Epidemiology of childhood cancer in a section of the private health sector of South Africa

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PREFACE

This dissertation is presented in article format. The chapters in this dissertation are outlined as follows:

- Chapter 1 provides an exhaustive background to the study, an outline of the aims and objectives and the research methods utilised in this study.
- Chapter 2 presents a literature review on childhood cancer, focusing on the types and classification, global trends in incidence rates of childhood cancers, risk factors associated with childhood cancers, treatment modalities employed in childhood cancers as well as the coexisting conditions and complications associated with childhood cancers and their treatment.
- Chapter 3 is made up of the results and discussions of the empirical study, which are presented in the form of manuscripts for submission and possible publication in the following journals:
  (a) Cancer epidemiology
  (b) Journal of epidemiology and global health
- Chapter 4 consists of the conclusions, recommendations and limitations of the study.

The references cited in this dissertation and annexures are indicated at the end of the dissertation.

The manuscripts presented in this dissertation were written and referenced in accordance with the author guidelines specified by the journals to which they were submitted. Other references indicated in this dissertation followed the Harvard referencing style, as prescribed by the North-West University.

The supervisor and co-supervisors of this study are indicated as co-authors in the manuscripts, and they revised and approved the final manuscript. The roles of each author are outlined in Chapter 3.

ABSTRACT

Epidemiology of childhood cancer in a section of the private health sector of South Africa

The study aimed at determining the incidence, prevalence and trends of childhood cancers over time, as well as identifying the common coexisting conditions in children and adolescents on treatment for cancer in the private health sector of South Africa.

A literature review, aimed at describing the types and classification of childhood cancer, elucidating the risk factors associated with childhood cancer, and identifying the treatment options, coexisting conditions and the complications of cancer and its treatment in children was carried out. The empirical investigation, utilising retrospective medicines claims data spanning the period of January 2008 to December 2017, obtained from a Pharmaceutical Benefit Management (PBM) company, followed a quantitative, descriptive, cross-sectional approach. The objectives of the empirical study were to:

1. Determine the incidence, prevalence and trends over time of childhood cancers in children younger than 19 years, stratified according to age group, gender, type of malignancy and geographic area.
2. Identify the common coexisting conditions in children and adolescents with cancer on the database.

The study population was categorised into five age groups, namely <1, 1-4, 5-9, 10-14 and 15<19 years using the age at last birthday on the database as the reference date.

The first objective was addressed in Manuscript one. Patients with International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes C00 to C97 for cancer in conjunction with claims for medicines reimbursed from patients' oncology benefit were selected for this study. Over the 10-year period, a total of 173 patients with cancer (0.01% of children younger than 19 years on the database) were identified. This translated into an age-standardised incidence rate (ASR) of 82.3 cases per million persons. The mean age of the study population was 10.0 ± 5.4 (95% CI, 9.2-10.9) years. Age-specific incidence rates were highest in 15<19 years' age group (112.8 cases per million persons) and lowest in the <1 year age group (13.2 cases per million persons). Higher incidence rates were estimated for males as compared to females, with ASRs of 112.3 and 51.9 cases per million persons, respectively. Leukaemias, lymphomas and central nervous system (CNS) neoplasms were the most frequently occurring cancers, with overall ASRs of 32.6, 11.7 and 9.1 cases per million persons,

respectively. Hepatic tumours were the least occurring cancers (ASR of 0.5 cases per million persons). The highest incidence rate of cancer was observed in the KwaZulu-Natal province (193.4 cases per million persons) followed by Gauteng (102.3 cases per million children). This may, however, not necessarily indicate a high incidence of cancers in those provinces since postal codes of prescribers were used as a proxy for geographic location. No new cases in the Eastern Cape, Mpumalanga, and Northern Cape provinces were identified on the database during the study period. Incidence rates of all childhood cancers combined decreased from 76.7 cases per million persons in 2008 to 58.2 cases per million persons in 2017. The prevalence of childhood cancers increased from 9 cases per 100 000 children in 2008 to 13.3 cases per 100 000 children in 2017. Leukaemias were consistently the most prevalent diagnostic group during the study period, with prevalence increasing from 25.0% of all cancer diagnostic groups in 2008 to 43.8% in 2017. With the exception of 2008, cancers were more prevalent in males as compared to females from 2009 to 2017.

Findings of the investigation into the coexisting conditions in children undergoing treatment for cancers were presented in manuscript two. A total of 2 631 non-cytotoxic medicine items were claimed for children and adolescents on cancer chemotherapy during the study period. Approximately 83% (n = 2 272) of these medicine items were claimed under non-specific diagnostic codes which included codes for repeat prescriptions, failure of patient or clinician to disclose clinical information, and encountering health services in unspecified conditions. A drug utilisation 90% (DU90) of medicine items claimed under non-specific diagnostic codes, using the Monthly Index of Medical Specialties (MIMS) classification indicated that antimicrobials, respiratory agents, analgesics, ear, nose and throat agents, gastrointestinal tract agents, central nervous system agents, autacoids, dermatological agents, endocrine agents, herbal preparations, musculoskeletal agents and anaesthetics, made up the top 90% medicines with these diagnostic codes. Diagnostic codes for diseases of the respiratory system, diseases of the gastrointestinal tract and disorders of the skin were associated with 7.15%, 1.60%, 0.95% and 0.91% of the medicine items, respectively. Antimicrobial agents were found to be the most frequently claimed medicines (17.4%, n = 458), followed by respiratory agents, (13.9%, n = 366) and analgesics (10.6%, n = 280), among all medicine claims. Overall, 82.1% (n = 2 160) of the medicine items claimed over the study period were reimbursed from patients' acute benefits and 0.5% (n = 13) were reimbursed from patients' chronic benefits.

In conclusion, this study provided an insight into the epidemiological trends of cancers in children and adolescents in a section of the South African private health sector, with specific reference to trends by gender, age group, malignancy type and geographic area. Coexisting

conditions in children and adolescents with cancer were also determined and results indicated that the majority of these coexisting conditions were acute rather than chronic.

Keywords: Incidence, childhood cancer, adolescents, incidence trends, coexisting conditions, utilisation patterns, South Africa.

LIST OF ABBREVIATIONS

5-HT3	5-hydroxytryptamine type 3
ACCIS	Automated Childhood Cancer Information System
AFCRN	African Cancer Registry Network
AIDS	Acquired immunodeficiency syndrome
ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukaemia
APC	Annual percentage change
ASR	Age-standardised incidence rate
CDC	Centers for Disease Control and Prevention
CINV	Chemotherapy-induced nausea and vomiting
CIPN	Chemotherapy-induced peripheral neuropathy
CNS	Central nervous system
DNA	Deoxyribonucleic acid
DU90%	Drug utilisation 90%
ENT	Ear, nose and throat
GIT	Gastrointestinal tract
GVHD	Graft-versus-host disease
HIV	Human immunodeficiency virus
HREC	Health Research Ethics Committee
HSCT	Haematopoietic stem cell transplantation
IACR	International Association of Cancer Registries
IARC	International Agency for Research on Cancer
ICCC	International Classification of Childhood Cancer
ICCC-3	International Classification of Childhood Cancer, third edition
ICD-10	International Classification of Diseases and Related Health Problems, 10th Revision
ICD-O	International Classification of Diseases for Oncology
IICC-1	International Incidence of Childhood Cancer, volume one

IICC-2	International Incidence of Childhood Cancer, volume two
IICC-3	International Incidence of Childhood Cancer, volume three
M/F	Male-to-female
MIMS	Monthly Index of Medical Specialties
MUSA	Medicine Usage in South Africa
NAPPI	National Approved Product Pricing Index
NCI	National Cancer Institute
NCR	National Cancer Registry
NCRI	National Cancer Registry of Ireland
NHL	Non-Hodgkin's lymphoma
NPCR	National Program for Cancer Registries
NWU	North-West University
PBM	Pharmaceutical benefit management
PMBs	Prescribed minimum benefits
PROMEC	Programme on Mycotoxin and Experimental Carcinogenesis
RNA	Ribonucleic acid
SACCSG	South African Childhood Cancer Study Group
SACTR	South African Children Tumour Registry
SEER	Surveillance, Epidemiology, and End Results
USA	United States of America
USD	United States Dollars
WHO	World Health Organization
ZAR	South African Rand

LIST OF DEFINITIONS

Cancer	A cluster of diseases characterised by uncontrolled proliferation of cells and the ability of the cells to migrate to both distant and nearby tissues from the original site (Gale Encyclopaedia of Medicine, 2008).
Carcinogen	Any agent or substance which induces the formation of cancer (NCI Dictionary of Cancer Terms, 2019).
Carcinoma	Cancer that originates from the skin or the lining of internal organs (NCI Dictionary of Cancer Terms, 2018).
Coexisting condition	A medical condition in a child with cancer which was present before or occurs after the diagnosis of cancer and which may or may not be caused by cancer (Aaberg *et al*., 2016).
Histology	The study of the minute structure of cells, tissues and organs and the relationship between their structure and function (Lowe & Anderson, 2015:1).
Immunosuppression	Impaired functioning of the immune response as a result of damage to the immune system, often augmenting the susceptibility to diseases (NCI Dictionary of Cancer Terms, 2019).
Malignancy	Condition which is characterised by uncontrolled growth of abnormal cells that has the ability to spread to other nearby tissues (NCI Dictionary of Cancer Terms, 2018).
Morphology	The form and structure of a particular organism, organ, tissue or cell (Miller-Keane Encyclopaedia and Dictionary of Medicine, Nursing and Allied Health, 2003).
Mutation	An alteration in the sequence of the genetic material of a cell (Griffiths, 2018).
Neoplasm	Abnormal tissue mass resulting from rapid uncontrolled cell division (NCI Dictionary of Cancer Terms, 2019).
New patient	Beneficiary of a medicial aid scheme with the first diagnosis code for cancer in conjunction with a claim reimbursed from oncology benefit in a particular year within the study period (2008-2017), but disease-free in the preceding year.
Prognosis	The anticipated outcome in a patient with a particular disease (Croft *et al*., 2015).

Registry	A place where a written record containing regular entries of items is kept (Merriam-Webster's Medical Dictionary, 2018).
Syndrome	A collection of signs and symptoms which occur simultaneously and are characteristic of an abnormal condition (Merriam-Webster's Medical Dictionary, 2019).

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CHAPTER 1: INTRODUCTION AND STUDY OVERVIEW

1.1 Introduction

This chapter presents an overview of the research project, providing the background and problem statement for the study. The questions to be answered by the study, the aims and the specific objectives, as well as the methodology will also be discussed. The chapter concludes with a description of the components of the next chapter in this study.

1.2 Background and problem statement

Childhood cancer, described as cancer occurring in children prior to their 19th birthday, forms part of the principal causes of mortality among children, with an approximated 80 000 annual deaths occurring worldwide (International Agency for Research on Cancer (IARC), 2016). The survival of these children has, however, increased in the last few decades in response to advancements in diagnostic procedures, cancer therapy and improved supportive care (Boman *et al*., 2010:1385; Seth *et al*., 2017:216; Hayek *et al*., 2018:127).

Childhood cancers, unlike adult cancers that are mostly carcinomas, are histologically disparate (Stiller, 2004:6429). Most of the cancers that occur in children and adolescents grow rapidly and are aggressively invasive (Anderson *et al*., 2000:573). They are usually not caused by mutable risk factors; the population-based screening and preventive programmes that are often employed in minimising cancers that occur in adults have, therefore, little benefits in the minimising of childhood cancers (Gupta *et al*., 2014). The histologically diverse nature of childhood cancers makes the classification thereof in accordance with their histology or morphology, instead of their initial site of origin as done in adults, more appropriate (Steliarova-Foucher *et al*., 2005:1457; Stiller, 2004:6429).

The incidence of childhood cancer exhibits marked geographic variations worldwide (Chirdan *et al*., 2009:127; Magrath *et al*., 2013:105), and has been linked to genetic, familial and environmental factors (Anderson *et al*., 2000:573; Howard *et al*., 2008:463; Lichtenstein *et al*., 2000:85). Cancer is comparatively rare among children globally, with approximately 0.5% prevalence in children aged younger than 15 years in developed countries (Fathi *et al*., 2015:5459; IARC, 2016; Stiller, 2004:6429). Nonetheless, the trend in the incidence of common childhood cancers has received much attention recently because of the concerns that they may be on the rise and certain environmental exposures may contribute to the occurrence of childhood cancer (Linet *et al*., 2003:218).

There have been publications of the International Incidence of Childhood Cancer (IICC-1) in 1988 (Parkin *et al*., 1988) and IICC-2 in 1998 (Parkin *et al*., 1998). For close to two decades after the second volume (IICC-2) was published, there had not been any data on the incidence of childhood cancer that could be used in international comparisons (Steliarova-Foucher, Colombet, Ries, Moreno *et al*., 2017:719). This necessitated an update on the incidence of childhood cancer by the IARC and the International Association of Cancer Registries (IACR), which is due to be published as the third volume of the International Incidence of Childhood Cancer (IICC-3) (Steliarova-Foucher, Colombet, Ries, Moreno *et al*., 2017:719-720). A significant update in IICC-3 is the addition of the 15 to 19-year age group, though cancers that occur in this age range differ from those in children with respect to type and distribution (Siegel, R.L. *et al*., 2018:27), as compared to the IICC-1 and IICC-2, which had an age range of between 0 and 14 years (Steliarova-Foucher, Colombet, Ries, Moreno *et al*., 2017:719). The addition of adolescents aged between 15 and 19 years, a transitional age group from childhood to adulthood, was necessitated by the lack of proper data for this age group, which could be used for comparisons (Steliarova-Foucher, Colombet, Ries, Moreno *et al*., 2017:720).

Data on the incidence of cancers are usually obtained from population-based or hospital-based registries and from cancer research publications (Howard *et al*., 2008:463; Steliarova-Foucher, 2019:460). The IARC, which is the specialised cancer agency for the World Health Organization (WHO) (IARC, 2018), conducts comprehensive studies into childhood cancers using information from multiple population-based tumour registries (Howard *et al*., 2008:463), providing a considerable source of information about the epidemiology of cancer in a number of countries. The worldwide childhood cancer incidence, according to IARC (2016), is reported to be increasing from previously estimated annual new cases of 16 500 to 215 000 cases in children younger than 15 years and 85 000 cases for those who are 15 to 19 years old. Table A.1 (Annexure A), which was used in the compilation of the IICC-3 (Steliarova-Foucher, Colombet, Ries, Hesseling *et al*., 2017), provides an overview of the incidence of childhood cancers in some countries across the globe. Incidence of childhood cancer is observed to be highest in England, followed by Germany and France for Europe, highest in India for the Asian countries, highest in the United States of America (USA), followed by Canada for North America, and highest in South Africa in comparison to other African countries. The highest incidence of childhood cancer is also recorded in adolescents aged between 15 and 19 years, followed by the one- to four-year age group. Although a number of researchers have observed this trend, the reason for the high incidence of cancer in adolescents between the ages of 15 and 19 years remains unknown (Burkhamer *et al.*, 2017; Noone *et al*., 2018).

Table 1.1 presents an overview of the incidence of childhood cancer in South Africa from 1998 to 2012, stratified by age group, gender and ethnic group as compiled by Steliarova-Foucher, Colombet, Ries, Hesseling *et al*. (2017). This study, however, did not include incidence among the newly introduced 15 to 19-year age group. Based on Table 1.1, the incidence of childhood cancer is observed to be highest in the one to four-year-old age group in all ethnic groups, with a significant male preponderance, and closely followed by the five to nine-year-old age group. The black population has always been the largest ethnic group in South Africa, with the recent general household survey in 2016 by Statistics South Africa estimating that 44 346 000 (approximately 80% of the population) of the total 55 176 000 South African population were black South Africans (Statistics South Africa, 2017). This could explain the observed high incidence of cancer in the black population across all age groups. The 2014 report on cancer statistics in South Africa by the National Cancer Registry also shows a higher incidence of childhood cancer in black South African children compared to all other ethnic groups (CANSA, 2018). Rates were also higher in males in comparison to their female counterparts. Other studies done in South Africa show similar trends in incidence rates with respect to age and ethnic groups (Erdmann *et al*., 2015:2631; Stefan *et al*., 2015:942).

The higher incidence of childhood cancer in the under-five-year age group, according to Table 1.1, has also been observed in other studies across the globe (Erdmann *et al*., 2018:24; Isaevska *et al*., 2017; Park *et al*., 2016:873; Siegel, D.A. *et al*., 2018; Youlden, 2014).

Table 1.1: Incidence of childhood cancer in South Africa from 1998-2012

	Asian		Black		Coloured		White		Total	Total population	Incidence rate (per million person-years)
Age group (years)	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**			
< 1	13	4	269	268	66	58	59	40	777	13 652 768	56.9
1-4	80	53	1 498	1 230	291	230	265	216	3 863	61 242 227	63.1
5-9	39	42	1 224	893	220	162	172	125	2 877	72 358 414	39.8
10-14	29	25	916	690	142	133	133	114	2 182	72 356 966	30.2
Total	**161**	**124**	**3 907**	**3 081**	**719**	**583**	**629**	**495**	**9 699**	**219 610 375**	**44.2**

Cancer continues to be the second-highest cause of death in the paediatric population in the USA, with an annual increase in incidence since 1975 and a seeming stabilisation from 2012 to date (Siegel, R.L. *et al*., 2018:28). Siegel, R.L. *et al*. (2018:27) estimated that 10 590 cases of cancer would be recorded in children younger than 15 years in the year 2018, with 1 180 deaths occurring in the same year.

Childhood cancer has received low publicity and priority in Africa, with many children continuing to die from the condition (Chirdan *et al*., 2009:127; Stefan, 2015a:35). This could be partly due to the lack of availability of proper data for comparative studies that could inform public health decisions (Stefan, 2015a:35). Another reason for the low publicity and priority of childhood cancer in Africa could also be due to the condition not being recognised as an important public health problem in a continent that is struggling with diseases such as tuberculosis, human immunodeficiency virus infection and acquired immunodeficiency syndrome (HIV/AIDS) and malaria, especially in children (Elhassan *et al*., 2018; Hadley *et al.,* 2012:138; Quilty, 2016:40; Stefan, 2010:317).

According to Chirdan *et al*. (2009:127), fewer than 20% of children living with cancer can access and afford therapy for cancers in the few established paediatric oncology centres, and consequently, more than 80% of these children die from these conditions. Other causes of the high mortality associated with childhood cancers in developing countries include late presentations to the hospital, poor nutritional status at time of presentation, absence of supportive care, irregular availability of drugs, frequent treatment interruptions and complete halting of treatment (Arora *et al*., 2007:941; Lam *et al*., 2019:1182). The belief of most parents of children with malignant conditions in traditional medicine and healing, especially in the rural areas, makes them prone to finding symptomatic care from traditional healers (Stefan *et al*., 2015:945). They mostly turn to the hospitals when the traditional remedies have failed; children, therefore, often present with advanced diseases (Chirdan *et al*., 2009:128; Hadley *et al*., 2012:140).

Even though developed countries have made great strides in its management, with survival rates of approximately 80% in both children and adolescents, childhood cancer remains a burden for most low-income countries, especially those in Africa (Chirdan *et al*., 2009:126; Hadley *et al.,* 2012:136*;* Siegel, R.L. *et al*., 2018:28; Stefan, 2010:317). Resources allocated by governments in Africa for cancer control are woefully inadequate (Hadley *et al*., 2012:138; Stefan, 2015a:35). The reason for this could be due to the general lack of recognition of these conditions and scarce national statistical data, although the low national *per capita* income of most African countries could also be the cause of the allocation of inadequate funds for cancer control (Stefan, 2015a:35). Some Northern African countries and South Africa are comparatively

wealthier than most African countries and are different in their social, political and economic environments (Hadley *et al*., 2012:137).

In the quest to advance the education, awareness and recognition of childhood cancer in South Africa and the whole of the South African region, the South African Children's Cancer Study Group (SACCSG) established the South African Children Tumour Registry (SACTR) in 1987 (Stefan & Stones 2012:605). The aim of establishing this registry was to obtain data to help estimate incidence and prevalence of childhood cancers in the various age groups and their distribution with regard to the geographical area, sex and ethnicity, which would, in turn, help in public health planning and scientific research (Stefan & Stones, 2012:605).

Another source of information about childhood cancer in South Africa is the National Cancer Registry (NCR), which was also established in 1986 (Stefan 2010:318). This registry has had inconsistencies with regard to childhood cancers (Stefan & Stones, 2012:605). This pathology-based registry collates data from both public and private laboratories, which implies that a number of cases that were only diagnosed clinically and not based on pathological reports were not registered. The register also does not distinguish between children and adults and consequently both children and adults were put in the same register, causing some data that are specific to children to be missed (Stefan, 2010:318). Private laboratories stopped providing data for the registry from 2006 onwards due to the fear of disclosing any confidential information (Erdmann *et al*., 2015:2629).

The Programme on Mycotoxin and Experimental Carcinogenesis (PROMEC) of the South African Medical Council also established the Eastern Cape Province Cancer Registry in the 1980s to study the trends and geographical disparities in the occurrence of oesophageal cancer in some magisterial areas of the Eastern Cape Province (African Cancer Registry Network (AFCRN), 2018; Singh *et al*., 2015:4). The registry broadened its scope to cover all other cancers and also some more magisterial areas in 1998 to be able to provide high-quality and comparable data to the research community, policy-makers and health professionals, to advance the health of the people living in the province (AFCRN, 2018; Singh *et al*., 2015).

Epidemiological data are important in the implementation of any cancer control strategy (Bhakta *et al*., 2019:e42; Gakunga & Parkin, 2015:2045; Segbefia *et al*., 2013:65). There have been limited epidemiological studies of childhood cancer in South Africa in recent years, one being published in 2010, using data from the SACTR and covering the years 1997 to 2007 (Stefan, 2010:318), another in 2013 covering the years 2003 to 2007 and using data from the Eastern Cape Province Cancer Registry (Somdyala *et al*., 2013), and another in 2015, covering years 2000 to 2006 (Erdmann *et al*., 2015), using data from the NCR. The latest statistical report from

the NCR is that of 2014 (NCR, 2018). Most epidemiological studies into childhood cancer in South Africa have been based on data from these registries and therefore the inconsistencies in the data and eventual lack of updates could be the reason for no current epidemiological studies in this field. There is, therefore, a need for current epidemiological studies to be conducted to be able to identify any variations in the pattern of incidence and prevalence of childhood cancers in South Africa in the last few years.

The acute and chronic nature of cancer and the resultant consequences on health and quality of life, due to the immunosuppression associated with it, make the presence of other coexisting conditions with cancer relatively common (Sarfati *et al*., 2016:338). While the associated immunosuppression with cancer predisposes patients to other conditions such as infections, there are paradoxically other conditions that predispose patients to cancer, especially those also linked to suppression of the immune system such as HIV and AIDS (Hensel *et al*., 2011:117). These immunosuppressive conditions are risk factors for the occurrence of some cancers including Kaposi's sarcoma and non-Hodgkin's lymphoma (Hensel *et al*., 2011:117). The presence of coexisting conditions sometimes results in the need for treatment protocol modification, which could influence treatment outcomes, while the treatment of cancer could also exacerbate coexisting conditions (Sarfati *et al*., 2016:340; Yang & Warnakulasuriya, 2016:1). There is, therefore, the need to investigate coexisting conditions associated with cancer when designing epidemiological studies into cancer.

The study aimed at addressing the following research questions:

- What are the current rates of incidence and prevalence of childhood cancer globally?
- What were the incidence and prevalence rates of childhood cancer in the section of the private health sector of South Africa?
- What are the common coexisting conditions present in children with cancer?

1.3 Research aims and objectives

Paragraphs in this section give the general research aim and the specific objectives of the study.

1.3.1 Research aims

The aim of the study was to determine the epidemiology of childhood cancer and to investigate the common coexisting conditions present in children and adolescents with cancer, in a section

of the private health sector of South Africa, using medicines claims data for the period of 1 January 2008 to 31 December 2017.

1.3.2 Specific research objectives

The study comprised a literature review and an empirical study.

1.3.2.1 Literature review

The objectives of the literature review were to:

- Conceptualise childhood cancer, describing the types and classification.
- Discuss the prevalence and incidence of childhood cancer in South Africa and internationally.
- Elucidate the causes of and risk factors associated with cancers of childhood.
- Identify the treatment options utilised in the management of childhood cancer.
- Identify the common coexisting conditions and the acute and long term complications associated with childhood cancer and its treatment.

1.3.2.2 Empirical investigation

The aims of the empirical investigation were to:

- Determine the incidence, prevalence and trends over time of childhood cancers in children younger than 19 years, stratified according to age group, gender, type of malignancy and geographic area[1] using a medicines claims database for the period 2008 to 2017.
- Identify the common coexisting conditions[2] in children and adolescents with cancer on the database.

1.4 Research methodology

In addressing the objectives of the study, the paragraphs subsequently outlined will focus on the research methods that were employed in the literature review and empirical study conducted.

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[1] Geographic area was defined as the province where children received treatment. Prescribers' postal codes were used as proxy measure to determine geographic area.

[2] Within the context of this study, coexisting condition was defined as a medical condition in a child with cancer that was present before or occurred after the diagnosis of the cancer and that may or may not have been caused by the cancer (Aaberg *et al*., 2016). Coexisting conditions were identified using the ICD-10 codes; in the absence of the ICD-10 codes, the main pharmacological classes for active ingredients of non-cytotoxic medications prescribed were noted.

1.4.1 Literature review

Literature from published work from reliable sources such as PubMed®, ScienceDirect®, Scopus®, GoogleScholar®, EBSCOhost® and books was reviewed in this study to help draw evidence-based conclusions from the findings of the study.

Combinations of keywords and phrases used for the internet search included, '*child', 'neoplasms', 'adolescent neoplasms', 'incidence', 'prevalence', 'epidemiology', 'antineoplastic', 'comorbidity' 'coexisting conditions', 'private health sector' and 'South Africa'.* The search was limited to the English language, and findings from 2000 to 2019 were used to identify relevant references.

1.4.2 Empirical investigation

The subsequent paragraphs cover the study design, data source, data fields, target and study population, study variables, and validity and reliability of the database that helped to attain the outlined objectives of the empirical investigation.

1.4.3 Study design

This study employed a descriptive retrospective observational study design, using medicines claims data from 2008 to 2017, obtained from one pharmaceutical benefit management (PBM) company with a substantial national representation.

Descriptive studies are used to depict the frequency of occurrence of a condition or phenomenon without regard to its causality (Waning & Montagne, 2001:46). When used in epidemiological research, they define the health of the population and open the way for further studies (Grimes & Schulz, 2002:145). A researcher undertaking an observational study observes individuals without any form of manipulation or intervention to achieve the outcome (Hartung & Touchette, 2009:399). Different study designs that were utilised to achieve the different specific objectives are summarised in Table 1.2.

Table 1.2: Study designs in conjunction with empirical objectives

Empirical objective	Study design
Determine the incidence, prevalence, and trends over time, of childhood cancers in children younger than 19 years, stratified according to age group, gender, type of malignancy and geographic area using medicines claims database for the period 2008-2017.	A retrospective open cohort study
Identify the common coexisting conditions in children and adolescents with cancer on the database.	Cross-sectional study

Hess (2004:1171) indicates that data that are used in retrospective studies are usually previously collected data and are not specifically collected for the purpose of research. These studies are relatively inexpensive because they use existing data and can be used to study diseases of rare occurrences.

In an open cohort study, the composition of the study population may change with time as a result of patients being recruited into or leaving the cohort at various time points (Messerlian & Basso, 2017:371).

Cross-sectional study designs focus on obtaining data of various variables at a single point in time and therefore have the advantage of allowing for the study of several variables and are helpful in estimating the prevalence of diseases (Thelle & Laake, 2015:291).

1.4.4 Study setting and data source

Data that were used for the analysis were received from the medicine claims database of a PBM company in South Africa. The database is an administrative claims database that is devoid of recall bias because it does not rely on interviewing patients to obtain information. The database, which is an electronic claims processing system, and used for managing medicine benefits, acts as an interface between the medical insurance scheme and the service providers.

The PBM company which provided data for the study is a large independent company that has been servicing the South African healthcare sector for more than 25 years. The company provides medicine claims processing services to over 1.8 million beneficiaries of about 42 medical schemes in South Africa and is integrated with approximately 16 different administrative platforms. Data covering the period of 1 January 2008 to 31 December 2017 were used in this study.

1.4.5 Data fields

Data fields on the PBM database that were used in the study include:

- patient demographics (gender, date of birth);
- encrypted patient number, encrypted dependant code;
- diagnosis code (based on the International Classification of Diseases and Related Health Problems, 10th revision, ICD-10 code);
- date prescription was dispensed;
- medicine prescribed (active substances);
- reimbursement category; and the
- postal code of provider (as a proxy to determine the geographic area of the patient).

1.4.6 Validity and reliability of data

Analysis of data from one source for the period of study provided results that could be generalised to the study population only. Data were checked thoroughly for duplication of claims and the exclusion criteria strictly enforced to make data reliable, although the study was carried out on the assumption that the data on the PBM database were correct and accurate.

Validity and reliability of the data were ensured through a validation process put in place by the PBM company. The process includes validation of the integrity of the data, management of the eligibility of the claims, review of drug utilisation and clinical management. Pre-authorisation services, including exception management and management of medicine pricing, are also carried out by the PBM company. All these processes are also intended to ensure that payments are made for claims meeting standards for claiming.

1.4.7 Target and study populations

The target population for this study was all patients, younger than 19 years with cancer, who were beneficiaries of a medical scheme in the South African private health sector, for the period 1 January 2008 to 31 December 2017.

The study population comprised an open cohort of patients younger than 19 years on the medicine claims database with a diagnosis code for cancer (ICD-10 code C00-C97) in conjunction with a claim for any medicine, reimbursed from the oncology benefit during the study period.

Patients who had incomplete demographics (age and gender) were excluded from the study.

1.4.8 Study variables

A variable refers to any measurable characteristic of a population whose value varies (Pagano, 2013:6). The variables that were used in this study are discussed in paragraphs 1.4.8.1 to 1.4.8.5.

1.4.8.1 Age group

In this study, the date of birth of the patients was used to calculate the patients' ages. Patients were then stratified by age at last birthday into age groups of <1 year, 1-4 years, 5-9 years, 10-14 years, and 15<19 years, based on the recent age range by the IARC for estimating the global incidence of childhood cancer (Steliarova-Foucher, Colombet, Ries, Hesseling *et al*., 2017).

1.4.8.2 Gender

The WHO (2018a) defines gender as the culturally accepted traits of women and men including the roles, societal standards and the relationship between men and women. Most epidemiological studies into cancers, especially childhood cancer, have reported a higher incidence in males compared to their female counterparts (Erdmann *et al*., 2015:2630; Lacour *et al*., 2010:174; Siegel *et al*., 2017:8; Ward *et al*., 2014:86). There was, therefore, the need to know if there would be a similar trend in this study. Categories of gender that were used in this study were male and female; any patient with an unknown gender was excluded.

1.4.8.3 Diagnosis

Diagnosis in this study was based on ICD-10 codes for both malignant and coexisting conditions. In the absence of ICD-10 codes, the main pharmacological drug classes for active substances prescribed, based on the Monthly Index of Medical Specialties (MIMS) classification system (Snyman, 2019), were noted.

1.4.8.4 Geographical area

The postal code of the service provider was used as a proxy for the geographical area of the study population.

1.4.8.5 Time/ year of study

The overall study period (2008-2017) was divided into annual periods.

1.5 Statistical analysis

Data were analysed using the Statistical Analysis System® SAS 9.4® programme (SAS Institute Inc., 2002-2012) and the Joinpoint Regression Program Version 4.7.0.0 (2019) by making use of descriptive and inferential statistics. Data were organised such as to enhance effective communication of the results and describe the characteristics of the variables.

1.5.1 Descriptive statistics

Descriptive statistics are used to depict, determine and abstract obtained data in such a way to make it meaningful (Vetter, 2017:1376). The arithmetic mean (average), standard deviation, frequency (n), percentages and confidence intervals (CI) were used to describe the data. Age-specific and overall crude incidence rates were expressed per million persons and standardised using the Segi World Standard Population (Ahmad *et al*., 2001).

1.5.2 Inferential statistics

Inferential statistics allow data obtained on a variable to be used to make conclusions or deductions about an unknown population framework and are, therefore, useful in establishing a cause and effect relationship between variables in a population (Vetter, 2017:1376).

1.5.1.1 Trend analysis

The change in the incidence of childhood cancers over time was investigated in this study. The change in trend over time was analysed using the joinpoint regression analysis. Joinpoint regression is used to analyse measures over time by identifying time point(s) where an observed trend changes, also known as joinpoint(s), and estimating the regression function of the identified joinpoints (Rea *et al*., 2017). The formula for the joinpoint regression model for the observations $(x_1,y_1),\ldots,(x_n,y_n)$, where $x_1<x_2<\ldots<x_n$ denotes the time variable and y_i (i=1,…,n) represent the response variable, is given as (Kim *et al*., 2000:336):

$$E[y|x] = \beta_0 + \beta_1 x + \delta_1 (x - \tau_1)^+ + \cdots + \delta_k (x - \tau_k)^+$$

Where:

$\tau_1<\ldots<\tau_k$ are the joinpoints

$$(x_i - \tau_k)^+ = \begin{cases} x_i - \tau_k \; for \; x_i > \tau_k \\ 0 \quad otherwise \end{cases}$$

Table 1.3 depicts the data analysis plan for the study.

Table 1.3: Data analysis plan for the study

Objective	Measurement	Variables		Statistical analysis		
		Dependent	Independent	Descriptive	Inferential	Effect size
Determine the incidence, prevalence and trends over time of childhood cancers in children younger than 19 years, stratified according to age group, gender, type of malignancy and geographic area using medicines claims database for the period 2008-2017	Demographic characteristics of the study population	Unique patients	Age Gender	Normal distribution: Mean (SD) (95% CI) Skew distribution: Median (IQR) Frequencies (%)		
	Number of patients as a % of the number of patients in the database (prevalence)	Patients	Age group Gender Malignancy type Geographical area Study period	Frequency (%)		
	Change in incidence over time	Patients	Study years 2008-2017	Frequency (%)	Joinpoint regression analysis	*p*-value <0.05
	Change in prevalence over time	Total number of patients	Study years (2008-2017) Age group Gender Malignancy type Geographical area	Frequency (%)		
	Total number of new patients with cancer per study year (incidence)	Patients	Age group Gender Diagnosis/malignancy type Geographical area Study year	Frequency (%)		

Objective	Measurement	Variables		Statistical analysis		
		Dependent	Independent	Descriptive	Inferential	Effect size
Identify the common coexisting conditions in children and adolescents with cancer on the database	Total number of patients with cancer and at least one medicine claim for a non-cytotoxic medication as a % of number of patients with cancer	Patients	Age group Gender Diagnosis/malignancy type	Frequency (%)		
	Prevalence of coexisting conditions with respect to number of medicine claims	ICD-10 codes		Frequency (%)		
		Main pharmacological group	ICD-10 codes (non-specific)	Frequency (%)		
	Prevalence of the main pharmacological classes of non-cytotoxic medications used in children and adolscents with cancer	Pharmacological class	Age group Gender	Frequency (%)		

1.6 Ethical considerations of the study

Permission to conduct the study was obtained from the PBM, the Scientific Committee of Medicine Usage in South Africa (MUSA) and the Health Research Ethics Committee (HREC) of the North-West University (NWU-00179-14-A1-08; Refer to Annexure B). Data received from the PBM for the study were anonymised prior to their release and, therefore, there was no information on the identity of patients, prescribers, medical schemes and service providers. This ensured the preservation of data privacy and confidentiality throughout the study. There were signed confidentiality agreements by the researcher and the study leaders for the use of the database.

The use of a retrospective database made the study one of low risk since patients whose information was used could not be identified or contacted. The benefits of the study, therefore, outweighed the risks involved.

1.7 Chapter summary

The rarity of childhood cancers in comparison with those occurring in adults, the lack of priority and publicity of childhood cancers especially in sub-Saharan Africa, and the seeming stabilisation in the occurrence of childhood cancers have been established in this chapter. There are, however, few recent epidemiological studies into childhood cancer in South Africa. The aims and objectives, as well as the methodology of the study, were also stated in this chapter. The subsequent chapter provides an extensive overview of the epidemiology of childhood cancer, risk factors associated with, the burden of, treatment of, and the coexisting conditions and complications associated with childhood cancers.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

This chapter focuses on the information obtained during the literature review. It provides an overview of the epidemiology of childhood cancer, the types, classification, treatment options, risk factors, and the coexisting conditions and complications that are associated with childhood cancer.

2.2 Definition of childhood cancer

Cancer is a group of diseases distinguished by the unrestrained reproduction of abnormal cells, which can invade both nearby and distant cells through the lymphatic system and the blood (Abotaleb *et al*., 2018:471; EPA, 2013:223; NCI Dictionary of Cancer Terms, 2018). The International Agency for Research on Cancer (IARC, 2016) further limits childhood cancer to cancer that presents in children who are younger than 19 years.

Childhood cancers are less common compared to cancers that occur in adults (Farazi *et al*., 2018:83; Murphy *et al*., 2013:95). Cancers occurring in children can be classified as haematopoietic tumours, which are the most frequently occurring cancers, tumours occurring in the central nervous system (CNS), and other solid tumours (Murphy *et al*., 2013:95; Pritchard-Jones *et al*., 2013:e97). These cancers also differ from those that occur in adults in their causes, rate of growth and spread, as well as the outcome of their treatment, making them not amenable to the risk prevention strategies employed in adults (Alibek *et al*., 2013; Gupta *et al*., 2014; Hopkins *et al*., 2013:e9; Murphy *et al*., 2013:95; NCI Dictionary of Cancer Terms, 2018).

Specific causes of childhood cancers are unknown, although genetic factors and some environmental exposures both in the prenatal (chemicals and radiation) and post-natal periods (viral infections and radiation) are thought to be associated with an increased risk of childhood cancers (Bhattacharya *et al*., 2014; Hewitt *et al*., 2003:20). Approximately 5% of these cancers are also considered to be associated with syndromes caused by genetic mutations (Moore, 2009:755; Murphy *et al*., 2013:97; NCI, 2017). The ontogenesis of childhood cancers is thought to begin with either germline mutations or damage to deoxyribonucleic acid (DNA) caused by exposure to a carcinogen, which eventually leads to uncontrolled cell division and growth (EPA, 2013:223). Common cancers that are present in children under the age of 15 years are leukaemias, CNS tumours and lymphomas, in descending order of frequency (NCI, 2017; Steliarova-Foucher, Colombet, Ries, Moreno *et al*., 2017:726). Lymphomas, however, are the

most commonly diagnosed cancers in adolescents who are 15 to 19 years old, followed by CNS tumours and leukaemias (NCI, 2017).

2.3 Classification of childhood cancer

Birch and Marsden (1987:622) were the first to propose a classification of childhood cancers, according to the coding of the International Classification of Diseases for Oncology (ICD-O), which was accepted internationally, in 1987. The second edition of the ICD-O (Percy *et al*., 1990) and the tenth revision of the International Classification of Diseases (ICD-10) of the WHO introduced an advanced and broadened coding of cancer, and this necessitated an update of the International Classification of Childhood Cancer (ICCC) to its second edition (Kramárová & Stiller, 1996:759). Improvements in diagnostic methods, as well as pathological and genetic studies as a result of advancements in technology, necessitated a revision of the second edition of the ICD-O, to its third edition (Fritz *et al*., 2000). The third edition of the ICD-O (ICD-O-3), which revised the morphological codes for lymphomas and leukaemias, in particular, prompted a revision of the second edition of the ICCC by Steliarova-Foucher and colleagues (2005:1458), to its third edition (ICCC-3).

The third edition of the ICCC (ICCC-3), which is currently the accepted classification system for childhood cancers, employs both the topographical and morphological codes of ICD-O-3 (Steliarova-Foucher *et al*., 2005:1458). Classification is done on three major levels, with Level 1 being the major diagnostic groups and designated by roman numerals; diagnostic subgroups making up Level 2, and designated by alphabets; and Level 3 being a sub-division of the subgroups of Level 2 (Steliarova-Foucher *et al*., 2005:1458). The sub-division of Level 2, although they allow homologous tumours in a group to be differentiated from each other, are not frequently used due to a deficiency of diagnostic methods (Steliarova-Foucher *et al*., 2005:1458). The various classifications of the ICCC-3, based on the classification by Steliarova-Foucher *et al*. (2005), are given in Table 2.1.

Table 2.1: International Classification of Childhood Cancer

Level 1	Level 2
I Leukaemias, myeloproliferative and myelodysplastic diseases	a. Lymphoid leukaemias b. Acute myeloid leukaemias c. Chronic myeloproliferative diseases d. Myelodysplastic syndrome and other myeloproliferative diseases e. Unspecified and other specified leukaemias
II Lymphomas and reticuloendothelial neoplasms	a. Hodgkin lymphomas b. Non-Hodgkin lymphomas (except Burkitt lymphoma) c. Burkitt lymphoma d. Miscellaneous lymphoreticular neoplasms e. Unspecified lymphomas
III CNS and miscellaneous intracranial and intraspinal neoplasms	a. Ependymomas and choroids plexus tumour b. Astrocytomas c. Intracranial and intraspinal embryonal tumours d. Other gliomas e. Other specified intracranial and intraspinal neoplasms f. Unspecified intracranial and intraspinal neoplasms
IV Neuroblastoma and other peripheral nervous cell tumours	a. Neuroblastoma and ganglioneuroblastoma b. Other peripheral nervous cell tumours
V Retinoblastoma	
VI Renal tumours	a. Nephroblastoma and other nonepithelial renal tumours b. Renal carcinomas c. Unspecified malignant renal tumours
VII Hepatic tumours	a. Hepatoblastoma b. Hepatic carcinomas c. Unspecified malignant hepatic tumours
VIII Malignant bone tumours	a. Osteosarcomas b. Chondrosarcomas c. Ewing tumour and related sarcomas of bone d. Other specified malignant bone tumours e. Unspecified malignant bone tumours
IX Soft tissue and other extraosseous sarcomas	a. Rhabdomyosarcomas b. Fibrosarcomas, peripheral nerve sheath tumours, and other fibrous neoplasm c. Kaposi sarcoma d. Other specified soft tissue sarcomas e. Unspecified soft tissue sarcomas

Level 1	Level 2
X Germ cell tumours, trophoblastic tumours and neoplasms of gonads	a. Intracranial and intraspinal germ cell tumours b. Malignant extracranial and extragonadal germ cell tumours c. Malignant gonadal germ cell tumours d. Gonadal carcinomas e. Other and unspecified malignant gonadal tumours
XI Other malignant epithelial neoplasms and malignant melanomas	a. Adrenocortical carcinomas b. Thyroid carcinomas c. Nasopharyngeal carcinomas d. Malignant melanomas e. Skin carcinomas f. Other and unspecified carcinomas
XII Other and unspecified malignant neoplasms	a. Other specified malignant tumours b. Other unspecified malignant tumours

2.4 Epidemiology of childhood cancer

Childhood cancers are uncommon and represent a small percentage of all cancers (Bhakta *et al*., 2019:e42; Israels *et al*., 2015:607; Yang *et al*., 2014:285). Their occurrence is, however, associated with psychological and medical distress, and represents an important public health problem (Bidwell *et al*., 2019; Kaatsch, 2010:277; Steliarova-Foucher, Colombet, Ries, Moreno *et al*., 2017:719). Several interventions have been put in place to control childhood cancers (WHO, 2018b). These include prioritising childhood cancer by raising its awareness at both national and global levels, and building the capacities of countries to improve on their childhood cancer care (WHO, 2018b). Notwithstanding the rarity of childhood cancers, a study by Steliarova-Foucher, Colombet, Ries, Moreno *et al*. (2017:727) showed a 13% increment in the incidence of childhood cancers from the 1980s to between 2001 and 2010.

2.4.1 Global trends and incidence rates

Studies on the trends in the incidence of childhood cancers may help to generate hypotheses for future epidemiologic studies as well as the development of robust policies and programmes for their control (Bhakta *et al*., 2019:e42; Ward *et al*., 2019:483; Xie *et al*., 2018:79; Ye *et al*., 2017). Again, to allow for a critical evaluation of the policies and strategies currently in use for the control and the prevention of childhood cancer, a description of the trends in the epidemiology over time is necessary (Hopkins *et al*., 2013:e10; Yang *et al*., 2014:285). Variations in the incidence of childhood cancers with respect to gender, diagnostic group and geographical regions have been reported in some studies (Steliarova-Foucher, Colombet, Ries, Moreno *et al*., 2017:727). Table 2.2 is a compilation of some epidemiological studies that have

been carried out in various parts of the globe. Paragraphs in this section give an overview of the trends in incidence rates of childhood cancers across the globe.

