Burden and causes of ongoing paediatric infectious disease morbidity and mortality in the Western Cape Province of South Africa

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Abstract

Under-five mortality has significantly decreased globally over the past 28 years, halving to 39 deaths per 1,000 live births in 2018, yet remains high, necessitating further progress to meet the Sustainable Development Goal of reducing it to below 25 deaths per 1,000 live births by 2030. Improvements in healthcare access, nutrition, vaccinations, and socioeconomic conditions have been key drivers of this observed reduction, but infectious diseases such as lower respiratory tract infections (LRTIs) including pneumonia, diarrhoea, and malaria continue to cause substantial childhood mortality. In South Africa, LRTIs, diarrhoea, meningitis, and tuberculous meningitis (TBM) remain leading causes of childhood morbidity and mortality. The Western Cape continues to bear a substantial burden from these infectious diseases, but the available data is outdated and lacks granularity. Therefore, the aim of this thesis was to explore the morbidity and mortality of LRTIs, diarrhoea, meningitis and TBM among children younger than five years in the public sector in the Western Cape.

After a brief background chapter which lays out the key issues and overview of the South African healthcare system, Chapter 2 provides a comprehensive literature review discussing the morbidity and mortality of LRTIs, diarrhoea and meningitis (including TBM where appropriate) in children under five years globally and in South Africa with a focus on the Western Cape. Chapter 3 provides a detailed description of the data management required to develop the de-duplicated dataset that was used for each of the results chapters (Chapter 4-7).

Chapter 4 explores causes of death using various death data sources, including routinely collected and detailed audits, and found that routine hospital information systems had accurate causes of death relying on International Classification of Diseases 10th Revision codes, particularly for LRTIs and diarrhoea. Chapters 5 and 6 explore the impact of COVID-19 public health and social measures (PHSM) on LRTI and diarrhoea admissions. COVID-19 surges and their associated measures, including PHSM, were linked to declining LRTI admissions and in-facility deaths, likely driven by a combination of reduced infectious disease transmission and reduced use of healthcare services. Lastly, Chapter 7 identified associations with repeat infectious disease admissions (LRTIs, diarrhoea and meningitis) among children who were first admitted for an infectious disease in the first six months of life. Male children with lower birthweight, whose first admission was due to LRTI or diarrhoea (versus meningitis), experienced a longer length of stay during their initial admission, and were living with HIV were more likely to be re-admitted for an infectious disease. Both individual- and population-

level interventions are needed to reduce the prevalence and impact of factors associated with infectious disease re-admissions and reduce infectious disease morbidity.

This thesis concludes that infectious disease morbidity and mortality persist among children under five years in the Western Cape by presenting up-to-date and comprehensive data. It highlights the need to address existing gaps to improve data quality and comprehensiveness, as well as healthcare and health outcomes for these children.

Declarations

This thesis is presented in fulfilment of the requirements for the degree of Doctor of Philosophy (PhD) in the School of Public Health and Family Medicine, Faculty of Health Sciences, University of Cape Town and Population Health Sciences, Bristol Medical School, University of Bristol.

I acknowledge that plagiarism is wrong, affirm that this dissertation is my own work with all contributions and quotations properly cited, and will not permit anyone to copy it.

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1. **Kehoe K**, Morden E, Jacobs T, Zinyakatira N, Smith M, Heekes A, Murray J, le Roux DM, Wessels T, Richards M, Eley B, Jones HE, Redaniel MT, Davies MA. Comparison of paediatric infectious disease deaths in public sector health facilities using different data sources in the Western Cape, South Africa (2007-2021). BMC Infect Dis. 2023 Feb 22;23(1):104.
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Acronyms and abbreviations

aHR	Adjusted hazard ratio
ART	Antiretroviral therapy
BCG	Bacillus Calmette-Guérin
CDR	Child Death Review
CFR	Case fatality rate
CHAMPS	Child Health and Mortality Prevention Surveillance
Child PIP	Child Healthcare Problem Identification Programme
CI	Confidence interval
COPC	Community-Oriented Primary Care
DHA	Department of Home Affairs
DHIS	District Health Information System
DN	Death Notification
EC	Eastern Cape
EPI	Expanded Programme on Immunisation
ESPID	European Society for Paediatric Infectious Diseases
FS	Free State
GP	Gauteng
HEU	HIV exposed uninfected
HIV	Human immunodeficiency virus
HR	Hazard ratio
HREC	Human Research Ethics Committee
HUU	HIV unexposed uninfected
ICD-10	International Classification of Diseases 10th Revision
ICU	Intensive care unit

IQR	Interquartile range
IRR	Incidence rate ratio
KZN	KwaZulu-Natal
LP	Limpopo
LRTI	Lower respiratory tract infections
MP	Mpumalanga
NC	Northern Cape
NHI	National Health Insurance
NW	North West
PCR	Polymerase chain reaction
PCV	Pneumococcal conjugate vaccine
PHSM	Public health and social measures
PVT	Prevention of vertical transmission
RHIS	Routine Health Information System
RSV	Respiratory syncytial virus
RV	Rotavirus vaccine
SA	South Africa
SAM	Severe acute malnutrition
SDG 3	Third Sustainable Development Goal
TB	Tuberculosis
TBM	Tuberculous meningitis
U5MR	Under-five mortality rate
UHC	Universal healthcare coverage
VR	Vital registration

WC	Western Cape
WCGHW	Western Cape Government Department of Health and Wellness
WCPHDC	Western Cape Provincial Health Data Centre
WHO	World Health Organization

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CHAPTER 1

Background

1.1 Introduction

Globally, under-five mortality has decreased significantly since 1990 more than halving to 38 deaths per 1,000 live births in 2019 (1,2). Despite this considerable progress, mortality among children remains high. Further advancement is still required to achieve the third Sustainable Development Goal (SDG 3), which aims to reduce under-five mortality to <25 deaths per 1,000 live births by 2030 (3). Infectious diseases are common causes of childhood mortality. Despite substantial reductions in the associated risk factors, children continue to suffer and succumb due to infectious diseases, particularly pneumonia, diarrhoea, meningitis, measles and malaria (4–6). Broadly, drivers of reductions in the mortality rate include improvements in access to healthcare, early diagnoses, breastfeeding, nutrition, vaccinations, programmes for prevention of vertical transmission (PVT) for human immunodeficiency virus (HIV), socioeconomic status and provision of water, sanitation and hygiene (7,8).

Stark differences exist across and within the nine provinces in South Africa relating to childhood infectious disease morbidity and mortality. Some of the variation may be driven by differences in the healthcare system, reporting and healthcare access, which will be described below, focusing on the Western Cape province, where this study is located.

1.2 Overview of South Africa's healthcare system

The South African public healthcare system is organised into national, provincial and local government levels (9). Within provinces, there is a divide between the management of public sector hospitals and metropolitan (or city) clinics, as is seen in the Western Cape province. The majority of healthcare facilities in the Western Cape are managed by the Provincial Department of Health, however approximately 30% of the province's clinics are managed by the City of Cape Town (10). The majority of provinces use the District Health Information System (DHIS) for reporting, unlike the Western Cape where multiple health information reporting systems are consolidated to generate the same indicators as the DHIS (10).

South Africa's healthcare system is divided, with clearly defined differences between the public and private sector (9,11). There is unequal resource distribution between these sectors, including the distribution of healthcare workers. Typically, the private sector has a higher ratio of healthcare workers per patient, with more specialists. There is also a disparate distribution

of healthcare workers (e.g. specialists, general practitioners, and nurses) across sectors and provinces (9). These striking disparities in healthcare sectors have resulted in disparities and inequities in the accessibility and affordability of healthcare (12).

Based on the current structure of the healthcare system, there are several inequities observed across and within provinces in South Africa. These inequities include unequal access to healthcare, with clear urban and rural differences, inadequate health infrastructure and the unequal distributions of healthcare professionals (8). Aiming to improve health equity in the country, it was proposed to have one integrated healthcare system to provide universal health coverage known as the National Health Insurance (NHI) (17). The NHI bill was signed into South African law in May 2024, and implementation timelines are currently unclear, especially as the fund required to finance this has not yet been set up (13). The District Health Barometer 2018/19 (the latest data available across the reports) reported on universal healthcare coverage (UHC) indices, ranging from 0-100, and aims to monitor essential healthcare service coverage (8,14). This includes health-related measurements from four broad categories: reproductive, maternal, newborn and child health; infectious diseases; non-communicable diseases and service capacity and access. The overall UHC service coverage index, a combination of these four categories, was 56.9 for South Africa, ranging from 44 to 62 across the 52 districts (8). Based on these measures, it is clear that heterogeneity and inequities persist (8,11). The best performing provinces were the Western Cape and KwaZulu-Natal, whereas Limpopo and the North West had the lowest UHC indices. In the Western Cape, the UHC service coverage index ranged from 51.1 in the West Coast district to 59.7 in the City of Cape Town (8). These differences observed inter-provincially and intra-provincially are likely due to varying access to healthcare and preventive child health services such as vaccinations, differences in case definitions and hospital admission criteria, lack of identification for diseases or conditions and varying accuracy of recording or reporting by healthcare workers (8). A combination of these factors may contribute to differences observed in infectious disease morbidity and mortality, particularly in children. Therefore, it is important to be mindful of these factors when investigating infectious disease burden among children, which will be described in Chapter 2.

1.3 Overview of the Western Cape

The Western Cape, one of South Africa's nine provinces, consists of six districts: City of Cape Town, Cape Winelands, Central Karoo, Garden Route, Overberg, and West Coast (Figure 1.1). The province had an estimated seven million people in 2020 (15) of whom 8% (563,590) were

children aged 0-4 years (16). About 80% of the child population utilise public sector services, with the remaining proportion accessing health services through the private sector. There are 52 hospitals and 272 primary care clinics, and the City of Cape Town manages an additional 82 clinics (10).

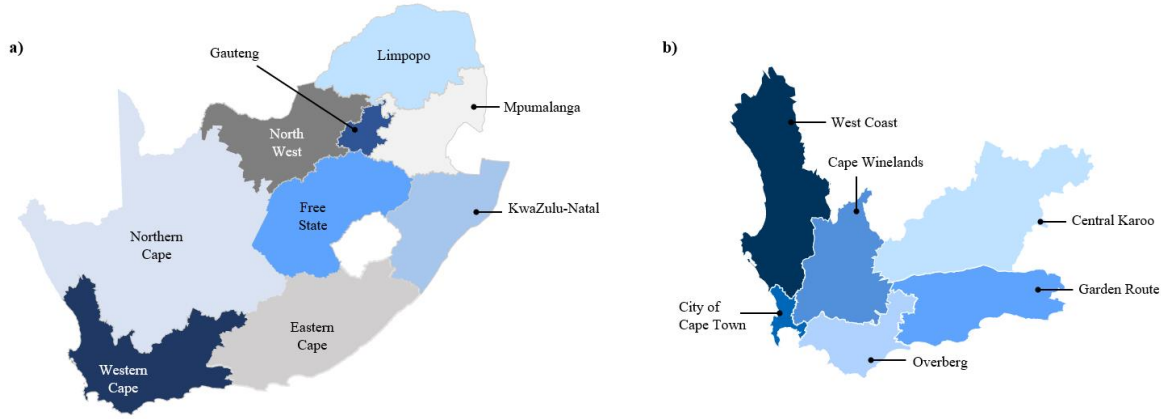


Figure 1.1. Map of a) the nine South African provinces and b) the six districts in the Western Cape Province.