2.4.1.1 Childhood cancer in Europe

The Automated Childhood Cancer Information System (ACCIS), a programme initiated with the aim of compiling and publicising information on the incidence and survival of childhood cancers in Europe, pools data from different geographical areas in Europe to provide enough statistical power to estimate the incidence and changing trends in childhood cancers (Kaatsch *et al*., 2006:1962). This method of data pooling is necessary due to the rarity of childhood cancers (Kaatsch *et al*., 2006:1962). Earlier epidemiological studies in Europe using data from ACCIS indicated an average annual increase of approximately 1% in all cancers (Kaatsch *et al*., 2006:1962; Steliarova-Foucher *et al*., 2004:2101), but there has been a seeming stabilisation in the incidence rates of childhood cancers in Europe in recent years (Desandes *et al*., 2014:976; Isaevska *et al*., 2017; Karim-Kos *et al*., 2016:74; Marcos-Gragera *et al*., 2017:306; Nakata *et al*., 2018:424). Average annual incidence rates in the last three decades have ranged between 140 cases per million person-years (n = 48 847) (Steliarova-Foucher *et al*., 2004:2098) and 140.9 cases per million person-years (n = 20 408) (Kaatsch *et al*., 2006:1962). A study by Steliarova-Foucher, Colombet, Ries, Moreno *et al*. (2017:722), however, reported 140 to 170 cases per million person-years for children aged younger than 15 years and 180 to 240 cases per million person-years for those aged 15 to 19 years.

Results of a number of studies done in Europe indicate that leukaemia has the highest incidence followed by lymphomas in children who are 0 to 14 years, while lymphomas are the most common cancer in the 15 to 19-year age group (Isaevska *et al*., 2017; Kaatsch, 2010:279; Kaatsch *et al*., 2006:1964; Peris-Bonet *et al*., 2010:iii106; Pesola *et al*., 2017:1866; Steliarova-Foucher, Colombet, Ries, Moreno *et al*., 2017:724-725; Steliarova-Foucher *et al*., 2018:1164). A study by Steliarova-Foucher *et al*. (2018:1164), covering the years 1991 to 2010, and using data from 53 registries across Europe, reported an average age-standardised incidence rate (ASR) of all cancers in children under the age of 15 years as 137.5 per million person-years (n = 118 265). The results showed an ASR of 46.9 per million person-years (n = 48 458) for leukaemia, and 15.8 per million person-years (n = 18 458) for lymphoma in this age group. For those aged 15 to 19 years, the average ASR of all cancers was 176.2 per million person-years (n = 35 138), with an ASR of 23.6 per million person-years (n = 4 702) for leukaemia, and 47.4 per million person-years (n = 9 446) for lymphoma. Data from the National Cancer Registry of Ireland (NCRI) also indicate a similar trend in the occurrence of leukaemia in children under the age of 15 years (30%, n = 137) and of lymphoma in children between 15 and 19 years (23%, n = 74), for cases recorded for the years 1994 to 2014 (NCRI, 2017).

A higher incidence of cancer is recorded in males compared to females for both the under 15 and 15 to 19-year age groups (Isaevska *et al*., 2017; Kaatsch, 2010:279). With the exception of germ cell tumour, which has a higher occurrence in females than males, a higher incidence in males is seen in all the other individual major diagnostic groups of childhood cancer (Isaevska *et al*., 2017; Kaatsch, 2010:279). Peris-Bonet *et al*. (2010:iii106), in a study in Spain covering the years 1983 to 2002, reported ASRs of 169.41 per million person-years (n = 3 311) in males under the age of 15 years, and 141.48 per million person-years (n = 2 625) in females for the same age group. Isaevska *et al*. (2017) in their study covering the years 1967 to 2011, which used data from the Childhood Cancer Registry of Piedmont, Italy, also showed a male-to-female ratio of 1.3:1 in the incidence of cancer in children under the age of 15 years, (total number of patients in this age group = 4 411). The overall male-to-female ratio in the incidence of cancer in all patients from 0 to 19 years was also 1.3:1 (total number of patients in this age group = 5 020) (Isaevska *et al*., 2017). A study in France covering the years 2000 to 2004 also reported an overall male-to-female ratio of 1.2:1 (n = 8 473) in the incidence of cancer (Lacour *et al*., 2010:176). The National Cancer Registry of Ireland (2017) estimated an ASR (using the world standard population) of 164 per million person-years for males (n = 73), and 152 per million person-years for females (n = 64) between the years 1994 and 2014.

Similar trends in incidence rates of childhood cancers indicating male predominance have also been observed in England. A report by Public Health England on the incidence of childhood cancer in England for the years 2001 to 2015, indicated an ASR of 166 per million (n = 11 617) in males under the age of 15 years, and 145 per million (n = 9 672) in females. Leukaemias constituted the highest occurring malignancy (31%, n = 6 514), followed by CNS neoplasms (25%, n = 5 231) (Public Health England, 2018).

2.4.1.2 Childhood cancer in America

The National Program for Cancer Registries (NPCR) of the Centers for Disease Control and Prevention (CDC), and the Surveillance, Epidemiology, and End Results (SEER) programme initiated by the National Cancer Institute (NCI), together cover the whole population of the USA and provide data on childhood cancers for epidemiological studies (CDC, 2018). Several epidemiological studies of childhood cancers have utilised data from these databases (Siegel, D.A. *et al*., 2018; Ward *et al.*, 2014:83).

Modest increases in the annual incidence rates of childhood cancers of approximately 0.6% have been observed since 1975 in the USA; estimates in recent years have, however, shown some level of stabilisation (Noone *et al*., 2018; Siegel, R.L. *et al*., 2018:27).

Results of the study by Siegel, D.A. *et al*. (2018), covering the period of 2003 to 2014, gave an overall incidence rate (ASR, adjusted by the 2000 US population) of 173.7 per million person-years (n = 171 432) in children and adolescents aged younger than 20 years. Higher incidence rates were recorded in males (ASR = 181.5 per million person-years, n = 91 667) in comparison to females (ASR = 165.5 per million person-years, n = 79 765). The diagnostic group with the highest incidence rate was leukaemias (ASR = 45.7 per million persons), followed by brain tumours (ASR = 30.9 per million persons) and lymphomas (ASR = 26.2 per million persons) (Siegel, D.A. *et al*., 2018). Stratification according to ethnic groups reported the highest incidence rates in Caucasians (ASR = 184.4 per million persons, n = 103 650) in comparison to African Americans (ASR = 133.3 per million persons, n = 20 188), Hispanics (ASR = 168.9 per million persons, n = 36 197), American Indian or Alaska Natives (ASR = 147.6 per million persons, n = 1 507) and Asian or Pacific Islanders (ASR = 144.6 per million persons, n = 7 089).

Similar trends in incidence rates were also reported by Ward *et al*. (2014:86), for the years 2006 to 2010. Incidence rates in males, 0 to 14 years, were higher (ASR = 178 per million persons, using the 2000 standard US population) compared to females of the same age group (ASR = 160.1 per million persons). Incidence rates were, however, similar for both males and females of the 15 to 19-year age group (ASR = 237.7 and 235.5 per million persons, respectively) (Ward *et al*., 2014:86). Incidence rates were highest in Caucasians when rates were stratified according to ethnic groups, with rates of 178.2 and 259.4 per million persons in the 0 to14-year and 15 to 19-year age groups, respectively. Incidence rates of 134.5 and 171.9 per million persons were recorded in African Americans, 167.3 and 220.7 per million persons in Hispanics, 131.9 and 167.8 per million persons in Asian or Pacific Islanders, and 117.1 and 200.1 per million persons in American Indian or Alaska Natives, for the <15 years and 15 to 19-year age groups, respectively.

Data used to compile the IICC-3, which covered the years 1998 to 2012 showed similar trends in incidence rates (Steliarova-Foucher, Colombet, Ries, Hesseling *et al*., 2017). Overall, higher incidence rates were recorded in males in comparison to females for the 0 to 19-year age group (ASR = 187.5 per million person-years, n = 115 586 and ASR = 171.4 per million person-years, n = 101 155 for males and females, respectively). Stratification according to the main diagnostic groups gave a higher incidence of leukaemias (ASR = 47.3 per million person-years, n = 54 132), followed by CNS neoplasms (ASR = 38.9 per million person-years, n = 46 710). The most frequently diagnosed cancer in children under the age of 15 years was leukaemia (n = 44 596, N = 146 015), while lymphoma constituted the most frequently occurring cancer in the 15 to 19-year age group (n = 15 498, N = 70 726) (Steliarova-Foucher, Colombet, Ries, Hesseling *et al*., 2017).

Canada recorded a gradual increase in the incidence of childhood cancers by an average annual rate of 0.4% from 1992 to 2010 (Ellison & Janz, 2015). Using data from the Canadian Cancer Registry and covering the years 2006 to 2010, results of the study by Ellison and Janz (2015) gave an average incidence rate of all cancers in children, 0 to 14 years, as 161 per million person-years per year (average annual incident cases = 905). Higher incidence rates were recorded in males compared to females (10 times higher in males than in females). Leukaemias were the most frequently diagnosed childhood cancer (32%, n = 292), followed by CNS tumours (19%, n = 173) and lymphomas (11%, n = 100) (Ellison & Janz, 2015).

Data used for the IICC-3 and covering the years 1992 to 2013 gave an overall estimated ASR of 176.4 per million person-years, for children aged 0 to 19 years in Canada (Steliarova-Foucher, Colombet, Ries, Hesseling *et al*., 2017). Rates were higher in males (ASR = 184.5 per million person-years, n = 14 667) compared to females (ASR = 168.0 per million person-years, n = 12 729). Overall, higher incidence rates were recorded for leukaemias (ASR = 48.1 per million person-years, n = 6 963), followed by CNS tumours (ASR = 30.8 per million person-years, n = 4 730) and lymphomas (ASR = 26.1 per million person-years, n = 4 500). However, the most frequently occurring cancer in children under the age of 15 years was leukaemia (n = 5 884, N = 18 309) while lymphomas were the highest occurring malignancy in the 15 to 19-year age group (n = 2 435, N = 9 087) (Steliarova-Foucher, Colombet, Ries, Hesseling *et al*., 2017).

In the study by Xie *et al*. (2018:81), covering the years 1992 to 2010 in children aged younger 15 years and using data from the Canadian Cancer Registry, overall incidence rates increased from 154.8 per million persons in 1992 to 169.7 per million persons in 2010, representing an average annual percentage increase of 0.4%. Incidence rates were higher in males in comparison to females (ASR = 168.0 per million persons, n = 9 380, and 150.7 per million persons, n = 8 000, respectively). Leukaemias were the most frequently diagnosed childhood cancers (ASR = 50.7 per million persons, n = 5 485) followed by CNS tumours (ASR = 30.4 per million persons, n = 3 345) and lymphomas (ASR = 17.0 per million persons, n = 1 905) (Xie *et al*., 2018:82).

Similar trends in incidence rates of childhood cancers have also been reported in some of the Latin American and Caribbean countries. Argentina recorded an ASR of 128.1 per million person-years (n = 18 067) between the years 2000 and 2013, for children aged <15 years. Higher rates were recorded in males (ASR = 140.6 per million person-years, n = 10 109) than females (ASR = 114.9 per million-person-years, n = 7 942). Leukaemias constituted the most frequently diagnosed childhood cancers (ASR = 48.1 per million person-years, n = 6 757), followed by CNS neoplasms (ASR = 23.8 per million person-years, n = 3 396) and lymphomas

(ASR = 14.6 per million person-years, n = 2 148) (Steliarova-Foucher, Colombet, Ries, Hesseling *et al*., 2017).

Moreno *et al*. (2013:468), in their study covering the period 2000 to 2008 in Argentina for children aged younger than 15 years, recorded similar trends. An overall ASR of 128.5 per million population was recorded for all childhood cancers during the study period. More males than females were diagnosed with cancers as evidenced by an overall male-to-female ratio of 1.3. Leukaemias were the most frequently diagnosed childhood cancers (ASR = 47.5 per million population), followed by brain and spinal neoplasms (ASR = 23.5 per million population), and then lymphomas (ASR = 15.6 per million population) (Moreno *et al*., 2013:468).

For the years 1995 to 2012, Brazil recorded an overall ASR of 151.0 per million person-years (n = 3 858) for children from 0 to 19 years, with a higher rate in males (ASR = 162.3 per million person-years, n = 2 085) than females (ASR = 139.7 per million person-years, n = 1 773). Leukaemias were the most frequently occurring cancer in all children from 0 to 19 years (ASR = 41.6 per million person-years, n = 1 001). Lymphomas were, however, the most prevalent cancers in the 15 to 19-year age group (ASR = 38.3 per million person-years, n = 281), followed by leukaemias (ASR = 25.2 per million-person-years, n = 185) and CNS neoplasms (ASR = 17.2 per million person-years, n = 126), whille leukaemias were the most common cancers in the <15 years age group (ASR = 46.4 per million person-years, n = 816), followed by CNS neoplasms (ASR = 24.8 per million person-years, n = 451) and lymphomas (ASR = 18.9 per million person-years, n = 361) (Steliarova-Foucher, Colombet, Ries, Hesseling *et al*., 2017).

Recent research conducted by Erdmann *et al*. (2018:24) on childhood cancer incidence in Costa Rica for the years 2000 to 2014 reported an ASR (using the Segi World Standard Population) of 140.0 per million persons for children aged younger than 15 years (n = 2 396). Higher incidence rates were observed in males compared to females (male-to-female ratio of 1.2). Leukaemias occurred more frequently than all the other childhood cancer types (ASR = 58.5 per million persons, n = 970), followed by CNS neoplasms (ASR = 19.4 per million persons, n = 334) and lymphomas (ASR = 16.6 per million persons, n = 304) (Erdmann *et al*., 2018:24). Estimates for Costa Rica by Steliarova-Foucher, Colombet, Ries, Hesseling *et al*. (2017), which covered a longer period from 1993 to 2012, reported an ASR of 133.9 per million person-years for children aged 0 to 14 years (n = 3 112), with a higher incidence rate in males (ASR = 142.6 per million person-years, n = 1 696) as compared to females (ASR = 124.8 per million person-years, n = 1 416). For stratification according to diagnostic groups, a higher incidence was observed for leukaemia (ASR = 55.5 per million person-years, n = 1 251), followed by CNS neoplasms (ASR = 18.4 per million person-years, n = 430) and then

lymphomas (ASR = 16.7 per million person-years, n = 413). Estimates of incidence rates were also made for adolescents aged 15 to 19 years by Steliarova-Foucher, Colombet, Ries, Hesseling *et al.* (2017). A total number of 1 443 incident cases of cancer were recorded for children aged 15 to 19 years for the period 1993 to 2012, with a higher number of males (n = 804) compared to females (n = 639). Stratification according to the diagnostic groups for adolescents aged 15 to 19 years, however, indicated that the most frequently occurring cancers in this age group were carcinomas and melanomas (n = 293), followed by the lymphomas (n = 268) and then leukaemias (n = 239).

2.4.1.3 Childhood cancer in Asia

A number of epidemiological studies have been carried out in Asian countries in recent times to estimate the incidence and trends of childhood cancers in these countries (Das *et al*., 2017:1035; Hossain *et al*., 2016; Hung *et al*., 2014:3547; Nakata *et al*., 2018:424; Park *et al*., 2016:870; Yang *et al*., 2014:286; Zheng *et al*., 2015:177).

A study done by Hung *et al*. (2014:3548) reported an overall ASR of 132.08 per million person-years (n = 12 315) for childhood cancers (0 to 19 years) in Taiwan, for the years 1995 to 2009. Higher incidence rates were recorded in males (ASR = 142.81 per million person-years, n = 6 896) compared to females (ASR = 120.43 per million person-years, n = 5 419), with leukaemias being the highest occurring cancer (ASR = 39.12 per million person-years, n = 3 520).

For the years 1993 to 2010, Nakata *et al*. (2018:427) reported an overall ASR of 121.1 per million person-years (n = 5 192) for children younger than 15 years in Japan. Leukaemias were the most frequently occurring childhood cancer (ASR = 42.0 per million person-years, n = 1 794), followed by CNS neoplasms (ASR = 18.0 per million person-years, n = 796) and neuroblastoma (ASR = 16.2 per million person-years, n = 604). Similar trends in the incidence rates of cancers stratified by the main childhood cancer diagnostic groups were shown in the data for the IICC-3 (covering years 1990 to 2013), with leukaemias being the most frequently occurring cancers for children aged 0 to 14 years (ASR = 44.5 per million person-years, n = 2 555), followed by CNS neoplasms (ASR = 26.4 per million person-years, n = 1 574) and neuroblastoma (ASR = 15.8 per million person-years, n = 798) (Steliarova-Foucher, Colombet, Ries, Hesseling *et al*., 2017). Incidence rates, however, were shown to be decreasing with time as evidenced by rates of 126.6 per million person-years for the years 1993 to 1998, 119.9 per million person-years for the years 1999 to 2004, and 115.9 per million person-years for the years 2005 to 2010 (Nakata *et al*., 2018:425).

Results of a study carried out by Zheng *et al*. (2015:177) for the period 2000 to 2010 in China, reported an ASR of 87.1 per million persons for children younger than 15 years, with higher rates in males (ASR = 96.2 per million persons) than in females (ASR = 76.4 per million persons). The most frequently occurring childhood cancer was leukaemia (ASR = 35.6 per million persons), followed by CNS neoplasms (ASR = 15.0 per million persons) and then lymphomas (ASR = 6.4 per million persons).

Incidence rates of childhood cancers in Bangladesh from 2001 to 2014 for children younger than 15 years, rose significantly from 2.0 per million person-years for the period 2001 to 2006, through 5.1 per million person-years for the period 2007 to 2010, to 7.8 per million person-years for the period 2011 to 2014 (Hossain *et al*., 2016). Incidence rates for adolescents in the 15 to 19-year age group increased from 1.5 per million person-years for the period 2007 to 2010, to 2.1 per million person-years for the years 2011 to 2014 (Hossain *et al*., 2016). Male predominance was observed in both children younger than 15 years (male-to-female ratio = 2.0) and adolescents aged 15 to 19 years (male-to-female ratio = 1.4). Leukaemia was the most prevalent type of childhood cancer in children younger than 15 years (27.56%, n = 804), followed by retinoblastoma (15.56%, n = 454), while bone tumours were the most frequently occurring cancer in adolescents (30.08%, n = 68), followed by lymphoma (19.91%, n = 45) (Hossain *et al*., 2016).

Similar trends in incidence rates were reported for children younger than 15 years in a study by Park *et al*. (2016:872) in Korea, for the period 1999 to 2011. The overall ASR was 134.9 per million persons (n = 15 113). Higher rates were recorded in males (ASR = 144.0 per million persons, n = 8 435) as compared to females (ASR = 124.9 per million persons, n = 6 678). Leukaemias were the most prevalent childhood cancers, with an ASR of 46.4 per million persons (n = 5 176), followed by CNS neoplasms (ASR = 18.3 per million persons, n = 2 121) and then lymphomas (ASR = 13.4 per million persons, n = 1 621) (Park *et al*., 2016:873).

In their study in Thailand, covering years 1990 to 2011, Bidwell *et al*. (2019) estimated an overall ASR of 98.5 per million person-years (n = 3 574) in children and adolescents aged 0 to 19 years. More males than females were diagnosed with cancers, as evidenced by ASRs of 104.8 per million person-years and 91.8 per million person-years, respectively. Leukaemias, brain and spinal neoplasms, and lymphomas constituted the most prevalent malignancies in the study population with ASRs of 36.1, 12.0, and 10.3 per million person-years, respectively.

2.4.1.4 Childhood cancer in Australia and New Zealand

Baade and colleagues (2010:622) reported an average annual incidence of 157.5 per million persons (n = 618.4) of childhood cancer (0-14 years) from 1997 to 2006. Leukaemias constituted the highest occurring malignancy (ASR = 53.1 per million persons per year, n = 207.2), followed by CNS neoplasms (ASR = 35.7 per million persons per year, n = 140.5) and lymphomas (ASR = 15.4 per million persons per year, n = 62.0). Higher incidence rates were recorded for males than females in this period (ASR = 167.2 and 147.2 per million persons per year, respectively) (Baade *et al*., 2010:623).

Recent estimates of the incidence of childhood cancer by Cancer Council Queensland, which oversees the Australian Childhood Cancer Registry, indicate a significant increment in the incidence of childhood cancer by a total of 35% from 1983 to 2014 (Cancer Council Queensland, 2018). The average incidence rate of cancers for children aged younger than 15 years was estimated to be 172 per million persons per year (n = 750) between 2010 and 2014 — a significant increase from the rates estimated by Baade *et al.* (2010:622). Leukaemias were the most frequently occurring childhood cancers for the five-year period, accounting for 33% of the total recorded cases, followed by CNS neoplasms (25%) and lymphomas (10%). More males than females were estimated to have cancer (55% versus 45%, respectively) (Cancer Council Queensland, 2018).

Estimates of the incidence of childhood cancers in New Zealand by Ballantine *et al*. (2017), for the years 2010 to 2014 and using data from the New Zealand Childhood Cancer Registry, reported an average annual ASR of 166.8 per million per year (number of cases recorded in the period = 762). Estimates were carried out in children under the age of 15 years. Rates were higher in males compared to females (ASR = 183.2 and 149.6 per million per year, respectively). Incidence of cancer was highest in the under-five years' age group (ASR = 243.6 per million per year), followed by the 10 to14 year age group (ASR = 131.5 per million per year) and the 5 to 9 years age group (ASR = 123.5 per million per year). Leukaemias were the most frequently occurring childhood cancer (ASR = 55.5 per million per year), followed by CNS tumours (ASR = 34.7 per million per year) and lymphomas (ASR = 18.0 per million per year).

Table 2.2 provides an overview of some of the epidemiological studies on childhood cancers carried out in Europe, America, Asia, Australia and New Zealand, detailing the country of study, year of inception, overall incidence rates and the most prevalent cancers in the various age groups. As reported in Table 2.2, most of the studies were carried out in children younger than 15 years, with leukaemias accounting for a higher proportion of malignancies in this age group. Lymphomas were the highest occurring cancers in the 15 to 19-year age group in most studies

that were carried out in this age group. Higher male-to-female ratios were observed in all the studies that measured incidence in both gender groups.

Table 2.2: Description of epidemiological studies on childhood cancers in Europe, America, Asia, Australia and New Zealand

Continent/ Country		Year of inception	Overall incidence rate for study period (per million person-years)		Most prevalent type of cancer		M/F ratio	Author and year of publication
			<15 years	15-19years	<15 years	15-19 years		
Europe	19 countries across Europe	1988–1997	138.5	N/A	Leukaemias	N/A	N/A	Kaatsch (2010)
	19 countries across Europe	1991–2010	137·5	176·2	Leukaemias	Lymphomas	N/A	Steliarova-Foucher *et al*. (2018)
	England	1993–2010	132.0	N/A	Leukaemias	N/A	N/A	Nakata *et al*. (2017)
	France	2000–2004	156.6	N/A	Leukaemias	N/A	1.2	Lacour *et al*. (2010)
	Italy	1967–2011 (2000–2011) for adolescents	156.9	281.7	Leukaemias	Lymphomas	1.3	Isaevska *et al*. (2017)
	Spain	1983–2002	155.8	N/A	Leukaemias	N/A	1.3	Peris-Bonet *et al*. (2010)
America	Canada	1992–2010	159.6	N/A	Leukaemias	N/A	1.1	Xie *et al*. (2018)
	Canada	1992–2013	164.9	216.3	Leukaemias	Lymphomas	1.2	Steliarova-Foucher, Colombet, Ries, Hesseling *et al*. (2017)
	Canada	2006–2010	161.0	N/A	Leukaemias	N/A	1.1	Ellison and Janz (2015)
	United States of America	1998–2012	166.9	223.5	Leukaemias	Lymphomas	1.1	Steliarova-Foucher, Colombet, Ries, Hesseling *et al*. (2017)

Continent/ Country		Year of inception	Overall incidence rate for study period (per million person-years)		Most prevalent type of cancer		M/F ratio	Author and year of publication
			<15 years	15-19years	<15 years	15-19 years		
America (*continued*)	Argentina	2000–2008	128.5	N/A	Leukaemias	N/A	1.3	Moreno *et al*. (2013)
	Argentina	2000–2013	128.1	N/A	Leukaemias	N/A	1.3	Steliarova-Foucher, Colombet, Ries, Hesseling *et al*. (2017)
	Brazil	1995–2012	145.2	171.1	Leukaemias	Lymphomas	1.2	Steliarova-Foucher, Colombet, Ries, Hesseling *et al*. (2017)
	Costa Rica	1993–2012	133.9	181.4	Leukaemias	Carcinomas and melanomas	1.2	Steliarova-Foucher, Colombet, Ries, Hesseling *et al*. (2017)
	Costa Rica	2000–2014	140.0	N/A	Leukaemias	N/A	1.2	Erdmann *et al*., (2018)
Asia	China	2000–2010	87.1	N/A	Leukaemias	N/A	1.3	Zheng *et al*. (2015)
	Japan	1990–2013	134.3	115.9	Leukaemias	Leukaemias	1.2	Steliarova-Foucher, Colombet, Ries, Hesseling *et al*. (2017)
	Japan	1993–2010	121.1	N/A	Leukaemias	N/A	N/A	Nakata *et al*. (2017)

Continent/ Country		Year of inception	Overall incidence rate for study period (per million person-years)		Most prevalent type of cancer		M/F ratio	Author and year of publication
			<15 years	15-19years	<15 years	15-19 years		
Asia (*continued*)	Korea	1999–2011	134.9	N/A	Leukaemias	N/A	1.2	Park *et al*. (2016)
Australia and New Zealand	Australia	1997–2006	157.5	N/A	Leukaemias	N/A	1.2	Baade *et al*. (2010)
	Australia	2010–2014	172	N/A	Leukaemias	N/A	1.2	Cancer Council, Queensland (2018)
	New Zealand	2010–2014	166.8	N/A	Leukaemias	N/A	1.2	Ballantine *et al*. (2017)

M/F: Male-to-female ratio; N/A: Not available

2.4.1.5 Childhood cancer in sub-Saharan Africa and South Africa

Africa, the second largest continent, has a population of approximately 1.25 billion, which represents 16.6% of the world population (Statista, 2018). Infectious diseases, including malaria, tuberculosis and HIV infection, constitute the largest magnitude of childhood diseases in Africa (Hadley *et al.,* 2012:139; Kruger *et al*., 2014:587). This has contributed to childhood cancer not perceived to be a vital public health problem in most countries on the continent (Stefan, 2010:317; Stefan *et al*., 2017). Estimating incidence rates of cancers of childhood in low- and middle-income countries, especially those in sub-Saharan Africa, is restricted by the inadequacy of dependable data, in comparison to the almost steady and adequately described incidence rates in developed countries (Erdmann *et al*., 2018:22; Ferlay *et al*., 2015:385; Frazier *et al*., 2017; Magrath *et al*., 2013:107; Stefan, 2015b:166; Steliarova-Foucher, Colombet, Ries, Moreno *et al*., 2017:719).

Recording of quality data in cancer registries, in terms of their accuracy, timeliness, comparability to other registries and their completeness, is essential in providing the basis for investigations and the formulation and appraisal of public health policies (Bray & Parkin, 2009:748; Parkin, 2008:103; Parkin & Bray, 2009:756). In view of this, the IARC, through its Global Initiative on Cancer Registration, has helped to advance the comprehensiveness of cancer registration through population-based registries (Stefan *et al*., 2017). This has improved the availability of data for epidemiological studies in Africa. Twenty-five registries from 18 countries in Africa which form the AFCRN, provide data for epidemiological studies into cancer in the various countries in which they are situated (Gakunga & Parkin, 2015:2046).

Table 2.3 provides a synopsis of the incidence of childhood cancer in Africa from the various registries of the AFCRN and some hospital series (compiled from Paintsil *et al*., 2015; Segbefia *et al*., 2013; Stefan, 2015b; Stefan *et al*., 2017).

Table 2.3: Childhood cancer incidence in sub-Saharan Africa

Country	Years	Number of registries	Number of cases	Most prevalent type of cancer
Botswana	2003-2008	1	267	Leukaemia
Ethiopia	2011-2013	1	160	Leukaemia
France Reunion	2002-2008, 2011	1	178	Leukaemia
Gambia	2002-2011	1	194	Hepatic tumours
Ghana	2008-2014	2	804	Burkitt's Lymphoma
Guinea	2001-2010	1	166	Lymphomas
Kenya	2007-2012	2	859	Non-Hodgkin's Lymphoma
Malawi	2003-2010	1	986	Burkitt's lymphoma
Mali	2006-2014	1	801	Retinoblastoma
Mauritius	2003-2012	1	270	Leukaemia
Mozambique	2000-2010	1	702	Kaposi sarcoma
Namibia	2003-2011	1	189	Leukaemia
Niger	2001-2009	1	175	Burkitt's Lymphoma
Nigeria	2003-2012	1	181	Burkitt's Lymphoma
Senegal	2008-2010	1	253	Nephroblastoma
South Africa	2003-2012	2	3596	Leukaemia
Uganda	2003-2012	1	1254	Burkitt's Lymphoma
Zambia	2006-2009	1	321	Non-Hodgkin's Lymphoma
Zimbabwe	2003-2013	1	504	Leukaemia

The paucity of information about childhood cancers in sub-Saharan Africa makes the true variation of childhood cancers largely unknown (Stefan, 2015b:166; Sullivan *et al*., 2013:e126). Nevertheless, estimates of incidence of childhood cancers have been reported by a number of studies in certain countries using data from different cancer registries (Erdmann *et al*., 2015; Somdyala *et al*., 2013; Stefan, 2010; Stefan, 2015b; Stefan *et al*., 2015; Stefan *et al*., 2017). The outcome of the study by Stefan (2015b) indicated that non-Hodgkin's lymphoma, specifically Burkitt's lymphoma, was the most predominant childhood cancer in sub-Saharan Africa. The occurrence of Burkitt's lymphoma is more prominent in the malaria-endemic countries (Chabay & Preciado, 2013:1289; Van den Bosch, 2004:738). Leukaemia followed as the second most common malignancy, while Kaposi's sarcoma formed the highest percentage

of the malignancies in the Southern African countries, with Mozambique for example, having Kaposi's sarcoma accounting for 15.8% of all childhood cancers in the country (Stefan, 2015b:169). Given that HIV infection is a recognised risk factor for the occurrence of Kaposi's sarcoma, this trend in incidence of Kaposi's sarcoma is not surprising due to the high prevalence of HIV infection in the Southern African countries (Vermund *et al*., 2015:191; Williams *et al*., 2015:198). A decrease in the incidence of Kaposi's sarcoma is, however, expected to be observed in a few years due to the numerous interventions that have been put in place to curtail the transmission of HIV infection in the Southern African countries (Stefan 2015b:172; Williams *et al*., 2015:202). These interventions include reduction of perinatal transmission and increased access to antiretrovirals (Vermund *et al*., 2015:191; Williams *et al*., 2015:202).

Current trends in the occurrence of childhood malignancies in South Africa are largely unknown as there are no recent epidemiological studies in the country; the most recent years of studies being 1987 to 2007, 1997 to 2007, 2003 to 2007 and 2000 to 2006 (Erdmann *et al*., 2015; Somdyala *et al*., 2013; Stefan, 2010; Stefan *et al*., 2015). Data used to compute incidence rates of childhood cancer in South Africa for the IICC-3 (Steliarova-Foucher, Colombet, Ries, Hesseling *et al*., 2017) span from 1998 to 2012, but data for individual years are not indicated and can, therefore, not be used to estimate the changes in the trend of incidence rates. Epidemiological studies in South Africa have demonstrated a higher incidence of childhood cancer in males in comparison to females across all ethnic groups, with an overall male-to-female ratio of between 1.2:1 and 1.3:1 (Erdmann *et al*., 2015:2631; Stefan *et al*., 2015:943; Steliarova-Foucher, Colombet, Ries, Hesseling *et al*., 2017). Table 2.4 compares the various epidemiological studies of childhood cancers carried out in South Africa, stratified according to gender and malignancy type, which show similar trends in incidence rates of cancer in males and females.

Incidence rates stratified according to age groups from the study by Erdmann *et al*. (2015:2631) gave results of 41.3, 59.81, 38.48 and 39.81 (per million person-years) for the <1, 1-4, 5-9 and 10-14 years' age groups, respectively. Results from the study by Stefan *et al*. (2015:942) showed incidence rates of 64.8, 38.1 and 26.9 (per million person-years) for the 0-4, 5-9 and 10-14 years' age groups respectively, indicating a higher incidence in the under-five age group. Table 2.5 similarly compares the various studies, but stratification is according to type of malignancy and age group.

Leukaemia has the highest incidence compared to all the other childhood malignancies in South Africa (Stefan, 2015b:169). Previous studies of childhood cancer in the country reported leukaemia as the most frequently occurring childhood cancer, with ASR of 11.9 (Stefan *et al*.,

2015:944), 8.5 (Erdmann *et al*., 2015:2633) and 11.4 per million person-years (Steliarova-Foucher, Colombet, Ries, Hesseling *et al*., 2017). This is confirmed by the study by Stefan (2015b:169), which reported leukaemia as the most frequently occurring malignancy in South Africa.

Results of the study by Stefan *et al.* (2015:944) indicate an overall childhood cancer incidence of approximately 45.2 per million person-years, with cancer occurring more frequently in white children (ASR ≈ 115.8) as compared to black children (ASR ≈ 36.9), coloured children (ASR ≈ 72.2) and Asians (ASR ≈ 79.5). Erdmann *et al*. (2015:2631) report a similar trend of incidence rates among the various ethnic groups in South Africa, with an overall incidence rate of approximately 45.7 per million person-years, with a higher rate in white children (ASR ≈ 114.96), in comparison to black children (ASR ≈ 37.17), coloured children (ASR ≈ 45.47) and Asians (ASR ≈ 82.97). Incidence rates of childhood cancers in South Africa, estimated by Steliarova-Foucher, Colombet, Ries, Hesseling *et al*. (2017), also show similar results, with an overall ASR of 45.6 per million person-years, ASR of 100.5 per million person-years in whites, 39.0 per million person-years in blacks, 71.5 per million person-years in children with mixed ancestry, and 78.2 per million person-years in Asians. Table 2.6 provides an overview of the comparison of the various studies of childhood cancers in South Africa, stratified according to malignancy type and ethnic group.

Table 2.4: Comparison of various studies of childhood cancer in South Africa stratified by type of malignancy and gender

Diagnostic group	Erdmann *et al*. (2015), 2000-2006					Stefan *et al*. (2015), 1987-2007					Steliarova-Foucher, Colombet, Ries, Hesseling *et al*. (2017), 1998-2012				
	Total number of cases	ASR (gender-specific)		M/F Ratio	ASR (overall)	Total number of cases	ASR (gender-specific)		M/F Ratio	ASR (overall)	Total number of cases	ASR (gender-specific)		M/F Ratio	ASR (overall)
		Male	Female				Male	Female				Male	Female		
Leukaemia	875	N/A	N/A	1.3	8.5	3113	13.5	10.3	1.3	11.9	2451	13.0	9.8	1.3	11.4
Lymphomas	725	N/A	N/A	2.1	6.9	1595	8.0	3.6	2.2	5.8	1357	8.5	3.7	2.4	6.1
CNS neoplasms	431	N/A	N/A	1.2	4.3	1334	5.4	4.8	1.1	5.1	1300	6.4	5.7	1.1	6.0
Neuroblastoma	209	N/A	N/A	1.3	2.3	748	3.4	2.7	1.3	3.1	533	2.9	2.4	1.2	2.7
Retinoblastoma	278	N/A	N/A	1.3	3.2	779	3.5	3.1	1.2	3.3	643	3.6	3.0	1.2	3.3
Renal tumours	542	N/A	N/A	1.1	5.9	1568	6.5	6.3	1.0	6.4	1247	6.1	6.3	1.0	6.2
Hepatic tumours	87	N/A	N/A	1.6	0.9	240	1.1	0.8	1.5	0.9	194	1.1	0.8	1.3	0.9
Bone tumours	260	N/A	N/A	0.9	2.2	473	1.7	1.6	1.1	1.6	391	1.8	1.5	1.2	1.6
Soft tissue sarcomas	630	N/A	N/A	1.3	6.2	1087	4.9	3.4	1.5	4.2	977	5.3	3.8	1.4	4.6
Germ cell tumours	118	N/A	N/A	0.3	1.1	436	1.1	2.3	0.5	1.7	341	0.9	2.3	0.4	1.6
Carcinoma & melanomas	350	N/A	N/A	0.9	3.2	223	0.8	0.8	1.0	0.8	218	0.9	1.0	0.9	0.9
Other and unspecified neoplasms	96	N/A	N/A	1.0	1.0	103	0.4	0.4	0.9	0.4	48	0.3	0.2	1.5	0.2

Diagnostic group	Erdmann *et al*. (2015), 2000-2006					Stefan *et al*. (2015), 1987-2007					Steliarova-Foucher, Colombet, Ries, Hesseling *et al*. (2017), 1998-2012				
	Total number of cases	ASR (gender-specific)		M/F Ratio	ASR (overall)	Total number of cases	ASR (gender-specific)		M/F Ratio	ASR (overall)	Total number of cases	ASR (gender-specific)		M/F Ratio	ASR (overall)
		Male	Female				Male	Female				Male	Female		
Total	**4 601**	**N/A**	**N/A**	**1.2**	**45.7**	**11 699**	**50.4**	**40.0**	**1.3**	**45.2**	**9 700**	**50.6**	**40.5**	**1.3**	**45.6**

ASR = Age-standardised incidence rates, per 1 000 000 person-years (estimated using the world standard population as reference); M/F = Male-to-female ratio- number of male cases/ number of female cases; N/A = Not available

Table 2.5: Comparison of various studies of childhood cancer in South Africa stratified by type of malignancy and age group

Diagnostic group	Erdmann *et al*. (2015), 2000-2006						Stefan *et al*. (2015), 1987-2007					Steliarova-Foucher, Colombet, Ries, Hesseling *et al*. (2017), 1998-2012					
	Total number of cases	§Age-specific incidence rates				ASR (overall)	Total number of cases	Age-specific incidence rates			ASR (overall)	Total number of cases	Age-specific incidence rates				ASR (overall)
		<1	1-4	5-9	10-14			0-4	5-9	10-14			<1	1-4	5-9	10-14	
Leukaemia	875	7.2	9.6	8.1	8.3	8.5	3113	15.5	11.3	7.7	11.9	2451	11.1	14.5	11.1	8.4	11.4
Lymphomas	725	1.3	6.3	8.4	7.3	6.9	1595	4.9	7.4	5.4	5.8	1357	0.6	5.6	7.8	6.2	6.1
CNS neoplasms	431	2.3	5.3	4.5	3.4	4.3	1334	5.9	6.0	3.0	5.1	1300	5.5	7.0	7.2	3.8	6.0
Neuroblastoma	209	6.0	4.5	1.1	0.4	2.3	748	6.3	1.3	0.6	3.1	533	8.1	5.1	1.1	0.4	2.7
Retinoblastoma	278	4.6	7.9	1.0	0.2	3.2	779	7.8	0.8	0.1	3.3	643	7.7	7.7	0.8	0.1	3.3
Renal tumours	542	6.2	12.6	3.9	1.0	5.9	1568	12.6	3.9	1.0	6.4	1247	8.6	13.2	3.7	0.7	6.2
Hepatic tumours	87	2.3	1.3	0.4	0.6	0.9	240	1.6	0.4	0.6	0.9	194	2.6	1.4	0.4	0.5	0.9
Bone tumours	260	0.6	0.4	1.4	5.5	2.2	473	0.5	1.5	3.2	1.6	391	0.1	0.4	1.4	3.6	1.6
Soft tissue sarcomas	630	1.3	7.4	5.7	5.8	6.2	1087	5.7	3.7	2.7	4.2	977	5.7	5.7	4.4	3.2	4.6
Germ cell tumours	118	1.1	1.1	0.9	1.4	1.1	436	2.8	1.0	1.1	1.7	341	6.1	1.7	0.9	1.2	1.6
Carcinoma & melanomas	350	3.7	2.0	2.3	5.3	3.2	223	0.6	0.6	1.3	0.8	218	0.2	0.6	0.7	1.8	0.9

Diagnostic group	Erdmann *et al*. (2015), 2000-2006						Stefan *et al*. (2015), 1987-2007					Steliarova-Foucher, Colombet, Ries, Hesseling *et al*. (2017), 1998-2012					
	Total number of cases	§Age-specific incidence rates				ASR (overall)	Total number of cases	Age-specific incidence rates			ASR (overall)	Total number of cases	Age-specific incidence rates				ASR (overall)
		<1	1-4	5-9	10-14			0-4	5-9	10-14			<1	1-4	5-9	10-14	
Other and unspecified neoplasms	96	1.4	1.5	0.7	0.6	1.0	103	0.6	003	0.2	0.4	48	0.6	0.3	0.2	0.1	0.2
Total	**4 601**	**41.39**	**59.81**	**38.48**	**39.81**	**45.7**	**11 699**	**64.8**	**38.1**	**26.9**	**45.2**	**9 700**	**56.9**	**63.1**	**39.8**	**30.2**	**45.6**

§ Age-specific incidence rates per 1 000 000 person-years; ASR = Age-standardised rates per 1 000 000 person-years

Table 2.6: Comparison of various studies of childhood cancer in South Africa stratified by type of malignancy and ethnic group

Diagnostic group	Erdmann *et al*. (2015), 2000-2006						Stefan *et al*. (2015), 1987-2007						Steliarova-Foucher, Colombet, Ries, Hesseling *et al*. (2017), 1998-2012					
	Total number of cases	ASR (Race-specific)				ASR (overall)	Total number of cases	ASR (Race-specific)				ASR (overall)	Total number of cases	ASR (Race-specific)				ASR (overall)
		W	B	M	A			W	B	M	A			W	B	M	A	
Leukaemia	875	23.5	6.9	N/A	N/A	8.5	3113	43.4	8.2	22.1	33.1	11.9	2451	35.1	8.4	21.3	37.5	11.4
Lymphomas	725	16.1	5.3	N/A	N/A	6.9	1595	13.5	4.9	9.5	8.3	5.8	1357	10.5	5.5	9.0	8.1	6.1
CNS neoplasms	431	15.4	2.9	N/A	N/A	4.3	1334	16.1	3.6	11.6	6.2	5.1	1300	15.4	4.7	13.2	8.7	6.0
Neuroblastoma	209	7.9	1.6	N/A	N/A	2.3	748	11.3	2.2	5.4	5.9	3.1	533	8.5	2.1	4.8	5.1	2.7
Retinoblastoma	278	3.6	3.1	N/A	N/A	3.2	779	2.8	3.4	3.3	2.6	3.3	643	3.4	3.3	3.3	2.2	3.3
Renal tumours	542	11.4	5.3	N/A	N/A	5.9	1568	9.2	6.2	6.8	6.8	6.4	1247	8.6	6.0	7.4	4.8	6.2
Hepatic tumours	87	2.2	0.7	N/A	N/A	0.9	240	1.7	0.7	2.3	1.2	0.9	194	1.9	0.8	1.5	2.0	0.9
Bone tumours	260	7.0	1.7	N/A	N/A	2.2	473	4.8	1.3	2.2	2.9	1.6	391	5.0	1.4	2.0	2.9	1.6
Soft tissue sarcomas	630	8.8	5.9	N/A	N/A	6.2	1087	6.5	4.0	4.3	6.6	4.2	977	5.7	4.5	4.7	4.2	4.6
Germ cell tumours	118	2.9	0.9	N/A	N/A	1.1	436	3.6	1.4	2.7	5.1	1.7	341	3.3	1.4	2.8	2.2	1.6
Carcinoma & melanomas	350	15.5	2.1	N/A	N/A	3.2	223	2.2	0.6	1.1	0.8	0.8	218	3.2	0.8	1.1	0.5	0.9
Other and unspecified neoplasms	96	0.7	1.0	N/A	N/A	1.0	103	0.4	0.4	0.6	N/A	0.4	48	0.1	0.2	0.4	N/A	0.2
Total	**4 601**	**114.9**	**37.2**	**45.5**	**82.9**	**45.7**	**11 699**	**115.8**	**36.9**	**72.2**	**79.5**	**45.2**	**9 700**	**100.5**	**39.0**	**71.5**	**78.2**	**45.6**

ASR = Age-standardised incidence rates, per 1 000 000 person-years; A = Children with Asian ancestry; B: Black children; M = Mixed or Coloured; N/A = Not available
W = White children

2.5 The burden of childhood cancer

There have been significant increases in the survival of children diagnosed and treated for cancer, representing a very remarkable achievement in paediatric oncology (Guy *et al*., 2016:S16; Hudson *et al*., 2014:2391; Mueller *et al*., 2015:490; Peikert *et al*., 2018; Sneha *et al*., 2017; Weaver *et al*., 2016:212; Westhoff *et al*., 2018). In spite of this, children who undergo treatment for cancers experience side effects related to treatment, during as well as years after treatment (DeSantis *et al*., 2014:258; Weaver & Samkari, 2017:60). Children treated with alkylating agents, epipodophyllin derivatives, anthracyclines and radiotherapy, especially, have a higher risk of developing secondary neoplasms (DeSantis *et al*., 2014:258). Increased survival has, therefore, not been able to fully reduce the burden of childhood cancers, as the problem of increased morbidity and diminished quality of life still persists (Kirch *et al*., 2016:405).