The Western Cape saw the second-largest net positive immigration in the most recent 2022 census, following Gauteng, with around 294,000 new residents since 2011 (17). Much of this migration occurs within the country, particularly from Gauteng and the Eastern Cape. This movement is often temporary, as people come to the Western Cape for job opportunities and other reasons (e.g. education, healthcare) and then return home during the holiday season or for significant life events like childbirth, especially those from the Eastern Cape.

Healthcare access in the Western Cape can vary significantly across different regions due to factors such as urbanicity, socioeconomic status, and safety concerns. Some residents may have to travel long distances or take time off work, losing income opportunities in the process. In certain areas, known as 'red zones,' safety is a significant issue, making it dangerous for residents to move around or for healthcare providers, like ambulances, to enter without police escorts (18). As a result, some people may experience delays or a complete lack of access to healthcare, leading to more severe conditions by the time they reach facilities or even death outside of them. These factors are crucial to consider when evaluating the health outcomes, which will be explored in more detail in Chapter 2.

1.4 Rationale

In South Africa, lower respiratory tract infections (LRTIs) including pneumonia, diarrhoea, and meningitis remain leading causes of morbidity and mortality amongst children (7,8). The

Western Cape province continues to report these infectious diseases as common causes of morbidity and mortality (7,19–23). Furthermore, infectious disease morbidity and mortality varies significantly across the six districts in Western Cape Province (7,23); Cape Town, Cape Winelands, Central Karoo, Garden Route, Overberg and West Coast (24). These differences are driven by inequities that exist within and outside of the healthcare system, referenced above (section 1.2). Despite the persistent morbidity and mortality caused by these infections, there is a scarcity of available data across the province. As the current national and provincial estimates may mask inequities in child health, there is a need for research in the Western Cape to better understand the burden of disease among children in and across geographic locations. This is vital for programme planning and resource allocation in the future.

1.5 Aim

This project aims to describe the burden and major drivers of infectious disease hospital admissions and mortality due to LRTIs, diarrhoea and meningitis in children aged younger than five years in public sector facilities using data from the Western Cape Provincial Health Data Centre (WCPHDC) in South Africa.

1.6 Objectives

1. To ascertain the completeness and accuracy of various death data sources, develop a de-duplicated dataset of deaths for children aged under five years and determine admission mortality rates for in-facility infectious disease deaths including LRTIs, diarrhoea, meningitis and tuberculous meningitis (TBM) in the public sector in the Western Cape province.

2. Describe the fluctuations in LRTI hospital admission and in-facility mortality rates among children under five years old in relation to COVID-19 surges and related measures within public sector facilities across the Western Cape province from January 2019 to November 2021.

3. Describe the fluctuations in diarrhoea hospital admission rates among children under five years old in relation to COVID-19 surges and related measures within public sector facilities across the Western Cape province from January 2019 to November 2021.

4. Identify risk factors for first repeat infectious disease hospital admissions due to LRTIs, diarrhoea, and meningitis among children under five years old over five years (2017-2021) in the Western Cape province.

CHAPTER 2

Literature review

2.1 Introduction

The purpose of this literature review is to provide an in-depth overview on infectious diseases morbidity and mortality globally, within South Africa and placing particular focus on the Western Cape province, the setting of this research project. This overview is a prerequisite to understanding the current burden of infectious diseases among children under five years and highlight the research gaps within the Western Cape to ultimately assist programme planning and resource allocation in the future.

This literature review primarily synthesises articles on paediatric infectious diseases that have a public health focus and draws on several reports in the public domain which release morbidity and mortality data annually or bi-annually. It will focus on the following infectious diseases: LRTIs including pneumonia, diarrhoea, and meningitis, including TBM where applicable. Data were mostly available for pneumonia, rather than all LRTIs. I searched for articles in PubMed as well as the internet for each infectious disease to ensure I could obtain relevant and comprehensive literature and/or reports to synthesise. The search was limited to articles available in English. The time period of the search was not limited to a particular timeframe and articles published up until May 2024 were included. Search terms included childhood mortality, under-five mortality, incidence, hospitalisation incidence, risk factors, vaccination and COVID-19 impact on child health. Each of the terms were searched for each of the infectious disease included in this thesis. I also searched bibliographies of the included studies and reports to identify additional, relevant resources.

2.2 Infectious disease mortality among children

Standardised indicators, including under-five mortality rates (U5MRs) and case fatality rates (CFRs), are used for mortality reporting among children, allowing for comparisons across settings. As these measures will be discussed in-depth in the below sections, understanding the potential limitations to these measures is useful. Differences in these measures may reflect variance in reporting of cases across different settings, which may also be influenced by changes in national case definitions (8). Alternatively, this may reflect better reporting systems, especially when comparing South Africa to other African settings. For children, South Africa has high coverage of both birth (>90%) and death (>75%) registrations and a minimum set of health indicators for reporting into health information systems, with a focus on quality control

(25). Differences in reporting can also be detected across South African provinces and its districts, as provinces have different reporting systems as discussed in section 1.2 of Chapter 1. These differences result in challenges when interpreting and comparing routine data from different settings across South Africa. Many observed inter-provincial and inter-district estimates may largely be driven by differences in reporting, access to healthcare services and health resources. These limitations will also apply to incidence and hospitalisation estimates discussed in sections 2.4 and 2.5 respectively.

2.2.1 Under-five mortality and case fatality rates

The U5MR is an important indicator of the health status of children and quality of child healthcare, and provides insight into the effectiveness of a country's healthcare system (26). Likewise, the U5MR is a useful index to assess factors which are related to child survival such as healthcare access and quality, nutrition and child safety (26,27). Recent evidence has shown that intervening and investing during early life is effective, not only in terms of cost benefit, but also in ensuring children grow, develop and achieve optimal health (27). These investments have the potential for long-term impact such as stimulating economic development and promoting social cohesion (27).

CFRs are also used to describe childhood mortality. This measure can be calculated in various ways, but is most often defined as the number of in-hospital deaths divided by the number of hospital admissions (8,19,20,28). For this thesis, CFRs will be defined as stated here unless otherwise specified. A limitation of this measure is that CFRs depend on children accessing healthcare services and being correctly identified and recorded as cases thereafter (7,8). Hence, these estimates should be interpreted with caution as not all cases in the population are accounted for, potentially influenced by the healthcare access issues discussed in section 1.2 of Chapter 1.

2.2.2 Global under-five mortality

In 2015, the 2030 Agenda for Sustainable Development was adopted by the member states of the United Nations. SDG 3, focusing on health and well-being, states that by 2030, all countries should reduce their U5MR to <25 deaths per 1,000 live births and decrease their neonatal (first 28 days of life) mortality rate to <12 deaths per 1,000 live births (3). Achieving this goal would ensure countries are reducing preventable child deaths and improving the overall health and well-being of children. Since the adoption of SDG 3, the global U5MR has reduced from 43 to

38 deaths per 1,000 live births from 2015 to 2019 and since 1990 there has been a 59% reduction in the U5MR from 93 to 38 deaths per 1,000 live births (1,2).

2.2.3 Under-five mortality in sub-Saharan Africa

The greatest burden of under-five mortality is in sub-Saharan Africa, which, in 2019, recorded an U5MR of 76 deaths per 1,000 live births, more than twice the global estimate (2). Compared to high-income countries (average of five deaths per 1,000 live births in 2018), significant efforts are required in sub-Saharan Africa to reduce childhood mortality (6,27). Despite a substantial reduction of 58% from 1990 (179 deaths per 1,000 live births) in the region (2), disparities exist in child health across different countries in the region.

Given the high U5MR in sub-Saharan Africa and Asia, the Child Health and Mortality Prevention Surveillance (CHAMPS) network was established in 2015 and includes the Chris Hani Baragwanath Hospital in Soweto, Gauteng province, South Africa. CHAMPS aims to better understand the causes of child deaths in these high-burden settings, using longitudinal mortality data collected using standardised methods across sites for data collection and abstraction (29,30). The network provides valuable insight into factors contributing to childhood mortality in an urban, informal settlement, which is similar to those in many parts of South Africa, including the Western Cape. The network aims to guide improvements in health systems and public health programmes by generating new information regarding the burden and causes of death in children (31).

2.2.4 Under-five mortality in South Africa

As of 2022, approximately 10% (5.8 million) of the South African population are children under five years (17). It is thus essential to prioritise and promote the health and well-being of this group to ensure our growing population not only survives, but thrives. Several key sources of data in the South African report on U5MRs, all show similar downward trends over the past 14 years (Figure 2.1) (4,5,32), as also observed in global mortality estimates (section 2.2.2). As for all people with identity numbers in South Africa, numbers of deaths in children with identity numbers, both in- and out-of-facilities, are recorded in the vital registration (VR) system in South Africa (26,33). Hospital reporting systems also capture under-five mortality occurring in-facilities which is mainly reported to the DHIS, the national health information system (5). The exception is the Western Cape, which makes use of their own consolidated individuated patient-level health data system, where the WCPHDC captures and tracks in-facility deaths (10). Additional death data sources include audit processes for child deaths to

specifically identify the modifiable factors associated with these deaths. Examples include the Child Healthcare Problem Identification Programme (Child PIP) across South Africa (28,34) and the Child Death Review (CDR) in the Western Cape (35,36). The CDR focuses on out-of-facility deaths aiming to obtain more information about these deaths, as half of child deaths occur outside of hospital settings in South Africa (20,36–38). Therefore, estimating deaths outside of hospital settings is of particular importance. Under-five mortality data sources used in this project are described in Chapter 3.

2.2.4.1 National under-five mortality rates in South Africa

The national U5MR was estimated at 34 deaths per 1,000 live births in 2018 (32), which represented a substantial decline since 1997 (estimated 65 deaths per 1,000 live births) (Figure 2.1) (4). Apart from a peak in 2004 (estimated 79 deaths per 1,000 live births) (4), continuous declines have been reported, although different evidence sources give different estimates for the same year, highlighting one of the limitations that currently exists in child mortality data. For example, estimates of the U5MR ranged from 40-42 deaths per 1,000 live births (average of 41 deaths per 1,000 live births) in 2012 (4,32) and from 37-40 deaths per 1,000 live births (average of 38.5 deaths per 1,000 live births) in 2015, an estimated 31,938 deaths (5,32). However, in the last three years, these rates have plateaued, with similar estimates reported in 2016-2018 (Figure 2.1) (32). After a slight increase in 2018 (estimated 36 deaths per 1,000 live births), the U5MR declined to an estimated 28 deaths per 1,000 live births in 2020 (Figure 2.1) (39). This is the lowest U5MR estimated for South Africa since 1997. It would be important to monitor it going forward as there may be biases present in the data due to the COVID-19 pandemic. For example, there was altered healthcare access during this time which may resulted in higher case fatality rates, children dying outside of facilities may not be captured and cause of death may have been incorrectly assigned or ill-defined. Additionally, a decrease in the in-hospital mortality rates and CFRs have been noted over time, with similar plateauing observed (8,19,20,23,28). The under-five mortality rate in-facilities (defined as children under five years who died in-facilities as a proportion of live births) has consistently been reported at 1.8% from 2017 to 2023, with the exception of 2021 (1.6%) which was likely impacted by the COVID-19 pandemic (23).