The diagnosis and treatment of childhood cancer significantly affect the quality of life of the affected children and their families, irrespective of the prognosis of cancer (Levine *et al*., 2017:1215). Childhood cancers have a huge impact on the affected children and their families psychologically, which goes beyond the treatment of the condition (Peikert *et al*., 2018; Pelletier *et al*., 2018:203; Tsimicalis *et al*., 2018:118). Diagnosis of childhood cancer has been described as a transformative ordeal for parents and families of these children (Sultan *et al*., 2016:618; Ward *et al*., 2014:83), as they have heightened anxiety after diagnosis of cancer has been made (Marcus, 2012:212). The side effects associated with treatment, coupled with the uncertainty of the prognosis of the condition, put significant stress on both the children and parents (Marusak, 2018). Siblings of these patients also undergo their fair share of distress as they often receive little attention from their parents after their siblings are diagnosed with cancer, as well as increased anxiety about the prognosis of their sibling's condition (Alderfer *et al*., 2010:799; Henry, 2012; Hosoda, 2014:18; Long & Marsland, 2011:59).

Due to their susceptibility to infections during treatment, the regular cycles for receiving chemotherapy or radiotherapy, as well as the side effects associated with therapy, most children stay away from school, making them fall behind their peers academically (Marusak, 2018; Tsimicalis *et al*., 2018:118). Most children also have low self-esteem and lose their identity due to the restrictions that cancer and some adverse effects of treatment, particularly the loss of hair during chemotherapy and radiotherapy, place on them (Griffiths *et al*., 2011:89; Sadruddin & Hameed-ur-Rehman, 2013). This makes it difficult for them to associate with their peers in school.

Treatment of childhood cancer is costly and this puts a financial burden on the already stressed parents or caregivers of children with cancer (Warner *et al*., 2015:12). This is especially

worrying for families who do not have insurance cover for health, as well as many patients from resource-limited countries, where cancer treatment is mostly not covered by most health insurance schemes (Sneha *et al*., 2017). This leads to a considerable reduction in savings of these families and a consequent reduction in the quality of life of parents and siblings of these children (Sneha *et al*., 2017). Families with insurance coverage for the treatment of cancer in their children are equally not spared, as they are not reimbursed for out-of-pocket payments they make for travel, accommodation and food during treatment cycles (Sneha *et al*., 2017:4). Apart from the increased utilisation of family resources during cancer treatment, sources of income continue to lessen due to the inability of most caregivers to work, as a result of their having to take care of their sick children (Bona *et al*., 2014:600; Sneha *et al*., 2017).

The average cost of diagnostic tests and treatment of nephroblastoma, one of the prevalent childhood cancers with a high cure rate of >90% (Davidoff, 2012:247; Szychot *et al*., 2014:12), was estimated by Stefan *et al*. (2014) to range between ZAR 9 304.97 (USD 1 093.40) and ZAR 46 422.94 (USD 5 455.10) in South Africa. Cost-effective diagnostic tests, treatments and procedures suggested by the authors for resource-limited countries, amounted to between ZAR 3 587.27 (USD 421.50) and ZAR 38 766.42 (USD 4 555.40) (Stefan *et al*., 2014). This amount is, however, still too high for parents of children diagnosed with cancer in resource-limited countries, whose average *per capita* is less than USD 2 000 (World Bank, 2018), to bear. Cost should not only be measured by the cost of treatment, radiological and laboratory investigations, but other indirect costs such as loss of productivity by the caregivers, and intangible costs such as psychological stress experienced by both patients and their families, should also be included in any assessment of the cost of treating childhood cancers (Aung *et al*., 2012:171; Bemis *et al*., 2015:734; Sneha *et al*., 2017; Tsimicalis *et al*., 2012:1115).

2.6 Risk factors for childhood cancers

The World Health Organization defines a risk factor as any determinant or peculiarity that predisposes an individual to an increased tendency of acquiring a disease (WHO, 2018c). Being cognisant of the factors that increase the risk of childhood cancers can help in proposing preventive measures to curb the disease (Erjaee *et al*., 2017:158). Global disparities in the incidence of childhood cancer are thought to be as a result of dissimilarities in the exposure to various risk factors for childhood cancers (Magrath *et al*., 2013:107). The established risk factors for the occurrence of childhood cancers, which include exposure to high doses of ionising radiation, some viral infections, and genetic mutations, can be classified as either external determinants or intrinsic risk factors (Bunin, 2004:91; IARC, 2001; Linet *et al*., 2003:223).

2.6.1 External agents

External agents that are risk factors for childhood cancer can be classified as physical, chemical or biological carcinogens (Belpomme *et al*., 2007:415).

2.6.1.1 Physical carcinogens

Physical carcinogens are mainly derived from radiation which may be either ionising or non-ionising (Belpomme *et al*., 2007:416; Teepen & van Dijck, 2012:770; Wakeford, 2004:6404). Children are specifically vulnerable to radiation; this may be because their tissues are still undergoing growth and development (Sadetzki & Mandelzweig, 2009:1022). These types of radiation are responsible for some thyroid, skin and lung cancers as well as some leukaemias and lymphomas (Cardis & Hatch, 2011:256; Wakeford, 2004:6404; Wild & Kleinjans, 2003:1390).

Ionising radiation has been found to have a causal relationship with some cancers in children and adolescents (Kutanzi *et al*., 2016; Murphy *et al*., 2013:96). Major exposure to ionising radiation is through its use for medical purposes such as x-rays and computed tomography (CT) scans (Harbron *et al*., 2018:400; Linet *et al*., 2009:23; Murphy *et al*., 2013:97; Wakeford, 2004:6405). These exposures have been observed to have a significant association with solid tumours — notable among them being brain tumour — acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML) in children (Bunin, 2004:94; Belson *et al*., 2007:138; Eden, 2010:290; Mahoney *et al*., 2004; Pauwels & Bourguignon, 2012:509; Ward *et al*., 2014:87).

Exposure to non-ionising radiation, including electromagnetic fields, has also been associated with some childhood leukaemias (Kheifets & Shimkhada, 2005:51; Schüz, 2011:341; Zhao *et al*., 2014:273), and this formed the basis for the classification of extremely low-frequency electromagnetic fields as carcinogens by the IARC (IARC, 2002).

2.6.1.2 Chemical carcinogens

Some chemicals to which humans are exposed, especially in the chemical industries, have been found to contain carcinogenic, mutagenic and reprotoxic molecules (Clapp *et al*., 2005:10). Children born to parents who work in industries where they are constantly exposed to chemicals such as asbestos, aflatoxin and arsenic, have a higher risk of childhood cancers (Belpomme *et al*., 2007:418). Scélo *et al*. (2009:136) found a significant association between childhood leukaemia and the exposure of parents of affected children to paints and petroleum solvents.

Most pesticides have also been found to be carcinogenic to humans and could be attributed to the close resemblance of their molecular structure to oestrogens and endocrine-disrupting mechanisms (Bassil *et al*., 2007:1708; Belpomme *et al*., 2007:419; Mnif *et al*., 2011:2267). Pesticides have also been found to promote carcinogenesis through immunosuppression (Duramad *et al*., 2006:464). An association between the presence of a high concentration of herbicides in household dust and the risk of ALL in children has also been found in some studies (Metayer *et al*., 2013:365). Chen *et al*. (2015:724) also found a significant association between residential indoor insecticides and risk of childhood leukaemia and lymphoma. An association between maternal prenatal exposure to pesticides and risk of childhood ALL has been found in some studies (Hyland *et al*., 2018:1299; Wang *et al*., 2019:151). Petrochemical exposure has also been linked to leukaemias (Belli *et al*., 2004:53; Yu *et al*., 2006:206).

Some studies have also found an association between smoking before and during pregnancy, and some childhood cancers, especially brain tumours (Rumrich *et al*., 2016; Tettamanti *et al*., 2016:69). Consumption of alcohol by women during pregnancy has also been found to be associated with a higher risk of brain tumours in their offspring (Georgakis *et al*., 2019:182). Cell adenocarcinoma of the cervix or vagina in females has been linked to in-utero exposure to diethylstilboestrol, a synthetic oestrogen used in the prevention of complexities in pregnancy (Hoover *et al*., 2011:1310; Laronda *et al*., 2012:257).

2.6.1.3 Biological carcinogens

Infections, especially those with viral causes, have been associated with the occurrence of some childhood cancers such as ALL, Burkitt's lymphoma, hepatocellular carcinomas and Kaposi's sarcoma (Autier, 2018:1136; Bunin, 2004:91; Spector *et al*., 2015:17). Epstein-Barr virus and HIV have been associated with Burkitt's lymphoma and ALL, and Kaposi's sarcoma, respectively (Alibek *et al*., 2013; Anderson, 2006:137; Jackson *et al*., 2016:393; Maeda *et al*., 2009:5; Magrath, 2012:748). Hepatitis B virus infection has been linked to hepatocellular carcinoma, and this has been confirmed by the significant reduction in its incidence with hepatitis B vaccination (Chang *et al*., 2009:1353; De Flora & La Maestra, 2015:E18; MacMahon *et al*., 2011:805; Magrath *et al*., 2013:108). Results of a study by Lu *et al*. (2018:152) showed a significant association between infection with hepatitis B virus and the occurrence of extrahepatic cancers in adolescents and young adults. The outcome of a study by Francis *et al*. (2017:1683) gave rise to the hypothesis that in-utero exposure to cytomegalovirus infection was linked to the occurrence of ALL in childhood. Results of the study by Baryawno *et al*. (2011:4045) also showed an association between the cytomegalovirus and medulloblastoma. This has led to the hypothesis that targeting human cytomegalovirus could yield significant results in the treatment of medulloblastoma (Hortal *et al*., 2017:57).

2.6.2 Internal risk factors

These are the inherent traits of individuals that are unmodifiable and include age, gender and genetic mutations.

2.6.2.1 Demographic risk factors

A considerable number of inherent traits of parents and their offspring have been associated with the development of childhood cancers (Spector *et al*., 2015:13). Several studies have shown an association between high birth weight and the risk of some childhood cancers including Wilms' tumour, brain tumours, neuroblastoma, ALL and AML, and low birth weight with risk of hepatocellular carcinoma (Caughey & Michels, 2009:2667; Dahlhaus *et al*., 2017; Harder *et al*., 2010:752; O'Neill *et al*., 2012:10; O'Neill *et al*., 2015:163; Oksuzyan *et al*., 2012:e363; Paltiel *et al*., 2015:340; Tran *et al*., 2017). Parental age, especially advanced maternal age, has also been positively linked to some childhood cancers including AML, retinoblastoma and Wilms' tumour (Johnson *et al*., 2009; Panagopoulou *et al*., 2019:160; Rios *et al*., 2018; Wang *et al*., 2017:847). Deficiencies in normal development, which is characteristic of a number of cancer predisposition syndromes, are observed in many paediatric cancers, giving rise to the hypothesis that birth defects increase the risk of childhood cancers (Autier, 2018:1136; Johnson *et al*., 2017).

Notable disparities in the occurrence of cancer according to age, sex and race have been observed in children, with the highest occurrence in infancy, followed by the 15 to 19-year age group and the least occurrence in the 5 to 9-year age group (Howlader *et al*., 2014; Spector *et al*., 2015:13). ALL has been noted to have a very high incidence in children aged between two and five years, while cancers of the bone have a high incidence in adolescents (Spector *et al*., 2015:13).

There is an observed overall male predominance in the incidence of childhood cancers from birth to 19 years, but there are differences in occurrence by gender in the various age groups (Dorak & Karpuzoglu, 2012; Siegel, D.A. *et al*., 2018; Spector *et al*., 2015:10). An example is seen with the higher incidence of Wilms' tumour in females compared to males (Spector *et al*., 2015:13; Varan, 2008:84).

Variations in the occurrence of childhood cancers have also been noted in different ethnic groups, with low occurrence in Asian, Africans and Hispanics, as compared to Caucasian children (Chow *et al*., 2010:3047; Peckham-Gregory *et al*., 2018:92; Siegel, D.A. *et al*., 2018; Spector *et al*., 2015:13). Differences in the incidence patterns of childhood cancer resulting from genetically-determined geographical differences could contribute to the generation of the

hypothesis of an association between geographical area or ethnic group and the risk of childhood cancer (Erdmann *et al*., 2018:21; Parkin & Stefan, 2017).

2.6.2.2 Predisposition to familial diseases

Several childhood and adolescent cancers have been attributed to intrinsic cancer predisposition syndromes, although the percentage of children with this predisposition has not been completely elucidated (Brozou *et al*., 2018:53; Kuhlen & Borkhardt, 2015:988). Cancer predisposition syndromes that could be caused by either inherited or *de-novo* germline mutations have been found to be highly linked to some childhood cancers (Davidoff, 2010:227; Gomy & Diz, 2016:184). These cancers include leukaemia, CNS tumours and non-CNS embryonal tumours[3] such as Wilms' tumour, rhabdomyosarcoma and retinoblastoma (De *et al*., 2011:E187; Moore, 2009:755; Zhang *et al*., 2015:2340). Knowledge of the cancer predisposition syndrome status of an index case could inform the risk of childhood cancer in the family line (Brozou *et al*., 2018:59; Wang, 2016:146). This is because the risk of childhood cancer is higher in a population with a familial predisposition compared to those without (Saletta *et al*., 2015:67). Treatment, surveillance and follow-up can also be improved in a child with a known cancer predisposition syndrome status (Brodeur *et al*., 2018:e2; Ripperger *et al*., 2017:1028).

2.6.2.3 Genetically determined features

De-novo genetic mutations in cancer predisposition genes, which are usually tumour suppressor genes, could result in the occurrence of cancers in very young children (Davidoff, 2010:229; Saletta *et al*., 2015:68). Work by Rahman (2014:302) identified 114 cancer predisposition genes, with mutations of some of these genes associated with childhood cancers. Mutations causing dominant and recessive genes lead to syndromes that are associated with some childhood cancers. Table 2.7 provides an overview of some gene mutations, the syndromes they cause and the childhood cancers associated with the mutations (compiled from Davidoff, 2010; Dumoucel *et al*., 2014; Jongmans *et al*., 2016; Malkin *et al*., 2014; Ogden, 2018; Scollon *et al*., 2017; Smith *et al*., 2014; Spinner *et al*., 2014; Xavier & Taub, 2010).

[3] Non-CNS embryonal tumours are defined as a collection of tumours that occur in embryonic cells and are particularly common in young children and infants (Zong *et al*., 2017:174).

Table 2.7: Childhood cancers associated with syndromes caused by genetic mutations

Syndrome	Mutated gene	Childhood cancer
Fanconi anaemia	*BRCA2/FANCD1*	AML, Hepatoma
Hereditary retinoblastoma	*RB1*	Retinoblastoma
Wilms' tumour syndrome	*WT1*	Nephroblastoma/Wilms' tumour
Gorlin syndrome	*PTCH1/SUFU*	Medulloblastoma
GATA2, haploinsufficiency syndrome	*GATA2*	AML
Ataxia telangiectasia	*ATM*	Lymphomas and leukaemia
Bloom syndrome	*BLM*	Non-Hodgkin's lymphoma, Wilms' tumour, osteosarcoma
Li-Fraumeni syndrome	*TP53*	Adrenocortical carcinoma, soft tissue carcinoma, osteosarcoma, CNS tumours
Beckwith-Wiedemann syndrome	*IGF-2 or CDKN1C*	Wilms' tumour, hepatoblastoma, neuroblastoma
Simpson-Golabi-Behmel syndrome	*GPC3*	Wilms' tumour, hepatoblastoma
Xeroderma pigmentosum	*XPC, ERCC2*	Skin carcinoma, melanoma
Down syndrome	*GATA1*	Acute leukaemias
Klinefelter syndrome	*47XXY*	Germ cell tumours
Nijmegen breakage syndrome	*NBN*	Medulloblastoma, glioma, T and B cell lymphomas, rhabdomyosarcoma
Perlman syndrome	*DIS3L2*	Wilms' tumour
Rubinstein-Taybi syndrome	*CREBBP*	Medulloblastoma

2.7 Treatment of childhood cancer

Oncologists employ several approaches in the management of cancer, which may be mainly through the use of medication (chemotherapy), radiation (radiotherapy) or by surgical means (Coura & Modesto, 2016:71; Hewitt *et al*., 2003:41; Israels *et al*., 2015:607; Ke & Shen, 2017:70; Saletta *et al*., 2014:156). The management of childhood cancers involves the use of one or more of these approaches, which is dependent on the type of cancer. Examples include the employment of chemotherapy alone in the treatment of some leukaemias and lymphomas, or the use of a combination of chemotherapy, surgery and radiotherapy in some solid tumours (Israels *et al*., 2015:607; Makin, 2018:183).

2.7.1 Chemotherapy

The field of paediatric oncology has witnessed a significant increase in the survival of children with cancers in the last five decades (Adamson, 2015:212; Saletta *et al*., 2014:157; Seth *et al*., 2017:216). This has been credited to the introduction and use of chemotherapy, either alone or in addition to radiotherapy and surgery, which are the main treatment options available for children with cancer (Davidoff *et al*., 2012:88; English, 2010:123; Makin, 2018:183; Oeffinger & Hudson, 2004:218; Ruggiero, *et al.*, 2017:2605; Saletta *et al*., 2014:156). The absence of damage to the DNA in childhood cancers makes them susceptible to chemotherapy as compared to adult cancers, which are characterised by several mutations and are, consequently, relatively less susceptible to chemotherapeutic agents (Makin, 2018:183; Westhoff *et al*., 2018). Chemotherapies for childhood cancers include the use of cytotoxic and biologic or targeted therapy.

2.7.1.1 Cytotoxic chemotherapy

Cytotoxic chemotherapy, which employs a combination of various classes of cytotoxics, forms the backbone for the treatment of childhood cancers (Makin, 2018:184; Oduro-Dominah & Brennan, 2013:158). The rationale for the use of a combination of various chemotherapeutic agents in the management of cancers is to prevent resistance to the drugs (Makin, 2018:184; Westhoff *et al*., 2018). Protocols utilised for various types of malignancies employ a combination of chemotherapeutic agents with distinctive modes of action but with synergistic effects for that particular malignancy and which do not potentiate the toxic effects of either of them (Corrie, 2011:721; Makin, 2018:184; Payne & Miles, 2018:45; Pritchard *et al*., 2012:171). The mechanism of action of cytotoxics involves the interruption of cell division of cancer cells, which undergo rapid division as compared to normal cells (English, 2010:123; Payne & Miles, 2018:39). The various agents can be classified according to their phase-specific toxicity (which are sub-classified into phase-specific, cell cycle-specific or cell cycle-nonspecific chemotherapy), or with respect to their specific mode of action, which is the most widely used classification (Baudino, 2015:5; Payne & Miles, 2018:42).

2.7.1.1.1 Alkylating agents

Alkylating agents act by forming inter- and intra-DNA links, which inhibit replication and consequently activate cell death, by covalently binding an alkyl group to the DNA of the cell (Abotaleb *et al*., 2018:468; Galluzzi *et al*., 2015:690; Makin, 2018:184; Mihlon *et al*., 2010:387; Payne & Miles, 2018:42). Drugs in this class of chemotherapeutic agents include oxazaphosphorines (e.g. cyclophosphamide, ifosfamide); nitrogen mustards (e.g. melphalan

and chlorambucil); nitrosoureas (e.g. carmustine and lomustine); tetrazines (e.g. dacarbazine) and procarbazine (English, 2010:126; Makin, 2018:185; Payne & Miles, 2018:42).

2.7.1.1.2 Antimetabolites

These agents act by competitive inhibition of naturally occurring substances, to which they bear structural similarities, for their receptor sites leading to halting of cell activity (Abotaleb *et al*., 2018:459; Makin, 2018:185; Masui *et al*., 2013:725; Mihlon *et al*., 2010:387; Payne & Miles, 2018:42). The macromolecules formed as a result of binding of antimetabolites to the receptor sites are non-functional and this results in cell death (Masui *et al*., 2013:725; Mihlon *et al*., 2010:387). Antimetabolites are often classified as cell-specific agents since their effects cause interference of the activities of actively dividing cells (Abotaleb *et al*., 2018:459). Drugs in this class of cytotoxics include folic acid analogues (e.g. methotrexate), purine analogues (e.g. 6-mercaptopurine and thioguanine) and pyrimidine analogues (e.g. 5-fluorouracil and cytarabine) (English, 2010:125; Makin, 2018:184; Payne & Miles, 2018:43).

2.7.1.1.3 Cytotoxic antibiotics

These antibiotics with cytotoxic properties are produced from the *Streptomyces* species and interrupt nucleic acid formation (Makin, 2018:185; Mihlon *et al*., 2010:388; Payne & Miles, 2018:43). Antibiotics in this group include anthracyclines (e.g. doxorubicin, daunorubicin and epirubicin), actinomycin D, bleomycin and mitomycin (Makin, 2018:185; Payne & Miles, 2018:43).

2.7.1.1.4 Topoisomerase inhibitors

These drugs inhibit the topoisomerase enzymes that are required for the breakdown of the enzyme-DNA bonds — a process required for cell replication — and this results in the breakage of strands of DNA (Goftar *et al*., 2014:2432; Makin, 2018:185; Payne & Miles, 2018:44). Drugs in this class are sub-classified as topoisomerase I or II inhibitors, with the topoisomerase II inhibitors being the most frequently utilised type and the topoisomerase I inhibitors employed in protocols of some recurrent cancers (English, 2010:126; Makin, 2018:185; Payne & Miles, 2018:44). Topoisomerase II inhibitors include etoposide and examples of the topoisomerase I inhibitors are irinotecan and topotecan (Makin, 2018:185; Payne & Miles, 2018:44).

2.7.1.1.5 Spindle poisons

The cytotoxic action of these drugs involves the inhibition of mitosis, by the interference of the formation of microtubules, through their binding to tubulin in the cells in the case of vinca alkaloids, and the stimulation of the aggregation of microtubules in the case of taxoids (English,

2010:123; Galluzzi *et al*., 2015:690; Makin, 2018:186; Mihlon *et al*., 2010:388; Payne & Miles, 2018:44). The most widely known drugs in this group, vincristine and vinblastine, are obtained from the periwinkle plant (English, 2010:123; Makin, 2018:186; Payne & Miles, 2018:43). Other examples of drugs in this group are paclitaxel, docetaxel and vinorelbine.

2.7.1.1.6 Platinum compounds

The chemotherapeutic effect of drugs in this group is derived from their covalent bonding to DNA, leading to the creation of both inter- and intra-strand linkages, which hampers its replication (Johnstone *et al*., 2014:472; Makin, 2018:186; Payne & Miles, 2018:42; Wang & Lippard, 2005:308). Drugs in this group include cisplatin, carboplatin and oxaliplatin, with cisplatin and carboplatin being the most widely used agents in childhood cancers (Makin, 2018:186; Payne & Miles, 2018:42).

2.7.1.2 Biologic or targeted therapy

Most of the agents used in conventional chemotherapy protocols act by restricting the formation and functions of DNA of rapidly replicating cells and are, therefore, mostly not tumour-specific, leading to a considerable number of adverse effects (Gore *et al*., 2013:e72; Mondal *et al*., 2014:3; Palumbo *et al*., 2013:4; Payne & Miles, 2018:49). Recent advances in the use of chemotherapeutic agents are aimed at targeting a particular pathway in the process of malignancy formation, which leads to the reversal of the process when halted (Gore *et al*., 2013:70; Joo *et al*., 2013:309; Payne & Miles, 2018:46; Westhoff *et al*., 2018). Targeted therapies are characterised by a lower side effect profile compared to the conventional chemotherapies due to their tumour-specific properties (Adamson, 2015:215; Gore *et al*., 2013:72; Joo *et al*., 2013:309; Palumbo *et al*., 2013:4). This type of therapy, initially developed for use in adults for the treatment of haematological malignancies, has also been found to be beneficial in the paediatric population (Makin, 2018:186; Payne & Miles, 2018:46; Stewart & Robinson, 2017:752). The aim of their use is to improve the rate of cure and to reduce adverse effects associated with treatment with conventional chemotherapy (Forrest *et al*., 2018:22). The paediatric population is more likely to benefit from molecular target therapies due to their relatively reduced likelihood of gene mutation and the presence of fewer comorbidities as compared to adults (Stewart & Robinson, 2017:753). Monoclonal antibodies and small molecules are the main drugs that are used in targeted therapy for cancers (Makin, 2018:186; Payne & Miles, 2018:46).

2.7.1.2.1 Monoclonal antibodies

The effects of monoclonal antibodies can be classified as either direct or indirect. Direct effects include the activation of apoptotic processes, inactivation of growth factor receptors required for cell growth, and antibody formation, while indirect effects include cellular toxicity caused by the fusion of antibodies to the tumour cells and cellular cytotoxicity which is dependent on complement formation (Baudino, 2015:4; Green *at al*., 2000:270; Huang *et al*., 2015). Monoclonal antibodies currently utilised in paediatric tumours target growth and tumour signalling pathways, and investigations into the development of monoclonal antibodies that will target T-cell inhibitory processes are ongoing (Capitini *et al*., 2014; Huang *et al*., 2015; Makin, 2018:186). Rituximab, brentuximab vedotin and gemtuzumab ozogamicin are some of the monoclonal antibodies utilised in some paediatric cancers (Huang *et al*., 2015; Payne & Miles, 2018:49; Saletta *et al*., 2014:159).

2.7.1.2.2 Small molecules

This class of drugs are mostly inhibitors of tyrosine kinases, a group of enzymes that mediate the signal transduction pathway required for cell replication and survival (Adamson, 2015:215; Makin, 2018:186; Mihlon *et al*., 2010:389; Paul & Mukhopadhyay, 2004:102). Tyrosine kinases constitute a large part of oncoproteins; their inhibition is, therefore, utilised as specific targets in cancer chemotherapy (Paul & Mukhopadhyay, 2004:107; Westhoff *et al*., 2018; Yan *et al*., 2011:1). Imatinib is one of the agents in this group that has been utilised and proven to be effective when combined with intensive conventional chemotherapy for the treatment of paediatric Philadelphia positive (Ph^+) ALL (Champagne *et al*., 2004:2659; Champagne *et al*., 2011; Hunger, 2011:362; Jeha *et al*., 2014:1517; Schultz *et al*., 2014:1469).

2.7.1.3 Miscellaneous pharmacotherapeutic agents in childhood cancers

These agents have selective action against lymphoma and leukaemia cells and are, therefore, an integral part of protocols for the treatment of these cancers especially ALL, Hodgkin's and non-Hodgkin's lymphoma. These agents include asparaginase and steroids.

2.7.1.3.1 Asparaginase

The cytotoxic effect of this enzyme is derived from its interference with the formation of ribonucleic acid (RNA) and DNA of cells, through its mechanism of action of converting L-asparagine, an endogenous substance required for the normal functioning of tumour cells, to aspartate and ammonia (Andrade *et al*., 2014:95; Makin, 2018:186; Piątkowska-Jakubas *et al*., 2008:664). L-asparagine can be produced by normal cells with the help of asparagine synthase,

while tumour cells, which require large amounts of L-asparagine to maintain the rapid replication, depend largely on extrinsically derived L-asparagine for cell growth (Andrade *et al*., 2014:96; Avramis, 2012:2426; Narta *et al*., 2007:210). Administration of asparaginase in the management of cancer, therefore, depletes the already limited levels of L-asparagine required for proliferation of tumour cells (Narta *et al*., 2007:210).

L-asparaginase is available in three forms, two being derived from *Escherichia coli* and *Erwinia chrysanthemi*, and the third form, pegasparaginase, derived from the covalent binding of the enzyme derived from *Escherichia coli* to polyethylene glycol (Chen, 2015:287). The addition of polyethylene glycol is to prolong its half-life, reduce the frequency of dosing and also to reduce the associated hypersensitivity (Makin, 2018:186; Narta *et al*., 2007:211; Piątkowska-Jakubas *et al*., 2008:664; Place *et al*., 2015:1688).

2.7.1.3.2 Glucocorticoids

Glucocorticoids activate apoptosis of cancer cells by binding to glucocorticoid receptors present in these cells and translocating the bound receptors to the nucleus, thereby halting the replication process of the cancer cells (Inaba & Pui, 2010:1096; Makin, 2018:186; Tissing *et al*., 2003:17). Their cytotoxic effect is particularly against lymphoma and leukaemia cells and is, therefore, employed in treatment protocols of ALL, Hodgkin's lymphoma, NHL, and Langerhans cell histiocytosis (LCH) (Makin, 2018:186; Pufall, 2015:316). Prednisolone and dexamethasone are the steroids mostly employed in the management of cancer (Inaba & Pui, 2010:1096; Makin, 2018:186).

2.7.1.4 Chemotherapy-induced side effects and management

Children diagnosed with and on treatment for cancer with various chemotherapeutic agents are at risk of serious adverse drug reactions (Parande *et al*., 2018:340). The general mechanism of action of chemotherapeutic agents, which involves the non-selective inhibition of cell proliferation of both cancer and normal cells, and the narrow therapeutic window of chemotherapeutic agents, lead to a myriad of adverse drug reactions (Helleday, 2017:2054; Lau *et al*., 2004:626; Masui *et al*., 2013:726; Poulopoulos *et al*., 2017:36). These effects are present even at normal doses (Sharma *et al*., 2005:93). Common adverse drug reactions associated with chemotherapeutic agents include alopecia, vomiting, constipation, neutropenia, diarrhoea, anaemia, mucositis and anorexia (Behera *et al*., 2017:594; Wahlang *et al*., 2017:63).

2.7.1.4.1 Alopecia

Alopecia remains one of the most frequently observed chemotherapy-related adverse drug reactions (Chopra *et al*., 2016; Gunawa *et al*., 2016:1717; Hedén *et al*., 2013:370; Komen *et al*., 2013:885; Wahlang *et al*., 2017:63). Chemotherapy-induced alopecia is thought to result from the toxic effect of the chemotherapeutic agent on the hair follicle, a rapidly dividing cell, causing interruption of the production of hair-shaft and growth cycle of hair follicles (Paus *et al*., 2013:e50; Shaw & Boyle, 2017; Trüeb, 2010). The pattern of hair shaft shedding is demonstrated by anagen effluvium (loss of hair during the growing phase of the hair growth cycle) or telogen effluvium (loss of hair during the resting phase of hair growth cycle) (Bleiker *et al*., 2005; Trüeb, 2010). Hair loss may occur on all parts of the body that have terminal hair such as the scalp, beard, eyelashes, eyebrows and pubic hair, but is more prominent on the scalp (Komen *et al*., 2013:885; Shaw & Boyle, 2017).

Alopecia caused by most chemotherapeutic agents can be reversed within three to six months of completing chemotherapy (Shin *et al*., 2014; Tallon *et al*., 2010:334; Trüeb, 2010; Yang & Thai, 2015). However, permanent alopecia, which is defined as the lack of, defective or inadequate resurgence of hair after more than six months of cancer therapy (Machado *et al*., 2007:979), has been reported in patients who had undergone high-dose conditioning therapy prior to haematopoietic stem cell transplantation (Choi, M. *et al*., 2014:502). Chemotherapeutic agents typically implicated in chemotherapy-induced alopecia include cyclophosphamide, etoposide, doxorubicin, paclitaxel, busulphan, carboplatin, vinorelbine, ifosphamide, cisplatin, topotecan and methotrexate (BNFC, 2017-2018; Rugo & Voigt, 2018:19).

Currently, the most widely utilised and clinically confirmed efficacious approach in preventing chemotherapy-induced alopecia is scalp cooling (Grevelman & Breed, 2005:352; Katikaneni *et al*., 2014:30; Mols *et al*., 2009:186; Rugo & Voigt, 2018:19; Shin *et al*., 2014). One of the mechanisms by which hypothermia, caused by cooling of the scalp, prevents hair loss is the reduction of blood flow to the hair follicles due to vasoconstriction while the patient is receiving chemotherapy. This causes a reduction in the uptake of the chemotherapeutic agent by the cells of the hair follicles (Grevelman & Breed, 2005:352; Sheikholeslami *et al*., 2015). Another mechanism is through the decrease in the biochemical activity of the hair follicles, making them less sensitive to the damaging effects of the chemotherapeutic agent (Grevelman & Breed, 2005:352).

2.7.1.4.2 Chemotherapy-induced nausea and vomiting

Chemotherapy-induced nausea and vomiting (CINV) are part of the dreadful adverse drug reactions observed during treatment in children with cancer (Ruggiero *et al*., 2018:2150; Warr, 2008:S4). Patients could, however, have nausea, which is defined as a patient's subjective feeling of wanting to vomit, without actually vomiting, although the two are related (Ruggiero *et al*., 2018:2150; Warr, 2008:S4). The time for the onset and duration of CINV is dependent on the type of chemotherapeutic agent the patient receives (Jordan, Hinke *et al*., 2007:1023; Navari, 2013:249). Chemotherapy-induced nausea and vomiting are thought to occur by the interactions of serotonin, whose release is stimulated by the free radicals generated after the administration of chemotherapy, with 5-hydroxytryptamine type 3 (5-HT3) receptors in the wall of the bowel (Navari, 2015a:2739). Impulses are then sent to the vomiting centre through the chemoreceptor trigger zone (CTZ), causing an increase in salivation, pharyngeal and gastrointestinal muscle contractions, leading to nausea and vomiting (Navari, 2015a:2739). Chemotherapy-induced nausea and vomiting can be classified into five specific syndromes (Ruggiero *et al*., 2018:2150). These are acute, delayed, anticipatory, breakthrough and refractory chemotherapy-induced nausea and vomiting.

- Acute chemotherapy-induced nausea and vomiting

This occurs while patients are receiving chemotherapy and subsides within 24 hours (Ruggiero *et al*., 2018:2150). This type of CINV is mainly mediated by the release of serotonin in the enterochromaffin cells in the intestines, which then interacts with the 5-HT3 receptors (Jordan, Hinke *et al*., 2007:1024; Navari & Aapro, 2016:1357). This forms the basis for the high sensitivity of acute CINV to 5-HT3 receptor antagonists. Recommendations for preventing acute CINV (Dupuis *et al*., 2017:327; Patel *et al*., 2017) are:

- A combination of 5-HT3 antagonist, dexamethasone and aprepitant, for children receiving highly emetogenic chemotherapeutic agents (e.g. cisplatin, dacarbazine, and cyclophosphamide).
- A combination of 5-HT3 antagonist and dexamethasone for those receiving moderately emetogenic chemotherapeutic agents (e.g. doxorubicin, methotrexate and ifosphamide).
- 5-HT3 antagonist alone for those children receiving low emetogenic chemotherapeutic agents (e.g. etoposide, fluorouracil and paclitaxel).

- Delayed chemotherapy-induced nausea and vomiting

This usually occurs 24 hours post-chemotherapy, peaks on the third-day post-chemotherapy, and could continue until a week after a cycle of chemotherapy (Rapoport, 2017; Ruggiero *et al*.,

2018:2150). It is usually observed in patients whose acute-onset CINV, after the administration of highly emetogenic agents such as cisplatin, is not well controlled (Navari, 2015a:2740; Ruggiero *et al*., 2018:2150). Delayed-onset CINV is mediated by substance P, which is responsible for activating neurokinin-1 (NK_1) receptors in the brain to cause nausea and vomiting (Navari & Aapro, 2016:1357; Garcia-Recio & Gascón, 2015). This forms the basis for the use of NK_1 receptor antagonists for delayed-onset CINV. The regimen for the management and prevention of delayed-onset CINV also includes 5-HT3 receptor antagonist, dexamethasone and aprepitant, with the 5-HT3 antagonists given only on day one of chemotherapy, and dexamethasone and aprepitant given on days one to four, and days one to three, respectively (NCCN, 2017).

- Anticipatory chemotherapy-induced nausea and vomiting

This type of CINV usually occurs before the patient receives the chemotherapeutic agent and is usually precipitated by the child's expectation of nausea and vomiting due to a previous experience (Dupuis *et al*., 2014:1506; NCCN, 2017; Ruggiero *et al*., 2018:2151). Good management of both acute and delayed CINV in children is, therefore, likely to subsequently reduce anticipatory nausea and vomiting in these patients (Dupuis *et al*., 2014:1508). Other recommendations for the management of anticipatory CINV in children are the methods of systematic desensitisation and hypnosis, and the use of benzodiazepines (lorazepam) the night before and on the day, some few hours prior to receiving chemotherapy (Dupuis *et al*., 2014:1507).

- Breakthrough chemotherapy-induced nausea and vomiting

Nausea and vomiting can be characterised as breakthrough when the cause is attributable to the chemotherapeutic agent the patient has received, after all other possible causes have been excluded, and occurs even after the patient has received adequate emetic prophylaxis (Flank *et al*., 2016:1146; Jordan, Sippel *et al*., 2007:1149). Treatment for breakthrough CINV includes the addition of olanzapine to the antiemetic regimen for those being administered highly emetogenic agents, and upgrades to the next higher level of treatment in those receiving moderately, low or minimally emetogenic agents (Flank *et al*., 2016:1147; Tamura *et al*., 2017:410).

- Refractory chemotherapy-induced nausea and vomiting

This refers to nausea and vomiting that occur subsequently in patients who have received previous cycles of chemotherapeutic agents and do not respond to antiemetic therapy nor

modifications in prophylactic treatment (Flank *et al*., 2016:1148; Navari, 2015b; Ruggiero *et al*., 2018:2151). Recommendations for the management of refractory CINV include:

- The upgrade of antiemetic therapy to the next higher level, as prophylaxis for acute CINV, in patients receiving minimally, low or moderately emetogenic chemotherapeutic agents (Flank *et al*., 2016:1148).
- Addition of olanzapine, metoclopramide or the stimulation of Nei Guan through acupressure, to the antiemetic regimen being used as prophylaxis for acute CINV, in patients receiving highly emetogenic drugs (Flank *et al*., 2016:1149).
- A benzodiazepine can also be added to the existing antiemetic regimen if anxiety is the main factor contributing to refractory nausea and vomiting (Navari, 2015b).

2.7.1.4.3 Neutropenia and fever

Chemotherapy-induced neutropenia is one of the dose-limiting side effects of cancer chemotherapy (Badr *et al*., 2016:300; Hashiguchi *et al*., 2015:1054; Lalami & Klastersky, 2017:163; Söderman *et al*., 2016; te Poele *et al*., 2009:46). Neutropenia is defined as an absolute neutrophil count with a value less than 500 neutrophils per microlitre of blood or a leucocyte count of less than 1 000 neutrophils per microlitre of blood (Gudiol *et al*., 2010:334; Lustberg, 2012:825; te Poele *et al*., 2009:46). Reduced counts of neutrophils are usually observed 10 to 14 days after a chemotherapy cycle and are expected to return to normal counts in about a month after treatment (Moore, 2016:765). Neutrophils, the largest component of granulocytes, are the first to appear during an inflammatory response (Mayadas *et al*., 2014:181). Chemotherapy-induced neutropenia, therefore, increases the risk of infections due to the reduced immunity associated with low counts of neutrophils (Burutaran *et al*., 2015:29; Badr *et al*., 2016:300). Fever, which is a primary sign of infection in children with neutropenia (febrile neutropenia), must be handled as an emergency (Burutaran *et al*., 2015:29; Castagnola *et al*., 2013:135; Reynders, 2010:328; te Poele *et al*., 2009:46). A study by Mueller *et al*. (2015:492) indicated chemotherapy-induced fever and neutropenia as one of the most common diagnoses in children with cancer, who present to the emergency ward.

Chemotherapy is usually withheld in patients who develop neutropenia, or they receive reduced doses of the chemotherapeutic agent in subsequent cycles and this could impact adversely on the expected patient outcome (Castagnola *et al*., 2016:5859; Kaplan *et al*., 2019:70; Lalami & Klastersky, 2017:164; Loeffen *et al*., 2015:143). Advances have been made in the prevention of chemotherapy-induced neutropenia and its associated fever, and these include the prophylactic administration of granulocyte-colony-stimulating factor, a cytokine that stimulates increased neutrophil production and function, and antibiotics (Badr *et al*., 2016:300; Gafter-Gvili *et al*.,

2012). These interventions are, however, associated with treatment costs and the potential for increased bacterial resistance (Alexander *et al*., 2012:17; Badr *et al*., 2016:300; Barone, 2011; Klastersky *et al*., 2016:42). Prophylaxis of fever and neutropenia should, therefore, be considered in patients with a high risk of fever and neutropenia, based on results of risk stratification measures (Badr *et al*., 2016:301; Haeusler *et al*., 2015:532).

The management of chemotherapy-induced neutropenia with fever involves the hospitalisation and administration of broad-spectrum antibiotics to the patient until the absolute neutrophil counts return to normal (Af Sandeberg *et al*., 2017; Boragina *et al*., 2007:521; Haeusler *et al*., 2015:532; Lehrnbecher *et al*., 2017:2084; Maxwell *et al*., 2017). Antibiotic treatment duration is dependent on the results of blood cultures done before the initiation of therapy and the clinical status of the patient (Sung & Johnston, 2007:19). Delaying the initiation of antibiotics in febrile neutropenia until the causative organism has been isolated, could worsen the infection-related mortality in these patients (Perron *et al*., 2014). The immediate initiation of empiric broad-spectrum antibiotics is encouraged (Miedema *et al*., 2016:17; Reynders, 2010:330).

2.7.1.4.4 Anaemia

Anaemia is one of the haematological adverse effects of cancer chemotherapy (Aapro *et al*., 2018:130). This may be caused by the impairment of the production of red blood cell precursors in the bone marrow, haemolysis, or indirectly through the nephrotoxic side effects of some chemotherapeutic agents (Bartucci *et al*., 2011:6185; Rodgers *et al*., 2012:642). The nephrotoxic side effects of the chemotherapeutic agents lead to a decreased production of erythropoietin by the kidneys (Rodgers *et al*., 2012:642). The standard approach in the management of chemotherapy-induced anaemia is the transfusion of red blood cells, but this is associated with effects such as haemolysis and the risk of infection transmission (Aldoss *et al*., 2008:24; Hiradfar & Banihosseinian, 2014:151; Ruggiero & Riccardi, 2002:452). Current trends in the management of chemotherapy-induced anaemia, which include the use of erythropoietin stimulating agents, have reduced the use of blood transfusions (Aldoss *et al*., 2008:24). This was confirmed in a study by Hiradfar and Banihosseinian (2014), which showed positive effects of recombinant human erythropoietin in the treatment of chemotherapy-induced anaemia in paediatric patients, and the resultant decrease in the need for blood transfusion.

2.7.1.4.5 Mucositis

Mucositis refers to the inflammation of the gastrointestinal tract, but is mostly seen and is severe in the oropharyngeal part of the gastrointestinal tract (Castagnola *et al*., 2013:132; Carreón-Burciaga *et al*., 2018). Inflammation of the oral mucosa, which precedes ulceration of the

tissues, after the administration of chemotherapy is regarded as one of the most severe non-haematological adverse effects of cancer chemotherapy, which may lead to treatment disruption and reduction of dose in children (Cheng *et al*., 2011:161; Miller *et al*., 2012:340; Ribeiro *et al*., 2017). The non-selective nature of chemotherapeutic agents on rapidly dividing cells makes the oral mucosa very prone to the toxic effects of chemotherapy (Chaveli-López & Bagán-Sebastián, 2016:201; Miller *et al*., 2012:340).

Inflammation is characterised by erythema and oedema, which may progress to ulceration within seven days, causing discomfort in the patients and will usually require administration of opioids (Chaveli-López & Bagán-Sebastián, 2016:202; Damascena *et al*., 2018; Miller *et al*., 2012:341; Scully & Sonis, 2006). The onset of mucositis is within three to ten days after the administration of chemotherapy and abates within three weeks after the administration of the offending agent (Chaveli-López & Bagán-Sebastián, 2016:202; Miller *et al*., 2012:341; Scully & Sonis, 2006). The break in mucosal barriers in children with mucositis predisposes them to oral and systemic infections (Girmenia & Menichetti, 2011:274; Miller *et al*., 2012:341). Different approaches are used to assess the severity of mucositis with regard to the extent of mucosal damage. Carreón-Burciaga *et al*. (2018) showed a correlation between the chemotherapeutic agent and the total number of cycles received, and the severity of mucositis. Severe neutropenia has also been shown to be a risk factor for the occurrence of mucositis (Cheng *et al*., 2011:161). Recommendations for the prophylaxis of mucositis in children receiving chemotherapy include cryotherapy, which involves the sucking of ice cubes by the children the whole time of receiving chemotherapy; low-level light therapy, which offers anti-inflammatory and analgesic effects; and the administration of keratinocyte growth factor (Sung *et al*., 2017:8). The use of combination mouth rinses, which are usually based on hospital protocols, and the use of low-level light therapy have been found to be effective in the treatment of severe oral mucositis (Ribeiro *et al*., 2015:468).