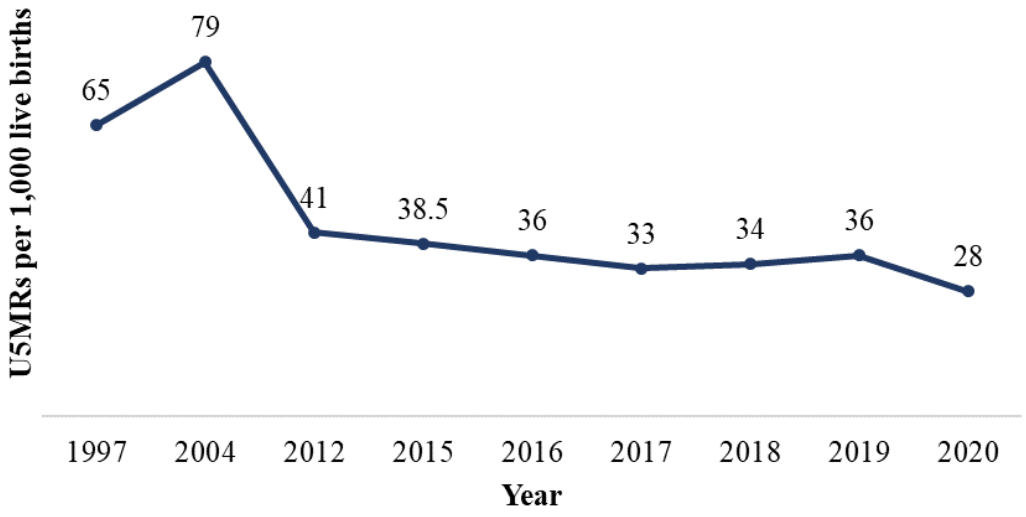


Figure 2.1. Estimated under-five mortality rates in South Africa from 1997-2020 using various data sources (4,5,32,39). Note: data were not available annually and therefore the timeframe between each data point is not equal for earlier years until 2015.

2.2.4.2 Provincial under-five mortality rates in South Africa

Across the nine provinces of South Africa, a similar trend is observed. However, despite the overall downward trend in childhood all-cause mortality, some provinces report higher estimates than others. The highest U5MR estimates were observed in KwaZulu-Natal, Free State, Mpumalanga and Eastern Cape in 2012 (4). It is of concern that by 2012, eight of the nine provinces had maintained U5MRs higher than 30 deaths per 1,000 live births (4). Conversely, the Western Cape, one of the wealthier provinces in South Africa, has consistently performed better since 1997, with a decrease in U5MR from 30 deaths per 1,000 live births in 1997 to an estimated 21 or 24 (alternative estimates from two different data sources) deaths per 1,000 live births in 2012 (4,37). The province achieved the SDG 3 in 2011, with one geographic service area, the Metro West region, reporting this in 2010 (4,20,37). Further published evidence shows that the Western Cape is performing well in comparison to the rest of the country (19). In a tertiary hospital in the Western Cape, there was a 60% reduction in the in-hospital U5MRs (estimated 32 deaths per 1,000 live births in 2008 to 14 deaths per 1,000 live births in 2013) (19). In 2022/23, the death rate under five years in-facilities (as a proportion of live births) exceeded the national average of 1.8% in six of the nine provinces (Free State, Northern Cape, Eastern Cape, Limpopo, Gauteng and North West). Mpumalanga and Kwa-Zulu Natal matched the national average, whereas the Western Cape (1.6%) was the only province with a mortality rate lower than the national average (23). These differences may be

driven by various socioeconomic factors and health related inequities, such as the proportion of mothers living with HIV, access to healthcare and availability of preventive child health such as vaccinations (4).

Despite lower provincial mortality in the Western Cape, mortality estimates for districts, subdistricts and within the City of Cape Town may differ and be slightly higher than reported due to existing heterogeneity and inequities, which may be masked when reporting at an aggregated level. Most districts have been able to reduce childhood mortality from 2009 to 2015, except for the Central Karoo, Garden Route and Overberg, where there has been minimal change (40). The majority of the districts (five out of the six) reported mortality rates in-facilities lower than the national average in 2022/23. However, the Central Karoo (2.7%) mortality rate in-facilities (as a proportion of live births) was three times higher when compared to the West Coast (0.9%) (23). In addition, the U5MR in the Western Cape remains five times higher than the estimate reported from high-income countries. Moreover, compared to similar middle-income countries, such as Brazil and Cuba, both of which have achieved low U5MRs (6), the Western Cape still needs to make significant improvements in child health.

2.2.5 Under-five mortality summary

Based on several data sources and the current trajectory, South Africa should be able to achieve <25 deaths per 1,000 live births by 2030 (SDG 3). Despite the Western Cape achieving SDG 3 in 2011 (4,37), childhood mortality appears to have plateaued in the province (20). Monitoring the morbidity associated with child mortality is important, as it provides an opportunity to implement a tailored care package aimed at preventing both deaths and one or more hospital admissions, ultimately reducing both morbidity and mortality.

2.3 Causes of mortality in children

Infectious diseases contribute substantially to under-five mortality. In 2018, the estimated global distribution of under-five mortality due to infectious diseases was: pneumonia (12%), diarrhoea (8%), malaria (5%), meningitis (2%) and measles (2%) (6). Common causes of death among children in South Africa include perinatal and neonatal conditions, pneumonia, diarrhoea, gastroenteritis, HIV, malnutrition, meningitis, septicaemia, tuberculosis (TB) and injuries (4,5,7,28,41). Leading causes of mortality in children have changed significantly over time in South Africa and correlate with the peak of the HIV/AIDS epidemic, rollout of the PVT of HIV programme, the antiretroviral therapy (ART) programme, the introduction of the

pneumococcal and rotavirus vaccines into the expanded programme of immunisation (EPI) in 2009, increased breastfeeding and improved water and sanitation (4,7).

2.3.1 Global lower respiratory tract infection under-five mortality

In 2019, the global mortality rate for LRTIs, including pneumonia, was estimated as 100 per 100,000 person years among children under five years (42). LRTIs are considered as a spectrum of disease including pneumonia, bronchitis and bronchiolitis. These conditions depend on the causative agent and host response, both of which alter the clinical and radiological manifestation (43,44). Of the global LRTI childhood deaths in 2015, approximately 56% were caused by pneumococcal pneumonia (45). Pneumonia persists as a leading cause of death in children aged under five years (excluding the neonatal period), with an estimated mortality rate of six deaths per 1,000 live births, causing approximately 15% of deaths in children under five years globally in 2015 (46). In comparison to other regions, sub-Saharan Africa has maintained high mortality rates and slower declines in pneumonia and LTRI incidence and mortality (42,45,46).

2.3.1.1 Lower respiratory tract infection under-five mortality in South Africa and the Western Cape

Across several data sources, ranging from research studies to reports, pneumonia remains a leading cause of child mortality and years of life lost in South Africa, both in- and out-of-facilities (4,5,7,28,36,41), raising concerns about the diagnosis, treatment and control of the disease. The mortality rate due to pneumonia in children under five years was estimated as 97 per 100,000 person years annually from 2005 to 2008, with the leading cause attributed to non-bacterial pneumonia disease (47). Thereafter, in 2012-2013, the introduction of the pneumococcal conjugate vaccine (PCV) decreased the U5MR by approximately two thirds (to 36 per 100,000 person years) (47). Respiratory syncytial virus (RSV) remains one of the leading causes of pneumonia globally (42), and has been the leading cause of pneumonia in South Africa since the introduction of PCV (48). The CFR of children hospitalised with pneumonia peaked during the COVID-19 pandemic increasing to 2.1% in 2020/21, although the estimated mortality rate in the population was relatively low at 0.1 pneumonia deaths per 1,000 children under five years (23). The high CFR may be due to reduced access to healthcare due to COVID-19 related movement restrictions and pressure on health services, with only the sicker children being admitted to hospital versus pre-pandemic. Most recently, the estimated

pneumonia mortality rate for children under five years was 0.2 per 1,000 children nationally, with a CFR estimated as 1.5% (939 deaths) in 2022/23 (23).

As with all-cause mortality (section 2.2), the pneumonia mortality rates varied across provinces, highlighting inequities in risk factors for disease and healthcare. Several provinces reported U5MRs for pneumonia which were the same or higher than the national average: Eastern Cape, Free State, KwaZulu-Natal, Limpopo, Mpumalanga, and Northern Cape (Figure 2.2) (8). The Western Cape province reported the lowest U5MR (0.1 per 1,000 children) and CFR (0.2%) due to pneumonia over time (8), with several associated factors including higher pneumonia hospital admissions contributing to a much lower CFR (8). However, disparities are observed within the province, with the Central Karoo and Garden Route districts reporting higher mortality due to pneumonia as well as consistently high all-cause mortality (section 2.2.4.2). Of concern, pneumonia persists as a leading cause of mortality among children in the province, and data suggests mortality rates have plateaued (7,8,23,40).

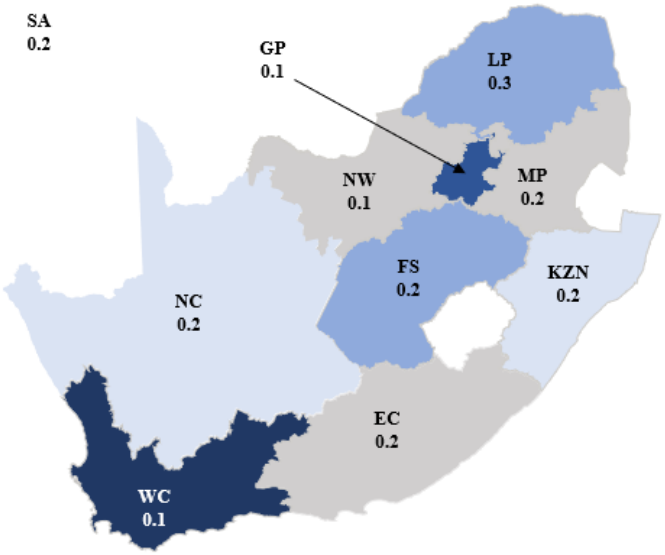


Figure 2.2. Estimated pneumonia mortality rates per 1,000 children under five years by provinces of South Africa. Adapted from the District Health Barometer 2022/23 (23). Note: the colour coding does not represent the mortality rates, but rather highlights the different provinces.

EC: Eastern Cape, FS: Free State, GP: Gauteng, KZN: KwaZulu-Natal, LP: Limpopo, MP: Mpumalanga, NC: Northern Cape, NW: North West, SA: South Africa, WC: Western Cape.

2.3.2 Global diarrhoea under-five mortality

Among children under five years, diarrhoea remains the second leading cause of infectious disease mortality globally (49). In 2017, the global mortality rate for diarrhoea was estimated to be 78 per 100,000 children; a 70% reduction since 1990 (49). Diarrhoeal mortality rates among children vary largely across regions, with the lowest number of deaths observed in high-income countries globally (one per 100,000 children across high-income countries in 2017). Sub-Saharan Africa remains disproportionally affected by diarrhoeal deaths, with an estimated diarrhoeal U5MR of 205 per 100,000 children, accounting for 62% of global child diarrhoeal deaths in 2017. Among the four sub-regions of sub-Saharan Africa, the lowest mortality rate was observed in southern sub-Saharan Africa (estimated 95 deaths per 100,000 children in 2017) (49).

2.3.2.1 Diarrhoea under-five mortality in South Africa and the Western Cape

Childhood mortality due to diarrhoea persists in South Africa, both in- and out-of-facilities (4,5,7,19,20,28,36–38,41). In 2016, the U5MR due to diarrhoea was estimated as 53 deaths per 100,000 children (50). In 2018/19, the most up-to-date data available, the national CFR for diarrhoea hospitalisations among children younger than five years was 2%, with 565 deaths recorded. As discussed in section 2.2.1, the CFR should be interpreted with caution as it does not reflect all diarrhoea cases for this population. The number of child deaths in-facilities due to diarrhoea nationally has decreased by approximately 78% since 2010/11 (CFR of 7% and 2,558 deaths in 2010/11) (7).

Across South Africa, Gauteng, Free State, Limpopo, North West and Eastern Cape reported the highest CFRs (Figure 2.3) (7). The lowest CFR was reported in the Western Cape in 2018/19 (0.4%) (7). The provincial CFR target of 0.3% was only achieved in two districts: the West Coast and Cape Town. The Overberg district reported high diarrhoea mortality, as seen for all-cause mortality (section 2.2.4), with the addition of the Cape Winelands; both reporting approximately double the target (8). It is evident that substantial disparities exist intra-provincially for diarrhoea outcomes among children.

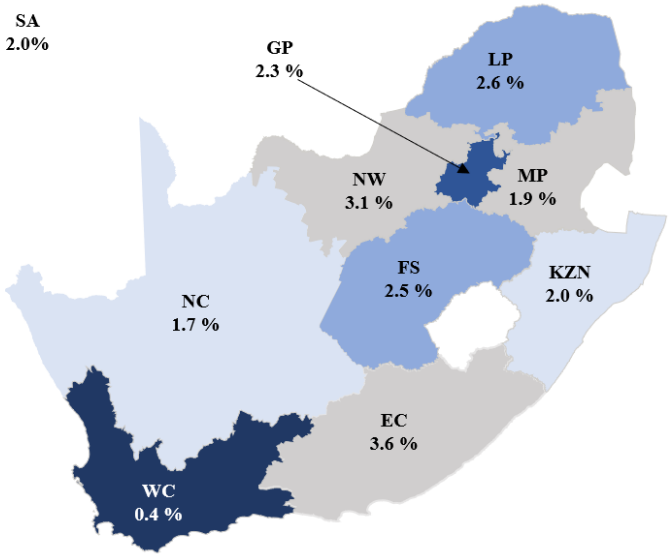


Figure 2.3. Estimated diarrhoea case fatality rates (%) for children under five years by province. Adapted from the District Health Barometer 2017/18 (8). Note: the colour coding does not represent the case fatality rates, but rather highlights the different provinces.

EC: Eastern Cape, FS: Free State, GP: Gauteng, KZN: KwaZulu-Natal, LP: Limpopo, MP: Mpumalanga, NC: Northern Cape, NW: North West, SA: South Africa, WC: Western Cape.

2.3.3 Global meningitis under-five mortality

The global U5MR in 2019 for meningitis was estimated as 0.8 per 1,000 live births, declining by approximately 60% since 1990 (51). Of all global meningitis deaths in 2019, almost 50% (estimated 112,000 deaths) were in children under five years (51). Among children aged under five years, the highest mortality rate globally has consistently been observed in Africa, mostly clustered across the meningitis belt, a hyperendemic area in sub-Saharan Africa which includes 26 meningitis hyper-endemic countries, extending from Senegal in West Africa to South Sudan and Ethiopia in East Africa (51,52).

2.3.3.1 Meningitis under-five mortality in South Africa and the Western Cape

The U5MR in southern sub-Saharan Africa was 88 per 100,000 population in 2019 – the lowest among all the four regions in sub-Saharan Africa which had an overall rate of 344 per 100,000 population (51). Within southern sub-Saharan Africa, approximately half of meningitis deaths were recorded in South Africa in 2016 (2,635 deaths) (53). The meningitis mortality rate in South Africa was estimated at 8 per 100,000 children in 2016, a 5% decrease since 1990 (54). The most recent estimate for the Western Cape was in 2011, with the proportion of child deaths attributed to meningitis (excluding TBM) reported as approximately 2% (37,38). Recent

estimates for the province and its districts are not known, a crucial knowledge gap, and this data would be beneficial for healthcare providers and service provision.

2.3.4 Summary

Infectious diseases remain a common cause of death globally and in South Africa, despite declining mortality over time. These causes of death are mostly preventable and should be further investigated to ensure that the years of life lost are reduced, especially in children, a vulnerable age group. Within South Africa, the Western Cape continues to report lower infectious disease mortality, where available, however, these estimates mask the intra-provincial differences in U5MRs and CFRs, specifically for the Central Karoo, Garden Route, Overberg and Cape Winelands districts.

2.4 Infectious disease morbidity among children

In conjunction with monitoring infectious disease mortality, it is important to also understand the burden of infectious diseases in children. In this section, infectious disease morbidity will be discussed in terms of the infectious disease incidence and hospitalisation incidence globally and in South Africa, with specific focus on the Western Cape where possible and using the most up-to-date estimates available.

2.4.1 Global lower respiratory tract infection incidence

Rates of LRTIs, including pneumonia and bronchiolitis, remain substantially high in comparison with other childhood infectious diseases (55). The global incidence of LRTIs was estimated as 12,198 per 100,000 children under five years in 2017, with one of the worst affected regions being sub-Saharan Africa (10,493 per 100,000 children) (55). In 2019, female (6,721 per 100,000 children) and male (6,877 per 100,000 children) children had similar LRTI incidence, with approximately 50% declines noted from 1990 (42). In southern sub-Saharan Africa, the incidence in children remains higher than what is observed in sub-Saharan Africa overall (7,357 per 100,000 children in 2017), despite a 30% reduction in incident cases since 1990 (55). Pneumonia contributes substantially to LRTI incidence globally, and developing countries continue to be severely affected by this disease. Across 132 developing countries, the estimated pneumonia incidence was 231 episodes per 1,000 children in 2015 among children younger than five years, despite declining 30% since 2000 (329 episodes per 1,000 children) (56).

2.4.1.1 Lower respiratory tract infection incidence in South Africa and the Western Cape

Although pneumonia incidence has decreased in South Africa (8,56), as in other developing countries, pneumonia remains a leading cause of infectious disease morbidity. Most recently, national pneumonia incidence among children younger than five years in 2022/23 was estimated as 275 cases per 1,000 children (23), a 40% decrease from 2014/15 (44 cases per 1,000 children) (8). The lowest pneumonia incidence was reported in 2020/21 (12 cases per 1,000 children), coinciding with the COVID-19 pandemic (23). In 2022/23, provinces reporting low incidence rates (Figure 2.4) (8) may have had improvements in pneumonia prevention and management. However, this lower pneumonia incidence was not universal, highlighting inter-provincial inequities in access to and quality of healthcare services (section 1.2). Despite a low pneumonia mortality estimate in the Western Cape, the estimated incidence rate was still more than triple the national estimate (111 cases per 1,000 children) (23). This incidence may be driven by better reporting and access to healthcare in the province, as discussed in section 1.2 of Chapter 2. As has been seen with all-cause and pneumonia mortality rates (section 2.2 and 2.3), incidence estimates are highly variable across districts, and highest in the City of Cape Town and Overberg in 2022/23. On the other hand, the West Coast and Garden Route reported estimates closer to the national incidence rate (8). These stark differences observed across districts may be driven by similar factors to those mentioned in Chapter 1 and highlight the inequities that exist across the province.

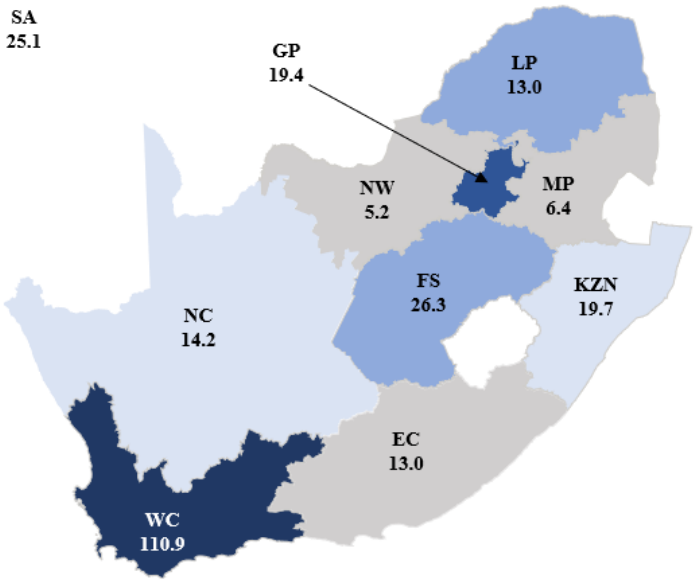


Figure 2.4. Estimated pneumonia incidence per 1,000 children under five years by province. Adapted from the District Health Barometer 2022/23 (23). Note: the colour coding does not represent the incidence, but rather highlights the different provinces.

EC: Eastern Cape, FS: Free State, GP: Gauteng, KZN: KwaZulu-Natal, LP: Limpopo, MP: Mpumalanga, NC: Northern Cape, NW: North West, SA: South Africa, WC: Western Cape.

2.4.2 Global diarrhoea incidence

Globally, acute diarrhoea incidence among children under five years of age was estimated as 1.75 episodes per child year in 2016 (50), a 10% decrease since 2000 (2 episodes per child year) (50). Despite global decreases in incidence, sub-Saharan Africa remains disproportionately affected by diarrhoea, reporting the highest incidence rates in 2016 among children (2.37 episodes per child year) (50). Notably, the incidence in children in sub-Saharan Africa was approximately 35% higher than the global estimate (50).

2.4.2.1. Diarrhoea incidence in South Africa

Among children under five years, South Africa reported the highest number of episodes and incidence (2 episodes per child year) in southern sub-Saharan Africa in 2016 (50). This estimate is fourfold higher than in high-income settings (0.58 episodes per child year) (50). These differences may be driven by multiple factors including non-exclusive breastfeeding, unsafe water and sanitation, poor hygiene, and poor nutritional status (50) or better reporting in South Africa (versus other sub-Saharan African countries). Disaggregated estimates across provinces and districts are currently unavailable and urgently needed in South Africa.