2.7.1.4.6 Chemotherapy-induced peripheral neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN), described as an acute and chronic injury to the peripheral nervous system, has been associated with some chemotherapeutic agents (Kandula *et al*., 2016:118). Vinca alkaloids, especially vincristine, and platinum compounds are associated with CIPN (Gilchrist, 2012:9; Kandula *et al*., 2016:118; Mora *et al*., 2016:2417). CIPN, which usually presents as deficiencies in the sensory, autonomic and motor functions of the peripheral nervous system, starts with the feet and hands (Gilchrist, 2012:9; Mora *et al*., 2016:2416). Symptoms include paresthesia, numbness, dysesthesias and tingling, and they are usually induced by cold and warm temperatures, and alterations in touch sensations (Gilchrist, 2012:9; Starobova & Vetter, 2017).

Chemotherapy-induced peripheral neuropathy is usually dose-related; reduction of the dose or prolongation of the interval between doses of the offending agent, therefore, minimises the risk of CIPN (Gilchrist, 2012:14; Starobova & Vetter, 2017). It is important for children to recover from CIPN since the symptoms associated with CIPN put them at high risk of secondary diseases and developmental disorders (Schlenke *et al*., 2018). Involving the expertise of occupational and physical therapists to evaluate the level of CIPN and its resultant effects on the functional ability of the affected child is encouraged (Gilchrist, 2012:14). Therapies such as foot massage and bathing, whole-body vibration and sensorimotor training are some of the physical therapies that have been found to be effective in controlling the symptoms of CIPN (Schlenke *et al*., 2018).

Table 2.8 presents an overview of the mode of action, adverse drug effects and type of malignancies for which they are utilised, of some of the common chemotherapeutic agents used in the management of childhood cancers (compiled from Avramis, 2012; BNFC, 2017-2018; Capitini *et al*., 2014; Goftar *et al*., 2014; Hijiya & van der Sluis, 2016; Huang *et al*., 2015; Makin, 2018; Mihlon *et al*., 2010 & Montecucco *et al*., 2015).

Table 2.8: Chemotherapeutic agents utilised in the management of childhood cancers

Cytotoxic class	General mechanism of action	Common drugs in class utilised in children	Adverse effects	Examples of cancers in which drug is utilised
Alkylating agents	Bind covalently to the alkyl or hydrocarbon group of DNA of cells, causing cross-links and breaks in DNA strands. This leads to necrosis or apoptosis.	Cyclophosphamide Chlorambucil Melphalan Dacarbazine Carmustine Lomustine	Alopecia Secondary malignancy Haemorrhagic cystitis Fluid retention and oedema	Wilms' tumour ALL NHL Hodgkin's lymphoma Neuroblastoma Retinoblastoma
Antimetabolites	Compete with, and bind to receptor sites of structurally similar physiological molecules to form non-functional macromolecules.	5-Fluorouracil Cytarabine Methotrexate Thioguanine 6-mercaptopurine	Alopecia Bone marrow suppression Oral mucositis	ALL AML Burkitt's lymphoma Hodgkin's lymphoma
Cytotoxic antibiotics	Intercalate between DNA strands, and interrupt the activities of topoisomerase leading to breakage in DNA strands	Doxorubicin Daunorubicin Epirubicin Actinomycin Bleomycin Mitomycin	Cardiotoxicity Bone marrow suppression Tissue necrosis after extravasation Alopecia	Wilms' tumour Neuroblastoma Retinoblastoma Hodgkin's lymphoma Rhabdomyosarcoma NHL
Topoisomerase inhibitors	Inhibit topoisomerase enzymes that are responsible for catalysing the breaking and re-assembling of DNA strands of normal cells	Etoposide Irinotecan Topotecan	Bone marrow suppression Alopecia Oral mucositis	Neuroblastoma Germ cell tumour Rhabdomyosarcoma NHL
Spindle poisons	Inhibit mitosis by preventing the formation of microtubules or stimulating the aggregation of microtubules	Vincristine Vinblastine Vinorelbine Docetaxel	Peripheral neuropathy Tissue necrosis after extravasation Oral mucositis	Lymphomas Acute leukaemias Hodgkin's lymphoma NHL

Cytotoxic class	General mechanism of action	Common drugs in class utilised in children	Adverse effects	Examples of cancers in which drug is utilised
		Paclitaxel		Wilms' tumour Neuroblastoma
Platinum compounds	Cause the formation of inter- and intra-DNA strands leading to cross-linkages in DNA and eventual cell apoptosis	Cisplatin Carboplatin Oxaliplatin	Nephrotoxicity Peripheral neuropathy Oral mucositis Ototoxicity	Neuroblastoma Germ cell tumours Wilms' tumour Retinoblastoma Hepatoblastoma
Monoclonal antibodies	Inactivating growth factor receptors needed for cell growth, thereby activating apoptotic processes Fusion of antibodies with tumour cells to induce cell death	Rituximab	Immune suppression	Leukaemia NHL Metastatic neuroblastoma
Small molecules	Targeting of specific signal transduction pathways required for cell survival and replication	Imatinib Everolimus	Growth suppression Immunosuppression	Ph^+ ALL Chronic phase of CML
Asparaginase	Converts L-asparagine to aspartate and ammonia, preventing the formation of RNA and DNA and normal functioning of tumour cells	L-asparaginase Pegasparaginase	Hypersensitivity reactions Hyperglycaemia Pancreatitis Thrombosis Myelosuppression Hepatic toxicity	ALL AML NHL
Glucocorticoids	Bind to glucocorticoid receptors on the surface of the tumour cells and translocate them to the nucleus, thereby activating cell apoptosis.	Prednisolone Dexamethasone	Bone toxicities Proximal myopathy Immunosuppression	Adjunctive therapy in: ALL Hodgkin's lymphoma NHL

DNA = Deoxyribonucleic acid; ALL = Acute lymphoblastic leukaemia; NHL = Non-Hodgkin's lymphoma; AML = Acute myeloid leukaemia
Ph^+ = Philadelphia positive; CML = Chronic myeloid leukaemia

2.7.2 Radiotherapy

This approach in the management of childhood cancers employs radiation (Paulino, 2013a:119) and is usually used in combination with chemotherapy or surgery (Rombi *et al*., 2013). Radiation in cancer therapy produces effects in two ways (Baskar *et al*., 2012:196; Baskar *et al*., 2014:2; Burns *et al*., 2016; Kirthi Koushik *et al*., 2013:255; Sánchez, 2015):

- By directly providing high energy for RNA and DNA of cells, resulting in the breakage of the bonds in their molecules.
- By indirectly ionising the water-soluble component of the cancer cells, producing free radicals in the process, which are toxic to the cells.

Although both fast-growing normal and tumour cells are affected by radiation, cancer cells are more sensitive to damage that radiation causes to the DNA (Baskar *et al*., 2014:2; Rodgers *et al*., 2013). The use of both low- and high-linear energy transfer radiation allows for extensive damage to tumour cells while reducing toxicity to normal cells through the reduction of doses absorbed by these cells (Niemantsverdriet *et al*., 2012:1294; Paulino *et al*., 2010:14; Zaghloul, 2013:2). The application of radiation in smaller fractions spanning several weeks allows for the reduction of toxicity to normal cells and also allows damage done to these cells to be repaired (Baskar *et al*., 2014:2; Kirthi Koushik *et al*., 2013:259; Sánchez, 2015). Treatment planning before the start of radiotherapy is also a necessary requirement that enables optimisation of radiation dose to the target and normal tissues (Jairam *et al*., 2013:e151; Kristensen, 2017:15).

Most of the cancers that occur in children are very responsive to radiation and, therefore, require lower doses compared to adults, especially when treatment involves the combination of chemotherapy and radiotherapy (Mukherji, 2018:37). Radiotherapy is generally delayed in children, especially those under the age of three years, since tissues that are still undergoing growth have a higher tendency of being affected by the radiation (Mukherji, 2018:37; Westhoff *et al*., 2018; Zaghloul, 2013:2). Effects of radiotherapy on children include diminished growth and developmental delay (especially neurocognitive defects in children younger than three years and receiving cranial radiation), and this has led to a reduction in its use over the last two decades (Ahmed *et al*., 2018:15; Jairam *et al*., 2013:e151; Kutanzi *et al*., 2016; Ward *et al*., 2014:93).

Clinical uses of radiotherapy include the use as neoadjuvant therapy (done before starting the main approach of treatment for the particular cancer), radical treatment (used as the main modality of treatment with the aim of a higher probability of cure), adjuvant treatment

(given together with either surgery or chemotherapy) and palliative treatment (aimed at improving the quality of life of the patient) (Kirthi Koushik *et al*., 2013:259). Paediatric malignancies for which radiation therapy is indicated include Erwing sarcoma, Hodgkin's lymphoma, neuroblastoma, medulloblastoma, craniopharyngioma, ependymoma, rhabdomyosarcoma, retinoblastoma and nephroblastoma (Sánchez, 2015).

Exposure of tumour cells to radiation can be done using two main techniques which are external beam radiation and internal radiation therapy (McGovern & Mahajan, 2012:323).

2.7.2.1 External beam radiation

This technique involves the targeting of high energy radiation to where the tumour is located, from outside the body, while sparing the normal tissues around the tumour (Baskar *et al*., 2012:194; Kirthi Koushik *et al*., 2013:256). Types of external beam radiation therapy include 3-D conformal radiation therapy, intensity-modulated radiation therapy (IMRT), stereotactic radiosurgery (SRS), image-guided radiotherapy (IGRT) and stereotactic body radiation therapy (SBRT) (Baskar *et al*., 2012:195).

Photons, electrons and protons are employed in external radiation therapy, but protons are preferred in children due to its advantage of distributing high doses of radiation to the tumour cells while sparing normal cells (Buchsbaum, 2015; Chang *et al*., 2014:358; Ho *et al*., 2017:1040; Merchant, 2013:97). Tumours in children for which external beam radiation is utilised include Erwing sarcoma, neuroblastoma, medulloblastoma, Hodgkin's lymphoma, retinoblastoma and craniopharyngioma (Kim & Younghee, 2015:1478; Merchant, 2013:98).

2.7.2.2 Internal radiation therapy

This technique of delivering radiation therapy, also known as brachytherapy, involves the introduction of radioactive materials in the form of implants, into the body, on the tumour or very close to it (Baskar *et al*., 2012:194; Kirthi Koushik *et al*., 2013:257). Application of a higher dose to a smaller area, which might be impossible with the external radiation technique, can be achieved using brachytherapy (Fijuth, 2010:81; Kirthi Koushik *et al*., 2013:257). Reduction in radiation dose to normal tissues and a decrease in treatment time can also be achieved using brachytherapy (Fijuth, 2010:81; Martinez-Monge *et al*., 2006:157). Late effects associated with radiation therapy such as growth retardation and developmental delay, which are usually characteristic of external beam radiation, are reduced with the use of brachytherapy (Fijuth, 2010:81). Techniques of brachytherapy utilised in children include low-dose-rate brachytherapy, pulsed-dose-rate or high-dose-rate

temporary brachytherapy, as well as intraoperative high-dose-rate brachytherapy (Martinez-Monge *et al*., 2006:158-159).

2.7.2.3 Radiotherapy-induced adverse effects

Adverse effects of radiotherapy are classified as early-onset, occurring during or immediately after treatment, or late-onset, which usually occurs months or years after radiation therapy (Berkey, 2010:381; Bourgier *et al*., 2015:313; Coura & Modesto, 2016:71; Otmani, 2007:257). Early-onset or acute adverse effects of radiation treatment include mucositis, xerostomia, emesis, proctitis, cystitis and taste disturbances. Late-onset effects, on the other hand, include the occurrence of secondary malignancies after treatment with radiation, cognitive dysfunction, musculoskeletal abnormalities, pulmonary toxicities and endocrine effects (Christopherson *et al*., 2014:475; Ducassou *et al*., 2015:607; Grosshans *et al*., 2018:76).

Children exposed to radiation are more susceptible to late effects of treatment, especially the development of secondary malignancies; some strategies have, therefore, been implemented to reduce these effects (Dracham *et al*., 2018:85; Kamran *et al*., 2016:1811; Paulino, 2013b:122; Rowe *et al*., 2017). These interventions include reducing the doses and volumes of radiation and adding chemotherapy to the treatment protocol, delaying or omitting radiotherapy in the very young, and lowering doses of radiation per fraction (Roddy & Mueller, 2016:240). Others include avoiding radiotherapy in children with favourable prognoses and use of modern techniques that allow delivery of radiation to tumours while sparing the surrounding normal tissues (Paulino, 2013b:122).

Radiation-induced endocrine effects are relatively common in children exposed to radiation, especially those treated for CNS tumours (Rowe *et al*., 2017). These effects are dependent on the dose, and how fractionation was done (Follin & Erfurth, 2016). Notable among these effects are growth hormone deficiency resulting in growth delay, thyroid hormone defects due to the high susceptibility of the thyroid gland to ionising radiation, gonadotropic hormone deficiency, and defects in the secretion of adrenocorticotropic hormone (Follin & Erfurth, 2016; Iglesias *et al.*, 2017:180; Rowe *et al*., 2017). Strategies aimed at reducing the incidence of radiation-related late effects must, therefore, be implemented.

The lungs are highly sensitive to radiation, and patients exposed to radiation for the treatment of lung malignancies are at a higher risk of radiation-induced pulmonary toxicities (Elbahlawan *et al*., 2017:768; Liles *et al*., 2008:535; Oda *et al*., 2017). The damage to DNA from radiation therapy during cancer treatment results in cell injury and necrosis of

pulmonary cells (Graves *et al*., 2010:201; Versluys & Bresters, 2016:64). The risk of pulmonary injury increases with increased doses of radiations, being female, and the co-administration of chemotherapeutic agents (Graves *et al*., 2010:203). Pulmonary effects of radiation therapy include pneumonitis and radiation-induced lung fibrosis (Elbahlawan *et al*., 2017:768; Krasin *et al*., 2010:22; Versluys & Bresters, 2016:64). These effects are characterised by dyspnoea on exertion, shortness of breath and cough, which may or may not be accompanied by fever (Liles, 2008:534). Pulmonary fibrosis may lead to chronic respiratory failure, which may eventually result in cor pulmonale or pulmonary hypertension (Versluys & Bresters, 2016:64). Planning before administration of radiation therapy, which involves the selection of appropriate technique and optimal radiation dose to reduce the amount of radiation to the normal lung tissue, is useful in reducing the toxicity associated with the treatment (Graves *et al*., 2010:204; Paulino, 2013b:124).

Radiation-induced brain necrosis, which could result in neurologic decline and fatal consequences, is seen as one of the most severe late adverse effects of radiation therapy in patients treated for CNS tumours (Grosshans *et al*., 2018:78; Smiley *et al*., 2016:1671; Verma *et al*., 2013:516). This begins as acute injury and death of endothelial cells, leading to aggregation of platelets, the formation of thrombus and eventual blockage of microvessels (Drezner *et al*., 2016:146). Symptoms associated with radiation-induced brain necrosis in children include ataxia, weakness, changes in vision and headache (Rowe *et al*., 2017). Treatment of radiation-induced necrosis involves the use corticosteroids, hyperbaric oxygen therapy (HBOT), or bevacizumab — a monoclonal antibody that inhibits vascular endothelial growth factor (Drezner *et al*., 2016:146; Song & Colaco, 2018). These can be used either singularly or in combination.

2.7.3 Surgical intervention

Surgical intervention was the main treatment modality for cancers until the advent of radiation therapy and chemotherapy some decades ago (Alcoser & Rodgers, 2003:107; Brierley & Collingridge, 2015:1187; Eden & Burns, 2015:1191). A multimodal approach, employing chemotherapy, radiotherapy and surgery, is currently used in the management of childhood cancers and this has helped to improve survival outcomes (Alcoser & Rodgers, 2003:107). The main goal of surgery in the resection of malignant tumours is the complete removal of the tumour in order to attain the best oncologic outcomes (Kelleher *et al*., 2013:1727). Oncologic outcomes include little or no cosmetic loss, normal functioning after surgery, and progression-free survival (Björk-Eriksson & Glimelius, 2005:871; Kelleher *et al*., 2013:1727). Surgery is employed in oncology for prevention (to excise tissues that have the likelihood of becoming malignant), diagnosis (the use of tissue biopsy to diagnose certain

cancers), treatment (removal of solid tumours), and palliative care (aimed at improving the quality of life of patients) (Eden & Burns, 2015:1192; Fernandez-Pineda *et al*., 2017; Sullivan *et al*., 2015:1193). Surgery is also required to insert central venous intravenous catheters in patients who would require long-term treatment for their cancers, in order to reduce the pain and discomfort that follow continuous venepuncture for various chemotherapy cycles (Hatakeyama *et al*., 2011:372). The use of central venous catheters also helps to reduce the extravasation of highly vesicant chemotherapeutic agents (Hatakeyama *et al*., 2011:372; Kreidieh *et al*., 2016:91).

Surgery is employed either as the main treatment modality or as adjunctive therapy for some solid tumours (Boo *et al*., 2017). For example, surgery is the first treatment modality employed in the management of medulloblastoma, and this is a means of confirming the type of tumour as well as improving treatment outcome (Kopecky *et al*., 2017:589).

The field of surgical oncology has witnessed advancements in the treatment of childhood cancers and this has led to the shift from traditional surgical procedures, which mainly involved primary resection, to procedures that are minimally invasive. These are used in initial biopsy for diagnosis and post-chemotherapy resection of tumours (Boo *et al*., 2017; Eden & Burns, 2015:1192; Fuchs, 2015:213; Fuchs *et al*., 2014). These techniques include thoracoscopic and laparoscopic techniques (Jackson & Kane, 2014:149; Lorenzo & Romao, 2016:180). Greater surgical precision is achieved with the use of these techniques since they offer the ability to directly visualise the detailed anatomy of a magnified tissue (Acker *et al*., 2015:1206; Oh *et al*., 2016). Other advantages with these techniques include a reduced risk of infections since only small incisions are required, reduced post-operative pain, and a shorter post-operative hospital stay (Phelps & Lovvorn, 2018; Saravanan *et al*., 2008:103; Yardley & Kenny, 2013:185).

2.7.4 Haematopoietic stem cell transplantation

Haematopoietic stem cell transplantation (HSCT) is used as a treatment modality for children with high risk solid tumours and haematologic malignancies (Bhatia, 2011:437; Chow *et al*., 2016:782; Majhail *et al*., 2015:1863; Munchel *et al*., 2011:233; Peters *et al*., 2015:1265; Ullrich *et al*., 2010:3879). These include leukaemias and lymphomas (Khandelwal *et al*., 2017:1346; Yeşilipek, 2014:92). Stem cell transplantation is also often used as second-line treatment when the use of conventional therapies including chemotherapy, surgery and radiotherapy, has been unsuccessful (Armenian *et al*., 2011:1413; Ceppi *et al*., 2016; Reinfjell *et al*., 2017).

This treatment modality employs the intravenous infusion of autologous (progenitor cells from the patient undergoing treatment) or allogeneic (progenitor cells from a donor) stem cells to a child with a defective immunological response, in order to induce normal haematopoietic function (Dulamea & Lupescu, 2018:945; Pulsipher *et al*., 2011:s140). To prevent the rejection of the stem cells by the host, patients who are to undergo HSCT receive conditioning therapy in the form of chemotherapy, radiotherapy or antilymphocyte antibodies, to suppress the patient's immune system (Hoare *et al*., 2017:349; Yeşilipek, 2014:92). The immunocompromised state of these patients leaves them vulnerable to latent and opportunistic infections (Hoare *et al*., 2017:349; Caldas Teixeira *et al*., 2018:69; Ghimire *et al*., 2017; Ullmann *et al*., 2016:1435). Prophylaxis against bacterial, viral and fungal infections in children undergoing HSCT is, therefore, necessary to reduce the morbidity and mortality associated with this treatment modality.

Graft-versus-host disease (GVHD), which is due to the recognition of the infused cells as foreign antigens by the host antigens, is another important complication of HSCT, especially with allogeneic transplant (Chao, 2017; Flinn & Gennery, 2017; Ghimire *et al*., 2017; Li *et al*., 2016:1368; Yeşilipek, 2014:95). The predominant risk factor for the occurrence of GVHD is the disparity between the human leucocyte antigen (HLA) of the donor and the recipient (Hierlmeier *et al*., 2018; Nassereddine *et al*., 2017:1548). The use of HLA-identical sibling donors is, therefore, preferable in allogeneic transplantation due to the better histocompatibility between donors and recipients (Lazaryan *et al*., 2016:137). Graft-versus-host disease could be either acute or chronic. Acute GVHD, which is known to occur within the first 100 days after HSCT, manifests as abdominal cramps, nausea and vomiting, maculopapular rash, and high levels of serum bilirubin (Chao, 2017; Hatzimichael & Tuthill, 2010:112). Chronic GVHD, which usually occurs after the first 100 days after HSCT, manifests as scleroderma, increasing serum bilirubin, ulceration of the oral mucosa and sclerosis of the gastrointestinal tract (Chao, 2017; Ferrara *et al*., 2009:1552). The management of acute GVHD involves the use of steroids, which produce both anti-inflammatory and immunosuppressive effects (Flinn & Gennery, 2017; Ferrara *et al*., 2009:1556). The use of prednisolone, in combination with cyclosporine and other therapies such as monoclonal antibodies, sirolimus and mycophenolate mofetil, has proven to be effective in the management of chronic GVHD (Baird *et al*., 2010:315).

Other complications of HSCT in children include pulmonary complications, cardiovascular complications, secondary malignancies, rejection of transplant, renal complications, neurological complications and endocrine disorders (Diab *et al*., 2016:260; Dulamea & Lupescu, 2018:946; Hierlmeier *et al*., 2018).

2.7.5 Palliative care

In spite of the increasing survival of children with childhood cancer, some children still die from these conditions (Erdmann *et al*., 2019; Gatta *et al*., 2014:42; Kirch *et al*., 2016:402; Misko *et al*., 2015:561; Siegel, R.L., *et al*., 2018:27). For children with advanced stages of various intractable cancers, palliative care offers a pragmatic and humane management option (Esmaili *et al*., 2018:1). Palliative care is defined as an all-inclusive approach with the aim of improving the quality of life of patients with lethal conditions together with their families, through the prevention and relieving of suffering associated with pain as well as other psychosocial, spiritual and physical problems (WHO, 2007). Palliative care was, in times past, only thought of when the child was not responding to curative treatment (Bergstraesser, 2013:31; Michelson & Steinhorn, 2007:213). The American Academy of Pediatrics (AAP), however, advocates for the offering of palliative care to children at diagnosis and throughout therapy, irrespective of the prognosis of cancer (AAP, 2013:968). This early introduction of palliative care in the management of childhood cancer is intended to address the physical, psychological and spiritual needs of the children and their families (Vern-Gross & Marcus, 2018:419; Weaver *et al*., 2015:829). The overall aim of palliative care in paediatric oncology is to improve the quality of life of the affected children and their families and, therefore, can be offered to children together with other treatment-alignment plans (Bradford *et al*., 2014). The all-inclusive approach employed in palliative care, therefore, requires a multidisciplinary team, which includes the medical team as well as social workers and chaplains (Niha & Vivek, 2016).

Children and adolescents diagnosed with cancer undergo both physical (symptomatic) and psychosocial stress due to the concurrence of the disease and their developmental stage (Kwak *et al*., 2013:2160; Weaver *et al*., 2015:829). Being offered relief from these stressors is, therefore, helpful. The optimal management of symptoms in children with cancer is usually made difficult by the inability of most of them to adequately communicate the extent of their suffering, requiring parents to act as proxies for communication with healthcare providers (Getz *et al*., 2018; van der Geest *et al*., 2016:599). Parents and families of these children also undergo psychosocial stress and, therefore, need to be included as beneficiaries of palliative care throughout the course of their child's illness (Barrera *et al*., 2018:159; Nafratilova *et al*., 2018:127; Weaver *et al*., 2015:832).

Relieving physical pain as well as other physical symptoms including nausea, anxiety and constipation is the fundamental component of palliative care (Israels *et al*., 2015:608; Michelson & Steinhorn, 2007:215; Postovsky *et al*., 2018:120). Although pain, which could be caused by an underlying tumour or from procedures involved in cancer treatment

constitutes the most common discomfort experienced by children with advanced cases of cancer, it is a challenging condition for healthcare professionals to manage (Long & Agrawal, 2019:113; Mercadante & Giarratano, 2014:93; Tutelman *et al*., 2018:198). Pain management involves a multidisciplinary approach that may include anaesthesia, sedation services, psychosocial and spiritual support (Postovsky *et al*., 2018:123). In the pharmacological management of the highly subjective experience of pain, the WHO recommends an incremental hierarchy approach which involves the use of mild analgesics and the steady progression into the use of more potent opioid analgesics (WHO, 2012). Appropriate dose increment of opioids and the administration of adjuvant analgesics are also recommended (WHO, 2012). Mild analgesics such as paracetamol and ibuprofen should be used for mild to moderate pain, while opiates such as morphine should be given to manage moderate to severe pain (WHO, 2012). These treatments must, however, be tailored according to individual patient needs through the use of pain scores (WHO, 2012). Administration of opioid analgesics is mostly confronted with the concerns of tolerance, withdrawal symptoms and side effects such as constipation (Michelson & Steinhorn, 2007:215). Opioid switching is recommended for the management of tolerance, and to a small extent side effects, while opioid weaning — which involves the slow tapering of doses — is recommended to reduce the risk of withdrawal syndrome (Mercadante & Giarratano, 2014:96; Michelson & Steinhorn, 2007:215; Postovsky *et al*., 2018:127; WHO, 2012).

In addressing the psychological needs of children with cancer, approaches including psycho-education, psychological support (involving empathic listening), cognitive-behavioural therapies (encouraging positive thinking) and distraction techniques have been employed in palliative care (Barrera *et al*., 2018). Economic hardship, due to the cost of treating childhood cancer as well as the likelihood of parents having to quit their jobs to take care of their sick children, has been established as a source of psychological distress in families of children with cancer (Creswell *et al*., 2014:508). Addressing this source of stress as an approach in palliative care can relieve the psychological burden of cancer on families during treatment (Pelletier *et al*., 2018:206). This intervention is also necessary even after treatment, as some parents still experience late psychological distress (Ljungman *et al*., 2014).

Spiritual care is recognised as an important component of healthcare in general (together with physical, social and emotional domains), and palliative care specifically (McNeil, 2016:55; Puchalski *et al*., 2019; Richardson, 2014:155; Weaver & Wratchford, 2017:270). Palliative care programmes for children with cancer and their families must, therefore, necessarily assess and meet the spiritual needs of the beneficiaries (Rego & Nunes,

2019:279). Spiritual care for children with cancer and their families help them to find the meaning and purpose of life, thereby improving the quality of their lives (Lima *et al*., 2013:1540). They must, therefore, be allowed to express their spirituality through rite simulations, the use of spiritual symbols, and allowing contact with chaplains and spiritual groups (Fitchett *et al*., 2011:706; Mueller, 2010:201; NCPQPC, 2013). These measures, which help children and their families deal with spiritual distress, do not postpone or hasten the anticipated death in patients with poor prognoses but give them some comfort (Barros Meireles *et al*., 2015).

2.8 Coexisting conditions and complications of childhood cancer

In spite of the tremendous improvement in the treatment and survival of childhood cancers, children undergoing treatment and survivors of childhood cancers continue to experience both acute and chronic complications, such as cardiotoxicity and endocrine side effects (Adamson, 2015:213; Armstrong *et al*., 2014:1225; Versluys, & Bresters, 2016:63). The increasing survival of children diagnosed and treated for various childhood cancers makes it important for the acute toxicity and long-term complications of the condition and its treatment to be recognised (Allodji *et al*., 2016:390; Goldsby *et al*., 2011:1468; Van Breeschoten *et al*., 2017:60). There is an increased risk of recurrence of the primary cancer, as well as the development of secondary malignancies in children who survive after five years of being diagnosed with and treated for cancer (Xie *et al*., 2018:79). These complications may be as a result of the malignancy or the interventions employed in their treatment (Jones *et al*., 2008:724; Weaver & Samkari, 2017:60). The risk of complications in survivors of childhood cancer, as a result of the therapies they received, has resulted in treatment modifications for childhood cancer (Gibson *et al*., 2018). This is aimed at improving the long-term survival of children with cancer and reducing the risk of complications (Gibson *et al*., 2018; Wijnen *et al*., 2016:R300). Long-term follow-up of survivors of childhood cancers is therefore necessary for early detection and prevention of some of these complications (AAP, 2009:907; Pritchard-Jones *et al*., 2013:e96; Signorelli *et al*., 2017:132).

2.8.1 Infectious complications

Treatment modalities, including chemotherapy, radiotherapy and HSCT, compromise the immunity of children with cancer, and predispose them to infections — a major cause of death in these children (Castagnola *et al*., 2013:122; Foster *et al*., 2018; Sasada *et al*., 2016; Vento & Cainelli, 2003:595; Weaver & Samkari, 2017:67). Chemotherapy-induced fever and neutropenia are common risk factors for infectious complications (refer to paragraph 2.7.1.4.3). Nonetheless, the underlying malignancy could also be a risk factor for

immunosuppression and predispose patients to infections (Benites *et al*., 2014:371; Weaver & Samkari, 2017:60).

A study by Perkins *et al*. (2014:2519) to investigate the risk of infectious complications in survivors of childhood cancers revealed that almost 33% of their study population had infectious complications after more than five years of being diagnosed with cancer. These infections included bronchitis, tonsillitis, pneumonia, colitis, hepatitis, genitourinary infections and gingivitis. They concluded that survivors of childhood cancer were at an increased risk of infections, with the increased risk being proportional to the time since diagnosis (Perkins *et al*., 2014:2520).

2.8.2 Cardiovascular complications

Cardiotoxicity has been noted as one of the severe complications of the treatment of childhood cancer with radiotherapy and chemotherapy (Marr *et al*., 2017:615; Olsen *et al*., 2014:122; Tukenova *et al*., 2010:1313; Walker *et al*., 2013:1801), and is a leading cause of morbidity and mortality among childhood cancer survivors (Chen *et al*., 2011:620; Mulrooney *et al*., 2009; Trachtenberg *et al*., 2011:342). Cardiovascular complications observed in survivors of childhood cancer include myocardial infarction, heart failure, pericardial diseases and valvular abnormalities (Feijen *et al*., 2019; Mulrooney *et al*., 2009; Purkayastha *et al*., 2017:83). Findings suggesting cardiotoxicity include lower left ventricular mass and higher left ventricular overload (Lipshultz *et al*., 2012:1051). Treatment of childhood cancer with anthracyclines, and exposure to cardiac irradiation, have been found to be associated with, and a major risk factor for, the development of cardiotoxic adverse effects during and years after the treatment (Angsutararux *et al*., 2015; Baker *et al*., 2011:1948; Trachtenberg *et al*., 2011:343; van der Pal *et al*., 2012:1435). This risk is increased with the presence of congestive heart disease during treatment of childhood cancer (van der Pal *et al*., 2012:1435). Long-term risk of cardiotoxicity has also been found in survivors who were not treated with cardiotoxic agents (Lipshultz *et al*., 2012:1056).

Being female and younger of age at time of diagnosis, higher cumulative doses of anthracyclines, and the presence of coexisting cardiovascular diseases have been found to be some of the risk factors associated with cardiotoxicity in survivors of childhood cancer (Franco & Lipshultz, 2015:110; Hutchins *et al*., 2017:457; McGowan *et al*., 2017:68). Identifying patients who are at a higher risk of cardiotoxic adverse effects can aid in appropriate regimen selection before treatment and a guide to follow-up screening after treatment (Trachtenberg *et al*., 2011:345).

Several mechanisms of chemotherapy-related cardiovascular complications, particularly anthracycline-induced cardiotoxicity, have been proposed (Angsutararux *et al*., 2015; Purkayastha *et al*., 2017:86). These include oxidative stress caused by free radical formation from the reduction of anthracyclines and the formation of iron complexes — leading to cardiac cell death — damaging of structural proteins responsible for the regulation of cardiac muscle contractility, and cardiomyocyte necrosis and dysfunction of sarcomere (Chen *et al*., 2011:622; Sadurska, 2015:1113; Trachtenberg *et al*., 2011:343; Walker *et al*., 2013:1802).

An approach employed in the prevention of cardiotoxicity associated with childhood cancer is the administration of dexrazoxane, an iron-chelator that prevents cardiotoxicity induced by anthracyclines through the interference of iron-mediated free radical formation (Loar *et al*., 2018:10). Other therapies for prevention include the use of liposomal or pegylated formulations of anthracyclines and administration of anthracyclines as a continuous infusion instead of bolus injections (Chen *et al*., 2011:623; Hutchins *et al*., 2017:461).

Risk factors for the occurrence of radiation-induced complications are addressed in paragraph 2.7.2.3. Another important risk factor for radiation-induced cardiotoxicity is the proportion of the heart situated in the radiation field (Loar *et al*., 2018:6; Walker *et al*., 2013:1806). Strategies implemented to reduce the adverse effects of radiation therapy (refer to paragraph 2.7.2.3) will help to reduce the risk of radiation-induced cardiotoxicity.

2.8.3 Neurological complications

A study by Kenborg *et al*. (2018) indicated that survivors of childhood cancers, especially those who were diagnosed and treated for CNS tumours, were at a higher risk of cognitive consequences. Complications involving the CNS, as a result of childhood cancer, may be due to the direct invasion of the cancer in the CNS or a consequence of the effects of the cancer treatment process (Cordelli *et al*., 2017; Duke *et al*., 2018:597; Kenborg *et al*., 2018; Weaver & Samkari, 2017:60; Sleurs *et al*., 2016:38). Neurocognitive complications arising from the cancer treatment processes are usually as a result of the use of protocols containing multiple cytotoxic agents and radiation treatment (Ikonomidou, 2018). These complications include infections (meningitis, encephalitis and abscesses), neurovascular complications (coagulopathy and thrombotic microangiopathy), neurotoxic effects (neuropathy, visual, auditory and taste disturbances), spinal cord injury from radiation therapy, and radiation-induced neurocognitive side effects (Cordelli *et al*., 2017; Neil *et al*., 2016; Reddy & Witek, 2003:137; Vossough, 2017:6; Weaver & Samkari, 2017). Symptoms of the complications, which could result from compression by the tumour, increase in

intracranial pressure, and interruptions in the environment of the tumour are dictated by the location of the tumour (Duke *et al*., 2018:599).

Toxicity resulting from the treatment of childhood cancer may range from mild and short-lived symptoms to serious and noxious syndromes (Cordelli *et al*., 2017). Headaches and seizures are a common manifestation of neurological complications associated with treatment of childhood cancers (Duke *et al*., 2018:601). Chemotherapy-induced peripheral neuropathy is another important complication associated with cancer treatment (refer to paragraph 2.7.1.4.6). Neurological adverse effects observed during treatment of childhood cancers may sometimes result in regimen modifications to alternatives that may be less effective (Sun & Cooper, 2018:33).

2.8.4 Pulmonary complications

Pulmonary complications of childhood cancer treatment can present during the treatment, immediately after the treatment or later on in the life of childhood cancer survivors (Versluys & Bresters, 2016:63). These complications may be as a result of the chemotherapeutic agents used in the treatment, surgeries of the lungs, or the involvement of the lungs in radiation therapy (Green *et al*., 2016:1577; Versluys & Bresters, 2016:63). Mechanism of radiation-induced pulmonary injury, risk factors associated with increased pulmonary injury from radiation therapy, and measures to reduce radiation-induced pulmonary complications are addressed in paragraph 2.7.2.3.

The use of some chemotherapeutic agents, notably bleomycin, alkylating agents (cyclophosphamide and busulphan) and the nitrosoureas (carmustine and lomustine) has been associated with lung fibrosis and pulmonary pneumonitis, which is observed during treatment or several months after chemotherapy is completed (De *et al*., 2014:1679; Raissy & Harkins, 2014:236; Versluys & Bresters, 2016:66). Reduction of the cumulative dose of chemotherapeutic agents noted to cause pulmonary toxicity remains the best way to prevent this complication (Reinert *et al*., 2013). Extensive follow-up of patients who received chemotherapeutic agents known to cause pulmonary toxicity is useful in monitoring and early management of patients who develop pulmonary toxicity (Versluys & Bresters, 2016:69). This is because long-term childhood cancer survivors have a higher risk of experiencing late-onset pulmonary toxicity (Dietz *et al*., 2016:3695).

2.8.5 Endocrine complications

Complications of the endocrine system from childhood cancer stem from the effects of cancer and its treatment on the thyroid gland, hypothalamic-pituitary axis, and gonads (refer

to paragraph 2.7.2.3). A decrease in bone mineral density and the disruption of the normal body homeostasis have also been observed (Chemaitilly & Sklar, 2010:141; González *et al*., 2016:332; Klika *et al*., 2018; Yuen, 2015:323). These complications are usually observed in patients who receive high doses of alkylating agents, radiation therapy as well as patients who survive Hodgkin's lymphoma and CNS tumours (Chemaitilly & Cohen, 2017:183; Yuen, 2015:323).

Complications associated with the thyroid gland include hypothyroidism, hyperthyroidism and thyroid neoplasms (Chemaitilly & Sklar, 2010:146; González *et al*., 2016:332; Lubin *et al*., 2017:2582; Ramanauskienė *et al*., 2014:279; Yuen, 2015:327). Effects on the hypothalamic-pituitary axis lead to deficiencies in growth-hormones, and luteinising and follicle-stimulating hormones (Chemaitilly & Sklar, 2010:144; González *et al*., 2016:332; Ramanauskienė *et al*., 2014:278; Yuen, 2015:324). Gonadal dysfunction involves Leydig cell and ovarian failure (Chemaitilly & Sklar, 2010:148; González *et al*., 2016:332; Yuen, 2015:328). Disruption of normal body homeostasis leads to obesity, increased insulin resistance and a decrease in the production of insulin by the pancreatic β-cells (Chemaitilly & Sklar, 2010:151; González *et al*., 2016:332; Ramanauskienė *et al*., 2014:279; Yuen, 2015:331).

Survivors of childhood cancer, particularly those treated with chemotherapeutic agents, radiation therapy and steroids, are at an increased risk of osteoporosis and osteopenia (Yuen, 2015:330). This is due to the reduction in the pituitary hormone production, decrease in vitamin D due to malabsorption and malnutrition, and reduction of calcium through its absorption in the intestine and increased renal excretion (Chemaitilly & Sklar, 2010:151; Van der Sluis & Van den Heuvel-Eibrink, 2008:475; Yuen, 2015:330). Development of osteoporosis in adult life is dependent on the maximum adolescent bone mass achieved. Children who are exposed to cancer therapies that reduce bone mineral density, therefore, have a higher risk of developing osteoporosis later in life (Khoshhal, 2011:69; Van der Sluis & Van den Heuvel-Eibrink, 2008:474). Supplementation with calcium and vitamin D, and increased physical activity during cancer treatment can help to increase bone mass and consequently reduce the risk of osteoporosis (Van der Sluis & Van den Heuvel-Eibrink, 2008:476).

2.8.6 Renal complications

A number of chemotherapeutic drugs including cisplatin, methotrexate, carboplatin and ifosphamide, surgical removal of the kidney(s), and radiation therapy involving the renal system are associated with renal complications (Jones *et al*., 2008:725; Skinner, 2018:215).

Complications of the renal system typically manifest as impaired renal function at the renal tubules or the glomerulus (Dekkers *et al*., 2013:922). Signs of renal impairment include proteinuria, hypertension and decreased glomerular filtration rate (Knijnenburg *et al*., 2012:1416; Tibúrcio *et al*., 2018). This was confirmed in a study by Knijnenburg *et al*. (2012:1425), which recorded a diminished glomerular filtration rate, albuminuria and elevated blood pressure (twice the prevalence in the general population) in survivors of childhood cancer, after over a decade of treatment completion. Cancer, *per se*, has the potential to cause renal impairment through the damaging of normal renal tissue by the infiltration by the tumour, tumour lysis syndrome or the obstruction of the urinary tract (Campbell *et al*., 2014:65; Skinner, 2018:215).

The role that the kidneys play in the elimination of toxic substances from the body, makes them particularly vulnerable to toxic insults from chemotherapeutic agents (Glezerman & Jaimes, 2016; Lameire, 2014:12; Skinner, 2018:215; Valika & Shirali, 2015:66). The toxic metabolites and reactive oxygen species formation during the metabolism of chemotherapeutic agents lead to renal injury (Perazella, 2012:1714). The potential of chemotherapeutic agents to cause nephrotoxicity is increased with the presence of pre-existing renal disease (Izzedine & Perazella, 2017:505; Lameire, 2014:12). Renal function should, therefore, be evaluated before and during chemotherapy to help in the early detection of renal toxicity (Sharbaf *et al*., 2017). Long-term follow-up of survivors of childhood cancer is necessary to be able to detect late-onset nephrotoxicity in patients receiving nephrotoxic agents during treatment (Ruggiero *et al*., 2017:2607; Skinner, 2018:221).

The renal tissue is particularly sensitive to radiation due to its dependence on the metabolically active cells and the complex vasculature of the kidneys (Skinner, 2018:216). Radiation-induced nephropathy also presents as an increase in blood pressure, a reduction in glomerular filtration rate and proteinuria (Dawson *et al*., 2010:108; Skinner, 2018:216). Risk factors for radiation-induced nephropathy, which are similar to those of other radiation-induced adverse effects, are discussed in paragraph 2.7.2.3. The main mechanism of action of radiation therapy, which involves free radical formation (refer to section 2.7.2), leads to kidney injury (Yurut-Caloglu *et al*., 2015:317).

Partial removal of renal tissue or total nephrectomy (common in the treatment of Wilms' tumour) results in a significant decrease in total renal mass and subsequent reduction in the surface area required for glomerular filtration (Kern *et al*., 2014:663; Ruggiero *et al*., 2017:2608; Skinner, 2018:216). This loss of kidney mass is associated with renal insufficiency and proteinuria (Basturk *et al*., 2015). There is a reduction in glomerular

filtration rate, which is then compensated for by an increased filtration in the remaining glomerulus (Dekkers *et al*., 2013:927). This compensatory mechanism eventually leads to kidney damage (Chapman *et al*., 2010:338).

2.8.7 Other effects of childhood cancer

2.8.7.1 Ototoxicity

Ototoxicity during and after treatment of childhood cancer is usually as a result of the toxic effects of chemotherapeutic agents — especially platinum compounds — and high doses of radiation to the cochlea (Clemens *et al*., 2017:470; Khan *et al*., 2018; Landier, 2016:1647). Hearing loss, a common manifestation of ototoxic effects associated with childhood cancer treatment, is associated with a delay in language acquisition, psychosocial functioning and academic performance in children (Hudson *et al*., 2013:2374; Khan *et al*., 2018; Landier, 2016:1647).

Risk factors associated with childhood cancer treatment-related ototoxicity include impaired renal function, use of multiple ototoxic agents during treatment, younger age during treatment, high doses of radiation, and combination of chemotherapy and radiation in treatment protocol (Langer *et al*., 2013:459; Liberman *et al*., 2016:626; Warrier *et al*., 2012:193). A study by Peleva *et al*. (2014:2013) in Quebec, indicated a 48% incidence (N = 306) of ototoxicity in children. Monitoring for audiologic function during and after cancer treatment is necessary to help in the early detection of any ototoxic side effects and possible treatment modifications to prevent severe damage (Landier, 2016:1655; Peleva *et al*., 2014:2016; Phanguphangu & Ramma, 2018).

2.8.7.2 Secondary malignancies

The development of secondary malignancies after the treatment of childhood cancers is one of the long-term effects in survivors of childhood cancers (Berendsen *et al*., 2013:147; Choi, D.K. *et al*., 2014:1764). A study by Ju *et al*. (2018) concluded that survivors of childhood cancers were at a 20-fold higher risk of developing a secondary neoplasm. Malignant neoplasms are referred to as secondary malignant neoplasms when they occur after the treatment of a primary malignancy has been completed, and are histologically distinct from the primary one (Bhatia, 2015:353; Shimatani *et al*., 2019:153; Wijnen *et al*., 2016:R300). These secondary malignancies are associated with specific exposures used in the treatment of the primary malignancy and are, therefore, classified as chemotherapy-related or radiotherapy-related (Bhatia, 2015:354; Choi, D.K. *et al*., 2014:1765). The location of the primary cancer, the presence of cancer predisposition syndromes, the age at which patient

was first diagnosed and exposed to treatment, and being female, have also been noted as important risk factors for the development of secondary malignancies (Bhatia, 2015:357; Choi, D.K. *et al*., 2014:1769; Dracham *et al*., 2018:87; Friedman *et al*., 2010:1088; Hayek *et al*., 2018:130; Ng & Shuryak, 2015:2; Zong *et al*., 2017:178).