2.4.3 Global meningitis incidence

Among children aged one to five years, global meningitis incidence was estimated as 192 cases per 100,000 population in 2019 (51), with the majority of global cases reported in children (53). From 1990 to 2016, global meningitis incident cases have increased by 13% across all ages (53). This may be due to increased awareness, especially in high burden areas, leading to better diagnoses and reporting over time. In 2019, sub-Saharan Africa reported the highest incidence rate among children (863 per 100,000 children) globally, despite an almost 50% decrease from 1990 (51). Although southern sub-Saharan Africa reported approximately 50% fewer cases than other areas of sub-Saharan Africa and an approximate 37% reduction in incident cases for all ages from 1990 to 2019, the burden of meningitis persists (51).

2.4.3.1 Meningitis incidence in South Africa

The incidence of meningitis in South African children aged one to four years in 2017 was 141 cases per 100,000 children (57). South Africa accounted for approximately half of the incident cases in the southern sub-Sharan region, recording a 16% reduction in cases since 1990 (53). The national incidence of invasive meningococcal disease, one common cause of acute bacterial meningitis, was estimated as 0.22 cases per 100,000 persons for all ages in 2018, similar to rates in 2017 and 2016 (21,58). Although estimates have plateaued in recent years, the national incidence decreased significantly since 2003 (0.97 cases per 100,000 persons) (58). Three provinces account for the majority of incident cases across all ages: Western Cape, Eastern Cape and Gauteng (21,58). The incidence of invasive meningococcal disease is higher in younger age groups (0.68 per 100,000 persons for children aged <15 years), specifically among children younger than age one year, for all serogroups (21,58). Among younger children, meningitis incidence, irrespective of cause, has not recently been quantified in the Western Cape and similar disparities across districts may be observed as seen with other infectious diseases discussed above.

2.4.4 Summary

The above-described incidence estimates for these infectious diseases further contribute to the understanding of the burden of disease based on mortality data as discussed in section 2.3. Similar to the mortality estimates, infectious disease incidence has decreased over time globally and within South Africa, with the exception of meningitis. Again, inter-provincial and intra-provincial differences were observed in South Africa and the Western Cape respectively.

2.5 Hospitalisation due to infectious diseases among children in South Africa and the Western Cape

Decreases in infectious disease morbidity over time have resulted in decreases in hospital admissions in children in a large tertiary hospital in the Western Cape, South Africa (19). The median length of stay decreased from nine to seven days in general medical wards from 2004-2013 (19). As infectious disease morbidity persists with severe disease resulting in hospitalisation, it is important to understand hospital admissions due to these infectious diseases in the Western Cape. When assessing hospitalisation rates, it is important to be aware that higher rates may not reflect greater morbidity overall, but rather better access to healthcare services, a lower threshold for admission, or better reporting and/or diagnostic coding practices.

2.5.1 Lower respiratory tract infections hospitalisation incidence

National pneumonia hospitalisation incidence has fluctuated recently: estimates were similar in 2014/15 (8.0 per 1,000 children) and 2018/19 (8.8 per 1,000 children), but lower in 2017/18 (6.2 per 1,000 children) (8,23). However, this lower 2017/18 rate may be due to changes in reporting as observed decreases may be due to the introduction of the updated National Indicator Dataset, which may have led to under-reporting of pneumonia cases in the early implementation phase (8). In 2022/23, the national incidence of pneumonia hospitalisations was an estimated 10.6 per 1,000 children under five years, approximately doubling from 2020/21 (5.1 per 1,000 children) (23).

As with the other statistics that have been examined (section 2.2-2.4), hospitalisation incidence estimates vary across provinces. The highest reported estimates in 2022/23 were in Western Cape (30.2 per 1,000 children), approximately three times higher than the national average (Figure 2.5) (23). Several sources have reported reductions for the incidence of pneumonia hospitalisation and lower rates of childhood HIV and improved rates of exclusive breastfeeding may also have contributed to this decline (8). However, the evidence is not consistent, with one study reporting a 40% increase in pneumonia hospitalisation incidence from 2010-2015 (20). Overall, the Western Cape reported the highest hospitalisation incidence due to pneumonia, despite reporting the lowest mortality in South Africa (section 2.2.4.2). As with the other conditions, there are disparities in hospitalisation incidence for pneumonia between districts in the Western Cape. The Central Karoo, Garden Route and Overberg districts reported the highest hospitalisation incidence (8). These three districts have also reported minimal change in all-cause mortality (section 2.2.4.2) (40). The Central Karoo and Garden Route districts also

reported the highest pneumonia related mortality in 2018/19 (8). The sustained burden of disease observed in these districts over time is concerning and should be further investigated. Once more, the heterogeneity across geographic location confirms that factors that improve the provinces' overall performance are not universal across districts and needs to be understood.

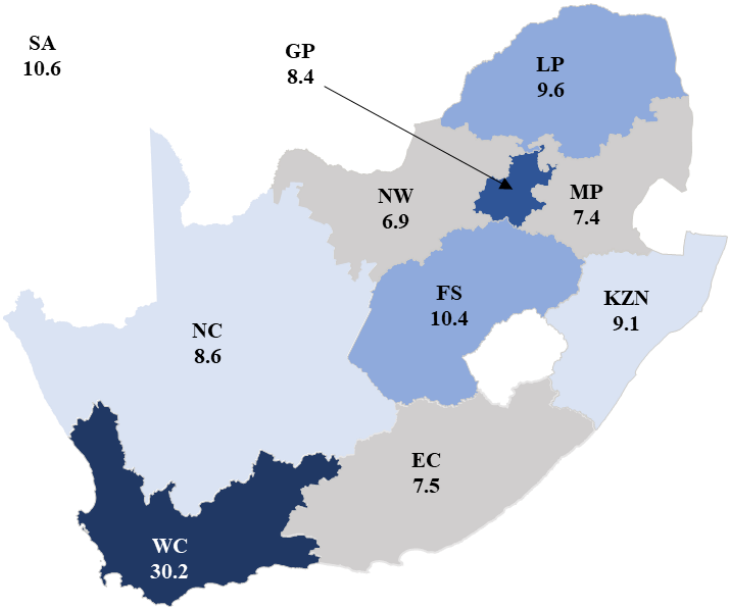


Figure 2.5. Estimated pneumonia hospitalisation incidence per 1,000 children under five years by province. Adapted from the District Health Barometer 2022/23 (23). Note: the colour coding does not represent the hospitalisation incidence, but rather highlights the different provinces.

EC: Eastern Cape, FS: Free State, GP: Gauteng, KZN: KwaZulu-Natal, LP: Limpopo, MP: Mpumalanga, NC: Northern Cape, NW: North West, SA: South Africa, WC: Western Cape.

2.5.2 Diarrhoea hospitalisation incidence

According to the District Health Barometer 2017/18 report, the most recent available data, 28,189 children under five years were hospitalised for diarrhoea in South Africa; a 35% decrease since 2010/11 (7). In 2014, the national incidence of diarrhoea hospitalisations was estimated at 6.9 hospitalisations per 1,000 children (59). At a large hospital in Gauteng, a similar incidence of diarrhoea hospitalisations was observed (676 and 612 per 100,000 children in 2015 and 2016 respectively) (60). Several South African studies have reported reductions in all-cause diarrhoeal hospitalisations ranging from 14-58% across different time periods from 2004 to 2015 (19,20,59,61). Provincial differences were observed in the number of hospitalisations, as seen with the other infectious diseases. The lowest number of admissions was observed in the Northern Cape (823 admissions) and the highest in the Western Cape (6,565 admissions) (7). Admission rates were not reported, and thus the higher absolute numbers in the Western Cape should be interpreted with caution as it may be reflective of being

one of the more populous provinces (higher denominator), better access to healthcare or better reporting (section 1.2, Chapter 1). Once more, this is the opposite pattern from mortality (Section 2.3.2.1), for which the Western Cape has reported the lowest estimates across provinces. Lower rates of HIV and severe acute malnutrition (SAM) among children in the province (8) may have contributed to improved outcomes among diarrhoeal cases. However, across districts in the Western Cape, the number of hospitalised cases due to diarrhoea varied substantially (7), suggesting that the hospitalisation incidence may range considerably as well.

2.5.3 Meningitis hospitalisation incidence

Meningitis has persisted in the top ten causes of childhood hospitalisation from 2008 to 2013 across the Western Cape (19). A tertiary hospital in the City of Cape Town recorded a 33% increase in meningitis hospitalisations (including TBM) in children <13 years between 2007 and 2009 (177 to 236 episodes) (62). This increase may in part be due to the increase in TB incidence in the province over the same time period, thus resulting in more TBM cases among susceptible children (62). This is supported by the median age of hospitalisation being 17 months; as younger children are mainly admitted for bacterial meningitis, whereas older children are admitted for aseptic/viral meningitis or TBM (62). A high proportion of children were admitted for TBM, with a doubling of cases since previous surveys in the same setting raising concerns about children's exposure to TB-infected individuals and the effect of not receiving Bacillus Calmette-Guérin (BCG) vaccine at birth due to stock shortages (62). These findings suggest poor TB control amongst this vulnerable group in this setting. Similar inequities may be observed at a district level, but the shortage of updated data for the Western Cape suggests a gap in current knowledge.

2.5.4 Summary

Pneumonia and diarrhoea hospitalisation incidence is persistently higher in the Western Cape, as compared to the rest of the country. This was also observed for the incidence of these infectious diseases, as discussed in section 2.4. The lack of updated hospitalisation incidence estimates makes the burden of disease in this vulnerable age group difficult to estimate. The geographic patterns for the above-described estimates, and estimates discussed in 2.2 and 2.3, are useful to track, as they provide information about the highest burdened areas which may require additional support and interventions. Furthermore, the lack of data on the burden of repeat infectious disease admissions makes it difficult to determine if children are experiencing

multiple admissions due to infectious diseases. Therefore, understanding re-admissions is crucial for implementing interventions to reduce these occurrences.

2.6 Infectious disease morbidity and mortality in South Africa summary

The persistence of these infectious diseases within low- and middle-income countries is concerning, especially as these deaths are mostly preventable through measures such as vaccinations, often included in national immunisation programmes such as the EPI in South Africa. It is vital to understand the contribution of these infectious diseases to morbidity and mortality, both in- and out-of-facilities. Furthermore, as child mortality continues to decline, we need an increasing focus on child morbidity to ensure that children grow and develop optimally, to ensure that they thrive and do not just survive (27).

There is a decreasing trend in infectious disease mortality and morbidity over time among children aged under five years globally, in South Africa and the Western Cape. There is heterogeneity in infectious disease morbidity and mortality among children within and across provinces in South Africa, which may be driven by inequities in the healthcare system as described is section 1.2 of Chapter 1. Some apparent differences between areas may be artificial, due to case diagnosis and recording/reporting issues, whereas some may be real, driven by differences in access to and quality of healthcare (7,8). When comparing the Western Cape to the other provinces, it appears that the province is performing better in terms of mortality, which may be driven by better access to healthcare, better case identification, potential differences in case definitions, early presentation with less severe disease, improvements in the quality of healthcare, increased vaccine coverage and improved breastfeeding rates. However, compared to wealthier countries, the province is still lagging. Furthermore, there is significant heterogeneity and inequity that exists across Western Cape districts, suggesting that factors associated with improved outcomes are not universal across the province. Certain districts, such as the Central Karoo, continue to report poor performance for mortality, incidence and hospitalisation estimates. In addition, the current evidence on mortality, incidence and hospital admissions in the Western Cape is outdated and/or not available for the whole province and its districts. Using updated data to assess temporal trends in these infectious diseases would identify changes in population vulnerability over time and quantify the district specific burden of disease, informing planning of programmes to improve child health.

2.7 Risk factors for infectious diseases morbidity and mortality globally and in South Africa

Common risk factors for morbidity and mortality across pneumonia, diarrhoea, and meningitis include health, environmental, social, nutritional, water, sanitation and hygiene related factors (7,8). Risk factors fall into two broad categories: those altering the risk of acquiring the infection, and those associated with poor health outcomes. An extensive list of risk factors for each disease is summarised in Table 2.1, with selected risk factors discussed below. Given the frequent clustering of these risk factors, many children experience one or more of these infectious diseases more than once throughout childhood, sometimes requiring one or more hospitalisations, especially in developing countries such as South Africa.

2.7.1 Lower respiratory tract infections

Pneumonia-related mortality is strongly correlated with age, rapidly declining from 67% of all deaths at six months of age to 6% of all deaths at 30-54 months of age in South Africa (63). Younger age is frequently reported as a major risk factor in children for acquiring pneumonia and experiencing adverse outcomes such as mortality and hospitalisation (47,63–65). In the Drakenstein Child Health Study, the incidence of LRTIs decreased from the first (0.51 episodes per child year, 95% confidence interval [CI] 0.47-0.55) to second year of life (0.25 episodes per child year, 95% CI 0.22-0.29) (64). One South African study reported that the risk of pneumonia mortality in infants (younger than one year of age) is approximately seven times higher compared to children one to four years old (relative risk 6.73, 95% CI 6.23-7.03) (47).

Birth related factors such as preterm birth and low birthweight have also been associated with pneumonia. In the Drakenstein Child Health Study, children born preterm had an increased risk of pneumonia when compared to full term births (incidence rate ratio [IRR] 1.52, 95% CI 1.04-2.20) (66). Furthermore, increased pneumonia incidence has been observed for children who were moderately and severely underweight (weight-for-age Z-score <-2: IRR 2.25, 95% CI 1.41–3.48 as compared to weight-for-age Z-score >-2) and stunted (length-for-age Z-score <-2: 1.76, 95% CI 1.17–2.58 as compared to length-for-age Z-score >-2). Being underweight or stunted in the first few months of life may be due to poor postnatal growth and/or low birthweight with poor catch-up growth (66).

Improvements in PVT of HIV and reductions in childhood HIV infections have substantially decreased the risk of acquiring pneumonia and the incidence of pneumonia (8,19,63,67,68). Pneumonia-related hospitalisations and mortality remain substantially higher in children living

with HIV in comparison to those who do not have HIV (47). In South Africa, where the prevalence of HIV remains high among children relative to other similar countries, the relative risk for mortality due to pneumonia in children living with HIV (under five years) was estimated to be 25 times higher (95% CI 21-26) in 2012-2013 compared to children living without HIV (47). ART data were not available for this analysis, but ART guidelines have progressively expanded from children meeting clinical or CD4 criteria in 2004, to all children under two years in 2010, under five years in 2013, and everyone by 2015, with early diagnosis through birth testing only becoming widely available from 2015/16 (69). This suggests that the risk for pneumonia should have been reduced due to improved immune function provided by ART at the time of the analysis. HIV exposure status has also been associated with LRTI morbidity: infants living without HIV who were exposed to HIV in-utero had a higher risk of LRTI hospitalisation particularly in the first six months of life when compared to HIV unexposed infants (64).

The odds of severe LRTI, including pneumonia, are higher in the first four months of life in non-exclusively breastfed infants in developing countries (odds ratio 2.7, 95% CI 1.7-4.4) (70). Consequently, the Global Action Plan for pneumonia and diarrhoea recommends exclusive breastfeeding for the first six months of life to significantly reduce the incidence and severity of both pneumonia and diarrhoea cases (8).

Historically, pneumonia morbidity and mortality have also been associated with low socioeconomic status. Related factors include household crowding and pollution, poor childhood nutrition and poor water, sanitation and hygiene, all of which increase the risk of acquiring pneumonia and experiencing adverse outcomes (8,63,67). Improvements in living and socioeconomic conditions have been associated with declining pneumonia incidence and mortality globally, as well as in South Africa (8,19,63,67). However, these improvements are not universal and they, along with other environmental factors, remain substantial risk factors of pneumonia morbidity and mortality in South Africa (64). Environmental changes are observed in South Africa, with pneumonia hospitalisations and deaths typically increasing in winter months (June to August) (19,32,64).

The Pneumonia Etiology Research for Child Health study developed a severity score for pneumonia, which discriminated between death and survival among pneumonia cases (C-statistic = 0.82). This severity score could assist in determining the likelihood of adverse outcomes based on identified risk factors. The factor with the highest discrimination was the

number of World Health Organization (WHO) dangers signs (Table 2.1), with the highest predicted mortality (33%) observed among children with ≥2 danger signs (65).

2.7.2 Diarrhoea

Major risk factors for diarrhoea morbidity and mortality are unsafe water, sanitation and hygiene, and improvements in these factors result in significant reductions in diarrhoeal related deaths globally (49,50). However, challenges remain: it has been estimated that 94% of global diarrhoeal deaths in 2017 could have been averted through providing safe water, sanitation and hygiene to children younger than five years (49). Similarly, in sub-Saharan Africa and South Africa, 96% of child deaths were reportedly due to these same factors (49).

Risk factors related to nutrition, including failure to grow/thrive and vitamin A and zinc deficiencies, as well as low use of oral rehydration solutions, are associated with diarrhoea morbidity and mortality (49,50). Estimates suggest that globally, enhancing nutrition could have prevented 88% of diarrhoeal deaths among children under five years old, while expanding the availability of oral rehydration solution could have prevented 58% (49). Similar proportions for these risk factors were reported in sub-Saharan Africa and in South Africa (49).

Non-exclusive breastfeeding remains a major risk factor for diarrhoea among children under five years (7). Improvements in breastfeeding practices have been correlated with improved child health outcomes. These improvements are suggested to have decreased diarrhoea-related mortality in children under five years with an estimated 2% decline in sub-Saharan Africa from 2010 to 2016 (50). Birth-related factors, such as prematurity and neonatal hospitalisations are thought to impact diarrhoea incidence and mortality (71). However, in the South African context, there is a paucity of data, with only one study reporting estimates for the association between diarrhoea and prematurity which were not statistically significant (72).

In South Africa, reductions in diarrhoeal hospitalisation may be due to improved management within primary healthcare facilities and seasonal increases in resources and staff in hospitals (20). Additionally, improvements in HIV management and socioeconomic conditions may have contributed to the reductions observed in the acquisition of all-cause diarrhoea and subsequent hospitalisations among children (59). Despite these improvements, the increase risk of adverse events, such as dying from diarrhoea, has been observed in children with HIV and in younger children (aged younger than six months) in South Africa (60).

The risks of acquiring diarrhoea and of having adverse outcomes such as requiring hospitalisation appear to be seasonal and differ across several studies. Overall, hospital admissions tend to increase from March to May (19,59), with one study reporting increases until August (61). However, this seasonal trend became less pronounced after the introduction of the rotavirus vaccine (RV) in 2009 (59). Diarrhoeal infections and deaths tend to peak around winter months as well (32,73). Overall, the surge season for diarrhoea cases has been observed from November to May annually, with specific interventions implemented each season to manage the increased case load in hospitals (74).

2.7.3 Meningitis

Childhood meningitis is associated with several factors which often occur in combination in many children in a particular community and subsequently result in an epidemic. Health-related risk factors in children include malnutrition, living with HIV, lack of immunisation against common causative agents, acute respiratory infections, sickle cell disease and a splenectomy (52,53,75,76). Higher incidence of meningitis has been observed in individuals living with HIV in South Africa across all age groups (58), with an estimated nine times higher incidence rate estimated in children living with HIV compared to children living without HIV (77). Younger age also increases the risk of acquiring meningitis, with children aged 0-4 years being at a higher risk of contracting meningococcal disease as compared to individuals older than 15 years (77).

Socioeconomic factors such as overcrowding, poor housing and low educational and income levels have been strongly associated with meningitis, particularly in African countries (52,53,75,76). Additionally, exposure to maternal or passive smoking is known to increase the risk of acquiring invasive meningococcal disease in children (75,76).

Environmental risk factors include seasonality, with dry seasons being associated with an increase in meningitis cases and epidemics, especially across the meningitis belt (52,76). In South Africa, meningococcal diseases typically spike between May to September (late autumn and winter), with an additional peak observed in December (summer) in South Africa across all age groups (21).

2.7.4 Summary

There are common risk factors for these infectious diseases which increase the likelihood of acquiring the infectious disease and to experiencing poor outcomes, such as hospitalisation and

death. While several risk factors have been identified for children in a South African setting, the relative contributions of these risk factors are not known at a population-level for children under five years of age. Identifying key risk factors that increase children's vulnerability to repeated poor outcomes, such as hospitalisation, is important, as it offers an opportunity to intervene, particularly during their first hospital admission. Reducing re-admissions is important to improve health outcomes and quality of care as well as implement interventions that could reduce the burden on health facilities (78,79). By understanding the risk factors for repeat admissions in these vulnerable children, it is possible to implement interventions aimed at: i) addressing population-level vulnerabilities, such as vaccinations, ii) mitigating specific risk factors, such as HIV prevention and treatment programmes, and iii) providing targeted interventions for those at highest risk during their first infectious disease admission by addressing the combination of risk factors.

2.8 Vaccinations for infectious diseases in South Africa

As mentioned, population-level interventions such as vaccinations play an important protective role against infectious diseases. As this research project will focus LRTIs, diarrhoea and meningitis, the following section will focus on the three related, routinely administered vaccines including the PCV, RV and BCG vaccine. The meningitis vaccine will also be discussed. Although not routinely administered, it is available in South Africa.

South Africa launched the EPI in 1974, which has expanded and currently includes childhood vaccines for polio, TB, rotavirus, diphtheria, tetanus, pertussis, *Haemophilus influenzae* type B, hepatitis B, pneumococcus, rubella and human papillomavirus as well as influenza for high risk patient groups, and maternal pertussis and diphtheria vaccines (23,80,81). In 2022/23, the national and Western Cape one-year vaccination coverage (proportion of children aged under one year who completed the primary course of immunisations) was 82.2% (23). The EPI has played a crucial role in reducing vaccine-preventable diseases in South Africa, a hyperendemic setting for many of these diseases. Incomplete vaccinations are not only a risk factor for infectious disease acquisition, but also for adverse outcomes. Additional prevention measures which aid in reducing infectious disease morbidity and mortality are listed in Table 2.1.