Secondary malignancies occurring in children diagnosed and treated for cancer include haematological malignancies, neurological tumours, thyroid tumours and bone cancers (Scholz-Kreisel *et al*., 2018:387). Surveillance of childhood cancer survivors in the immediate years following completion of treatment is usually done to detect relapse of cancer. Surveillance, however, should not only focus on the identification of relapse of primary cancer but also on the possible occurrence of a secondary malignancy. This requires the evaluation of the patients' risk of developing secondary malignancies and taking appropriate measures for early detection (Choi, D.K. *et al*., 2014:1770; Husmann, 2019:6; Ju *et al*., 2018).

2.9 Chapter summary

This chapter presented an overview of the concept of childhood cancer with a description of the types and classification. The epidemiology, risk factors and treatment modalities employed in childhood cancers were discussed. The burden of childhood cancer on the patients and their families, as well as the coexisting conditions and complications associated with childhood cancer and its treatment, were further discussed.

Chapter 3 will focus on the results of the empirical investigation and their discussions.

CHAPTER 3: RESULTS AND DISCUSSION

3.1 Introduction

This chapter presents the results and discussion of the empirical investigation of this study in the form of two manuscripts and an "additional results section". Table 3.1 gives an overview of the format for the presentation of the results of the empirical study.

Table 3.1: Format for the presentation of the results of the empirical study

Objective	Paragraph
Determining the incidence, prevalence and trends over time of childhood cancers in children younger than 19 years, stratified according to age group, gender, type of malignancy and geographic area.	Manuscript 1 (paragraph 3.2) Paragraph 3.3
Identifying the common coexisting conditions in children and adolescents with cancer on the database.	Manuscript 2 (paragraph 3.4)

The objective, determining the incidence, prevalence and trends of childhood cancers over time, stratified according to age group, gender, type of malignancy and geographical area using a medicines claims database for the period 2008 to 2017, was addressed in manuscript 1 and the 'additional results section'. Manuscript one consists of results and discussions of incidence and trends in the incidence of childhood cancers over time, while the results and discussions of the prevalence of childhood cancers are presented in the "additional results section". Manuscript one, titled "Childhood cancers in a section of the South African private health sector: Analysis of medicines claims data", was submitted to *Cancer epidemiology*. Author guidelines for and proof of submission of manuscript one to *Cancer epidemiology* can be found in Annexures C and D, respectively.

Identifying the common coexisting conditions in children and adolescents with cancer on the database, which was the second objective of the empirical investigation, was addressed in manuscript 2, which was entitled "Coexisting conditions in children and adolescents with cancer in a section of the South African private health sector". Manuscript two was submitted to the *Journal of Epidemiology and Global Health*[4]. The author guidelines for and proof of submission of manuscript two to *Journal of Epidemiology and Global Health* can be found in Annexures E and F, respectively.

[4] Journal of Epidemiology and Global Health accepts manuscripts written in American-English.

Each of the manuscripts was prepared in conformity to the prescribed guidelines for authors of each journal. References cited in each of the manuscripts appear in both the reference list of the respective manuscripts, in the format stated in the respective journal guidelines, and in the Harvard format in the complete reference list at the end of the dissertation.

The role of each author for both manuscripts is provided in Table 3.2.

Table 3.2 Author contributions to manuscripts

Author	Role in the study
Ms MN Otoo (Researcher)	Concept of research Manuscript planning and design Interpretation of results Writing up of results
Prof JR Burger (Supervisor)	Concept of research Supervision of results interpretation Supervision of manuscript writing Reviewing the manuscript for important information and final approval
Prof MS Lubbe (Co-supervisor)	Concept of research Data and statistical analyses Guidance on writing of manuscript Reviewing the manuscript for important information and final approval
Mrs H Steyn (Co-supervisor)	Guidance on writing of manuscript Reviewing the manuscript for important information and final approval

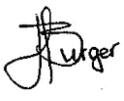
The following statement provided by the co-authors confirms their roles in the study and sanction the inclusion of the manuscripts in the dissertation.

I declare that I have approved the above-mentioned manuscripts and that my role in this study, as indicated above, is a representation of my actual contribution, and I hereby give my consent that it may be published as part of the MPharm study of MN Otoo.

MN Otoo

Prof MS Lubbe

Mrs H Steyn



Prof JR Burger

3.2 Manuscript one

Childhood cancers in a section of the South African private health sector: Analysis of medicines claims data

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Highlights: 43 words

Abbreviations:

ICD-10, International Classification of Diseases, Tenth Revision; SACTR, South African Childhood Tumour Registry; ASR, Age-standardised incidence rates; APC, Annual percentage change

Highlights:

- Incidence of childhood cancers decreased by 24.1% from 2008 to 2017 in the South African private health sector
- Incidence rates were highest in the 15<19-year age group.

- Incidence of childhood cancers was mainly driven by the high incidence of leukaemias.
- Leukaemias constituted 39.9% of incident cases identified.

Abstract

Background: Although childhood cancers are rare, increases in incidence have been observed in recent times. There is a paucity of data on the incidence of childhood cancers in South Africa. This study describes the epidemiology of childhood cancers in a section of the private health sector of South Africa, using medicines claims data.

Method: A longitudinal open-cohort study employing children younger than 19 years and diagnosed with cancers between 2008 and 2017 was conducted using medicine claims data from a South African Pharmaceutical Benefit Management company. Cases were identified using International Classification of Diseases, Tenth Revision (ICD-10) diagnostic codes C00 to C97, together with a medicine claim reimbursed from oncology benefits. Crude incidence rates were calculated per million persons younger than 19 years on the database and standardised using the Segi 1960 world population. Temporal trends in incidence rates, analysed using the joinpoint regression, were reported as annual percentage changes (APC).

Results: Overall, 173 new cases of childhood cancers were identified in the database, translating into an age-standardised incidence rate (ASR) of 82.3 per million. Annual incidence of cancer decreased from 76.7 per million in 2008 to 58.2 per million in 2017. More incident cases were identified in males (68.8%). The highest proportion of incident cases were recorded for leukaemias (39.9%), the 5-9 year age group (34.1%) and the Gauteng Province (49.7%), respectively.

Conclusion: The incidence of childhood cancers decreased over time in the section of private health sector studied. Leukaemias were the major drivers of childhood cancer incidence.

Keywords: Epidemiology, childhood cancer, adolescent, incidence, incidence trends, private health sector, South Africa.

1 Introduction

Childhood cancers, which are described as a varied collection of malignancies, are uncommon and form only a small proportion of all cancers [1,2,3,4]. There are, however, approximately 300 000 newly diagnosed cases of cancers annually in children aged 0 to 19 years globally [5], with over 80% of these cases occurring in resource-limited countries [6,7]. Notwithstanding the rarity of childhood cancers, increases in incidence have been observed in recent times in some parts of the globe [8,9,10]. A study using data from 153 registries in 62 countries across the globe indicated an increase in the incidence of childhood cancers from 124.0 cases per million person-years in the 1980s to 140.6 cases per million person-years in 2010, in children younger than 15 years [8].

Childhood cancers are not regarded as a high priority public concern in most developing countries due to the presence of malnutrition and infectious diseases such as tuberculosis (TB), malaria and human immunodeficiency virus (HIV) infection [11,12,13]. The paucity of data for comparable studies, which could inform public health decisions, could also contribute to childhood cancers not perceived to be a high priority public health concern [5,14].

The rarity of childhood cancers makes the estimation of their occurrence reliable only if a large population of children is studied [15,16]. Data for the estimation of childhood cancer incidence are usually obtained from population-based or hospital-based registries [17,18]. The incidence of childhood cancers is not adequately described in low and middle-income countries (LMIC), especially those in sub-Saharan Africa, due to a lack of high-quality data [6,19]. This makes the true variation of childhood cancer incidence on the continent largely unknown [20]. This is in contrast with the adequately described incidence rates in developed countries [21-26].

Some epidemiological studies of childhood cancer in South Africa have utilised data from the South African Childhood Tumour Registry (SACTR) [27] and the National Cancer Registry (NCR) [1], although this registry is not child-specific [28]. The NCR has also had inconsistencies regarding data on childhood cancer, resulting in a statistic which is not up-to-date [29]. The most recent data used in epidemiological studies of childhood cancer in South Africa are up to 2012 [30]. Most epidemiological studies of childhood cancers in South Africa have also not described the changing patterns of childhood cancers. Current epidemiological studies are required for any cancer control strategy, to monitor changes in disease burden, and to assess the effectiveness of implemented policies [18,31,32,33]. We therefore aimed at determining the incidence and temporal trends in the incidence of childhood cancers in a

section of the private health sector of South Africa by analysing medicine claims data over a 10-year period.

2 Materials and methods

2.1 Study design and data source

This study followed a longitudinal open cohort study design. Medicines claims data for a 10-year period from 1 January 2008 to 31 December 2017 were obtained from a South African Pharmaceutical Benefit Management (PBM) company. This PBM company is one of the largest electronic claims processing and medicine benefit management companies for medical aid schemes in South Africa and covers over 1.8 million beneficiaries.

Data fields on the database that were used for this study included gender, date of birth, patient encrypted number, date prescription was dispensed, dispensed active substances, International Classification of Diseases, Tenth Revision (ICD-10) diagnostic codes, reimbursement category and the postal code of prescriber. Prescribers' postal codes were used as proxy for geographic location to identify where the patient received treatment.

2.2 Study population

The study population comprised children younger than 19 years at the time of diagnosis, stratified by age at last birthday into age groups of <1, 1-4, 5-9, 10-14 and 15<19 years. Cases were identified based on ICD-10 codes C00 to C97 on claims for medicine(s) reimbursed from patients' oncology benefits, and were categorised into the 12 main diagnostic groups of childhood cancers [34].

Denominator data for the estimation of incidence rates were obtained from the database of the PBM company and consisted of the total number of patients under the age of 19 years, annually from 2008 to 2017. A total of 178 564 patients younger than 19 years was obtained for 2008 compared to 249 843 for 2009, 223 267 for 2010, 195 953 for 2011, 179 901 for 2012, 188 568 for 2013, 201 723 for 2014, 215 245 for 2015, 220 066 for 2016, and 240 766 for 2017. These were further categorised by age groups (<1, 1-4, 5-9, 10-14 and 15<19 years), gender and geographic location.

2.3 Definition of geographical location

Prescribers' postal codes were used to identify municipalities, which were then categorised into the nine provinces of South Africa and used as a proxy for geographic location since the residential address of patients are not indicated on the database. The nine provinces of South Africa include the Eastern Cape, Free State, Gauteng, KwaZulu-Natal, Limpopo,

Mpumalanga, Northern Cape, North West and Western Cape, as demarcated by the Municipal Demarcation Board in 2000 [35].

2.3 Statistical analysis

Data were extracted and analysed using SAS® version 9.4 [36]. Frequencies, gender ratios and incidence rates were used to describe the study population. Age-specific and overall crude incidence rates were expressed per million persons younger than 19 years on the database. Age-standardised incidence rates (ASR), also expressed per million persons, were estimated as the weighted average of the age-specific incidence rates of the 0-4, 5-9, 10-14 and 15<19 age groups, using the corresponding weights of the Segi 1960 World Standard Population [37]. Temporal trends in the incidence of all cancers, and leukaemia separately, were estimated using the Joinpoint Regression Program [38].

2.4 Ethical considerations

Ethical approval was obtained from an authorised, licensed Health Research Ethics Committee (ethical approval number: 00179-14-A1-08). The requirement for informed consent from patients whose data were used in this study was waived by the HREC due to the retrospective design of the study and the use of administrative data. Permission was also granted by the PBM company for the use of the data from their database.

3 Results

3.1 Childhood cancer incidence

3.1.1 Incident cases

A total of 173 incident cases of childhood cancers were identified during the 10-year period, representing 0.01% of children aged below 19 years on the database (average annual population of children younger than 19 years = 209 390). Table 1 depicts the characteristics of the study population. There were more incident cases in males (68.8%) compared to females, resulting in a male-to-female (M/F) ratio of 2.2. The mean age of the study population at diagnosis was 10.0 ± 5.4 years. The highest proportion of incident cases (34.1%) was identified in the 5-9 years age group compared to 0.6% among patients <1 year. Leukaemias were the most frequently identified cancers (39.9%), followed by lymphomas (13.9%) and CNS neoplasms (11.0%). The highest proportion of incident cases was identified in Gauteng (49.7%), followed by KwaZulu-Natal (29.5%) and the Western Cape Province (13.3%).

Table 1: Incident case counts and case frequencies from 2008 to 2017 stratified by age, gender, geographic area and malignancy type

Subgroup	Case counts (%)
Gender	
Male	119 (68.8)
Female	54 (31.2)
Age groups (years)	
<1	1 (0.6)
1-4	26 (15.0)
5-9	59 (34.1)
10-14	40 (23.1)
15<19	47 (27.2)
Province	
Eastern Cape	0 (0.0)
Free State	8 (4.6)
Gauteng	86 (49.7)
KwaZulu-Natal	51 (29.5)
Limpopo	2 (1.2)
Mpumalanga	0 (0.0)
North West	2 (1.2)
Northern Cape	0 (0.0)
Western Cape	23 (13.3)
Not indicated	1 (0.6)
Malignancy type	
I. Leukaemias	69 (39.9)
II. Lymphomas	24 (13.9)
III. CNS neoplasms	19 (11.0)
IV. Neuroblastoma	3 (1.7)
V. Retinoblastoma	6 (3.5)
VI. Renal tumours	7 (4.0)
VII. Hepatic tumours	1 (0.6)
VIII. Bone tumours	12 (6.9)
IX. Soft tissue sarcomas	7 (4.0)
X. Germ cell tumours	6 (3.5)
XI. Carcinoma and melanomas	17 (9.8)

XII. Other and unspecified neoplasms	2 (1.2)
Total	**173 (100)**

3.1.2 Incidence rates

Age-standardised incidence rate for all cancers was estimated at 82.3 per million persons based on the 173 cases identified over the 10-year period (Table 2). Overall, the highest age-specific incidence rate was estimated for adolescents aged 15<19 years (112.8 cases per million persons), followed by children aged 5-9 years (101.7 cases per million persons). The lowest age-specific incidence rate was estimated in children who were diagnosed at <1 year (13.2 cases per million persons). Leukaemias, lymphomas and CNS neoplasms were the most frequently occurring childhood cancers, with ASRs of 32.6, 11.7 and 9.1 cases per million persons.

The age-standardised incidence rate for children younger than 15 years was 73.4 cases per million persons. Leukaemias, CNS neoplasms, and carcinomas and melanomas constituted the three most frequently diagnosed cancers in this age group, with ASRs of 30.2, 8.9 and 8.9 cases per million persons, respectively (Table 2).

Table 2: Childhood cancers on the database from 2008 to 2017 stratified by malignancy type, age-specific, crude and age-standardised incidence rates.

Malignancy type[a]	Number of cases in age group (in years)					n (%)	Age-specific incidence rates[b]					Crude incidence[c]		ASR[d]	
	<1	1-4	5-9	10-14	15<19		<1	1-4	5-9	10-14	15<19	0-14	0<19	0-14	0<19
Leukaemias	1	10	26	15	17	69 (39.9)	13.2	19.3	44.8	29.6	40.8	31.0	33.0	30.2	32.6
Lymphomas	0	1	6	6	11	24 (13.9)	0.0	1.9	10.3	11.9	26.4	7.8	11.5	7.4	11.7
CNS neoplasms	0	5	6	4	4	19 (11.0)	0.0	9.7	10.3	7.9	9.6	8.9	9.1	8.9	9.1
Neuroblastoma	0	2	1	0	0	3 (1.7)	0.0	3.9	1.7	0.0	0.0	1.8	1.4	1.9	1.4
Retinoblastoma	0	3	3	0	0	6 (3.5)	0.0	5.8	5.2	0.0	0.0	3.6	2.9	3.7	2.8
Renal tumours	0	1	6	0	0	7 (4.0)	0.0	1.9	10.3	0.0	0.0	4.2	3.3	4.0	3.1
Hepatic tumours	0	0	0	1	0	1 (0.6)	0.0	0.0	0.0	2.0	0.0	0.6	0.5	0.6	0.5
Bone tumours	0	0	1	4	7	12 (6.9)	0.0	0.0	1.7	7.9	16.8	3.0	5.7	2.8	6.0
Soft tissue sarcomas	0	0	3	2	2	7 (4.0)	0.0	0.0	5.2	4.0	4.8	3.0	3.3	2.8	3.3
Germ cell tumours	0	0	1	2	3	6 (3.5)	0.0	0.0	1.7	4.0	7.2	1.8	2.9	1.7	2.9
Carcinoma and melanomas	0	4	5	6	2	17 (9.8)	0.0	7.8	8.6	11.9	4.8	8.9	8.1	8.9	7.9
Other and unspecified neoplasms	0	0	1	0	1	2 (1.2)	0.0	0.0	1.7	0.0	2.4	0.6	1.0	0.5	1.0
Total	**1**	**26**	**59**	**40**	**47**	**173 (100)**	**13.2**	**50.4**	**101.7**	**79.1**	**112.8**	**75.1**	**82.6**	**73.4**	**82.3**

[a] Childhood cancers categorised using the International Classification of Childhood Cancers, Third Edition (ICCC-3).
[b] Age-specific incidence rates expressed per 1 000 000 persons younger than 19 years.
[c] Crude rates expressed per 1 000 000 persons aged 0-14 and all patients younger than 19 years.
[d] Age-standardised incidence rate expressed per 1 000 000 persons aged 0-14 and all patients younger than 19 years.

A higher overall ASR was estimated for males (112.3 cases per million persons) compared to females (51.9 cases per million persons) (Table 3). Leukaemias, lymphomas and CNS neoplasms were the most frequently occurring cancers in both males and females, with ASRs of 48.0 and 14.8, 11.4 and 17.0, and 8.7 and 6.9 cases per million persons in males and females, respectively. With the exception of neuroblastoma, soft tissue sarcomas and other and unspecified neoplasms, the incidence rates of all other cancers were higher in males compared to females.

Table 3: Childhood cancers identified on the database from 2008 to 2017 by malignancy type, gender ratio, and gender-specific crude and age-standardised incidence rates.

Malignancy type	Number of cases in gender groups		M/F[a]	Crude incidence rates[b]		ASR[c]	
	Male n (%)	Female n (%)		Male	Female	Male	Female
Leukaemias	51 (29.5)	18 (10.4)	2.8	47.9	17.4	47.5	17.5
Lymphomas	15 (8.7)	9 (5.2)	1.7	14.1	8.7	14.2	9.0
CNS neoplasms	12 (6.9)	7 (4.0)	1.7	11.3	6.8	11.6	6.6
Neuroblastoma	1 (0.6)	2 (1.2)	0.5	0.9	1.9	0.8	2.1
Retinoblastoma	5 (2.9)	1 (0.6)	5.0	4.7	1.0	4.6	0.9
Renal tumours	5 (2.9)	2 (1.2)	2.5	4.7	1.9	4.3	1.8
Hepatic tumours	1 (0.6)	0 (0.0)	0.0	0.9	0.0	0.9	0.0
Bone tumours	11 (6.4)	1 (0.6)	11.0	10.3	1.0	11.0	1.1
Soft tissue sarcomas	3 (1.7)	4 (2.3)	0.8	2.8	3.9	3.1	3.6
Germ cell tumours	3 (1.7)	3 (1.7)	1.0	2.8	2.9	3.1	2.9
Carcinoma and melanomas	11 (6.4)	6 (3.5)	1.8	10.3	5.8	10.4	5.5
Other and unspecified neoplasms	1 (0.6)	1 (0.6)	1.0	0.9	1.0	0.8	1.1
Total	**119 (68.8)**	**54 (31.2)**	**2.2**	**111.6**	**52.4**	**112.3**	**51.9**

[a] M/F: Male-to-female ratio.
[b] Crude incidence rates expressed per 1 000 000 persons younger than 19 years.
[c] ASR: Age-standardised incidence rates expressed per 1 000 000 persons younger than 19 years.

3.2 Geographical trends in childhood cancer incidence

Using the prescriber's postal codes as a proxy measure, differences in the incidence of childhood cancers were observed in the various geographical regions on the database. No new cases of cancers in Eastern Cape, Mpumalanga and Northern Cape, based on prescribers' postal codes, were identified in the database during the study period (Table 1). Leukaemias were the most frequently identified childhood cancers in the Free State, Gauteng, KwaZulu-Natal and the Western Cape. Only one new case of hepatic tumour was identified during the study period and this was recorded in the Western Cape.

Incidence rates (per million persons) were highest in KwaZulu-Natal (193.4 per million persons), followed by Gauteng (102.3 per million persons) and the Western Cape (77.3 per million persons). With the exception of North West and Limpopo, leukaemias were the most frequently identified cancers, with incidence rates ranging from 29.0 to 56.9 cases per million persons, across provinces that recorded new cases of childhood cancers during the study period (Table 4).

Table 4: Geographical trends in the incidence of childhood cancers over the study period.

Malignancy type	Incidence[a] in province (2008-2017)										
	Eastern Cape	Free State	Gauteng	KwaZulu-Natal	Limpopo	Mpumalanga	Northern Cape	North West	Western Cape	Other[b]	All provinces
Leukaemias	0.0	38.0	47.6	56.9	0.0	0.0	0.0	0.0	29.0	61.0	32.6
Lymphomas	0.0	0.0	11.9	34.1	8.6	0.0	0.0	17.0	6.5	0.0	11.7
CNS neoplasms	0.0	0.0	7.1	37.9	0.0	0.0	0.0	0.0	9.7	0.0	9.1
Neuroblastoma	0.0	0.0	1.2	0.0	0.0	0.0	0.0	0.0	6.5	0.0	1.4
Retinoblastoma	0.0	9.5	4.8	3.8	0.0	0.0	0.0	0.0	0.0	0.0	2.8
Renal tumours	0.0	0.0	7.1	3.8	0.0	0.0	0.0	0.0	0.0	0.0	3.1
Hepatic tumours	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	3.2	0.0	0.5
Bone tumours	0.0	9.5	4.8	11.4	8.6	0.0	0.0	0.0	9.7	0.0	6.0
Soft tissue sarcomas	0.0	9.5	4.8	0.0	0.0	0.0	0.0	0.0	6.5	0.0	3.3
Germ cell tumours	0.0	9.5	3.6	7.6	0.0	0.0	0.0	0.0	0.0	0.0	2.9
Carcinoma and melanomas	0.0	0.0	7.1	37.9	0.0	0.0	0.0	0.0	3.2	0.0	7.9
Other and unspecified neoplasms	0.0	0.0	2.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0
Total	**0.0**	**76.0**	**102.3**	**193.4**	**17.2**	**0.0**	**0.0**	**17.0**	**74.4**	**61.0**	**82.3**

[a] Incidence rates expressed per 1 000 000 persons younger than 19 years.
[b] Case(s) with missing prescriber postal code.

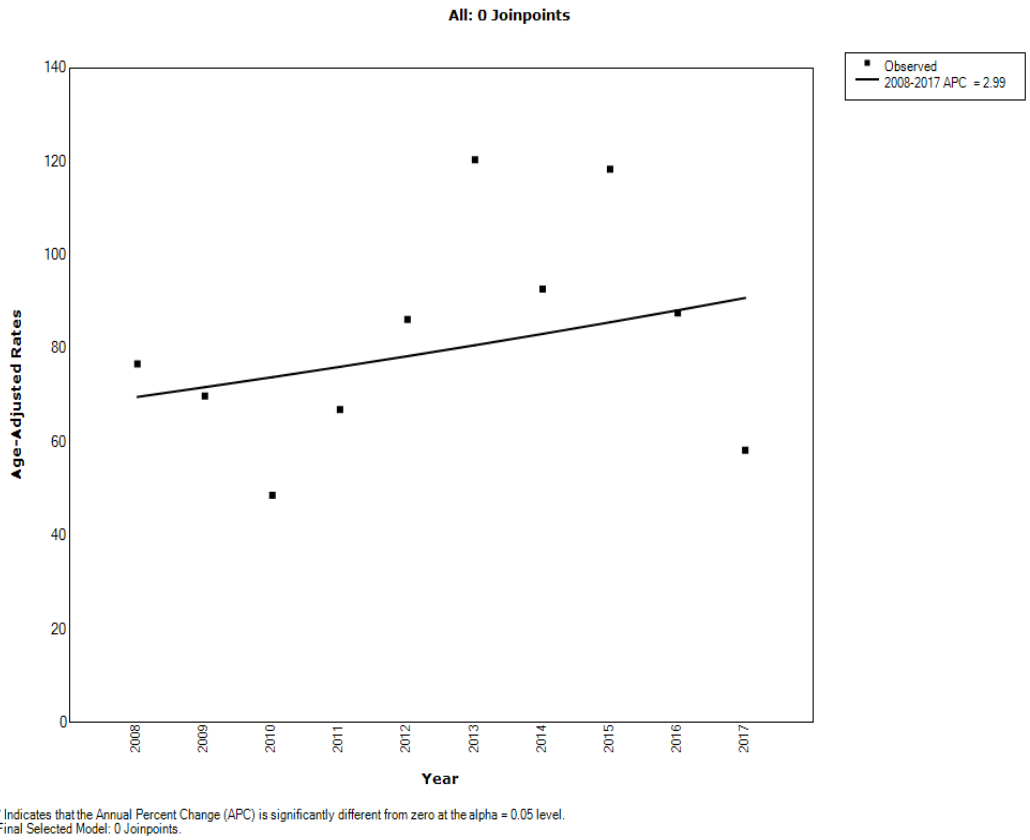
3.3 Time trends in childhood cancer incidence

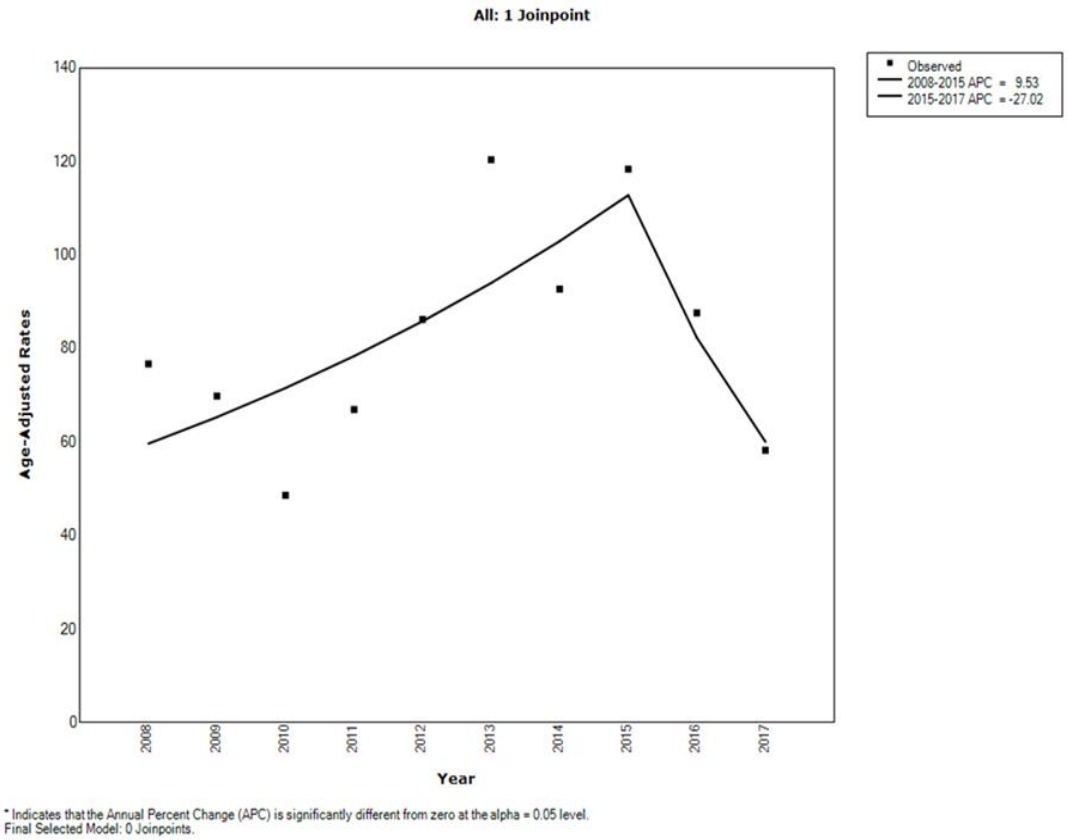
Table 5 indicates the incidence rates of all childhood cancers from 2008 to 2017. Figure 1a and Figure 1b indicate the trend in ASR of all cancers combined and leukaemia, respectively with their corresponding annual percentage changes (APC). Overall, incidence rates of childhood cancers decreased from 76.7 cases per million persons in 2008 to 58.2 cases per million children in 2017; however, peaking at 120.3 cases per million persons in 2013. Incidence rates for all cancers combined increased from 2008 to 2015 (APC of 9.53%; 95%CI: -2.9–23.6) (p = 0.1) and decreased thereafter from 2015 to 2017 (APC of -27.0%; 95%CI:-70.5–80.3) (p = 0.4). With the exception of 2008, in which carcinomas and melanomas were the most frequently diagnosed cancer, leukaemias were consistently found to be the most frequently diagnosed cancer, annually, from 2009 to 2017. Temporal trends in the incidence of leukaemias were similar to those of all cancers combined, with an APC of 10.67% (95%CI -2.9–26.2) (p = 0.1) from 2008 to 2015 and an APC of -25.0% (95%CI -71.9–99.8) (p = 0.5) from 2015 to 2017.

Table 5: Age-standardised incidence rates of childhood cancers over the study period.

	Annual age-standardised incidence rates[a]									
Malignancy type	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**
Leukaemias	18.7	27.7	25.9	36.3	26.6	46.0	25.1	47.0	45.8	21.0
Lymphomas	14.4	7.6	8.9	5.2	5.1	30.1	6.2	22.0	11.9	9.3
CNS neoplasms	0.0	7.6	4.7	4.8	20.8	12.6	4.9	19.9	3.9	11.4
Neuroblastoma	0.0	0.0	0.0	0.0	0.0	0.0	9.2	0.0	4.5	0.0
Retinoblastoma	0.0	3.9	0.0	0.0	0.0	0.0	14.1	0.0	8.4	0.0
Renal tumours	5.0	0.0	0.0	0.0	5.6	4.8	4.4	4.0	0.0	7.1
Hepatic tumours	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	4.3	0.0
Bone tumours	0.0	0.0	4.7	0.0	0.0	16.3	18.5	10.5	8.7	5.4
Soft tissue sarcomas	0.0	4.0	4.3	5.6	10.5	0.0	4.4	4.5	0.0	0.0
Germ cell tumours	4.7	0.0	0.0	9.6	6.3	0.0	6.2	4.5	0.0	0.0
Carcinoma and melanomas	33.9	11.1	0.0	5.2	11.1	10.5	0.0	6.0	0.0	4.2
Other and unspecified neoplasms	0.0	7.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Total	**76.7**	**69.8**	**48.6**	**66.9**	**86.2**	**120.3**	**92.7**	**118.3**	**87.6**	**58.2**

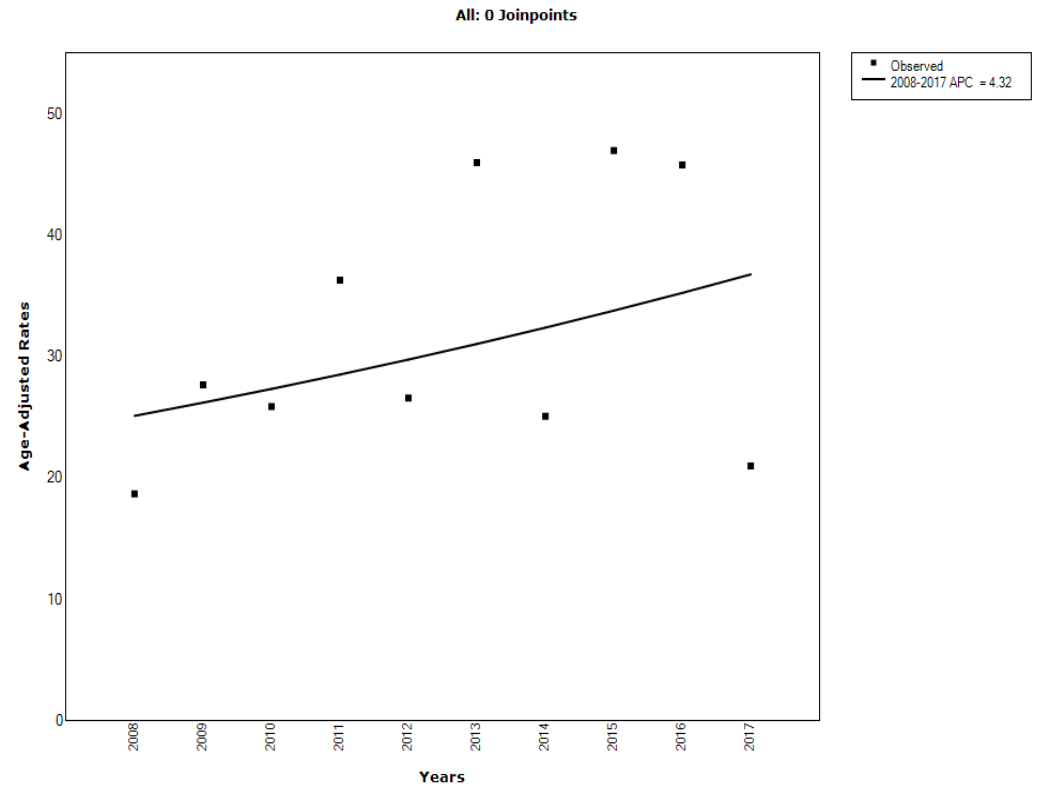
[a] Age-standardised incidence rate expressed per 1 000 000 persons younger than 19 years

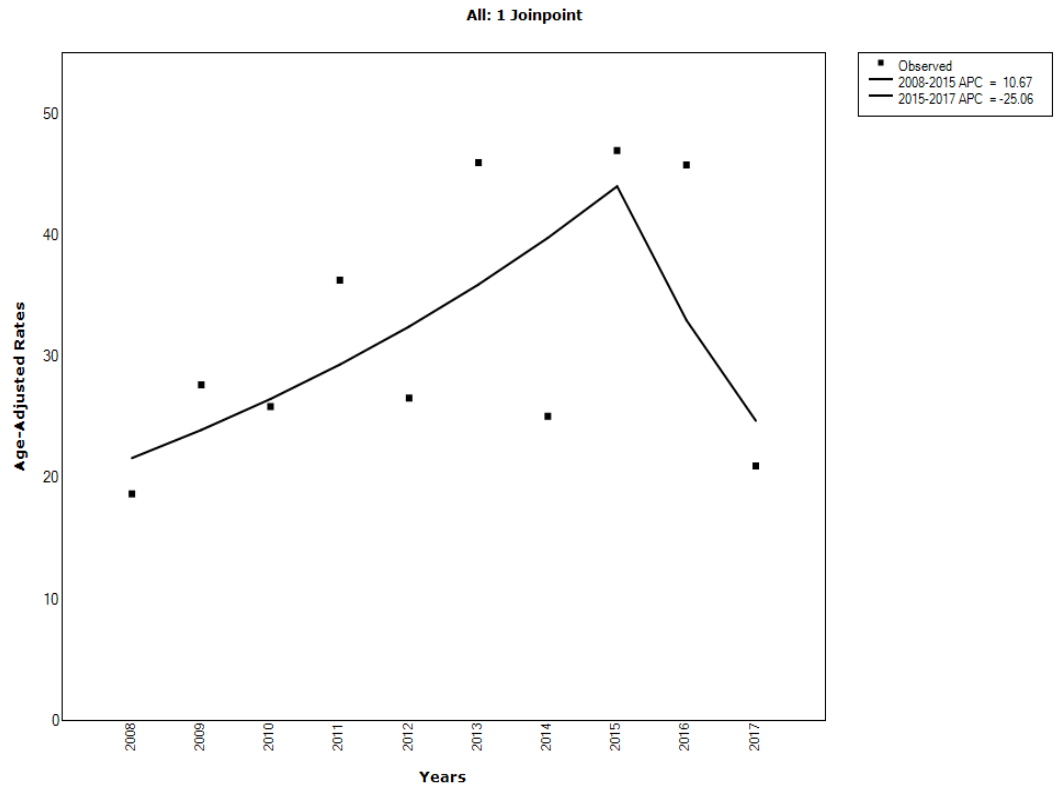




Age-adjusted rates expressed per 1 000 000 persons younger than 19 years

Fig 1a Temporal trends in the incidence of all childhood cancers combined from 2008 to 2017





Age-adjusted rates expressed per 1 000 000 persons younger than 19 years

Fig 1b. Temporal trends in the incidence of leukaemias from 2008 to 2017

4 Discussion

This study reports on the incidence and temporal trends in the incidence of cancers in children aged younger than 19 years in a section of the South African private health sector over a 10-year period. The overall ASR for all childhood cancers over the study period was 82.3 per million persons, with leukaemias, lymphomas and CNS neoplasms constituting the top three most frequently identified cancers.

Previous epidemiological studies into childhood cancers in South Africa have been carried out in children younger than 15 years [1,27,30]. These studies by Erdmann et al [1], Stefan et al. [27] and Steliarova-Foucher et al., [30] reported ASRs of 45.7, 45.6 and 45.2 cases per million population, respectively. Estimated ASR for all cancers in children aged younger than 15 years in our study population was 73.4 cases per million over the 10-year period; a rate higher than those reported in previous studies in South Africa. It should, however, be noted that the most recent year under review for the previous studies is 2012 [30], this higher estimate in our study is, therefore, possible considering the increasing incidence of childhood cancers in recent times [8]. Again, patients subscribed to private medical schemes are likely to have access to modern diagnostic procedures and, therefore, more incident cases of cancers, when present, will be identified. Furthermore, the study population consisted of only beneficiaries who claimed medications during the study period. Patient population used as denominator for the estimation of incidence rates therefore included only claiming individuals and not all patients whose medicine benefits are managed by the PBM company. This could account for the higher ASRs recorded in this study as compared to other studies in South Africa.

The 5-9 year age group recorded the highest age-specific incidence rate (112.1 per million) among all other age groups in children aged 0-14 years. This is in contrast to the highest age-specific incidence rate in the under-five years' age group in all previous studies in South Africa [1,27,30] as well as most countries around the globe [8,9,19].

The observed male preponderance in the incidence of childhood cancers in this study is to be expected, as the incidence of childhood cancers is generally higher in males than females [23,39,40]. This trend has also been demonstrated in previous studies conducted in South Africa, although relatively lower M/F ratio of between 1.2 and 1.3 were reported in these studies [1,27,30].

Leukaemias were observed to be the most frequently diagnosed childhood cancer across all age-groups and in both males and females in this study, and this is similar to the results of previous studies in South Africa [1,27,30]. This is, however, in contrast to the higher incidence of lymphomas, compared to leukaemias, in other countries in sub-Saharan Africa [20]. Lymphomas are usually the most frequently occurring cancers in adolescents [8]. The higher

incidence of leukaemias, in comparison to lymphomas, in the adolescent age group in this study confirms a predominance of leukaemias among childhood cancers in our patient population.

Overall, there was a 24.1% decrease in the incidence rate of all childhood cancers combined from 2008 to 2017, although the decrease was not homogenous throughout the study period. This is in contrast to the increasing trend in the incidence of childhood cancers observed by Steliarova-Foucher et al. [8]. The database used for this study contains medicine claims of patients subscribed to medical aid schemes whose medicine benefits are managed by the PBM company. Composition of the database is, consequently, likely to change annually and this could explain the fluctuations in the incidence of cancers observed in this study. Furthermore, annual changes in health plan or benefit design of beneficiaries could account for the annual fluctuations in incidence rates observed in this study, as benefit design defines the composition of a population at a given time [39]. An interesting observation is the highest incidence of carcinomas and melanomas, among all other diagnostic groups in 2008 (33.9 cases per million). Mandatory coding of diseases for reimbursement purposes using ICD-10 codes started in 2008 in South Africa; this observation may, therefore, reflect less precision in the coding processes in 2008 and not necessarily a high incidence of this diagnostic group since carcinomas in children are relatively rare [11]. This was confirmed by a reduction in the incidence of carcinomas and melanomas in subsequent years.

Based on prescribers' postal codes, incidence rates of children and adolescents receiving treatment for cancers were found to be highest in KwaZulu-Natal followed by Gauteng and Western Cape although the largest proportion of incident cases was identified in Gauteng. This is in contrast to a previous study in South Africa which reported the highest ASR of childhood cancer in Western Cape [27]. Treatment of childhood cancers in South Africa is carried out in specialised centres which are mostly located in the major metropolitan municipalities. This implies that patients may receive cancer treatment at locations other than their province of residence. The leukaemias were the diagnostic group with the highest incidence rates in four out of the six provinces which recorded cases of childhood cancers, further confirming leukaemias as the most prevalent cancer in the section of private health sector studied.

4.1 Strengths and limitations

The study population was drawn from the database of only one PBM company in South Africa. The external validity of this study is therefore limited since results cannot be generalised to the total private health sector or South Africa as a whole. Further research using population-based data may have the potential of confirming these findings and describing the general trends in the whole South African population. Although higher incidence rates were recorded in this study, under-ascertainment of cases cannot be ruled out since data used were reimbursed

claims. Patients diagnosed with cancers which are not captured in their prescribed minimum benefits, and who do not have comprehensive health plans with oncology benefits would have to make out-of-pocket payments for cytotoxic medication. Data on these patients will, therefore, not be included in the database. The use of prescribers' postal codes as proxy for the geographic location of patients has the potential of introducing bias into the analysis of geographical trends. This is because most oncologists have their practices located in metropolitan municipalities and, therefore, patients may travel to those provinces for treatment. Higher incidence rates in those provinces may, therefore, reflect a higher diagnostic rate of cancers and not necessarily the true incidence of cancers.

Notwithstanding the limitations of this study, results obtained provide baseline information on the current trends of childhood cancers in a section of the private health sector of South Africa and have the potential to stimulate further research into childhood cancers in the whole South African population.

5 Conclusions

This preliminary research provides an insight into the epidemiological trends of cancers in children and adolescents in a section of the South African private health sector. The highest incidence rate of cancers was estimated for the adolescent age group. The overall incidence rate observed in this study was largely driven by leukaemias which contributed more than one-third of the cases identified on the database. Results of the temporal trend analysis do not support the observed increasing rates of childhood cancers in global communities. Data used for this study was, however, obtained from only one database. Future studies using a larger and more nationally representative database should be carried out to establish the true epidemiological trends in childhood cancers in South Africa.

Competing interests

The authors have no potential conflict of interest to declare.

Author contributions

The study was conceived by JRB, MNO, HS and MSL. MSL extracted and analysed the medicine claims data. MNO interpreted findings and drafted the report under the supervision of JRB, which was reviewed and modified with input from all authors over a number of versions. All authors reviewed and approved the final version.

Role of funding source

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Data availability statement

The authors do not have permission to share the research data.

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3.3 Prevalence of childhood cancers on the database

The study population consisted of children under the age of 19 years identified annually on the database from 2008 to 2017, with diagnostic codes for cancer (C00-C97) and claims for medicines reimbursed from their oncology benefits. Patients were categorised annually, by gender, age group (<1, 1-4, 5-9, 10-14 and 15<19 years), geographic area and malignancy type.

The prevalence rates of cancers in the total population and in the various subgroups on the database for each year were calculated using the total population of children aged <19 years and the population of the various subgroups on the database for each respective year, as denominators (Table 3.3).

Prevalence of all childhood cancers combined increased from 9 cases per 100 000 persons in 2008 to 19.8 cases per 100 000 persons in 2014 and decreased to 13.3 cases per 100 000 persons in 2017. Overall, there was a 47.8% increase in the prevalence of childhood cancers from 2008 to 2017 (Table 3.3).

With the exception of 2008, the prevalence rates of childhood cancers were consistently higher in males as compared to females (Table 3.3). The prevalence rate of cancers in males was highest in 2013 (32.4 cases per 100 000 persons) whilst it was highest in 2014 (12.1 cases per 100 000 persons) for females. This trend, indicating male predominance, is consistent with global trends given that males are at a higher risk of being diagnosed with childhood cancers as compared to females (Dorak & Karpuzoglu, 2012).