2.8.1 Pneumonia

To reduce childhood pneumonia related morbidity and mortality in South Africa, PCV7 was introduced into the EPI in April 2009. The vaccination was scheduled at six and 14 weeks of age, and a booster dose at nine months with no catch-up campaign (47,82–84). Due to the

persistent high burden of pneumonia in low- and middle-income countries, PCV13 was later designed to address additional serotypes which commonly cause disease in these countries (83). South Africa introduced PCV13 into the EPI in April/May 2011, following the same schedule, with a single-dose catch-up campaign for children 18-36 months (47,82–84). At the end of 2023, South Africa switched to PCV10, which is considered to have comparable immunogenicity and safety to PCV13 (85).

National coverage of the third dose of PCV increased from 64% in 2010 to 99% in 2012 (82). In South Africa, both PCV7 and PCV13 serotypes have effectively prevented childhood (under five years of age) pneumonia cases and hospitalisation, with PCV13 reportedly more effective (83,84,86). Pneumonia hospitalisations reduced over time (section 2.5.1), which coincided with the introduction of PCV. Before the introduction of PCV, studies reported high incidences of pneumonia hospitalisations among children under five years including 2,074 per 100,000 person years from 2005-2008 (47), 31 per 1,000 children in 2006 and 36 per 1,000 children in 2009 (84). Thereafter, the incidence of pneumonia hospitalisations decreased to 16 per 1,000 children under five years in 2014 (84). Significant declines were also observed among adults aged 25-44 years for all PCV7 serotypes, suggesting both direct and indirect effects of the introduction of PCV in South Africa (68). Based on model estimates and the incidence of pneumococcal disease pre-vaccine, the introduction of PCV was estimated to have decreased cases and deaths nationally by 65,800 and 3,100 respectively in children in 2012-2013 (47). Among children under five years who were HIV-exposed but uninfected or had an unknown HIV status, the introduction of PCV7 and PCV13 averted 2 and 7-9 pneumonia admissions per 1,000 children respectively (84).

A case-control study using national surveillance data estimated that two or more doses of PCV13 were 85% effective against pneumococcal disease caused by all serotypes included PCV13 (83). However, this finding did not persist among non-PCV13 serotypes, after adjustment among children with HIV aged ≥16 weeks (83). Timely administration and completion of all vaccines are essential, as late or missed vaccinations are a risk factor for pneumonia hospitalisation (64).

2.8.2 Diarrhoea

The RV was shown to be highly efficacious in Latin America, Europe, and the United States in the early 2000s (87–89). However, little was known about the efficacy of the vaccine in many developing countries (90). In a double-blinded, randomised, placebo-controlled trial conducted

in South Africa, the vaccine efficacy of Rotarix® in South African children in the first year of life was approximately 77% and 44% for severe rotavirus and all-cause severe gastroenteritis respectively (90). Although lower efficacy was observed when compared to other low- and middle-income countries, the Strategic Advisory Group of Experts recommended introducing the RV into African national immunisation programmes together with other diarrhoea prevention strategies (90). The live oral RV was subsequently implemented into the South African EPI in August 2009, with a recommended two doses: one at six weeks to induce partial immunity as soon as possible and another at 14 weeks to ease logistics with the concurrent introduction of PCV (82).

National coverage rates for the second dose of the RV increased by 29% over one year (67% in 2010 to 96% in 2011) (82). Notably, among children younger than two years, it was estimated that the RV averted 13,000-20,000 hospitalisations in 2010 and 2011 (61), with studies reporting reductions in hospitalisations ranging from 24% to 58% (19,20,59,61). The reduction in non-rotavirus hospitalisations has been more modest: 14% in 2010 and 2011 (61). Despite all-cause diarrhoeal hospitalisations being used as a proxy, this evidence provides a sense of the public health impact that the RV has had in South Africa (59). Reductions in diarrhoea related hospitalisations have been the greatest in children aged under one year compared to older children (25-29 months) (59,61). The RV appears to provide protection in South Africa, where 5% of diarrhoeal deaths were due to low RV coverage among children under five years (49).

Evidence on the duration of the protective effect is varied. A study in several South African hospitals from 2010 to 2012 estimated the adjusted vaccine effectiveness of the second dose of Rotarix® as 57%, and similar across the two age groups (18 weeks to 11 months and 12-23 months) (91). This evidence suggests there may be continued protection for up to two years against acute rotavirus diarrhoeal hospitalisation (91). However, another South African study suggests the protective effect diminishes after the first year of life (61). Although two doses of the vaccine were more effective, protection was provided through a single dose only. This is reassuring as single dose administrations are likely to occur in many low- and middle-income settings such as South Africa (91).

2.8.3 Meningitis

Tetravalent polysaccharide and protein-conjugate meningococcal vaccines have been licensed in South Africa since 2014, but are not administered routinely in the EPI (58,92). A monovalent

conjugate meningococcal (MenAfriVac) vaccine has been used across African settings since 2010, specifically along the meningitis belt. The vaccine is safe to administer and effective in reducing meningitis outbreaks, significantly decreasing meningitis incidence (52,93). More recent advances for controlling meningococcal disease in the African meningitis belt has been the multivalent conjugate vaccine, Men5CV, which has been recommended by the WHO (94). Toward the end of 2023, Nigeria has started using this vaccine and it is recommended that other countries in the African meningitis belt use the same or similar vaccines to further reduce the incidence of invasive meningococcal disease by 2030 (94,95). Vaccinations against other common causes of bacterial meningitis include the *Haemophilus influenzae* type b conjugate vaccine and PCV, both routinely available in the South African EPI (96). Globally, these two vaccines have been associated with declines in meningitis cases due to increased vaccine coverage (53).

The BCG vaccine protects children against miliary TB and TBM, but provides little protection against adult TB (97,98). The BCG vaccine was first available in South Africa from the early 1960s and was administered routinely at birth through the percutaneous route (99). Since 2000, the route of administration changed to an intradermal route and high coverage rates have since been reported in South Africa (80,100). Since 2013, there have been global issues in obtaining the BCG vaccine due to production shortages or stockouts (98), resulting in a drop in BCG vaccination coverage in the Western Cape from 95% in 2014 to 89% in 2015. Thereafter, a large tertiary hospital saw an increase in hospital admissions due to TBM and tuberculomas (98). It is critical to ensure a continued supply of the BCG vaccine in the EPI, as the BCG vaccine may play a crucial role in controlling certain severe forms of childhood TB in South Africa.

2.8.4 Summary

Since the implementation of PCV and RV, studies have shown great reductions in hospitalisations and good vaccine effectiveness in South Africa. Widespread use of these vaccines should continue to be promoted in South Africa as part of pneumonia and diarrhoea prevention strategies to reduce infectious disease morbidity and mortality in this setting. Furthermore, it is important to monitor BCG stockouts in this setting, as an anecdotal report suggests increases in severe forms of childhood TB during BCG stockouts (98). To control meningitis in South Africa, it is important to vaccinate eligible children and continue vaccinating against common bacterial causes.

2.9 Impact of the COVID-19 pandemic on infectious diseases

COVID-19 hit African shores in February 2020 and the estimated number of hospitalisations and deaths, and requisite de-escalation of routine services to cope with the COVID-19 surge, were expected to impact the already strained healthcare services across the continent (101). To mitigate virus transmission, the South African government implemented strict public health and social measures (PHSM) which included school closures, physical distancing, wearing of face masks/coverings, promotion of hand hygiene and provision of alcohol-based sanitisers, curfews and limits on gathering sizes (102,103). Many of the PSHM implemented was expected to reduce infectious disease transmission which contributes to ongoing morbidity and mortality in children.

However, an unintended consequence of these measures was reduced access to routine healthcare services. At the start of the epidemic, emerging evidence from South Africa, suggested that child healthcare access decreased significantly in rural KwaZulu-Natal during the 34 days of the strictest PHSM implementation in the country (101). The study found that the number of child healthcare visits halved among children younger than one year and 1-5 years, with approximately seven fewer visits per day per clinic, on average, for all children younger than five years. In the next implementation of PHSM, which allowed somewhat more movement, this number slightly increased, with approximately 1.1 more visits per day per clinic for each week. The reduction in child healthcare visits was expected to have reduced childhood immunisation (101). However, this was not the case for the entire pandemic period. A national study found that most provinces experienced a decline in immunisation coverage in 2020, which subsequently recovered in 2021 (102). This was also observed in the national immunisation under one year coverage, where it declined by 4% from 2019/20 (83.5%) to 2020/21 (79.5%) but subsequently recovered to 85.5% in 2021/22 (19). Despite immunisation coverage rebounding, there may have been a resultant immune gap in children who did not receive their vaccinations on time. Therefore, restoring child health services to implement catch-up campaigns for immunisation became important. The Western Cape implemented a catch-up drive in 2020 to increase immunisation coverage and observed higher immunisation coverage when compared to 2018 and 2019 (19,103). This is important given that the childhood vaccinations in the EPI are protective against pneumonia and diarrhoea, which are prevalent across South Africa.

The immune gap may have played a role in the resurgence of infectious diseases, especially those that children were traditionally vaccinated against. For example, there was a sharp decline in pneumonia hospitalisations across South Africa in 2020/21 (5.1 admissions per 1,000 children) when compared 2019/20 (8.5 admissions per 1,000 live births) (19), as discussed in section 2.5.1. Changes in healthcare access may have also contributed to the observed reduction in hospital admissions. PHSM implemented across South Africa restricted movement of individuals, particularly in the strongest implementation of these measures (100), and there was fear of acquiring COVID-19 at facilities. Both these factors could have contributed to reduced healthcare access, as well as the direct effect of PHSM in actually reducing transmissions of infectious diseases. As PHSM eased, there was an increase in pneumonia hospitalisations in 2021/22 (7.1 admission per 1,000 children), with hospitalisation rates increasing beyond pre-pandemic levels in 2022/23 (10.6 admissions per 1,000 children) (19). It is vital to monitor short- and long-term impacts of the changes in childhood infectious diseases to better plan for future pandemics.

2.10 Summary and the need for further evidence in South Africa

2.10.1 Literature review summary

The U5MR in South Africa has declined from 1997 to 2018, dropping from an estimated 65 deaths per 1,000 live births to 34 deaths per 1,000 live births (4). However, fluctuations occurred over the years, with a peak in 2004 at an estimated 79 deaths per 1,000 live births (4). While continuous declines were noted, there were variations in estimates for certain years, reflecting limitations in data accuracy. In the Western Cape, despite fluctuations, a consistent downward trend in U5MR was observed from 1997 to 2012, with estimates ranging from 21 to 24 deaths per 1,000 live births (4,37). Notably, the Western Cape had already achieved the 3rd SDG in 2011.

In terms of childhood mortality within facilities, the Western Cape consistently reported lower rates compared to the national average (23). However, within the province, there were disparities across districts, with some areas exhibiting slightly higher mortality rates than reported for the province overall due to heterogeneity and inequities.

LRTIs, including pneumonia, are a leading cause of child mortality nationally and in the Western Cape (23), despite decreasing incidence over time (8,56). Disparities in pneumonia mortality and hospitalisation rates were observed across provinces and districts, with the Western Cape reporting the lowest mortality rate but the highest hospitalisation incidence (23).

Factors contributing to these variations include proportion of children with HIV and on ART, exclusive breastfeeding practices, and healthcare access.