Prevalence rates were highest in the 5-9 year age group in six out of the ten years under study, (2008, 2012-2014 and 2016-2017), with rates ranging from 16.1 and 36.3 cases per 100 000 persons. The 15<19 year age group recorded the highest prevalence rates of cancers in the remaining four years under study (2009-2011 and 2015) with rates of ranging from 19.7 to 29.3 cases per 100 000 persons. Prevalence rates of cancers were lowest in children aged < 1 year, with only one case of cancer recorded in this age group in the entire study period.

Using prescriber codes as a proxy measure for geographic location, most children received treatment in KwaZulu-Natal from 2008 to 2015, and Gauteng for the years 2016 and 2017 (Table 3.3). No cases of childhood cancers were treated in the Eastern Cape and Northern Cape over the study period. This, however, may not necessarily indicate an absence of childhood cancers in patients on the database who reside in those provinces, since patients are likely to travel to other provinces with oncologist practices for treatment.

Prevalence rates of childhood cancers stratified by malignancy type followed similar trends as the incidence rates, with leukaemias being the most prevalent cancer from 2009 to 2017 (refer to paragraph 3.2; manuscript one, Table 5). Carcinomas and melanomas were the most prevalent cancers in 2008, with a prevalence rate of 3.9 cases per 100 000 persons younger than 19 years and representing 43.8% of all cancer cases in 2008. This could be attributed to possible errors in the coding of cases since carcinomas and melanomas are relatively rare (Elhassan *et al*., 2018). Hepatic tumours were the least prevalent tumour over the study period with less than 1 case per 100 000 children in both 2016 and 2017 (Table 3.3).

Table 3.3: Prevalence of childhood cancers on the database from 2008 to 2017 by gender, age group, geographic area, and malignancy type

Patients <19 years on the database	2008 N=178 564	2009 N=249 843	2010 N=223 267	2011 N=195 953	2012 N=179 901	2013 N=188 568	2014 N=201 723	2015 N=215 245	2016 N=220 066	2017 N=240 766
Study population										
Patients with diagnostic codes for cancer, n(P[§])	16 (9.0)	24 (9.6)	25 (11.2)	23 (11.7)	25 (13.9)	35 (18.6)	40 (19.8)	39 (18.1)	39 (17.7)	32 (13.3)
Gender, n(P[†])										
Male	7 (7.7)	15 (11.8)	17 (15.0)	16 (16.0)	17 (18.6)	31 (32.4)	28 (27.3)	31 (28.4)	30 (26.9)	23 (18.7)
Female	9 (10.2)	9 (7.3)	8 (7.3)	7 (7.3)	8 (9.1)	4 (4.3)	12 (12.1)	8 (7.5)	9 (8.3)	9 (7.6)
Age group (years), n(P[†])										
<1	0 (0.0)	1 (11.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1-4	0 (0.0)	0 (0.0)	1 (1.8)	2 (4.0)	5 (10.8)	2 (4.0)	7 (13.1)	4 (7.2)	7 (12.3)	3 (4.8)
5-9	8 (16.1)	4 (6.2)	5 (8.6)	4 (7.7)	11 (22.7)	19 (36.3)	19 (33.2)	17 (27.1)	17 (26.4)	14 (19.8)
10-14	3 (5.8)	8 (12.6)	7 (12.9)	7 (5.1)	7 (16.7)	8 (18.7)	5 (10.8)	7 (13.9)	8 (15.5)	11 (19.2)
15<19	5 (10.4)	11 (19.7)	12 (25.2)	10 (25.1)	2 (5.6)	6 (16.8)	9 (24.6)	11 (29.3)	7 (18.4)	4 (9.6)
Province, n(P[†])										
Eastern Cape	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Free State	0 (0.0)	0 (0.0)	0 (0.0)	4 (43.4)	2 (21.8)	1 (9.8)	2 (21.5)	1 (7.0)	3 (24.5)	0 (0.0)
Gauteng	6 (8.8)	12 (11.4)	11 (11.6)	7 (8.4)	11 (14.7)	19 (24.2)	22 (24.5)	22 (25.3)	23 (30.7)	20 (23.4)
KwaZulu-Natal	10 (34.0)	12 (32.0)	12 (39.2)	8 (31.7)	6 (27.7)	9 (38.3)	8 (33.7)	9 (37.8)	7 (29.6)	5 (20.4)
Limpopo	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.0)	1 (11.3)	2 (20.6)	0 (0.0)	0 (0.0)	0 (0.0)
Mpumalanga	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.2)
North West	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.4)	1 (10.4)

Patients <19 years on the database	2008 N=178 564	2009 N=249 843	2010 N=223 267	2011 N=195 953	2012 N=179 901	2013 N=188 568	2014 N=201 723	2015 N=215 245	2016 N=220 066	2017 N=240 766
Northern Cape	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Western Cape	0 (0.0)	0 (0.0)	1 (4.0)	4 (17.8)	5 (22.9)	5 (20.3)	6 (24.5)	7 (22.6)	5 (9.0)	5 (8.1)
Not indicated	0 (0.0)	0 (0.0)	1 (63.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Malignancy type, n(P[§])										
Leukaemias	4 (2.2)	8 (3.2)	12 (5.4)	15 (7.7)	10 (5.6)	18 (9.5)	17 (8.4)	21 (9.8)	19 (8.6)	14 (5.8)
Lymphomas	3 (1.7)	3 (1.2)	4 (1.8)	1 (0.5)	2 (1.1)	6 (3.2)	5 (2.5)	5 (2.3)	3 (1.4)	3 (1.2)
CNS neoplasms	0 (0.0)	2 (0.8)	2 (0.9)	1 (0.5)	4 (2.2)	3 (1.6)	1 (0.5)	4 (1.9)	5 (2.3)	5 (2.1)
Neuroblastoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)	1 (0.5)	0 (0.0)
Retinoblastoma	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.5)	1 (0.5)	2 (0.9)	2 (0.8)
Renal tumours	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	2 (1.1)	1 (0.5)	2 (0.9)	1 (0.5)	2 (0.8)
Hepatic tumours	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.4)
Bone tumours	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	3 (1.6)	6 (3.0)	2 (0.9)	4 (1.8)	3 (1.2)
Soft tissue sarcomas	0 (0.0)	1 (0.4)	2 (0.9)	2 (1.0)	2 (1.1)	0 (0.0)	1 (0.5)	1 (0.5)	1 (0.5)	0 (0.0)
Germ cell tumours	1 (0.6)	1 (0.4)	1 (0.4)	3 (1.5)	3 (1.7)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	1 (0.4)
Carcinoma and melanomas	7 (3.9)	6 (2.4)	1 (0.4)	1 (0.5)	3 (1.7)	3 (1.6)	2 (1.0)	2 (0.9)	2 (0.9)	1 (0.4)
Other and unspecified neoplasms	0 (0.0)	2 (0.8)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)

[§]Prevalence expressed per 100 000 children and calculated using the total number of patients <19 years on the database (N), for each respective year, as the denominator

[†]Prevalence expressed per 100 000 children and calculated using the total number of patients in the various sub-groups on the database, for each respective year, as the denominator

3.4 Manuscript two

Coexisting conditions in children and adolescents with cancer in a section of the South African private health sector

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Abstract

Coexisting conditions are relatively common in children with cancer. This cross-sectional study aimed at investigating the common coexisting conditions in children and adolescents younger than 19 years being treated for cancers in a section of the South African private health sector. Medicine claims data from 1 January 2008 to 31 December 2017 were queried to identify coexisting conditions using the International Classification of Diseases, Tenth Revision (ICD-10) codes indicated on reimbursed claims. Where ICD-10 codes per claim were non-specific, the pharmacological drug classes of medications claimed alongside these codes were analyzed using the drug utilization 90% (DU90%) principle. Pharmacological classes were categorized using the Monthly Index of Medical Specialties (MIMS) classification system and stratified according to gender, age group and sub-pharmacological class. Reimbursement category of these medicines was noted. Data were analyzed descriptively. A total of 173 participants were included in the study. ICD-10 codes were available for 13.65% of medicine claims. Diseases of the respiratory system (J00-J99, 7.15%), gastrointestinal tract (K00-K95, 1.60%), and skin disorders (L00-L99, 0.95%) were the most prevalent specific diagnoses identified. Non-specific ICD-10 codes were recorded on 86.35% (n = 2 272) of non-cytotoxic medicine claims. The most frequently utilized pharmacological classes of medications included antimicrobial agents (17.40%), respiratory system agents (13.91%) and analgesics (10.64%). As determined from ICD-10 codes and medication claimed on reimbursed claims, children and adolescents being treated for cancers mostly suffered from acute conditions, in particular, microbial infections and diseases of the respiratory system.

Keywords: Children, adolescent, coexisting condition, South Africa, medicine utilization patterns, childhood cancer

1 Introduction

The resultant consequences of cancer, particularly immunosuppression, makes the presence of coexisting conditions — described as any medical condition that co-occurs with an index condition of interest in an individual — relatively common [1,2,3]. These conditions may arise from the malignancy itself or the treatment interventions employed in the management of cancer [4,5]. For example, the immunosuppression associated with cancer predisposes children to conditions such as infections [6]. Children exposed to anthracyclines and cardiac irradiation are at risk of developing cardiotoxic complications such as valvular abnormalities and pericardial diseases during and after the treatment of cancer [7]. The use of high doses of alkylating agents and platinum compounds have also been identified as risk factors for lung fibrosis, pulmonary pneumonitis, thyroid abnormalities, ototoxicity and impairment of renal function [8,9,10,11].

The risk of cancer, on the other hand, may be increased by the presence of other preexisting conditions — especially those which are similarly associated with immunosuppression — such as human immunodeficiency virus (HIV) infection [12]. HIV infection has been found to be a risk factor for some cancers including Kaposi sarcoma and non-Hodgkin's lymphoma [12] while hepatitis B virus infection has been linked to hepatocellular carcinoma [13]. Conditions that are characterized by chronic inflammation have also been found to stimulate tumorigenesis [14].

The prevalence of conditions coexisting in adults with cancer, especially chronic conditions such as hypertension, diabetes, peptic ulcer and other cardiovascular conditions has been described in literature [15,16,17,18]. There is, however, a paucity of information on the prevalence of coexisting conditions in children with cancer in South Africa. Cognizance of coexisting conditions in patients with cancer is important due to their possible influence on treatment decisions — by the modification of treatment protocols — and consequent impact on treatment outcome [1,15,19,20,21]. This study therefore aimed at identifying conditions that coexist with cancer in children and adolescents in the South African private health sector.

2 Materials and methods

2.1 Study design and data source

This study followed a descriptive cross-sectional design. Retrospective medicine claims data from 1 January 2008 to 31 December 2017, obtained from one of the largest South African PBM companies for medical aid schemes, were used for the analysis. This PBM company

has a substantial national representation and is currently responsible for the medicine benefits of 1.8 million beneficiaries enrolled in approximately 42 medical schemes in South Africa.

Information on the database, which was extracted and used in this study, included date of birth (age), gender, the National Pharmaceutical Product Index (NAPPI) codes, prescription treatment dates, diagnoses (inferred from the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) codes), and the active substances (trade or generic name and pharmacological class) per reimbursed medicine item.

2.2 Study population

The study population consisted of all children aged younger than 19 years with diagnostic codes for cancers (C00 to C97) in addition to at least one ICD-10 code recorded on non-cytotoxic medicine claims reimbursed from patients' acute, chronic, over the counter (OTC) or prescribed minimum benefits (PMB), over the study period.

2.3 Measurements

Medicines claims data for the study population were queried to identify coexisting conditions, using ICD-10 diagnostic codes recorded on claims for non-cytotoxic medicine items reimbursed over the study period. Where ICD-10 diagnostic codes were missing or non-specific, we examined the non-cytotoxic medicine claimed to determine the main pharmacological classes, using the drug utilization 90% principle (DU90%), i.e. drugs accounting for 90% of those claimed when ranked in descending order based on frequency. Non-specific ICD-10 diagnostic codes refer to those that do not indicate a specific diagnosis and include repeat prescriptions (Z76), encountering health services in unspecified conditions (Z76.9), and failure of the patient or provider to disclose clinical information, (U98.0 and U98.1, respectively).

The main pharmacological classes of medicines were classified into 22 main pharmacological groups based on the Monthly Index of Medical Specialties (MIMS) classification system [22]. Non-cytotoxic medicine items included all medicines not classified as cytostatics (MIMS® classification 23).

Age groups were categorized into four age groups, namely 0-4 years, 5-9 years, 10-14 years, and 15<19 years, using the age at last birthday on the database as the reference date.

2.4 Statistical analyses

The study population was stratified by gender and age group for analysis. The data were described using basic descriptive statistics such as frequencies, percentages, mean and standard deviation. Analyses of data were carried out using the SAS® program, version 9.4. [23].

2.5 Ethical considerations

Ethical approval was obtained from an authorized, licensed Health Research Ethics Committee (ethical approval number: 00179-14-A1-08). Permission for the use of the database for this study was granted by the board of directors of the South African PBM company.

3 Results

3.1 Demographic characteristics of the study population

Table 1 summarizes the demographic characteristics of the study population. The study population consisted of a total of 173 patients, identified out of 209 390 patients younger than 19 years on the database from 2008 to 2017. The mean age of the study population was 10.05 ± 5.40 years. The majority were males (68.79%, n = 119), and in the 5-9-year age group (34.10%, n = 59). Patients aged 0-4 years comprised the smallest proportion of the study population at 15.61% (n = 27). Leukemias were the most prevalent cancers (39.88%, n = 69) followed by lymphomas (13.87%, n = 24).

3.2 Coexisting conditions based on ICD-10 codes

Table 2 depicts the number and type of coexisting conditions based on ICD-10 diagnostic codes recorded on reimbursed medicine claims. A total of 2 631 medicine items were claimed for children and adolescents aged younger than 19 years on the database from 2008 to 2017. Specific diagnostic codes were only available for 13.65% (n = 359) of these medicine claims (N = 2 631). Overall, 0.38% (n = 10) of medicine items claimed had diagnostic codes for chronic conditions; these included asthma (J45.9, 0.11%, n = 3), essential hypertension (I10, 0.04%, n = 1), major depressive disorders (F32.2 and F32.3, 0.15%, n = 4), anxiety disorders (F41.9, 0.04%, n = 1) and epilepsy (G40.2, 0.04%, n = 1).

The most prevalent acute coexisting conditions identified in the study population included diseases of the respiratory system (J00-J99, 7.15%, N = 188), in particular, acute tonsillitis (J03.9, 17.55%, n = 33) and bronchitis (J20.9, 10.11%, n = 19), and diseases of the

gastrointestinal tract (GIT) (K00-K95, 1.60%, N = 42), particularly non-infective gastroenteritis (K52.9, 19.05%, n = 8) and gastric ulcer (K25.9, 14.29%, n = 6). Others included skin disorders (L00-L99, 0.95%, N = 25), particularly dermatitis (L30.9, 24.00%, n = 6) and impetigo (L01.0, 16.00%, n = 4), and disorders of the musculoskeletal system (M00-M99, 0.91%, N = 24), particularly osteomyelitis (M86.25, 16.70%, n = 4).

3.3 Pharmacological drug classes constituting the DU90%

The majority of medicine items, representing 86.35% (n = 2 272) of the total non-cytotoxic medicine items utilized by the study population, were claimed under non-specific diagnostic codes. Table 3 depicts the DU90% of medicine claims with non-specific diagnostic codes over the study period. The main pharmacological classes constituting the DU90% included antimicrobials (17.47%, n = 397), respiratory system agents (13.25%, n = 301), analgesics (10.26%, n = 233), ear, nose and throat (ENT) agents (9.73%, n = 221), GIT agents (7.75%, n = 176) and central nervous system (CNS) agents (6.65%, n = 151). Others included autacoids (6.34%, n = 144), dermatological agents, (4.97%, n = 113), endocrine agents (4.84%, n = 110), herbal preparations (3.57%, n = 81), musculoskeletal agents (3.26%, n = 74) and anesthetics (2.82%, n = 64) (Table 3).

3.4 Pharmacological drug classes of all medicine claims

Table 4 depicts the breakdown of the main pharmacological classes of all medications claimed at least once by the study population during the study period, by gender and sub-pharmacological class. Antimicrobial agents were the most prevalent pharmacological group of medicines (17.41%, n = 458), followed by respiratory system agents (13.91%, n = 366), analgesics (10.64%, n = 280), ENT agents (9.65%, n = 254), GIT agents (7.49 %, n = 197), CNS agents (6.46%, n = 170), autacoids (6.31%, n = 166) and dermatological agents (5.32%, n = 140). Special foods were the least claimed agents (0.11%, n = 3).

Beta-lactam antimicrobials were the most prevalent antimicrobial agents (N = 458) accounting for 49.12% (n = 225) of antimicrobial claims. This was followed by sulphonamides and sulphonamide-containing combinations (14.19%, n = 65), and erythromycin and other macrolides (10.70%, n = 49). Medicines for the treatment of coughs and colds (63.93%, n = 234) were the most prevalent class of medications among respiratory system agents (N = 366), followed by bronchodilators (21.58%, n = 79) and mucolytics (8.47%, n = 31). Analgesic combination products (56.79%, n = 159) were the most frequently received analgesics (N = 280), followed by analgesics and antipyretics (35.71%, n = 100) (Table 4).

Analysis by gender shows that the majority of medications (64.88%, n = 1 707) were claimed for males. Antimicrobials (11.71% and 5.70%), respiratory system agents (9.39% and 4.52%), and analgesics (6.80% and 3.84%) were the three most prevalent pharmacological classes received in males and females, respectively (Table 4). Beta-lactams, medicines for coughs and colds, and combination analgesics were the most prevalent sub-pharmacological classes in the antimicrobial, respiratory system agents, and analgesic classes, respectively in both gender groups.

With respect to age group, the highest proportion of medicine items (38.50%, n = 1 013) was claimed for the 5-9 year age group over the study period. This was followed by the 15<19 year age group (30.06%, n = 791), and the 10-14 year age group (18.02%, n = 474). The smallest proportion of medications (13.42%, n = 353) was claimed for the 0-4-year age group. Beta-lactams, medicines for colds and coughs, and combination analgesics were the most frequently received antimicrobial, respiratory system agents, and analgesics respectively, across all age groups (Table 5).

Table 6 illustrates the reimbursement categories from which medicine claims of patients were paid. A total of 2 160 medicine items, representing 82.10% of the total medicines utilized by the patient population in this study, were reimbursed from the patients' acute benefits. This was followed by medicines classified as over-the-counter medications (9.84%, n = 259). Medicines classified as chronic medications were the least claimed class of medicines, accounting for 0.49% (n = 13) of the medicine items claimed during the study period. This trend was observed across all gender and age groups with the exception of the 10-14-year age group in which prescribed minimum benefits (PMB) was the category with the fewest reimbursements (Table 6).

4 Discussion

This study aimed at identifying coexisting conditions in children and adolescents with cancer using the ICD-10 codes recorded on claims for non-cytotoxic medicines. In the absence of specific ICD-10 codes, the main pharmacological classes claimed were analyzed. Results of this study indicate that specific ICD-10 codes were available for only 13.65% of the total medicine claims over the study period. Non-specific ICD-10 codes indicated on the majority of medicine claims included those for repeat prescriptions (Z76.0), encountering health services in unspecified conditions (Z76.9) and failure of patient or provider to disclose clinical information (U98.0 and U98.1). ICD-10 codes, developed by the World Health Organization, are standard codes used to describe medical and health information and were introduced in the South African private health sector in 2005 [24]. Medical schemes utilize these standard

codes for easy identification of diagnoses, especially those classified as PMBs and chronic, and appropriate reimbursements. The absence of or use of non-specific ICD-10 codes limits the ability to identify important patient health information to support public health research and reporting [25]. There may, therefore, be an underestimation of the prevalence of coexisting conditions in our study.

Secondly, our results showed that the majority (97.21%) of medicine items reimbursed with specific ICD-10 codes were indicated for acute conditions while only about 3% were for chronic conditions. This is supported by the higher proportion (82.10%) of all medicine claims reimbursed from patients' acute benefits. This is to be expected because increasing age has been found to be a very important non-modifiable risk factor for chronic conditions [26,27]. Children are, therefore, less likely to develop chronic conditions. However, taking into account the potential complications of cancer and its treatment, chronic conditions may be identified in children on antineoplastic therapy. Chronic conditions identified in our study included hypertension which could be as a result of the nephrotoxicity associated with the use of some chemotherapeutic agents such as cisplatin and ifosfamide [28]. Corticosteroids, which are mostly used as adjunct therapy for some childhood cancers, have also been associated with hypertension in these patients [29]. Major depressive disorders (MDDs) and anxiety were also identified in our patient population and this could be attributed to psychological stress associated with cancer diagnosis and treatment [30]. Depression resulting from psychological stress is more prevalent in older children and adolescents with cancer due to the concurrence of the disease and their developmental stage [31]. This was confirmed in a study by Akimana et al [32] which established that patients aged 10-17 years were four times more likely to be diagnosed with MDD in comparison to younger children. This high prevalence of depression in older children and adolescents is confirmed by the prevalent use of antidepressants in the 10-14 and 15<19 year age groups, compared to the other age groups in our study population.

Other chronic conditions identified in the study included epilepsy and asthma. Coexistence of epilepsy and cancer in our study is supported by the relatively high use of antiepileptic drugs as observed from our analysis based on the main pharmacological classes of all medicine claims. Epilepsy, which is mostly characterized by seizures, may be drug-induced, result from metastasis of primary brain tumour, or may be a complication of leukemia with brain involvement [33,34]. Epilepsy has been indicated as the most common chronic neurological condition in children [35] with a prevalence of 0.7% reported in rural South African children [36]. Some studies in South Africa have demonstrated a 9-34% prevalence of asthma in children in the general population, with a higher rate in residents of urban

communities [37,38]. This confirms asthma as one of the prevalent chronic diseases in children. Asthma as a coexisting condition in our study population is supported by the prevalent use of anti-asthmatics, bronchodilators, antihistamines and corticosteroids. This is in contrast with previous studies that established a possible reduction in the prevalence of asthma symptoms and the need for asthma preventive therapies in children receiving chemotherapeutic agents [39,40]. It should, however, be noted that data for this study were expressed descriptively, and comparison with prevalent use of asthma preventive therapy in patients unexposed to chemotherapeutic agents is outside the scope of this study.

Thirdly, diseases of the respiratory system were the most prevalent acute conditions overall, followed by diseases of the GIT, disorders of the skin and diseases of the musculoskeletal system. Acute tonsillitis, acute upper respiratory tract infection and acute bronchitis were the most common respiratory system diagnoses recorded on medicine claims. In support of these results, the DU90% analysis showed that antimicrobial agents, respiratory system agents and analgesics, i.e. agents that are mainly used in the management of respiratory infections [41], were the three most prevalent pharmacological classes of medicines claimed with non-specific diagnostic codes. This may suggest a higher prevalence of respiratory diseases than was recorded in our patient population based on specific ICD-10 codes. Respiratory diseases have been found to be one of the leading causes of morbidity in children in the general population and represent approximately 25% of primary care consultations [42,43]. The immunosuppression associated with chemotherapeutic agents makes children undergoing cancer treatment more susceptible to respiratory diseases, notable among them being infections [44]. This is confirmed by results of previous studies which indicated the respiratory system as the common site of infections in children on antineoplastic therapy, with respiratory infections representing 16-23% of infectious episodes in these patients [45,46]. These infections may be from bacterial, viral or fungal origins [44]. Respiratory infections of bacterial origin, together with possible superinfection of respiratory viral infections with bacteria [47], is supported by the high prevalence of antimicrobial agents. Respiratory viral infections, especially influenza and respiratory syncytial virus (RSV) infections which are common in immunocompromised children [48,49,50,51], are characterized by symptoms such as cold and cough [52,53]. This could also explain the prevalent use of medicines for coughs and colds (63.93%) among the respiratory system agents. The use of analgesics and antipyretics for the management of fever, a primary sign of infection resulting from neutropenia in children receiving chemotherapeutic agents [54,55], could explain the prevalent use of analgesics in this study.

Acute toxicities of the GIT, which include constipation, nausea, vomiting, diarrhea and susceptibility to gastrointestinal infections, are often associated with cancer chemotherapy [56,57]. Chemotherapeutic agents such as cyclophosphamide have been found to be associated with mucosal ulceration, which predisposes patients to gastroenteritis [58]. Gastroenteritis is characterized by diarrhea, nausea, vomiting and abdominal pain, and is an important cause of morbidity in children especially those who are immunocompromised [59,60,61]. Mucosal ulceration and its associated gastroenteritis from chemotherapeutic agents are supported by the high proportion of medicine claims associated with gastric ulcer (21.4%) and non-infective gastroenteritis (19.0%) among the diseases of the GIT in this study. This is also confirmed by the high prevalence of acid reducers among the GIT agents in our population.

The skin is prone to toxicities of chemotherapeutic agents since their mode of action involves targeting rapidly growing cells. Dermatological events, therefore, although rarely life-threatening, are usually reported in patients undergoing chemotherapy [62,63], with skin rashes, hyperpigmentation and pruritus being the most prevalent. This could account for skin disorders being the third most prevalent disease group in our patient population.

The higher proportion of males as compared to females (68.79% vs. 31.21%) in the study population could account for the higher proportion of non-cytotoxic medicine claims in males. Comparison of the prevalence of coexisting conditions in males and females was, however, limited by the incomplete ICD-10 diagnostic codes on medicine claims. The highest proportion of non-cytotoxic medicine claims over the study period in the 5-9-year age group can be attributed to the majority of the study population (34.10%) falling within this age group. The majority of medications classified as CNS agents, musculoskeletal agents, genital system agents, dermatological agents and urinary system agents, are mostly utilized in the adolescent age group. This may, therefore, account for the high prevalence of these pharmacological classes among the adolescent age group. For example, the high prevalence of acne in adolescents [64] makes the use of acne preparations and contraceptives relatively common in this age group. Contraceptives are also used in the management of menstrual disorders such as amenorrhea and menorrhagia in adolescents [65].

4.1 Study strengths and limitations

The study population was drawn from the database of only one PBM company covering a section of the private health sector of South Africa and therefore results of this study cannot be generalized to the whole South African population. The use of the main pharmacological

group prescribed as a proxy for diagnoses in cases where medicines were claimed with non-specific ICD-10 diagnostic codes has the potential of introducing bias as some medications may be used for secondary indications or may be used off-label for other conditions not indicated on product labels [66]. Under-ascertainment of the prevalence of the use of the various pharmacological classes is likely because data used for this study were reimbursed claims. Medicine items used by the study population that are not covered under the health plan for which they are subscribed to on their medical schemes are not reimbursed and, consequently, will not be included in the database.

In spite of the limitations indicated, this study provides preliminary findings of the burden of diseases in children and adolescents being treated for various childhood cancers. Again, it highlights the utilization patterns of the major pharmacological classes of non-cytotoxic medications for the management of these conditions.

5 Conclusion

Most coexisting conditions in children and adolescents on cancer therapy in the section of the private health sector studied were acute conditions and included microbial infections and diseases of the respiratory system. Antimicrobial agents, respiratory system agents, analgesics, ENT agents and GIT agents were the top five most prevalent pharmacological classes of non-cytotoxic medications utilized by the study population. The high prevalent use of antimicrobial agents in this study indicates the need for the integration of antimicrobial surveillance programs into childhood and adolescent cancer care to curb antimicrobial infections.

Competing interests

The authors have no potential conflict of interest to declare.

Author contributions

The study was conceived by JRB, MNO, HS and MSL. MSL extracted and analyzed the medicine claims data. MNO interpreted findings and drafted the report under the supervision of JRB. All authors reviewed and approved the final version.

Role of funding source

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Data availability statement

The authors do not have permission to share the data.

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Table 1 Demographic characteristics of the study population

Characteristics	**n (%)[a]**
Overall population	**173 (100)**
Gender	
Male	119 (68.79)
Female	54 (31.21)
Age groups (years)	
0-4	27 (15.61)
5-9	59 (34.10)
10-14	40 (23.12)
15<19	47 (27.17)
Malignancy type	
Leukemias	69 (39.88)
Lymphomas	24 (13.87)
CNS neoplasms	19 (10.98)
Neuroblastoma	3 (1.73)
Retinoblastoma	6 (3.47)
Renal tumours	7 (4.05)
Hepatic tumours	1 (0.58)
Bone tumours	12 (6.94)
Soft tissue sarcomas	7 (4.05)
Germ cell tumours	6 (3.47)
Carcinoma and melanomas	17 (9.83)
Other and unspecified neoplasms	2 (1.16)

[a] Percentages calculated based on the total study population

Table 2 Coexisting conditions based on ICD-10 diagnostic codes associated with medicine claims

Conditions based on ICD-10 codes	**Number of medicine items associated with ICD-10 codes, n (%)[a]**
Total medicine items claimed, N	**2 631**
Conditions with specified diagnostic codes	**359 (13.65)**
Diseases of the respiratory system	188 (7.15)
Diseases of the gastrointestinal tract	42 (1.60)
Skin disorders	25 (0.95)
Disorders of the musculoskeletal system	24 (0.91)
Pain	17 (0.65)
Genitourinary system disorders	15 (0.57)
Diseases of the ear	13 (0.49)
Infectious diseases	9 (0.34)
Fever of unknown origin	6 (0.23)
Behavioral and mental disorders	5 (0.19)
Central nervous system disorders	3 (0.11)
Ascites	3 (0.11)
Anemia	2 (0.08)
Ocular diseases	2 (0.08)
Diseases of the circulatory system	2 (0.08)
Immunizations against infectious diseases	2 (0.08)
Hepatic abnormalities	1 (0.04)
Conditions with non-specified diagnostic code[b]	**2 272 (86.35)**

[a] Percentages calculated based on the total number of medicine items claimed during the study period (N = 2 631).

[b] These include diagnostic codes for repeat prescriptions (Z76.0), failure for patient or provider to disclose clinical information (U98.0 and U98.1), encountering health services in unspecified conditions (Z76.9) and missing codes.

Table 3 Pharmacological classes within DU 90% of medicines claimed under unspecified diagnostic codes.

Pharmacological class	**n (%)[a]**
Antimicrobials	397 (17.47)
Respiratory agents	301 (13.25)
Analgesics	233 (10.26)
Ear, nose and throat agents	221 (9.73)
Gastrointestinal tract agents	176 (7.75)
Central nervous system agents	151 (6.65)
Autacoids	144 (6.34)
Dermatological agents	113 (4.97)
Endocrine agents	110 (4.84)
Herbal preparations	81 (3.57)
Musculoskeletal agents	74 (3.26)
Anesthetics	64 (2.82)

[a] Percentages calculated based on the total number of medicine items claimed under non-specific diagnostic codes (N = 2 272).

Table 4 Pharmacological classes of non-cytotoxic medications used in children and adolescents with cancer in overall study population and by gender groups according to the Monthly Index of Medical Specialties classification.

Prevalence of main pharmacological classes in overall study population and gender groups				**Prevalence of sub-pharmacological classes in overall study population and gender groups**			
Main pharmacological classification	Overall prevalence n (%)	Prevalence in males n (%)	Prevalence in females n (%)	Sub-pharmacological classification	Overall prevalence n (%)	Prevalence in males n (%)	Prevalence in females n (%)
Antimicrobials	458 (17.40)	308 (11.71)	150 (5.70)	Beta-lactams	225 (8.55)	156 (5.93)	69 (2.62)
				Sulphonamides and combinations	65 (2.47)	44 (1.67)	21 (0.80)
				Erythromycin and other macrolides	49 (1.86)	35 (1.33)	14 (0.53)
				Anti-fungal agents	46 (1.75)	27 (1.03)	19 (0.72)
				Anti-viral agents	25 (0.95)	17 (0.65)	8 (0.30)
				Quinolones	24 (0.91)	15 (0.57)	9 (0.34)
				Anti-protozoal agents	13 (0.49)	6 (0.23)	7 (0.27)
				Tetracyclines	5 (0.19)	4 (0.15)	1 (0.04)
				Others	6 (0.23)	4 (0.15)	2 (0.08)
Respiratory system agents	366 (13.91)	247 (9.39)	119 (4.52)	Coughs and colds	234 (8.89)	154 (5.85)	80 (3.04)
				Bronchodilators	79 (3.00)	53 (2.01)	26 (0.99)
				Mucolytics	31 (1.18)	22 (0.84)	9 (0.34)
				Anti-asthmatics	22 (0.84)	18 (0.68)	4 (0.15)

Prevalence of main pharmacological classes in overall study population and gender groups				Prevalence of sub-pharmacological classes in overall study population and gender groups			
Main pharmacological classification	Overall prevalence n (%)	Prevalence in males n (%)	Prevalence in females n (%)	Sub-pharmacological classification	Overall prevalence n (%)	Prevalence in males n (%)	Prevalence in females n (%)
Analgesics	280 (10.64)	179 (6.80)	101 (3.84)	Combination products	159 (6.04)	95 (3.61)	64 (2.43)
				Analgesics and antipyretics	100 (3.80))	67 (2.55)	33 (1.25)
				Narcotic analgesics	14 (0.53)	11 (0.42)	3 (0.11)
				Other agents	7 (0.27)	6 (0.23)	1 (0.04)
Ear, nose and throat agents	254 (9.65)	163 (6.20)	91 (3.46)	Topical nasal preparations	156 (5.93)	106 (4.03)	50 (1.90)
				Mouth and throat preparations	79 (3.00)	41 (1.56)	38 (1.44)
				Ear drops and ointments	19 (0.72)	16 (0.61)	3 (0.11)
Gastrointestinal tract (GIT) agents	197 (7.49)	132 (5.02)	65 (2.47)	Acid reducers	91 (3.46)	62 (2.36)	29 (1.10)
				Antispasmodics	32 (1.22)	22 (0.84)	10 (0.38)
				Laxatives	30 (1.14)	19 (0.72)	11 (0.42)
				Antidiarrhoeals	23 (0.87)	16 (0.61)	7 (0.27)
				Other GIT agents	13 (0.49)	9 (0.34)	4 (0.15)
				Suppositories and anal ointments	8 (0.30)	4 (0.15)	4 (0.15)
Central nervous system agents	170 (6.46)	106 (4.03)	64 (2.43)	Anti-vertigo and antiemetics	54 (2.05)	29 (1.10)	25 (0.95)

Prevalence of main pharmacological classes in overall study population and gender groups				Prevalence of sub-pharmacological classes in overall study population and gender groups			
Main pharmacological classification	Overall prevalence n (%)	Prevalence in males n (%)	Prevalence in females n (%)	Sub-pharmacological classification	Overall prevalence n (%)	Prevalence in males n (%)	Prevalence in females n (%)
				Anti-epileptics	34 (1.29)	25 (0.95)	9 (0.34)
				Antidepressants	29 (1.10)	18 (0.68)	11 (0.42)
				Sedative hypnotics	24 (0.91)	15 (0.57)	9 (0.34)
				Anxiolytics	16 (0.61)	11 (0.42)	5 (0.19)
				Antipsychotics	6 (0.23)	3 (0.11)	3 (0.11)
				CNS stimulants	4 (0.15)	3 (0.11)	1 (0.04)
				Anti-Parkinson agents	2 (0.08)	2 (0.08)	0 (0.0)
				Anti-migraine agents	1 (0.04)	0 (0.0)	1 (0.04)
Autacoids	166 (6.31)	112 (4.26)	54 (2.05)	Antihistamines	112 (4.26)	71 (2.70)	41 (1.56)
				Serotonin antagonists	50 (1.90)	38 (1.44)	12 (0.46)
				NK1 antagonists	4 (0.15)	3 (0.11)	1 (0.04)
Dermatological agents	140 (5.32)	80 (3.04)	60 (2.28)	Corticosteroids	49 (1.86)	30 (1.14)	19 (0.72)
				Fungicides	27 (1.03)	16 (0.61)	11 (0.42)
				Anti-bacterial antiseptic agents	24 (0.91)	15 (0.57)	9 (0.34)
				Other dermatologicals	16 (0.61)	9 (0.34)	7 (0.27)

Prevalence of main pharmacological classes in overall study population and gender groups				Prevalence of sub-pharmacological classes in overall study population and gender groups			
Main pharmacological classification	Overall prevalence n (%)	Prevalence in males n (%)	Prevalence in females n (%)	Sub-pharmacological classification	Overall prevalence n (%)	Prevalence in males n (%)	Prevalence in females n (%)
				Emollients and protectives	12 (0.46)	5 (0.19)	7 (0.27)
				Acne preparations	11 (0.42)	5 (0.19)	6 (0.23)
				Psoriasis	1 (0.04)	0 (0.0)	1 (0.04)
Endocrine system agents	122 (4.64)	85 (3.23)	37 (1.41)	Corticosteroids	116 (4.41)	81 (3.08)	35 (1.33)
				Antidiabetic agents	4 (0.15)	4 (0.15)	0 (0.0)
				Sex hormones	2 (0.08)	0 (0.0)	2 (0.08)
Musculoskeletal agents	91 (3.45)	52 (1.98)	39 (1.48)	Non-Steroidal anti-inflammatory agents	70 (2.66)	42 (1.60)	28 (1.06)
				Topical agents	10 (0.38)	7 (0.27)	3 (0.11)
				Anti-gout agents	9 (0.34)	3 (0.11)	6 (0.23)
				Centrally acting muscle relaxants	2 (0.08)	0 (0.0)	2 (0.08)
Herbal preparations	85 (3.23)	61 (2.32)	24 (0.91)	Natural products	85 (3.23)	61 (2.32)	24 (0.91)
Anaesthetics	72 (2.74)	43 (1.63)	29 (1.10)	Local anaesthetics	41 (1.56)	21 (0.80)	20 (0.76)
				General anaesthetics	30 (1.14)	22 (0.84)	8 (0.30)
				Muscle relaxants	1 (0.04)	0 (0.0)	1 (0.04)

Prevalence of main pharmacological classes in overall study population and gender groups				Prevalence of sub-pharmacological classes in overall study population and gender groups			
Main pharmacological classification	Overall prevalence n (%)	Prevalence in males n (%)	Prevalence in females n (%)	Sub-pharmacological classification	Overall prevalence n (%)	Prevalence in males n (%)	Prevalence in females n (%)
Vitamins, tonics, minerals and electrolytes	59 (2.24)	39 (1.48)	20 (0.76)	Minerals and electrolytes	44 (1.67)	28 (1.06)	16 (0.61)
				Vitamins	13 (0.49)	9 (0.34)	4 (0.15)
				Vitamins with minerals	1 (0.04)	1 (0.04)	0 (0.00)
				Tonics	1 (0.04)	1 (0.04)	0 (0.00)
Ophthalmics	37 (1.41)	25 (0.95)	12 (0.46)	Anti-infectives	16 (0.61)	14 (0.53)	2 (0.08)
				Anti-infective and corticoid combinations	12 (0.46)	6 (0.23)	6 (0.23)
				Corticoids	3 (0.11)	2 (0.08)	1 (0.04)
				Decongestants	3 (0.11)	2 (0.08)	1 (0.04)
				Others	2 (0.08)	1 (0.04)	1 (0.04)
				Glaucoma	1 (0.04)	0 (0.0)	1 (0.04)
Urinary system	30 (1.14)	16 (0.61)	14 (0.53)	Diuretics	10 (0.38)	5 (0.19)	5 (0.19)
				Urinary alkalinizers	6 (0.23)	1 (0.04)	5 (0.19)
				Urinary antiseptics	1 (0.04)	0 (0.0)	1 (0.04)
				Others	13 (0.49)	10 (0.38)	3 (0.11)

Prevalence of main pharmacological classes in overall study population and gender groups				Prevalence of sub-pharmacological classes in overall study population and gender groups			
Main pharmacological classification	Overall prevalence n (%)	Prevalence in males n (%)	Prevalence in females n (%)	Sub-pharmacological classification	Overall prevalence n (%)	Prevalence in males n (%)	Prevalence in females n (%)
Biologicals	29 (1.10)	17 (0.65)	12 (0.46)	Biologicals	29 (1.10)	17 (0.65)	12 (0.46)
Blood and haematopoetic agents	23 (0.87)	14 (0.53)	9 (0.34)	Anticoagulants	15 (0.57)	9 (0.34)	6 (0.23)
				Haematinics	5 (0.19)	4 (0.15)	1 (0.04)
				Haemostatics	3 (0.11)	1 (0.04)	2 (0.08)
Anthelmintics	18 (0.68)	9 (0.34)	9 (0.34)	Anthelmintics	18 (0.68)	9 (0.34)	9 (0.34)
Cardiovascular agents	15 (0.57)	13 (0.49)	2 (0.08)	Antihypertensive agents	7 (0.27)	7 (0.27)	0 (0.0)
				Anti-arrythmics	4 (0.15)	3 (0.11)	1 (0.04)
				Anti-anginal agents	1 (0.04)	0 (0.00)	1 (0.04)
				Other vasodilators	1 (0.04)	1 (0.04)	0 (0.00)
				Vasoconstrictors	1 (0.04)	1 (0.04)	0 (0.00)
				Hipolipidaemic agents	1 (0.04)	1 (0.04)	0 (0.00)
Genital system	9 (0.34)	0 (0.0)	9 (0.34)	Contraceptives	8 (0.30)	0 (0.00)	8 (0.30)
				Vaginal preparations	1 (0.04)	0 (0.00)	1 (0.04)
Autonomic agents	7 (0.27)	5 (0.19)	2 (0.08)	Anticholinergics	4 (0.15)	3 (0.11)	1 (0.04)
				Sympathomimetics	2 (0.08)	2 (0.08)	0 (0.00)

Prevalence of main pharmacological classes in overall study population and gender groups				Prevalence of sub-pharmacological classes in overall study population and gender groups			
Main pharmacological classification	Overall prevalence n (%)	Prevalence in males n (%)	Prevalence in females n (%)	Sub-pharmacological classification	Overall prevalence n (%)	Prevalence in males n (%)	Prevalence in females n (%)
				Cholinergics	1 (0.04)	0 (0.00)	1 (0.04)
Special foods	3 (0.11)	1 (0.04)	2 (0.08)	Special foods	3 (0.11)	1 (0.04)	2 (0.08)
Total main class	**2361 (100.00)**	**1707 (64.88)**	**924 (35.12)**	**Total sub-class**	**2361 (100.00)**	**1707 (64.88)**	**924 (35.12)**

Table 5: Distribution of the pharmacological classes of non-cytotoxic medications used in children and adolescents with cancer, by age group, according to the Monthly Index of Medical Specialties classification

Prevalence of pharmacological classes in age groups					**Prevalence of sub-pharmacological classes in age group**				
Main pharmacological classification	Prevalence in 0-4 years n (%)	Prevalence in 5-9 years n (%)	Prevalence in 10-14 years n (%)	Prevalence in 15<19 years n (%)	Sub-pharmacological group	Prevalence in 0-4 years n (%)	Prevalence in 5-9 years n (%)	Prevalence in 10-14 years n (%)	Prevalence in 15<19 years n (%)
Antimicrobials	61 (2.32)	225 (8.55)	62 (2.36)	110 (4.18)	Beta-lactams	43 (1.63)	113 (4.29)	31 (1.18)	38 (1.44)
					Sulphonamides and combinations	7 (0.27)	41 (1.56)	8 (0.30)	9 (0.34)
					Erythromycin and other macrolides	7 (0.27)	27 (1.03)	6 (0.23)	9 (0.34)
					Anti-fungal agents	2 (0.08)	18 (0.68)	8 (0.30)	18 (0.68)
					Anti-viral agents	1 (0.04)	17 (0.65)	1 (0.04)	6 (0.23)
					Quinolones	0 (0.00)	2 (0.08)	4 (0.15)	18 (0.68)
					Anti-protozoal agents	1 (0.04)	6 (0.23)	0 (0.00)	6 (0.23)
					Tetracyclines	0 (0.00)	0 (0.00)	2 (0.08)	3 (0.11)
					Others	0 (0.00)	1 (0.04)	2 (0.08)	3 (0.11)
Respiratory system agents	48 (1.82)	167 (6.35)	58 (2.2)	93 (3.53)	Coughs and colds	28 (1.06)	89 (3.38)	43 (1.63)	74 (2.81)
					Bronchodilators	13 (0.49)	43 (1.63)	10 (0.38)	13 (0.49)
					Mucolytics	3 (0.11)	20 (0.76)	3 (0.11)	5 (0.19)
					Anti-asthmatics	4 (0.15)	15 (0.57)	2 (0.08)	1 (0.04)
Analgesics	41 (1.56)	106 (4.03)	50 (1.90)	83 (3.15)	Combination products	16 (0.61)	46 (1.75)	32 (1.22)	65 (2.47)
					Analgesics and antipyretics	25 (0.95)	53 (2.01)	14 (0.53)	8 (0.30)

Prevalence of pharmacological classes in age groups					**Prevalence of sub-pharmacological classes in age group**				
Main pharmacological classification	Prevalence in 0-4 years n (%)	Prevalence in 5-9 years n (%)	Prevalence in 10-14 years n (%)	Prevalence in 15<19 years n (%)	Sub-pharmacological group	Prevalence in 0-4 years n (%)	Prevalence in 5-9 years n (%)	Prevalence in 10-14 years n (%)	Prevalence in 15<19 years n (%)
					Narcotic analgesics	0 (0.00)	7 (0.27)	2 (0.08)	5 (0.19)
					Other agents	0 (0.00)	0 (0.00)	2 (0.08)	5 (0.19)
Ear, nose and throat agents	24 (0.91)	103 (3.91)	53 (2.01)	74 (2.81)	Topical nasal preparations	20 (0.76)	63 (2.39)	32 (1.22)	41 (1.56)
					Mouth and throat preparations	2 (0.08)	33 (1.25)	17 (0.65)	27 (1.03)
					Ear drops and ointments	2 (0.08)	7 (0.27)	4 (0.15)	6 (0.23)
Gastrointestinal tract (GIT) agents	20 (0.76)	57 (2.17)	55 (2.09)	65 (2.47)	Acid reducers	7 (0.27)	17 (0.65)	26 (0.99)	41 (1.56)
					Antispasmodics	5 (0.19)	11 (0.42)	9 (0.34)	7 (0.27)
					Laxatives	3 (0.11)	14 (0.53)	7 (0.27)	6(0.23)
					Antidiarrhoeals	3 (0.11)	7 (0.27)	6 (0.23)	7 (0.27)
					Other GIT agents	2 (0.08)	4 (0.15)	5 (0.19)	2 (0.08)
					Suppositories and anal ointments	0 (0.00)	4 (0.15)	2 (0.08)	2 (0.08)
Central nervous system (CNS) agents	12 (0.46)	35 (1.33)	37 (1.41)	86 (3.27)	Anti-vertigo and antiemetics	4 (0.15)	14 (0.53)	11 (0.42)	25 (0.95)
					Anti-epileptics	6 (0.23)	12 (0.46)	7 (0.27)	9 (0.34)
					Antidepressants	0 (0.00)	2 (0.08)	10 (0.38)	17 (0.65)
					Sedative hypnotics	0 (0.00)	2 (0.08)	2 (0.08)	20 (0.76)
					Anxiolytics	1 (0.04)	3 (0.11)	3 (0.11)	9 (0.34)

Prevalence of pharmacological classes in age groups					**Prevalence of sub-pharmacological classes in age group**				
Main pharmacological classification	Prevalence in 0-4 years n (%)	Prevalence in 5-9 years n (%)	Prevalence in 10-14 years n (%)	Prevalence in 15<19 years n (%)	Sub-pharmacological group	Prevalence in 0-4 years n (%)	Prevalence in 5-9 years n (%)	Prevalence in 10-14 years n (%)	Prevalence in 15<19 years n (%)
					Antipsychotics	0 (0.00)	1 (0.04)	2 (0.08)	3 (0.11)
					CNS stimulants	1 (0.04)	1 (0.04)	0 (0.00)	2 (0.08)
					Anti-Parkinson agents	0 (0.00)	0 (0.00)	2 (0.08)	0 (0.00)
					Anti-migraine agents	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.04)
Autacoids	24 (0.91)	75 (2.85)	31 (1.18)	36 (1.37)	Antihistamines	18 (0.68)	53 (2.01)	15 (0.57)	26 (0.99)
					Serotonin antagonists	6 (0.23)	22 (0.84)	15 (0.57)	7 (0.27)
					NK1 antagonists	0 (0.00)	0 (0.00)	1 (0.04)	3 (0.11)
Dermatological agents	17 (0.65)	44 (1.67)	28 (1.06)	51 (1.94)	Corticosteroids	8 (0.30)	18 (0.68)	9 (0.34)	14 (0.53)
					Fungicides	5 (0.19)	12 (0.46)	6 (0.23)	4 (0.15)
					Anti-bacterial antiseptic agents	2 (0.08)	9 (0.34)	4 (0.15)	9 (0.34)
					Other dermatologicals	2 (0.08)	3 (0.11)	4 (0.15)	7 (0.27)
					Emollients and protectives	0 (0.00)	2 (0.08)	4 (0.15)	6 (0.23)
					Acne preparations	0 (0.00)	0 (0.00)	1 (0.04)	10 (0.38)
					Psoriasis	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.04)
Endocrine system agents	14 (0.53)	54 (2.05)	21 (0.80)	33 (1.25)	Corticosteroids	14 (0.53)	54 (2.05)	21 (0.80)	27 (1.03)
					Antidiabetic agents	0 (0.00)	0 (0.00)	0 (0.00)	4 (0.15)

Prevalence of pharmacological classes in age groups					**Prevalence of sub-pharmacological classes in age group**				
Main pharmacological classification	Prevalence in 0-4 years n (%)	Prevalence in 5-9 years n (%)	Prevalence in 10-14 years n (%)	Prevalence in 15<19 years n (%)	Sub-pharmacological group	Prevalence in 0-4 years n (%)	Prevalence in 5-9 years n (%)	Prevalence in 10-14 years n (%)	Prevalence in 15<19 years n (%)
					Sex hormones	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.08)
Musculoskeletal agents	10 (0.38)	25 (0.95)	15 (0.57)	41 (1.56)	Non-Steroidal anti-inflammatory agents	7 (0.27)	22 (0.84)	9 (0.34)	32 (1.22)
					Topical agents	0 (0.00)	2 (0.08)	3 (0.11)	5 (0.19)
					Anti-gout agents	3 (0.11)	1 (0.04)	2 (0.08)	3 (0.11)
					Centrally acting muscle relaxants	0 (0.00)	0 (0.00)	1 (0.04)	1 (0.04)
Herbal preparations	19 (0.72)	37 (1.41)	9 (0.34)	20 (0.76)	Natural products	19 (0.72)	37 (1.41)	9 (0.34)	20 (0.76)
Anaesthetics	21 (0.80)	15 (0.57)	18 (0.68)	18 (0.68)	Local anaesthetics	8 (0.30)	10 (0.38)	8 (0.30)	15 (0.57)
					General anaesthetics	12 (0.46)	5 (0.19)	10 (0.38)	3 (0.11)
					Muscle relaxants	1 (0.04)	0 (0.00)	0 (0.00)	0 (0.00)
Vitamins, tonics, minerals and electrolytes	10 (0.38)	20 (0.76)	15 (0.57)	14 (0.53)	Minerals and electrolytes	9 (0.34)	15 (0.57)	10 (0.38)	10 (0.38)
					Vitamins	0 (0.00)	5 (0.19)	4 (0.15)	4 (0.15)
					Vitamins with minerals	0 (0.00)	0 (0.00)	1 (0.04)	0 (0.00)
					Tonics	1 (0.04)	0 (0.00)	0 (0.00)	0 (0.00)
Ophthalmics	10 (0.38)	15 (0.57)	4 (0.15)	8 (0.30)	Anti-infectives	7 (0.27)	8 (0.30)	0 (0.00)	1 (0.04)
					Anti-infective and corticoid combinations	3 (0.11)	4 (0.15)	2 (0.08)	3 (0.11)

Prevalence of pharmacological classes in age groups					**Prevalence of sub-pharmacological classes in age group**				
Main pharmacological classification	Prevalence in 0-4 years n (%)	Prevalence in 5-9 years n (%)	Prevalence in 10-14 years n (%)	Prevalence in 15<19 years n (%)	Sub-pharmacological group	Prevalence in 0-4 years n (%)	Prevalence in 5-9 years n (%)	Prevalence in 10-14 years n (%)	Prevalence in 15<19 years n (%)
					Corticoids	0 (0.00)	1 (0.04)	1 (0.04)	1 (0.04)
					Decongestants	0 (0.00)	0 (0.00)	1 (0.04)	2 (0.08)
					Others	0 (0.00)	1 (0.04)	0 (0.00)	1 (0.04)
					Glaucoma	0 (0.00)	1 (0.04)	0 (0.00)	0 (0.00)
Urinary system agents	2 (0.08)	8 (0.30)	3 (0.11)	17 (0.65)	Diuretics	0 (0.00)	2 (0.08)	0 (0.00)	8 (0.30)
					Urinary alkalinizers	1 (0.04)	0 (0.00)	0 (0.00)	5 (0.19)
					Urinary antiseptics	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.04)
					Others	1 (0.04)	6 (0.23)	3 (0.11)	3 (0.11)
Biologicals	9 (0.34)	7 (0.27)	2 (0.08)	11 (0.42)	Biologicals	9 (0.34)	7 (0.27)	2 (0.08)	11 (0.42)
Blood and haematopoetic agents	2 (0.08)	4 (0.15)	3 (0.11)	14 (0.53)	Anticoagulants	2 (0.08)	3 (0.11)	2 (0.08)	8 (0.30)
					Haematinics	0 (0.00)	1 (0.04)	1 (0.04)	3 (0.11)
					Haemostatics	0 (0.00)	0 (0.00)	0 (0.00)	3 (0.11)
Anthelmintics	3 (0.11)	11 (0.42)	4 (0.15)	0 (0.00)	Anthelmintics	3 (0.11)	11 (0.42)	4 (0.15)	0 (0.00)
Cardiovascular agents	2 (0.08)	5 (0.19)	0 (0.00)	8 (0.30)	Antihypertensive agents	1 (0.04)	3 (0.11)	0 (0.00)	3 (0.11)
					Anti-arrythmics	1 (0.04)	2 (0.08)	0 (0.00)	1 (0.04)
					Anti-anginal agents	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.04)

Prevalence of pharmacological classes in age groups					**Prevalence of sub-pharmacological classes in age group**				
Main pharmacological classification	Prevalence in 0-4 years n (%)	Prevalence in 5-9 years n (%)	Prevalence in 10-14 years n (%)	Prevalence in 15<19 years n (%)	Sub-pharmacological group	Prevalence in 0-4 years n (%)	Prevalence in 5-9 years n (%)	Prevalence in 10-14 years n (%)	Prevalence in 15<19 years n (%)
					Other vasodilators	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.04)
					Vasoconstrictors	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.04)
					Hipolipidaemic agents	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.04)
Genital system	0 (0.00)	0 (0.00)	1 (0.04)	8 (0.30)	Contraceptives	0 (0.00)	0 (0.00)	0 (0.00)	8 (0.30)
					Vaginal preparations	0 (0.00)	0 (0.00)	1 (0.04)	0 (0.00)
Autonomic agents	4 (0.15)	0 (0.00)	3 (0.11)	0 (0.00)	Anticholinergics	2 (0.08)	0 (0.00)	2 (0.08)	0 (0.00)
					Sympathomimetics	1 (0.04)	0 (0.00)	1 (0.04)	0 (0.00)
					Cholinergics	1 (0.04)	0 (0.00)	0 (0.00)	0 (0.00)
Special foods	0 (0.00)	0 (0.00)	2 (0.08)	1 (0.04)	Special foods	0 (0.00)	0 (0.00)	2 (0.08)	1 (0.04)
Total main groups	**353 (13.42)**	**1013 (38.50)**	**474 (18.02)**	**791 (30.06)**	**Total sub-groups**	**353 (13.42)**	**1013 (38.50)**	**474 (18.02)**	**791 (30.06)**

Table 6 Classification of medicine items according to reimbursement category

	Acute	Chronic	OTC[a]	PMB[b]	Other	Total	
Total population, n (%)[c]	2160 (82.10)	13 (0.49)	259 (9.84)	32 (1.22)	167 (6.35)	2631	
Gender, n (%)[c]							*p*-value
Male	1366 (51.92)	2 (0.08)	184 (7.00)	20 (0.76)	135 (5.13)	1707 (64.88)	<0.0001
Female	794 (30.18)	11 (0.42)	75 (2.85)	12 (0.46)	32 (1.22)	924 (35.12)	
Age groups, n (%)[c]							
0-4 years	312 (11.86)	0 (0.00)	29 (1.10)	0 (0.00)	12 (0.46)	353 (13.42)	<0.0001
5-9 years	804 (30.56)	0 (0.00)	102 (3.88)	19 (0.72)	88 (3.34)	1013 (38.50)	
10-14 years	388 (14.75)	7 (0.27)	60 (2.28)	1 (0.04)	18 (0.68)	474 (18.02)	
15<19 years	656 (24.93)	6 (0.23)	68 (2.58)	12 (0.46)	49 (1.86)	791 (30.06)	

a OTC: Over-the-counter

b PMB: Prescribed minimum benefits

c Percentages calculated using the total number of medicine items utilized (N = 2631)

3.5 Chapter summary

In this chapter, two manuscripts and an ‘additional results’ section that addresses the specific objectives outlined for the empirical investigation were presented. The subsequent chapter concludes the study and focuses on the conclusions, strength and limitations of the study, and proposes recommendations for further studies.

CHAPTER 4: CONCLUSIONS, STRENGTHS, LIMITATIONS AND RECOMMENDATIONS

4.1 Introduction

This final chapter of the dissertation focuses on drawing conclusions from the study in relation to the outlined specific objectives. A synopsis of the content of the dissertation will be provided. The strengths and limitations of the study will also be highlighted, with the chapter concluding with proposed recommendations for further studies.

4.2 Outline of the presentation

This dissertation comprised four chapters. Chapter 1 presented a general overview of the study by providing the background and rationale of the study, the research questions to be answered, the aim, specific objectives and methodology of the study, as well as the ethical considerations pertaining to the study.

Chapter 2, the literature review component of the dissertation, provided a summary of the types and classification of childhood cancers according to literature. The epidemiology of cancers occurring in childhood across the globe was extensively discussed. This was followed by a conceptualisation of the burden of childhood cancers, a discussion of the risk factors associated with childhood cancers, and the various treatment modalities available for the management of childhood cancers. The chapter concluded with a discussion of the coexisting conditions and complications associated with childhood cancer and its treatment.

The results and discussions of the empirical investigation, which were the main component of Chapter 3, were presented in the format of manuscripts and an 'additional results section'. Two manuscripts, with the following titles, were presented:

- Manuscript 1: Childhood cancers in a section of the South African private health sector: Analysis of medicines claims data.
- Manuscript 2: Coexisting conditions in children and adolescents with cancer in a section of the South African private health sector.

4.3 Conclusions from the study

The overall objective of the study was to determine the epidemiology of childhood cancers and to identify the common coexisting conditions in children and adolescents with cancer in a section of the private health sector of South Africa, using a medicines claims database. To achieve this objective, a literature review and an empirical investigation were employed. The subsequent paragraphs outline the conclusions of the various sections of this study based on the specific objectives.

4.3.1 Conclusions from the literature review

The specific objectives of the literature review, which were achieved in Chapter 2 of this dissertation, included:

- Conceptualising childhood cancer by describing the types and classification;
- Discussing the prevalence and incidence of childhood cancer in South Africa and internationally;
- Elucidating the causes of and risk factors associated with cancers of childhood;
- Identifying the treatment options utilised in the management of childhood cancer; and
- Identifying coexisting conditions and complications associated with childhood cancer and its treatment.

The subsequent paragraphs address the conclusions drawn from the literature review.

4.3.1.1 Conceptualisation of childhood cancer, types and classification

Childhood cancer was defined as cancer that occurs in children before they attain the age of 19 years (IARC, 2016). It was established that cancers that occur in children are uncommon and are distinct from those that are seen in adults, with reference to their causes, rate of growth and spread, and outcome of treatment (Murphy *et al*., 2013:95). This makes these conditions unresponsive to the risk preventive approaches that are utilised in adults (Gupta *et al*., 2014).

The literature review revealed that the development of childhood cancers stems from germline mutations or destruction of DNA induced by the exposure to a carcinogen, resulting in unrestrained cell division and growth (EPA, 2013:223). The major types of childhood cancers are classified as haematopoietic tumours, CNS tumours and other solid tumours (Murphy *et al*., 2013:95). Childhood cancers, which commonly occur in children under the age of 15 years,

were found to include leukaemias, CNS tumours, and lymphomas in decreasing order of prevalence, while those commonly found in adolescents aged 15 to 19 years are the lymphomas, followed by CNS tumours and leukaemias (NCI, 2017; Steliarova-Foucher, Colombet, Ries, Moreno *et al*., 2017:726) (refer to section 2.2).

The classification of childhood cancer has undergone several changes since Birch and Marsden (1987:622) proposed a classification system in 1987. These changes were necessitated by changes and updates in the morphological coding of cancer. The classification of childhood cancers is currently done according to ICCC-3, which employs both the topographical and morphological codes of ICD-O-3 (Steliarova-Foucher *et al*., 2005:1458). Classification is done on three levels, which are the main diagnostic group, sub-group of the major diagnostic group, and the sub-division of the subgroup (refer to section 2.3).

4.3.1.2 Global trends in the incidence and prevalence of childhood cancers

Cancers occurring in children and adolescents are rare and form only a small proportion of all cancers (Israels *et al*., 2015:607; Yang *et al*., 2014:285). Its occurrence is, however, associated with distress in both the children and their families; this, therefore, poses a critical public health concern (Steliarova-Foucher, Colombet, Ries, Moreno *et al*., 2017:719). Interventions, including increasing the awareness of childhood cancers and capacity building of countries to improve the management of childhood cancers, have been put in place in the bid to prioritise childhood cancers (WHO, 2018b). To allow for the generation of hypotheses for further studies into childhood cancer, the establishment of policies and interventions for their control, and the appraisal of such interventions, insight into the epidemiology of childhood cancers is vital (Xie *et al*., 2018:79). The epidemiology of childhood cancers in different geographical regions around the globe was extensively discussed to accomplish the aim of the study.

Variations in the incidence of childhood cancers with respect to age, gender and geographical locations were identified in the literature review. It was established from the literature that incidence rates of childhood cancers were highest in the under-five year age group and least in the 5 to 9 years age group. Leukaemia occurred more frequently in children aged younger than 15 years, followed by lymphomas, while lymphomas were the most frequently occurring malignancy in adolescents aged 15 to 19 years. More males than females were also found to be diagnosed with childhood cancers in both children aged younger than 15 years and adolescents who are 15 to 19 years old. These trends in incidence of childhood cancers with respect to gender, malignancy type and age group were found in epidemiological studies in Europe, North America, countries in Latin America and the Caribbean, Asia, Australia and South Africa (Baade *et al*., 2010:623; Ellison & Janz, 2015; Erdmann *et al*., 2015:2631; Erdmann *et al*., 2018:24;

Hossain *et al*., 2016; Hung *et al*., 2014:3548; Isaevska *et al*., 2017; Kaatsch, 2010:279; Moreno *et al*., 2013:724-725; Nakata *et al*., 2018:427; Park *et al*., 2016:872; Pesola *et al*., 2017:1866; Siegel, D.A. *et al*., 2018; Stefan *et al*., 2015:943; Steliarova-Foucher, Colombet, Ries, Hesseling *et al*., 2017; Steliarova-Foucher *et al*., 2018:1164; Ward *et al.*, 2014:86; Xie *et al*., 2018; Zheng *et al*., 2015:177) (refer to sections 2.4.1.1 to 2.4.1.5).

From the literature study, it was found that childhood cancer was not perceived to be a vital public health concern in Africa, because most countries on the continent are still striving to eradicate infectious diseases such as HIV, malaria and tuberculosis (Stefan, 2010:40; Stefan *et al*., 2017). Epidemiological studies on childhood cancers are therefore limited by the absence of reliable data, making the variations in the trends of childhood cancers unknown (Stefan 2015b:166; Sullivan *et al*., 2013:e126). Improvement has, however, been observed with the establishment of AFCRN, which is an initiative of IARC (Stefan *et al*., 2017).

Epidemiological studies in South Africa indicated that incidence rates of childhood cancer were higher in the white population, followed by children with Asian ancestry, the Coloured population and then the Black population (Erdmann *et al*., 2015:2631; Stefan *et al*., 2015:944; Steliarova-Foucher, Colombet, Ries, Hesseling *et al*., 2017). The incidence of cancers with respect to age group, gender and malignancy type in South Africa followed similar trends as those observed in most parts of the globe (Erdmann *et al*., 2015:2633; Stefan 2015b:169; Stefan *et al*., 2015:944; Steliarova-Foucher, Colombet, Ries, Hesseling *et al*., 2017) (Refer to Table 2.4 to Table 2.6).

From the various epidemiological studies around the globe, which were extensively expounded on in sections 2.4.1.1 to 2.4.1.5, it can be concluded that there are disparities in the incidence of childhood cancers with respect to age, gender and ethnicity.

4.3.1.3 Elucidating the causes of and risk factors associated with cancers of childhood

Definitive causes of childhood cancers are unknown; some environmental and genetic factors are, however, hypothesised to be linked with an elevated risk of childhood cancers (Hewitt *et al*., 2003:20). Risk factors encompass all conditions or exposures that increase a person's chance of developing a disease (refer to section 2.6). From the literature, disparities in the incidence of childhood cancers are proposed to be a result of differences in the exposure of children to these risk factors (Magrath *et al*., 2013:107). Risk factors hypothesised to be associated with cancers occurring in childhood are classified as either external or internal risk factors (Bunin, 2004:91; Linet *et al*., 2003:223).

External risk factors for childhood cancers, according to literature, include ionising and non-ionising radiations, chemicals including petrochemical solvents, pesticides and herbicides, and

infections, especially those of viral origins (refer to sections 2.6.1.1 to 2.6.1.3). Internal risk factors, on the other hand, are those factors inherent in the individual and are unmodifiable. These include age, gender, ethnicity, birth defects, high or low birth weight, presence of cancer predisposition syndromes, as well as genetic mutations (refer to sections 2.6.2.1 to 2.6.2.3).

Approximately 5% of childhood cancers are linked to syndromes that occur as a result of genetic mutations (Murphy *et al*., 2013:97). Tumour suppressor genes restrict the proliferation of cells and are, therefore, required for the prevention of the formation of tumours (Eldridge, 2019). Syndromes resulting from mutations in tumour suppressor genes have been found to be risk factors for some childhood cancers (Davidoff, 2010:229; Saletta *et al*., 2015:68). Childhood cancers arising from some of these syndromes caused by genetic mutations are indicated in Table 2.7.

From the summary of risk factors associated with childhood cancers established from the literature search, it can be deduced that although the specific causes of cancers that occur in children are not known, certain environmental exposures and genetic mutations increase the risk of childhood cancers.

4.3.1.4 Identifying the treatment options utilised in the management of childhood cancer

Current trends in the management of cancers of childhood involve chemotherapy, radiation therapy or surgical resection, either alone or in combination with the other approaches (Coura & Modesto, 2016:71; Hewitt *et al*., 2003:41; Israels *et al*., 2015:607; Ke & Shen, 2017:70; Saletta *et al*., 2014:156). Haematopoietic stem cell transplantation is employed in high-risk tumours or haematological malignancies, or as a second-line option when conventional therapies are ineffective (Armenian *et al*., 2011:1413; Ceppi *et al*., 2016; Reinfjell *et al*., 2017).

One approach of chemotherapy, which employs cytotoxic drugs, is the main treatment option for childhood cancers (Makin, 2018:184; Oduro-Dominah & Brennan, 2013:158). Cytotoxic drugs act by restricting the normal cell division process of cancer cells, which undergo rapid cell division (English, 2010:123; Payne & Miles, 2018:39). Examples of these drugs include vincristine, etoposide, doxorubicin, cisplatin and methotrexate (refer to sections 2.7.1.1.1 to 2.7.1.1.6). The non-specific action of these cytotoxic drugs on all rapidly dividing cells, including normal cells, leads to a myriad of adverse drug reactions, which include nausea and vomiting, alopecia, anaemia, neutropenia, mucositis and chemotherapy-induced peripheral neuropathy (refer to sections 2.7.1.4.1 to 2.7.1.4.6).

The non-tumour-specific action of cytotoxic drugs has resulted in the development of therapies that are aimed at targeting a specific pathway in the tumour formation process (Gore *et al*.,

2013:70; Joo *et al*., 2013:309; Payne & Miles, 2018:46; Westhoff *et al*., 2018). The tumour-specific activity of targeted therapies, therefore, leads to a reduction in the adverse drug reaction profile of these agents (Adamson, 2015:215; Gore *et al*., 2013:72; Joo *et al*., 2013:309; Palumbo *et al*., 2013:4). Examples of these agents include rituximab, gemtuzumab ozogamicin and imatinib (refer to sections 2.7.1.2.1 and 2.7.1.2.2). Asparaginase and glucocorticoids are other pharmacotherapeutic agents that are used in chemotherapy (refer to sections 2.7.1.3.1 and 2.7.1.3.2).

Radiotherapy involves the use of radiation and this approach in the management of cancer is usually done in combination with chemotherapy or surgery (Paulino, 2013a:119; Rombi *et al*., 2013). Radiation acts by either breaking the molecular bonds in RNA and DNA by providing high energy, or by producing toxic free radicals through the ionisation of the water-soluble component of tumour cells (Baskar *et al*., 2012:196; Baskar *et al*., 2014:2; Burns *et al*., 2016; Kirthi Koushik *et al*., 2013:255; Sánchez, 2015). Two main techniques are employed in radiation therapy; these include external beam radiation and internal radiation therapy. External beam radiation targets tumours through the application of high energy radiation from outside the body (Baskar *et al*., 2012:194; Kirthi Koushik *et al*., 2013:256). Examples of techniques used in external radiation therapy are intensity-modulated radiation therapy (IMRT), image-guide radiotherapy (IGRT) and sterotactic body radiation therapy (SBRT) (Baskar *et al*., 2012:195) (refer to section 2.7.2.1). Internal radiation therapy, on the other hand, involves introducing implants that contain radioactive materials into the body, either directly on the tumour or close to it (Baskar *et al*., 2012:194; Kirthi Koushik *et al*., 2013:257). Examples of this technique include low-dose-rate brachytherapy, intraoperative high-dose-rate brachytherapy and pulsed-dose-rate or high-dose-rate temporary brachytherapy (Martinez-Monge *et al*., 2006:158-159) (refer to sections 2.7.2.1 and 2.7.2.2).

Due to the effect of radiation on both tumour cells and normal tissues, radiation therapy is also characterised by a number of adverse effects which include mucositis, emesis, proctitis, cognitive dysfunction, endocrine effects and the development of secondary malignancies (Christopherson *et al*., 2014:475; Ducassou *et al*., 2015:607; Grosshans *et al*., 2018:76). Interventions to reduce radiotherapy-induced adverse effects include reduction of the total volumes of radiation, application of radiation in smaller fractions and the use of modern techniques that deliver radiation directly to the tumour while avoiding the normal tissues (Dracham *et al*., 2018:85; Paulino, 2013b, 122; Rowe *et al*., 2017). Radiation therapy, however, is usually avoided in children who are younger than three years old, due to the possible effects of the radiation on the growth and development of these children (Mukherji, 2018:37; Zaghloul, 2013:2) (refer to section 2.7.2.3).

Surgery was the main treatment option for cancers some decades ago until the discovery of chemotherapy and radiotherapy (Alcoser & Rodgers, 2003:107; Brierley & Collingridge, 2015:1187; Eden & Burns, 2015:1191). The main application of surgery in paediatric cancer treatment includes prevention, diagnosis, treatment, and as an approach in palliative care (Eden & Burns, 2015:1192; Sullivan *et al*., 2015:1193). Advancements in technology have led to the use of minimally invasive thoracoscopic and laparoscopic techniques in surgical oncology (Jackson & Kane, 2014:149; Lorenzo & Romao, 2016:180). These techniques offer the advantages of minimal post-operative pain, shorter hospital stay and reduced risk of post-operative infection (Phelps & Lovvorn, 2018; Saravanan *et al*., 2008:103; Yardley & Kenny, 2013:185) (refer to section 2.7.3).

Haematopoietic stem cell transplantation involves the infusion of progenitor stem cells to a child with compromised immunity, to activate normal haematopoietic function (Dulamea & Lupescu, 2018:945; Pulsipher *et al*., 2011:s140). The stem cells could either be from the same child, which is referred to as autologous stem cell transplantation, or from a compatible donor, which in this case is referred to as allogeneic stem cell transplantation. Complications of HSCT include infections, GVHD, secondary malignancies, transplant rejection, pulmonary, cardiovascular, renal, neurological and endocrine complications (Diab *et al*., 2016:260; Dulamea & Lupescu, 2018:946; Flinn & Gennery, 2017; Ghimire *et al*., 2017; Hierlmeier *et al*., 2018; Hoare *et al*., 2017:349) (refer to section 2.7.4).

Palliative care, which aims to improve the quality of life of children diagnosed with and on treatment for cancers, and their families, was found to be recommended for children irrespective of the prognosis of cancer (AAP, 2013:968; Bradford *et al*., 2014). This approach focuses on the physical, psychological and spiritual needs of the children and their families (Vern-Gross & Marcus, 2018:419; Weaver *et al*., 2015:829). The fundamental components of palliative care include relieving symptoms such as pain, nausea, vomiting, anxiety, psychological stress and spiritual distress (Michelson & Steinhorn, 2007:215; Postovsky *et al*., 2018:120; Rego & Nunes, 2019:279). This, therefore, requires the engagement of a multidisciplinary team that is made up of medical professionals, social workers and chaplains (Niha & Vivek, 2016). The components of palliative care were extensively discussed in section 2.7.5.

The various treatment options available for the management of childhood cancers were extensively discussed in Chapter 2, with a summary of their related adverse effects. It can be deduced that various approaches are available for the management of cancers of childhood. Each of these approaches is, however, associated with a myriad of adverse effects. Measures have therefore been put in place to reduce these adverse effects. Treatment of childhood

cancers does not only involve eradicating the tumour, but also relieving the physical symptoms, psychological distress and addressing the spiritual needs of the children and their families.

4.3.1.5 Identifying coexisting conditions and complications associated with childhood cancer and its treatment

Coexisting conditions and complications associated with childhood cancers and their treatment were extensively discussed in Chapter 2. Coexisting conditions were defined as conditions in children with cancer, which could have been present before or occurred after the diagnosis of cancer and which may or may not have been caused by cancer (Aaberg *et al*., 2016:2). It was established from the literature that, in spite of the improvement in the treatment of and increased survival of children diagnosed with cancer, these children continue to experience complications during and after treatment (Adamson, 2015:213; Armstrong *et al*., 2014:1225; Versluys & Bresters, 2016:63).

Most of the approaches used in the treatment of cancers in children, including chemotherapy, radiotherapy and HSCT, compromise the immunity of these children and put them at risk of infections (Foster *et al*., 2018; Sasada *et al*., 2016; Vento & Cainelli, 2003:595; Weaver & Samkari, 2017:67). Cancer itself also causes immunosuppression in these children (Benites *et al*., 2014:371; Weaver & Samkari, 2017:60).

Cardiovascular complications, especially cardiotoxicity, are part of the major complications arising from the treatment of childhood cancers with radiotherapy and chemotherapeutic agents (Olsen *et al*., 2014:122; Tukenova *et al*., 2010:1313; Walker *et al*., 2013:1801). Major contributing factors for cardiotoxicity were established to be the use of high doses of anthracyclines, cardiac irradiation, being female, younger age at diagnosis, and technique employed in radiation therapy (Angsutararux *et al*., 2015; Baker *et al*., 2011:1948; Boerma & Hauer-Jansen, 2011; Franco & Lipshultz, 2015:110; Hutchins *et al*., 2017:457; Loar *et al*., 2018:6; McGowan *et al*., 2017:68; Trachtenberg *et al*., 2011:343; van der Pal *et al*., 2012:1435; Walker *et al*., 2013:1806). The mechanism of anthracycline-induced cardiotoxicity and measures to prevent chemotherapy- and radiation-induced cardiotoxicity were extensively discussed in section 2.8.2.

Neurological complications arising from childhood cancer and its treatment, according to literature, are thought to be as a result of the infiltration of cancer in the CNS or due to the effects of the therapy on the CNS (Cordelli *et al*., 2017; Duke *et al*., 2018:597; Kenborg *et al*., 2018; Weaver & Samkari, 2017:60; Sleurs *et al*., 2016:38). These complications were found to include infections, neurocognitive side effects, neurovascular complications, neuropathy, visual

and auditory disturbances (Cordelli *et al*., 2017; Neil *et al*., 2016; Reddy & Witek, 2003:137; Vossough, 2017:6; Weaver & Samakri, 2017). These complications may result in alterations in treatment (Sun & Cooper, 2018:33).

Damage to DNA caused by chemotherapeutic agents and radiation, leads to necrosis of pulmonary cells, pneumonitis and lung fibrosis (Graves *et al*., 2010:201; Versluys & Bresters, 2016:64). It was established that factors associated with an increased risk of pulmonary complications resulting from childhood cancers include increased doses of radiation, co-administration of chemotherapeutic agents and radiation, and being female (Graves *et al*., 2010:203). Chemotherapeutic agents associated with pulmonary injury and measures to prevent pulmonary complications were discussed in section 2.8.4.

The effects of cancer treatment on the thyroid gland, hypothalamic-pituitary axis, bone mineral density, and normal body homeostasis, result in complications involving the endocrine system (Chemaitilly & Sklar, 2010:141; González *et al*., 2016:332; Klika *et al*., 2018; Yuen, 2015:323). These complications were found to include thyroid neoplasms, hypothyroidism, hyperthyroidism, growth hormone deficiency, deficiency in follicle-stimulating and luteinizing hormones, increased insulin resistance, osteoporosis, and osteopenia (Chemaitilly & Sklar, 2010:144; González *et al*., 2016:332; Ramanauskienė *et al*., 2014:278; Yuen, 2015:330).

The role of the kidneys in the elimination of chemotherapeutic agents from the body and the high sensitivity of the tissues of the kidney to radiation make the kidneys susceptible to toxicity from these treatment modalities (Glezerman & Jaimes, 2016; Lameire, 2014:12; Skinner, 2018:215; Valika & Shirali, 2015:66). The presence of pre-existing renal diseases, high doses of radiation and removal of tissues in nephrectomy — which leads to reduction in surface area for glomerular filtration — were found to increase the risk of renal toxicity in childhood cancers (Dawson *et al*., 2010:109; Izzedine & Perazella, 2017:505; Kern *et al*., 2014:663; Lameire, 2014:12; Ruggiero *et al*., 2017:2608; Skinner, 2018:216).

It was gathered that other complications arising from childhood cancers include secondary malignancies and ototoxicity (Berendsen *et al*., 2013:147; Choi, D.K. *et al*., 2014:1764; Clemens *et al*., 2017:470; Khan *et al*., 2018; Landier, 2016:1647). Secondary malignancies were defined as malignancies occurring after the treatment of a primary malignancy and that are histologically different from the primary cancer (Bhatia, 2015:353). These secondary malignancies were found to be as a result of the treatment modality employed in the primary malignancy (Bhatia, 2015:354; Choi, D.K. *et al*., 2014:1765). Ototoxicity, according to literature, is associated with poor academic performance, a lag in language acquisition and compromise in psychosocial functioning (Hudson *et al*., 2013:2374; Khan *et al*., 2018; Landier, 2016:1647). Risk factors for

the development of ototoxicity and secondary malignancies were discussed in sections 2.8.7.1 and 2.8.7.2, respectively.

It can be deduced from the discussion on the coexisting conditions and complications of childhood cancer that children undergoing treatment and who have completed treatment for cancers are at risk of complications in spite of the improvements in treatment and survival. Measures put in place to prevent these complications during treatment, as well as follow up of survivors must, therefore, be adhered to.

4.3.2 Conclusions of the empirical investigation

The specific objectives of the empirical investigation, which were achieved in Chapter 3 of this dissertation, included:

- Determining the incidence, prevalence and trends of childhood cancers over time, stratified according to age group, gender, type of malignancy and geographical area using a medicines claims database for the period 2008 to 2017.

- Identifying coexisting conditions among children and adolescents with cancer on the database.

Subsequent paragraphs summarise the findings and conclusions of the empirical investigations.

4.3.2.1 Determining the incidence, prevalence and trends over time of childhood cancers in children younger than 19 years, stratified according to age group, gender, type of malignancy and geographic area

A total of 173 cases of newly diagnosed cancers in children and adolescents aged below 19 years were identified in the database over the 10-year study period. This represented 0.01% of children below the age of 19 years on the database, confirming the rarity of childhood cancers (Bhakta *et al*., 2019:e42; Israels *et al*., 2015:607). The ASR of all childhood cancers over the study period was estimated to be 82.3 cases per million persons, a result higher than those reported in previous studies in South Africa (Erdmann *et al*., 2015; Stefan *et al*., 2015; Steliarova-Foucher, Colombet, Ries, Hesseling *et al*., 2017). Incidence of cancer was higher in males (112.3 cases per million persons) compared to females (51.9 cases per million persons), and this is consistent with several studies that show male preponderance in the incidence of childhood cancers (Baade *et al*., 2010:623; Bidwell *et al*., 2019; Erdmann *et al*., 2018:24; Hossain *et al*., 2016; Isaevska *et al*., 2017; Moreno *et al*., 2013; Siegel, D.A. *et al*., 2018; Stefan *et al*., 2015:943; Steliarova-Foucher, Colombet, Ries, Hesseling *et al*., 2017; Xie *et al*., 2018).

The highest age-specific incidence rate was identified in the 15<19-year age group (112.8 cases per million persons), followed by the 5-9-year age group (101.7 cases per million persons). The lowest incidence rate was identified in the <1-year age group (13.2 cases per million persons). For children aged younger than 15 years, incidence rates were highest in the 5-9 years age group. This is in contrast to the results of many studies reporting the highest incidence rate of cancers in the under-five-year age group (Bidwell *et al*., 2019; Erdmann *et al*., 2015:2631; Erdmann *et al*., 2018:24; Stefan *et al*., 2015:943).

Leukaemias were the most frequently identified childhood cancers with an ASR of 32.6 cases per million persons, followed by lymphomas and CNS neoplasms with ASRs of 11.7 and 9.1 cases per million persons, respectively. The highest ASR estimated for leukaemias is consistent with previous studies in South Africa, which indicated leukaemias as the most frequently occurring childhood cancer (Erdmann *et al*., 2015:2633; Stefan, 2015b; Stefan *et al*., 2015:944; Steliarova-Foucher, Colombet, Ries, Hesseling *et al*., 2017). Hepatic tumours were the least occurring childhood cancers during the study period, with an ASR of 0.5 cases per million persons. This is similar to the ASR of 0.9 cases per million persons reported in all previous studies of childhood cancers in South Africa (Erdmann *et al*., 2015:2633; Stefan *et al*., 2015:944; Steliarova-Foucher, Colombet, Ries, Hesseling *et al*., 2017).

The KwaZulu-Natal Province recorded the highest incidence rates of childhood cancers among the provinces of South Africa, with a rate of 193.4 cases per million persons. This was followed by Gauteng and the Free State, with incidence rates of 102.3 and 76.0 cases per million persons, respectively. The postal codes of prescribers were used as a proxy measure for the geographic location of patients (where patient received treatment) since information on geographic location of patients is not recorded in the database. Most oncologists have their practices located in the metropolitan municipalities which are mostly located in the KwaZulu-Natal, Gauteng, Free State and Western Cape Provinces. The higher incidence rate of cancers in KwaZulu-Natal, Gauteng and the Free State on the database may, therefore, not necessarily indicate a high incidence of cancer in those provinces as patients may travel to those provinces for cancer care.

The incidence of childhood cancers decreased from 76.7 cases per million persons in 2008 to 58.2 cases per million persons in 2017, peaking at 120.3 cases per million persons in 2013 (refer to manuscript 1). The joinpoint regression analysis of the trends in incidence of all cancers showed an APC of 9.53% (95%CI: -2.9–23.6) from 2008 to 2015, and -27.0% (95%CI: -70.5–80.3) from 2015 to 2017. Similar results were recorded in the trend analysis of leukaemias, with an APC of 10.67% (95%CI -2.9–26.2) from 2008 to 2015 and -25.0% (95%CI -71.9–99.8) from 2015 to 2017. It can be concluded that the incidence of childhood cancers in the section of

private health sector studied is highest in adolescents, higher in males, and is largely driven by leukaemias.

Prevalence rates of childhood cancers increased from 9 cases per 100 000 persons in 2008 to 13.3 cases per 100 000 persons in 2017, representing a 47.8% increase in the prevalence of cancers over the study period (refer to Table 3.3). With the exception of 2008, cancers were more prevalent in males as compared to females, with between 62.5% and 88.6% of cancers identified in males in the remaining years of the study. The highest prevalence rate of cancers was identified in the 5-9 year age group in six out of the 10 years under study, with rates ranging from 16.1 to 36.3 cases per 100 000 persons. Again, with the exception of 2008 in which carcinomas and melanomas were the most prevalent childhood cancer, leukaemias were consistently the most prevalent cancers among the main diagnostic groups from 2009 to 2017. The prevalence of leukaemias with respect to the other diagnostic groups of childhood cancers increased from 25% in 2008 to 43.8% in 2017. KwaZulu-Natal recorded the highest prevalence rates of childhood cancers among the provinces of South Africa in seven out of the 10 years under study, with prevalence rates ranging from 27.7 cases per 100 000 persons to 39.2 cases per 100 000 persons (refer to section 3.3). It should, however, be noted that prescriber codes were used as proxy for geographic location (where patient received treatment) of patients and, therefore, the highest prevalence rate of cancer in KwaZulu-Natal in the database may not reflect the actual prevalence in this province.

4.3.2.2 Identifying the common coexisting conditions among children and adolescents with cancer on the database

All 173 patients diagnosed with cancers from 2008 to 2017 on the database claimed at least one non-cytotocxic medication over the study period. A total of 2 631 non-cytotoxic medicine items were claimed for these patients. Of these, 86.4% were claimed under non-specified diagnostic codes, which included codes for repeat prescriptions (Z76.0), refusal of patient or clinician to disclose clinical information (U98.0 and U98.1) and encountering of health services in unspecified conditions (Z76.9). Specific ICD-10 diagnostic codes associated with medicine claims included those for diseases of the respiratory system (7.15%), gastrointestinal tract (1.60%), skin disorders (0.95%) and musculoskeletal disorders (0.91%) (refer to section 3.4, Table 2). A DU90% analysis on medicine items associated with non-specific diagnostic codes indicated that antimicrobials, respiratory system agents, analgesics, ENT agents, GIT agents, CNS agents, autacoids, dermatological agents, endocrine agents, herbal preparations, musculoskeletal agents and anaesthetics, in order of decreasing frequencies, made up approximately the top 90% medicine items claimed under these codes (refer to section 3.4, Table 3). Asthma (J45.9), essential hypertension (I10), major depressive disorders (F32.2 and

F32.3), anxiety disorders (F41.9) and epilepsy (G40.2) were the chronic conditions associated with medicine claims over the study period. These diagnostic codes were associated with only 0.38% (n = 10) of the total medicine items.

Analysis of the main pharmacological groups of all medicine claims indicated that 17.40% (n = 458), 13.91% (n = 366) and 10.64% (n = 280) of the total medicine items were antimicrobials, respiratory agents and analgesics, respectively, according to the MIMS classification (Snyman, 2019). Patients mostly received beta-lactams, cough and cold preparations, and combination analgesic products, among the antimicrobials, respiratory agents and analgesics respectively (refer to section 3.4, Table 4). The prevalent use of antimicrobial agents among the 22 pharmacological classes of medicines could be attributed to a high prevalence of microbial infections in the study population. This is in agreement with some studies that found a high prevalence of infectious episodes in children undergoing cancer chemotherapy (Af Sandeburg *et al*., 2017), and this could be attributed to the immunosuppression associated with most chemotherapeutic agents (Steele, 2012:202).

Among the infections commonly present in children undergoing chemotherapy, viral infections of the respiratory system, which are characterised by symptoms such as colds, coughs and fever, are the most prevalent (Hakim *et al*., 2016:804; Kou *et al*., 2018:276; Meissner, 2016:62; Tregoning & Schwarze, 2010:74). This could explain the high prevalence of respiratory system agents after antimicrobials in this study and the prevalent use of cough and cold preparations among respiratory system agents.

A total of 2 160 medicine items, representing 82.10% of medicine items claimed over the study period, were reimbursed from patients' acute benefits, and less than 1% of these medicines from patients' chronic benefits. This indicates that most of the coexisting conditions present in children undergoing cancer chemotherapy were acute conditions.

It can be concluded from the overall findings of this study that most medicine claims are associated with non-specific ICD-10 diagnostic codes and the majority of these medicine items are utilised for the management of acute conditions.

4.4 Study strengths and limitations

External validity of the study was limited in that the study population was drawn from the database of only one PBM company in South Africa and, therefore, results cannot be generalised to the entire population of South Africa. Again, although the results of the study indicated higher incidence rates of childhood cancers than previous studies in South Africa, under-ascertainment is possible since data used were only those from paid claims. Patients with

cancers that are not PMBs, and who do not have comprehensive health plans with oncology benefits would have to make out-of-pocket payments for their medications, which will not be captured in the database. The use of prescriber codes as a proxy for the geographic location of patients has the potential of introducing bias into the analysis of geographical trends. Most medical aid schemes require beneficiaries to consult specific oncologists who may have their practices located in different provinces from those in which beneficiaries reside. Interpretation of results on the geographical variation must, therefore, be done with caution.

The majority of medicine claims for non-cytotoxic medications were associated with non-specific ICD-10 codes, especially Z76.9 (encountering health services in unspecified conditions). This, together with the absence of clinical data, limited the estimation of the prevalence of coexisting conditions in the study population, as some medicine items may be used for secondary indications or off-label. Furthermore, medicine items used by the study population, which are not covered under the health plan for which they are subscribed to on their medical schemes, are not reimbursed and will, therefore, not be included in the database. Under-ascertainment of the prevalence of the use of the various pharmacological classes is likely because data used for this study were reimbursed claims.

Notwithstanding these limitations, this study represents the first epidemiological study into childhood cancers to be carried out in the private health sector of South Africa using a medicines claims database, to the knowledge of the researchers. The results obtained provide baseline information on the epidemiology of childhood cancers and coexisting conditions in children and adolescents with cancer in a section of the private health sector of South Africa. Another strength of this study also centres on the use of administrative database as these databases are acknowledged resources for pharmacoepidemiological, drug utilisation and health services research (Chini *et al*., 2011; Toh *et al*., 2013:124). The database used in this study contains medicine claims for patients from all provinces in South Africa. The PBM company which provided data for this study has in place eligibility checks and audits, which ensure reliable and valid data for research purposes (refer to paragraph 1.4.6).

4.5 Recommendations

Recommendations proposed from this study include the following:

- Further studies describing the current epidemiological trends of childhood cancers in the whole of South Africa should be carried out. This could help in predicting future incidence rates and the implementation of childhood cancer control strategies.

- A study into the survival trends of childhood cancers using data over a longer period will help to better understand the overall burden of childhood cancers in South Africa and possibly predict future survival rates.
- Interventions should be put in place to encourage prescribers to indicate specific ICD-10 diagnostic codes on prescriptions to facilitate pharmacoepidemiological studies.
- With high prevalent use of antibiotics among children on treatment for cancer, antibiotic stewardship programmes should be incorporated into cancer care to curb antibiotic resistance in these patients.

4.6 Chapter summary

This final chapter of the dissertation provided a detailed summary of the findings of the study and correlated the findings with the outlined objectives of the study. The strengths and limitations of the study were outlined and recommendations for further studies were also proposed.

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ANNEXURE A: GLOBAL INCIDENCE OF CHILDHOOD CANCER

Table A1: Incidence of childhood cancers in some countries across the globe

Country	Period	Number of new cases in the various age groups (in years)					Total number of new cases
		<1	1-4	5-9	10-14	15-19	
Algeria	1996-2014	54	575	463	566	982	**2 640**
Argentina	2000-2013	1 706	6 369	4 991	5 001	–	**18 067**
Australia	1992-2014	1 357	4 884	3 211	3 738	7 318	**20 508**
Botswana	1999-2007	6	93	111	102	138	**450**
Brazil	1995-2012	189	874	770	770	1 255	**3 858**
Cameroun	2004-2006	5	79	120	94	75	**373**
Canada	1992-2013	1 910	6 568	4 606	5 225	9 087	**27 396**
China	1990-2013	677	2 308	1 697	2 382	4 124	**11 188**
Egypt	1999-2010	105	599	564	544	785	**2 597**
England	1990-2013	2 810	11 098	7 753	8 158	12 693	**42 512**
France	2000-2012	2 437	7 761	5 935	6 451	–	**22 584**
France Reunion	1990-2011	31	162	133	133	198	**657**
Germany	1996-2012	3 169	10 557	8 310	8 734	–	**30 770**
India	1990-2013	469	5 384	5 167	5 220	6 430	**22 670**
Italy	1992-2013	699	2 435	2 015	2 368	4 146	**11 663**
Japan	1990-2013	1 135	2 492	1 967	2 161	2 809	**10 564**
Kenya	2000-2012	25	375	382	383	455	**1 620**
Libya	2003-2008	13	129	96	80	102	**420**
Mali	2005-2014	16	466	360	316	312	**1 470**
Mauritius	2001-2013	4	144	103	118	182	**551**
Morocco	2005-2012	54	384	337	371	542	**1 688**
South Africa	1998-2012	777	3 864	2 877	2 182	–	**9 700**
Tunisia	1993-2007	53	571	569	637	882	**2 712**
Uganda	1996-2013	48	540	707	582	617	**2 494**
U.S.A	1998-2012	15 384	5 125	36 853	42 523	70 726	**216 741**
Zimbabwe	1995-2013	61	371	337	313	372	**1 454**

Adapted from IICC-3 (Steliarova-Foucher, Colombet, Ries, Hesseling *et al*., 2017).

ANNEXURE B: CERTIFICATE OF ETHICS APPROVAL

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South Africa 2520

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Fax: 018 299-4910
Web: http://www.nwu.ac.za

Research Ethics Regulatory Committee
Tel: 018 299-4849
Email: nkosinathi.machine@nwu.ac.za

ETHICS APPROVAL LETTER OF STUDY

Based on approval by the North West University Health Research Ethics Committee (NWU-HREC) on 08/10/2018, the NWU Health Research Ethics Committee hereby approves your study as indicated below. This implies that the North-West University Research Ethics Regulatory Committee (NWU-RERC) grants its permission that, provided the special conditions specified below are met and pending any other authorisation that may be necessary, the study may be initiated, using the ethics number below.

Study title: Pharmacoepidemiology of childhood cancer in the private health sector of South Africa.
Study Leader/Supervisor (Principal Investigator)/Researcher: Prof JR Burger
Student: MN Otoo

Ethics number:

N	W	U	-	0	0	1	7	9	-	1	4	-	A	1	-	0	8
Institution				Study Number						Year			Status				

Status: S = Submission; R = Re-Submission; P = Provisional Authorisation; A = Authorisation

Application Type: Sub study
Commencement date: 2018/10/08 **Risk:** Minimal
Expiry date: 2019/10/31
Approval of the study is initially provided for a year, after which continuation of the study is dependent on receipt and review of an annual (or as otherwise stipulated) monitoring report and the concomitant issuing of a letter of continuation.

Special in process conditions of the research for approval (if applicable): None

General conditions:
While this ethics approval is subject to all declarations, undertakings and agreements incorporated and signed in the application form, the following general terms and conditions will apply:

- *The study leader/supervisor (principle investigator)/researcher must report in the prescribed format to the NWU-HREC:*
  - *annually (or as otherwise requested) on the monitoring of the study, whereby a letter of continuation will be provided, and upon completion of the study; and*
  - *without any delay in case of any adverse event or incident (or any matter that interrupts sound ethical principles) during the course of the study.*
- *The approval applies strictly to the proposal as stipulated in the application form. Should any amendments to the proposal be deemed necessary during the course of the study, the study leader/researcher must apply for approval of these amendments at the NWU-HREC, prior to*

implementation. Should there be any deviations from the study proposal without the necessary approval of such amendments, the ethics approval is immediately and automatically forfeited.

- *Annually a number of studies may be randomly selected for an external audit.*
- *The date of approval indicates the first date that the study may be started.*
- *In the interest of ethical responsibility the NWU-RERC and NWU-HREC reserves the right to:*
  - *request access to any information or data at any time during the course or after completion of the study;*
  - *to ask further questions, seek additional information, require further modification or monitor the conduct of your research or the informed consent process;*
  - *withdraw or postpone approval if:*
    - *any unethical principles or practices of the study are revealed or suspected;*
    - *it becomes apparent that any relevant information was withheld from the NWU-HREC or that information has been false or misrepresented;*
    - *submission of the annual (or otherwise stipulated) monitoring report, the required amendments, or reporting of adverse events or incidents was not done in a timely manner and accurately; and / or*
    - *new institutional rules, national legislation or international conventions deem it necessary.*
- *NWU-HREC can be contacted for further information or any report templates via Ethics-HRECApply@nwu.ac.za or 018 299 1206.*

The NWU-HREC would like to remain at your service as scientist and researcher, and wishes you well with your study. Please do not hesitate to contact the NWU-HREC or the NWU-RERC for any further enquiries or requests for assistance.

Yours sincerely

Prof Wayne Towers
Chair NWU Health Research Ethics Committee

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3 December 2018

File reference: 9.1.5.4.2

ANNEXURE C: AUTHOR GUIDELINES FOR CANCER EPIDEMIOLOGY

ELSEVIER

CANCER EPIDEMIOLOGY

Cancer determinants, prevention, prognosis and outcomes

AUTHOR INFORMATION PACK

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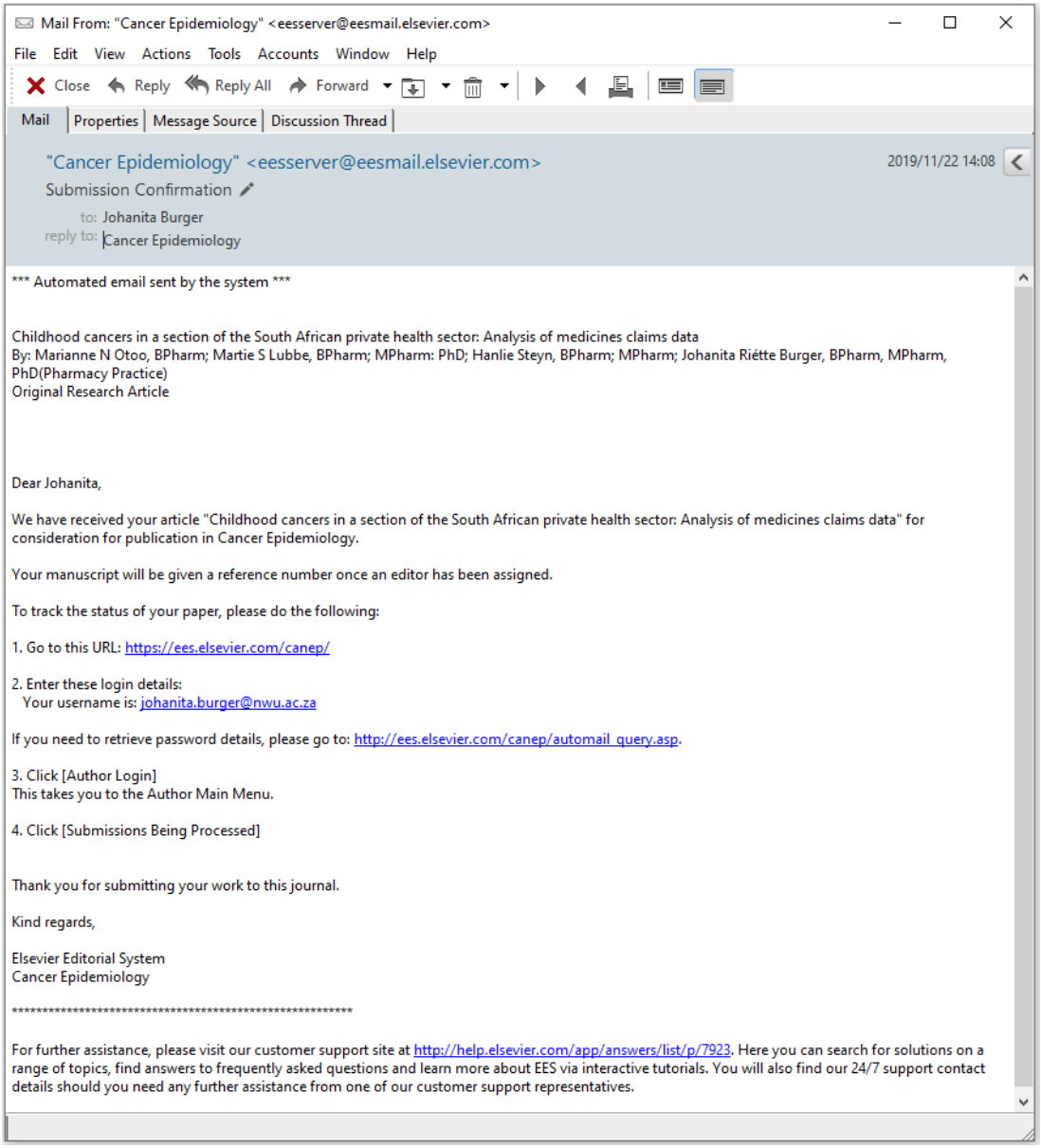
There are no strict formatting requirements but all manuscripts must adhere to the word limits for manuscripts set out above and contain the essential elements needed to convey your manuscript, for example Abstract (of no more than 250 words), Keywords, Introduction, Materials and Methods, Results, Conclusions, Artwork and Tables with Captions. If your article includes any Videos and/or other Supplementary material, this should be included in your initial submission for peer review purposes. Divide the article into clearly defined sections.

ANNEXURE D: PROOF OF SUBMISSION OF MANUSCRIPT 1



Mail From: "Cancer Epidemiology" <eesserver@eesmail.elsevier.com>

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Close Reply Reply All Forward

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"Cancer Epidemiology" <eesserver@eesmail.elsevier.com> 2019/11/22 14:08

Submission Confirmation

to: Johanita Burger

reply to: Cancer Epidemiology

*** Automated email sent by the system ***

Childhood cancers in a section of the South African private health sector: Analysis of medicines claims data
By: Marianne N Otoo, BPharm; Martie S Lubbe, BPharm; MPharm: PhD; Hanlie Steyn, BPharm; MPharm; Johanita Riétte Burger, BPharm, MPharm, PhD(Pharmacy Practice)
Original Research Article

Dear Johanita,

We have received your article "Childhood cancers in a section of the South African private health sector: Analysis of medicines claims data" for consideration for publication in Cancer Epidemiology.

Your manuscript will be given a reference number once an editor has been assigned.

To track the status of your paper, please do the following:

1. Go to this URL: https://ees.elsevier.com/canep/

2. Enter these login details:
Your username is: johanita.burger@nwu.ac.za

If you need to retrieve password details, please go to: http://ees.elsevier.com/canep/automail_query.asp.

3. Click [Author Login]
This takes you to the Author Main Menu.

4. Click [Submissions Being Processed]

Thank you for submitting your work to this journal.

Kind regards,

Elsevier Editorial System
Cancer Epidemiology

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For further assistance, please visit our customer support site at http://help.elsevier.com/app/answers/list/p/7923. Here you can search for solutions on a range of topics, find answers to frequently asked questions and learn more about EES via interactive tutorials. You will also find our 24/7 support contact details should you need any further assistance from one of our customer support representatives.

ANNEXURE E: AUTHOR GUIDELINES FOR JOURNAL OF EPIDEMIOLOGY AND GLOBAL HEALTH

Author Guidelines

Introduction

The *Journal of Epidemiology and Global Health* (JEGH) is an open access, peer-reviewed, multidisciplinary journal which aims to impact global epidemiology and international health with articles focused on innovative scholarship and strategies to advance global health policy. The journal seeks to improve regional and global health by informing efforts to reduce the risk of communicable and non-communicable diseases and takes special interest in publishing rigorous assessments of policies which have been implemented based on epidemiological and public health research. We welcome original studies (laboratory, epidemiological or clinical), reviews, perspectives and commentaries from all aspects of communicable and non-

communicable diseases, in particular those identified as priorities by the World Health Assembly. The journal does not accept case reports and submissions purely focused on basic (bench) science.

Manuscript Submission Checklist

Before you submit your manuscript to the journal for review, please ensure that all the items listed below have been checked and uploaded with your submission. In case you require more information about any of the items in this list, please refer to the relevant section in these Author Guidelines or contact the Publisher directly at author-support@atlantis-press.com.

- A title page which shows: (i) a concise and informative article title; (ii) the name(s) of the Author(s); (iii) the affiliation(s) and complete permanent address(es) of the Author(s) – the address at which the research was conducted must be kept as the main affiliation address; any current address (if different) can be included as a footnote to the Author's name; (iv) clear indication of the designated Corresponding Author with contact details including email address, full postal address and telephone number (including country code); (v) a total word count for the article; and (vi) a total table and figure count for the article.
- Keywords have been included in the manuscript.
- All figures (including relevant captions).
- All tables (including title, description, footnotes).
- All figure and table citations in the text match the files provided.
- References are in accordance with the journal reference style.
- All references mentioned in the reference list are cited in the text and vice versa.
- Author Declaration of Potential Conflict form. *Note that this competing interest declaration needs to be provided, even if the Author(s) have no competing interests to declare.*
- Data Availability Statement.
- Any supplementary files/materials (where applicable).
- Manuscript has been "spell checked" and "grammar checked" in the word processor tool used.
- Permission has been sought and obtained for the use of copyrighted materials from other sources (including the Internet).

- Referee suggestions and contact details have been provided as per the journal's requirements.
- Journal policies detailed in these Author Guidelines have been reviewed.

Article Types

The *Journal of Epidemiology and Global Health* (JEGH) publishes a range of article types with the following specifications:

- **Research Article**. A research article describes an original study which is of interest to the readership of the journal. *Specifications: unstructured abstract required of max. 250 words, main body of text (i.e. excluding abstract, tables, figures and references) not to exceed 4,000 words, max. 8 tables and/or figures, max. 100 references.*
- **Review Article**. A review article is a comprehensive and balanced survey of recent developments in a given field which is of interest to the readership of the journal. Review articles are often commissioned, although pre-submission enquiries for reviews are also welcome. *Specifications: unstructured abstract required of max. 250 words, main body of text (i.e. excluding abstract, tables, figures and references) not to exceed 6,000 words, max. 12 tables and/or figures, max. 150 references.*
- **Perspective**. A perspective is intended to provide a forward-looking and/or speculative approach to a given research topic which is of interest to the readership of the journal. Perspectives should always remain balanced and aim to stimulate discussion within the relevant research community. Pre-submission enquiries for perspectives are encouraged. *Specifications: unstructured abstract required of max. 150 words, main body of text (i.e. excluding tables, figures and references) not to exceed 2,000 words, max. 2 tables and/or figures, max. 15 references.*
- **Correspondence**. A correspondence is a concise communication which provides a forum to address new or hot issues which are relevant to the readership of the journal. *Specifications: no abstract required, main body of text (i.e. excluding tables, figures and references) not to exceed 1,200 words, max. 2 tables and/or figures, max. 20 references.*
- **Commentary**. A commentary is a short manuscript that provides information about a recent development or innovation in the field or opinions on unresolved and timely issues. The nature of such an article lends itself to opinion, thus appropriate evidence should be provided, excessive speculation should be avoided and the topic should be of interest to the readership of the journal. *Specifications: no abstract required, main body*

of text (i.e. excluding tables, figures and references) not to exceed 1,500 words, max. 2 tables and/or figures, max. 10 references.

- **Letter to the Editor**. This is a letter addressed to the Editor which is related to an article published in the journal. It must be submitted within 6 weeks of online publication (under no circumstances will exceptions be made). The Editor may choose to invite the Authors of the article in question to write a correspondence reply. Such letters are not appropriate for publishing new data without peer review. *Specifications: no abstract required, main body of text (i.e. excluding tables, figures and references) not to exceed 1,000 words, max. 2 tables and/or figures, max. 10 references.*

Submission Process

Manuscripts are submitted to the *Journal of Epidemiology and Global Health* using the Editorial Manager online submission and peer review system. Please click on the Submit your Paper button in the left-hand menu on the journal homepage for a link to access this system. Instructions will be provided on screen for uploading all the relevant information and files associated with your submission. All manuscripts must be in the English language and Authors are advised to ensure clarity, brevity and accuracy of the information provided.

Note that the submission of a manuscript means that the research described has not been published previously in other journals, that it is not under consideration for publication elsewhere, that its publication is approved by all Authors – either tacitly or explicitly – and by the responsible authorities where the work was carried out, and that upon acceptance the article will not be published elsewhere in the same form, either in English or in any other language, including in any electronic medium, without the written permission of the journal owner. The editorial team of the *Journal of Epidemiology and Global Health* verifies the originality of submitted manuscripts using similarity detection software.

Submission to the journal proceeds in an online environment only where Authors will be stepwise guided through the process of entering article details and uploading submission files. The online submission system automatically converts all source files into a single PDF file which is used in the peer review process. Please note that even though source files are converted to PDF at submission, the original editable files (e.g. in Word or LaTeX) are still needed for further processing and typesetting after acceptance. All correspondence, including notification of the Editor's decision and requests for revision, is sent via email.

Open Researcher and Contributor ID (ORCID)

The *Journal of Epidemiology and Global Health* supports ORCID in its publication workflow, enabling researchers to apply for a unique ID which is connected to their work. Similar to DOIs for articles, ORCID for Authors will help researchers to distinguish their research from others, to get appropriate recognition and to enhance the discovery of their work. Corresponding authors are required to register for an ORCID identifier (free of charge) and to link this identifier to their submission. Any co-authors are encouraged to do the same.

If you have registered with ORCID, you can link your personal ID to your existing Editorial Manager account by going to your account details and entering your ORCID identifier. After you validate and confirm your details, you will be directed to the ORCID website to sign in (make sure you have your username and password ready). You will then be requested to agree to attach your ORCID details to your Editorial Manager account. In the event that the number is invalid (you will see a red cross next to the ORCID identifier) you can click on the link to “Update ORCID iD” and follow the instructions to authorize the link between the journal submission system and your ORCID iD.

Manuscript Preparation

Use of Word Processing Software

It is important that your manuscript text file is saved in the native format of the word processor used. The text should be in a single-column format and the layout should be kept as simple as possible. Most formatting codes will be removed and replaced on processing the article. In particular, do not use the word processor’s options to justify text or to hyphenate words. However, you can use bold face, italics, subscripts, superscripts, etc. When preparing tables, if you are using a table grid, use only one grid for each individual table and not a grid for each row. If no grid is used, use tabs and not spaces to align columns. Note that source files of figures, tables and text graphics will be required regardless of whether you embed your figures in the text or not. To avoid unnecessary errors you are strongly advised to use the “spell-check” and “grammar-check” functions of your word processor.

LaTeX Submissions

Manuscripts, for example those which contain a lot of mathematical formulas, can also be submitted in LaTeX. All source files that are uploaded to the submission system will be automatically compiled into a single PDF file to be approved by the Author at the end of the submission process. While the compiled PDF will be used during peer review, the uploaded source files will be sent to the Publisher for publication upon acceptance. Please do not use

subfolders for your LaTeX submission, e.g. for figures or bibliographic files. Should you require additional technical information for uploading and compiling your LaTeX submission, please refer to the following resource: http://www.editorialmanager.de/pdf/latex.

Article Structure and Organization

Cover Letter

Including a cover letter with your submission gives you a chance to convince the Editors that your article is suitable for publication in the journal and of importance to its readership. A cover letter should be no more than two pages long and should include all the standard elements which are to be expected in an official letter (for example, the date and the address of the recipient, etc.). The Author(s) should confirm that the submission is original (include the title of the manuscript and the journal name) and not under consideration for publication in another journal. Furthermore, you should briefly mention the focus of the manuscript (no more than 4-5 sentences). Note that while we ask the Author(s) to provide competing interest information separately, you are welcome to also include this information in the cover letter.

Abstract

The abstract of your article should briefly state the purpose of the research, the main results and the major conclusions. An abstract is often presented separately from the article, so it must be able to stand alone. It should therefore not contain any undefined abbreviations or unspecified references. If references are still deemed essential, then cite the Author(s) and year(s). Also, if non-standard or uncommon abbreviations cannot be avoided they must be defined at their first mention in the abstract itself.

Keywords

Immediately after the abstract, provide a maximum of 7 keywords, using American-English spelling and avoiding general and plural terms and multiple concepts (for example, avoid “and”, “of”, etc.). Also avoid using abbreviations unless they are firmly established in the field. Note that these keywords will be used for indexing purposes.

Subdivision – Numbered Sections

Divide your article into clearly defined and numbered sections. Subsections should be numbered 1.1 (then 1.1.1, 1.1.2, ...), 1.2, etc. Note that the abstract should not be included in the section numbering. Use the section numbering also for internal cross-referencing: do not just refer to 'the text'. Any subsection may be given a brief heading. Each heading should appear on its own separate line.

Abbreviations

Abbreviations which are non-standard in the field should be defined at their first mention in the text and used consistently thereafter. Definitions can be placed in a footnote on the first page of the article.

Introduction

An introduction should state the objectives of the work and provide an adequate background. Make sure you explain the nature of the problem and provide the context of why the work is important. Avoid a detailed literature survey or a summary of the results and make sure you include all the relevant references.

Materials and Methods

This section is important to allow reproducibility of your work by an independent researcher. You should therefore provide sufficient details and a description of the techniques and equipment used. Standard techniques and methods used during the work should just be mentioned at the beginning of the section and descriptions of these are not needed. Methods that are already published should be summarized and indicated by a reference. If quoting directly from a previously published method, use quotation marks and cite the source. Any modifications to existing methods should also be described. If lengthy descriptions of experimental procedures are required, the Authors are encouraged to include them in a supplementary file. Where applicable, Authors must confirm whether all ethical approvals for a procedure have been obtained. For clinical trials, Authors have to clarify the study design (prospective, retrospective or other).

Results

Present your results and experimental data in a clear, consistent and concise manner. Only essential results should be included in the text and only points which are important for the discussion should be highlighted. Do not attempt to hide data; any secondary data can be included in a supplementary file.

Discussion

This section should contain an interpretation of what the results mean and explore their significance. Highlight the impact of your results compared with recent work and relate it back to the problem or original question in your study. Do not repeat the results in this section and avoid extensive citations or a discussion of published literature.

Conclusion

The main conclusions of the study may be presented in a short Conclusions section. Recommendations or plans for future studies can be included in this section as well.

Competing Interests

All Authors must disclose any financial and personal relationships with other people or organizations that could inappropriately influence or bias their work. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications or registrations, and grants or other funding. The *Journal of Epidemiology and Global Health* follows the recommendations of the International Committee of Medical Journal Editors (ICMJE) with regard to Authors' responsibilities for reporting conflicts of interest. Authors submitting to the journal are required to complete an *Author Declaration of Potential Conflict* form and upload it as a mandatory submission item together with their manuscript. Any potential competing interests must also be mentioned in an explicit statement within the manuscript itself: this statement should describe all potential conflicts of interest (or lack thereof) for each contributing Author.

Contributors

Each Author is encouraged to declare his/her individual contribution to the work submitted: all Authors should have materially participated in the research and/or article preparation and as such the roles of each Author should be clearly described. The statement that all Authors have approved the final article should be true and included in the disclosure. For more information, please refer to the Author Statement of Contribution section in the Atlantis Press Submission & Author Guidelines policy.

Role of Funding Source

Authors are required to disclose and list any parties which have made a financial contribution to the research and/or the preparation of the article and to briefly describe the role that such party may have had in the work (if any). If the funding source(s) had no involvement in the work beyond providing a financial contribution, then this should be explicitly stated as well.

Acknowledgements

Where applicable, Authors can collate a list of grants, funds and/or individuals who provided help during the research or writing of the manuscript in a separate Acknowledgements section at the end of the article before the references. Names of funding organizations should be written in full. Do not include acknowledgements on the title page, as a footnote to the title or otherwise.

Research Data

The *Journal of Epidemiology and Global Health* encourages Authors to deposit their research data in a relevant data repository and to cite and link to this dataset in their article. In cases where data sharing is not possible for some reason, Authors are requested to make a statement to explain why the research data cannot be shared. Authors are required to provide a *Data Availability Statement* along these lines as a mandatory item in the submission process. For more information, please refer to the Research Data Policy section in the Atlantis Press Transparency & Research Data policy.

Figure Captions

Authors must ensure that each illustration has a caption. Captions must be supplied separately and not attached to the figure itself. A caption should comprise a brief title (not on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum, but explain all symbols and abbreviations used. Note that captions should contain the figure number as cited in the text.

Tables

Tables should be numbered consecutively in accordance with their appearance in the text and cited accordingly. They can be placed either next to the relevant text in the article or on separate pages at the end. For each table, please supply a caption consisting of the table number, a brief title and a description of the data shown in the table. Any previously published material must be identified by providing the original source in the form of a reference at the end of the table caption after ensuring that permission has been sought from the copyright owner (where required). Any footnotes to tables should be indicated by superscript lower-case letters and placed below the table body. Tables should be submitted as editable text and not as images. Avoid using vertical rules and shading in table cells and make sure that the data presented in a table does not duplicate results described elsewhere in the article.

References

Authors are responsible for the accuracy of the references used. References should be numbered consecutively in the order in which they are first cited. References used in tables or figure captions must be numbered in sequence with those in the text.

- *Citations in text*. Please ensure that every reference cited in the text is also present in the reference list and vice versa. Any references cited in the abstract must be specified in full. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If such references are included in the

reference list they should follow the standard reference style of the journal and should include a substitution of the publication date as either ‘Unpublished results’ or ‘Personal communication’. Citation of a reference as ‘in press’ implies that the item has been accepted for publication.

- *Web references*. As a minimum, the full URL should be given and the date when the reference was last accessed. Any further information, if available (e.g. DOI, author names, dates, reference to a source publication, etc.) should also be mentioned. Web references can be listed separately under a different heading, if desired, or can be included in the reference list as well.
- *References in a special issue*. Please ensure that the words ‘this issue’ are added to any references in the list (and any citations in the text) to other articles in the same special issue.
- *Citing Research Data*. Datasets, program code and other methods should be recognized as original intellectual contributions and afforded recognition through citation. The journal therefore encourages Authors to appropriately cite underlying or relevant datasets in their manuscript by citing them in the text and including a data reference in the reference list. Data references should include the following elements: author name(s), dataset title, data repository, version (where available) and year. References to datasets and program code should also include a persistent identifier (e.g. a DOI). Persistent identifiers ensure future access to published digital objects and are assigned to datasets by digital archives, such as institutional repositories, or by partners in various digital preservation initiatives (e.g. Data-PASS).

Reference Style

In text: Designate references by number(s) in square brackets in line with the text. The actual Author(s) can be mentioned, but the reference number(s) must always be included.

In reference list: Number the references (with numbers in square brackets) in the list in the order in which they appear in the text.

Example of reference to a journal publication:

[1] Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. N Engl J Med. 2002; 347(4):284-7.

Example of reference to a book:

[2] Lawhead JB, Baker MC. Introduction to veterinary science, 2nd edition. Cengage Learning, Boston (MA), 2008.

Example of reference to a chapter in an edited book:

[3] Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93-113.

Example of web reference:

[4] Abrams EM, Becker AB, Gerstner TV. Anaphylaxis related to avocado ingestion: a case and review. Allergy, asthma & clinical immunology [Internet], 2011, Volume 7:12, DOI: https://doi.org/10.1186/1710-1492-7-12. Available from: BioMed Central.

Example of research data citation:

[5] Campbell A, Robert K. American national election study, 1948. ICPSR07218v3 [dataset]. Ann Arbor (MI): Inter-university consortium for political and social research [distributor], 1999. DOI: http://doi.org/10.3886/ICPSR07218.v3.

Notes:

- Note the shortened form for last page numbers, e.g. 284-7 in the first example above.
- In case of more than 6 Authors, the first 6 Authors should be listed followed by “et al.”.
- For further details on this reference style, please refer to “Uniform Requirements for Manuscripts Submitted to Biomedical Journals” (J Am Med Assoc. 1997; 277:927-934) and Samples of Formatted References for Authors of Journal Articles.

Supplementary Materials

The journal accepts electronic supplementary materials – such as applications, presentations, data sheets, images and sound clips – to support and enhance the circulation and presentation of your research. Submitted supplementary items will be published exactly as they are received (Excel and PowerPoint files will appear as such online) alongside the electronic version of the article. Please submit your supplementary materials together with the article and provide a concise and descriptive caption for each supplementary file. If you wish to make changes to supplementary materials during any stage of the publication process, please make sure to provide an updated file. Do not annotate any corrections on a previous version. Please switch off the ‘Track Changes’ option in Microsoft Office files as these will appear in the published version.

Footnotes

Footnotes can be used to give additional information and may include citations of references included in the reference list. They should be numbered consecutively throughout the article. Many word processors can build footnotes into the text and this feature may be used. If this is not the case, please indicate the position of footnotes in the text and list the footnotes themselves separately at the end of the article. Do not include footnotes in the reference list. Footnotes cannot contain a table or a figure. Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and placed below the table body instead. Footnotes to the title or Authors of an article are not given reference symbols. Authors are advised to always use footnotes instead of endnotes.

Journal Abbreviations

Journal names should be abbreviated according to:

- ISSN International Centre's "LTWA" (List of Title Word Abbreviations): https://www.issn.org/services/online-services/access-to-the-ltwa/
- Index Medicus journal abbreviations: http://www2.bg.am.poznan.pl/czasopisma/medicus.php?lang=eng

Referees

Together with your manuscript, please submit the names, institutional addresses and email addresses of at least three potential referees which would be qualified to review your article. Make sure to exclude reviewers with grounds for potential bias. Note that the Editor(s) of the journal retain(s) the sole right to decide whether the suggested reviewers will be used or not.

Artwork

Image Manipulation

Authors are permitted to manipulate images for the purpose of clarity only. Manipulation for purposes of deception or fraud will be regarded as scientific ethical abuse and will be dealt with accordingly. For graphical images, the *Journal of Epidemiology and Global Health* applies the following policy: no specific feature within an image may be enhanced, obscured, moved, removed or introduced. Adjustments of brightness, contrast or color balance are acceptable if and as long as they do not obscure or eliminate any information present in the original. Nonlinear adjustments (e.g. changes to gamma settings) must be disclosed in the figure legend.

Electronic Artwork

- Make sure you use uniform lettering and sizing of your original artwork.
- Save text in illustrations as “graphics” or embed the fonts used if your application provides that option.
- Number illustrations according to their sequence in the text.
- Use a logical naming convention for your artwork files.
- Provide captions to illustrations separately.
- Size your illustrations close to the desired dimensions in the published version.
- Submit each illustration as a separate file.

Image Formats

If your electronic artwork is created in a Microsoft Office application (Word, PowerPoint, Excel) then please supply the file “as is” in the native document format. For any application other than Microsoft Office which is used for creating artwork, once your electronic artwork is finalized please click “Save as” or convert the images to one of the following formats (note the resolution requirements for line drawings, halftones and line/halftone combinations):

- **EPS (or PDF)**: Vector drawings; embed the fonts or save the text as “graphics”.
- **TIFF (or JPEG)**: Color or grayscale photographs (halftones); keep to a minimum of 300 dpi.
- **TIFF (or JPEG)**: Bitmapped (pure black & white pixels) line drawings; keep to a minimum of 1000 dpi.
- **TIFF (or JPEG)**: Combinations bitmapped line/halftone (color or grayscale); keep to a minimum of 500 dpi.

Please do not:

- Supply files that are optimized for screen use (e.g. GIF, BMP, PICT, WPG); these typically have a low number of pixels and limited set of colors;
- Supply files that are too low in resolution;
- Submit graphics that are disproportionately large for the content.

Journal Editorial Standards

Peer Review

The *Journal of Epidemiology and Global Health* applies a single-blind peer review process, meaning that the names of Reviewers are hidden from the Authors. All submissions will be initially assessed by an Editor to ensure that they fall within the Aims & Scope of the journal, are of reasonable scientific quality and meet the basic criteria for publication. Papers which are deemed suitable are then typically sent to a minimum of two independent subject experts to assess the scientific quality. These Reviewers then submit review reports with recommendations back to the assigned Editor who makes a decision on the manuscript based on the reports received. If the recommendations from Reviewers are conflicting or no final decision can be made based on the reports received, then the assigned Editor may consult another senior Reviewer and/or the Editorial Board members of the journal. Note that the Editor-in-Chief is ultimately responsible for the final decision regarding acceptance or rejection of articles and that the Editor-in-Chief's decision is final in this regard.

Editorial Procedure and Timeline

After submitting an article, the Corresponding Author will receive a confirmation of receipt. Due to the many papers we are currently receiving, the peer review process may take up to 2-3 months, but this depends strongly on the subject and the details of the article. The journal's main policy is not to compromise on quality, so in some cases the review time can be longer. Once a paper has been accepted for publication, the Corresponding Author will be asked to sign a *Journal Publishing Agreement* (JPA) and to pay the *Article Publication Charge* (APC) for making the article open access. Upon receipt of the signed JPA and the APC payment, the accepted manuscript goes into production. Prior to publication, a set of page proofs in PDF format will be sent to the Corresponding Author via email for proofreading.

Authorship

All Authors should have made substantial contributions to each of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be submitted. The statement that all Authors have approved the final article should be true and included in the disclosure. For more information, please refer to the Author Statement of Contribution section in the Atlantis Press Submission & Author Guidelines policy.

Authorship Changes

The *Journal of Epidemiology and Global Health* adheres to the COPE guidelines for authorship changes. Authors are expected to carefully consider the list and order of all the Authors of a manuscript before submitting it and to provide the definitive list of Authors at the time of the original submission. Any addition, deletion or rearrangement of Author names in the authorship list should only be made before the manuscript has been accepted and only if approved by the journal Editor. To request such a change, the Editor must receive the following from the Corresponding Author of the manuscript: (i) the reason for the change in the authorship list; and (ii) written confirmation – via email or letter – from all Authors that they agree with the addition, removal or rearrangement. In the case of addition or removal of Authors, this includes confirmation from the Author being added or removed. Only in exceptional circumstances will the Editor consider the addition, deletion or rearrangement of Authors after the manuscript has been accepted. While the Editor considers the request, publication of the article will be suspended. If the article has already been published in an online issue, any requests approved by the Editor will result in a corrigendum.

Journal Ethical Standards

The *Journal of Epidemiology and Global Health* adheres to the ethical standards as outlined in the guidelines of the Committee on Publication Ethics (COPE). For more information, please refer to the Atlantis Press Publishing Ethics & Misconduct policy.

Human Subjects

If the work submitted involves the use of human subjects, Authors should ensure that the research described has been carried out in accordance with the Ethical Principles for Medical Research Involving Human Subjects (Declaration of Helsinki) of the World Medical Association. The manuscript should adhere to the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals of the International Committee of Medical Journal Editors (ICMJE) and aim for the inclusion of representative human populations (sex, age and ethnicity) as per these recommendations. The terms ‘sex’ and ‘gender’ should be used correctly. Authors should include a statement in the manuscript that informed consent was obtained for experimentation with human subjects. The privacy rights of human subjects must always be observed. For more information, please refer to the Human Subjects section in the Atlantis Press Submission & Author Guidelines policy and to the Ethical Standards: Authors’ Responsibilities section in the Atlantis Press Publishing Ethics & Misconduct policy.

Animal Subjects

All animal experiments should comply with the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines and should be carried out in accordance with the UK Animals (Scientific Procedures) Act 1986 and associated guidelines, or EU Directive 2010/63/EU on the protection of animals used for scientific purposes, or the U.S. Public Health Service Policy on Humane Care and Use of Laboratory Animals and, as applicable, the Animal Welfare Act. As per ARRIVE guidelines, Authors should clearly indicate in the appropriate section of the submitted article that such guidelines have been followed during the course of the research. The sex of animals must be indicated, and where appropriate, the influence (or association) of sex on the results of the study. For more information, please refer to the Animal Subjects section in the Atlantis Press Submission & Author Guidelines policy and to the Ethical Standards: Authors' Responsibilities section in the Atlantis Press Publishing Ethics & Misconduct policy.

Clinical Trial Results

In accordance with the position of the International Committee of Medical Journal Editors (ICMJE), the journal will not consider results posted in the same clinical trials registry in which primary registration resides to be prior publication if the results posted are presented in the form of a brief structured (less than 500 words) abstract or table. However, divulging results in other circumstances (e.g. investors' meetings) is discouraged and may jeopardize consideration of the manuscript. Authors should fully disclose all posting in registries of results of the same or closely related work. For more information, please refer to the Reporting Research section in the Atlantis Press Submission & Author Guidelines policy.

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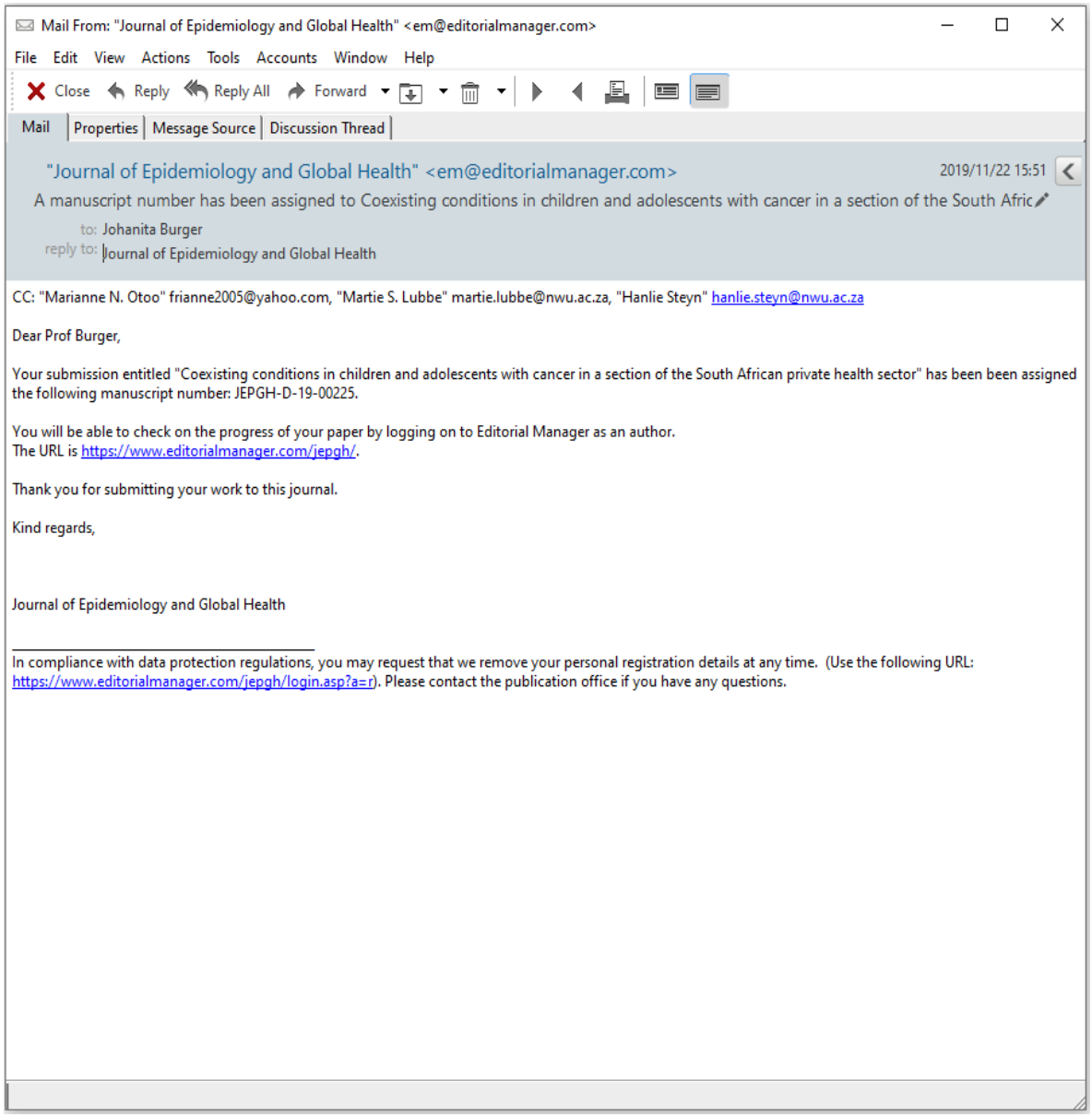

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CC: "Marianne N. Otoo" frianne2005@yahoo.com, "Martie S. Lubbe" martie.lubbe@nwu.ac.za, "Hanlie Steyn" hanlie.steyn@nwu.ac.za

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ANNEXURE G: PROOF OF LANGUAGE EDITING

Cecile van Zyl
Language editing and translation
Cell: 072 389 3450
Email: Cecile.vanZyl@nwu.ac.za

12 November 2019

To whom it may concern

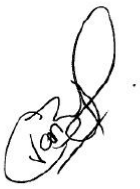
Dear Mr / Ms

Re: Language editing of master's dissertation: Epidemiology of childhood cancer in a section of the private health sector of South Africa

I hereby declare that I language edited the above-mentioned master's dissertation by Ms Marianne Naana Otoo (student number: 30901979).

Please feel free to contact me should you have any enquiries.

Kind regards



Cecile van Zyl

Language practitioner

BA (PU for CHE); BA honours (NWU); MA (NWU)
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