Similarly, diarrhoea persisted as a significant cause of childhood mortality, despite substantial reductions in hospitalisations nationally since 2010/11 (7). However, provincial- and district-level disparities existed, with the Western Cape reporting the highest number of admissions but the lowest mortality rates among provinces.

Meningitis remains a concern, particularly in the Western Cape, where a notable increase in hospitalisations was recorded between 2007 and 2009 (62). This increase was attributed, in part, to rising TB incidence (62), highlighting challenges in TB control among vulnerable populations.

Overall, while the Western Cape generally outperforms other provinces in child mortality indicators, significant intra-provincial disparities exist, underscoring the need for targeted interventions at the district-level. Additionally, gaps in data availability underscore the importance of continuous monitoring and research to address ongoing health challenges effectively.

2.10.2 Limitations of reporting of infectious diseases in South Africa and the Western Cape

Reporting of infectious disease morbidity and mortality among children in South Africa is mainly focused on pneumonia and diarrhoea (7,8,32), which contribute substantially to childhood disease, as discussed in sections 2.3-2.5. However, these estimates are often outdated and have not been reported across the Western Cape province, especially for diarrhoea. The findings of reduced pneumonia and diarrhoea morbidity and mortality may not be generalisable and uniform across the Western Cape, given intra-provincial heterogeneity in health outcomes.

The high burden of meningitis in Africa highlights the need for good surveillance data on interventions to reduce meningitis-related morbidity and mortality in children. However, given the paucity of published data or reports, further research is needed to understand the current burden.

Hospitalisations are not well characterised across the Western Cape province, with previous studies focusing on selected hospitals and all-cause hospitalisation (19,20). Furthermore, larger age ranges are often reported and not disaggregated for children under five years, making it hard to understand the ongoing burden of diseases in this age group (19,22,58). Beyond this, it is currently not known what the risk factors are for repeat infectious disease admissions,

making it hard to develop effective interventions aimed at reducing these admissions among children. There is also limited data available on the changes in childhood hospitalisations due to COVID-19 and the associated PHSM. Investigating this would be crucial to inform future pandemic planning.

2.11 Conclusion

Given the current limitations of the data, studies and reports, this study aims to investigate the key diseases contributing to childhood (under five years) infectious disease morbidity and mortality in the Western Cape province of South Africa, in line with the rationale and aim presented in section 1.3 and 1.4. As childhood mortality continues to decrease, there has been an increased focus on childhood morbidity. Limited and outdated data are available for these infectious diseases across the Western Cape province. Therefore, recent data are required to understand the burden and drivers of these infectious diseases between 2007-2021 in the Western Cape province. This would provide valuable insight to healthcare providers and policy makers to ensure children receive optimal healthcare in order to thrive in life.

Table 2.1. Summary of key characteristics for lower respiratory tract infections (including pneumonia), diarrhoea, and meningitis.

Infectious disease	Definition	Causative agent/aetiology	Risk factors	Specific prevention strategies	Diagnosis and management
Lower respiratory tract infections (including pneumonia)	*According to the WHO*: Pneumonia: tachypnoea and/or chest indrawing. Severe pneumonia: cough or difficulty breathing with either central cyanosis or oxygen saturation <90%; severe respiratory distress; or any general danger sign. No pneumonia: no signs of pneumonia (104,105). Other definitions rely on the diagnosis by a physician, which relies on their clinical knowledge or on the respiratory rate of the patient (63). WHO danger signs (63): 1) for children younger than 2 months of age: unable to drink, breastfeed or feed well, vomiting all food, convulsions, lethargy, unconsciousness, no movement, cyanosis, stridor, grunting, severe chest in-drawing, ≥60 breaths per minute, fever (≥38ºC) and low body temperature (<35.5ºC). 2) for children ≥2 months: unable to drink/breastfeed, vomiting all food, convulsions, stridor, lethargy and unconsciousness	Bacteria: *Staphylococcus aureus, Haemophilus influenzae, Streptococcus pneumoniae, Mycobacterium tuberculosis, Bordetella pertussis, Klebsiella pneumoniae* Viruses: RSV, Rhinovirus, Influenza, Human metapneumovirus, Adenovirus, Parainfluenza virus, Measles virus Herpes viruses (Cytomegalovirus, Epstein–Barr virus), Coronaviruses Fungi: *Pneumocystis jirovecii* (105).	Infancy, low PCV and *Haemophilus influenzae* type b conjugate vaccine coverage, malnutrition, having or being exposed to HIV, winter season, exposure to smoke or indoor air pollution, passive smoke, maternal smoking, zinc deficiency, no handwashing, low socioeconomic status, lack of exclusive breastfeeding, low birthweight, stunting, underweight, severe wasting, younger maternal age, low maternal education, poor antenatal care (55,63,64,105,106).	Childhood immunisation (pneumococcal conjugate vaccine [PCV7, PCV10 or PCV13], *Haemophilus influenzae* type b conjugate vaccine, RSV vaccine), maternal immunisation (pertussis, and influenza), nutrition supplements (zinc and vitamin A) and promoting breastfeeding (105,107).	Diagnosis: clinical signs, chest imaging, blood tests, aetiological diagnosis (nasopharyngeal aspirates/swabs, blood, urine), lung ultrasound (63,105). Management: antibiotics, corticosteroids, oxygen, continuous positive airway pressure, and micronutrients (105,107).

Infectious disease	Definition	Causative agent/aetiology	Risk factors	Specific prevention strategies	Diagnosis and management
Diarrhoea	*According to WHO* (104)*:* Acute/watery diarrhoea: >3 stools per day/24 hours and no blood in stools Dysentery: reported or observed blood in stool Persistent diarrhoea: diarrhoea enduring for 14 days or longer Diarrhoea with severe malnutrition: any type of diarrhoea plus signs of severe malnutrition Diarrhoea associated with recent antibiotic use: diarrhoea due to resent use of broad-spectrum oral antibiotics Intussusception: presence of blood in stool, abdominal mass and attacks of crying in pale infant Cholera: stool positive for *Vibrio cholerae* and diarrhoea with severe dehydration during a cholera outbreak	Common diarrhoea aetiologies in children younger than five years: Bacteria: *Aeromonas*, *Campylobacter*, *Vibrio cholera*, *Clostridium difficile*, Enteropathogenic *Escherichia coli*, Enterotoxigenic *Escherichia coli*, non-typhoidal *Salmonella*, S*higella*. Viruses: Adenovirus, Rotavirus, Norovirus Parasite: Amoebiasis, *Cryptosporidium* (50).	Childhood wasting, underweight and stunting; unsafe sanitation, low coverage of oral rehydration solution, unsafe water sources, underweight, stunting, low coverage of RV, no access to handwashing facilities or poor handwashing, non-exclusive or suboptimal breastfeeding, low coverage of zinc treatment or zinc deficiency, vitamin A deficiency, low birthweight and shorter gestation (49,50). Rotavirus infections and all-cause diarrhoea are more common in dry and cool winter months in southern Africa, specifically South Africa (59,73).	Safe water, hygiene and sanitation, handwashing, rotavirus, typhoid and cholera vaccine, improving nutritional supplementation (49,73,90).	Diagnosis: laboratory tests, clinical features (73). Management: oral rehydration solution, intravenous fluid replacement to restore electrolytes, supplementary nutrition (49,73).

Infectious disease	Definition	Causative agent/aetiology	Risk factors	Specific prevention strategies	Diagnosis and management
Meningitis	Meningitis is the inflammation of the meninges surrounding the brain or spinal cord and signs included: drowsiness or unconsciousness, stiff neck, irritability, less frequent feeding, high pitched, excessive or unexplained crying, recurring apnoeic episodes, bulging fontanelle, fever, hypothermia, vomiting, seizures, convulsions, headaches, respiratory distress, jaundice (96,104).	Bacteria: *Neisseria meningitidis, Streptococcus pneumoniae, Haemophilus influenzae, Escherichia coli, Mycobacterium tuberculosis, Klebsiella pneumoniae, Staphylococcus aureus* Viruses: Herpes simplex, Cytomegalovirus, Enterovirus, Varicella Zoster Fungi: Cryptococcal meningitis (62,96).	Common risk factors include malnutrition, household crowding, indoor air pollution, HIV infection, lack of immunisation and sickle cell disease (53,75). Various risk factors including environmental, host and organism factors which often occur in combination to result in an epidemic and include: susceptibility of the population, seasonality (dry seasons), low socioeconomic status (poor housing and low education and income level), crowding, virulence of the transmission strain, acute respiratory infections (52,76).	Vaccines targeting bacterial causes of meningitis include *Haemophilus influenzae* type b conjugate vaccine and PCV13/10, both used in the South African EPI(96). There are also Neisseria meningitidis vaccines (conjugate or polysaccharide vaccines) that have been licensed in South Africa but not used in the South African EPI (58).	Diagnosis: lumbar puncture, bacterial antigen tests on cerebrospinal fluid, chest X-ray, fungal culture of blood and urine, cryptococcal antigen test, ophthalmological assessments, electrolyte testing, polymerase chain reaction for suspected viral meningitis (96). Management: antibiotics, fluid management, treating other symptoms, specifically for viral meningitis (96).

EPI: Extended Programme on Immunisation, HIV: human immunodeficiency virus, PCV: Pneumococcal conjugate vaccine, RSV: Respiratory syncytial virus, WHO: World Health Organization.

CHAPTER 3

Data management

3.1 Overview

Given the large volume of data and multiple data sources, I needed to undertake and complete a substantial amount of data management to develop a base dataset that could be used as a starting point for each of the respective analyses outlined for each Objective. This chapter will detail the data sources, data variables and calculations, data quality checks, data governance, and data management and analyses software.

3.2 Data sources

Several data sources were utilised across the four Objectives in this thesis and are described in more detail below: WCPHDC, DHIS, and population estimates.

3.2.1 Western Cape Provincial Health Data Centre

The WCPHDC is a single consolidated environment that links individuated patient-level health data from different health information systems. It uses a unique identifier available in all patient administration systems in public health facilities in the Western Cape, South Africa (10). Data sources include hospitals (both inpatient and outpatient visits), primary healthcare facilities (outpatient visits), diagnostic laboratories, pharmacies, disease management systems, community data, partner systems, and mobile health systems (10). An overview of the architecture is summarised in Figure 3.1.

The primary focus of the WCPHDC is to provide data for service delivery and support clinical care. These data enable the identification of patient health service contacts (e.g. outpatient visits or admissions), and healthcare utilisation for and outcomes of health conditions (e.g., HIV, TB, pregnancy). Health conditions are inferred with varying levels of certainty using multiple data sources (e.g. diagnostic or disease specific laboratory tests, medication, disease management system data and diagnostic codes). Depending on the source, data are updated and linked either daily, monthly, quarterly or on an ad hoc basis (10). Integration of this data improves the data quality, reducing the concerns regarding a single data source.

I used the following data sources that are consolidated within the WCPHDC (Table 3.1): Routine Health Information System (RHIS), Child PIP, and Death Notification (DN) Surveillance data. Each dataset comprises multiple data variables, as described below. Table

3.1 provides an overview of these three data sources within the WCPHDC as well as the variables extracted for each of the analyses. Using all available data, I created a de-duplicated dataset for this project's analyses, as described in Section 3.3.

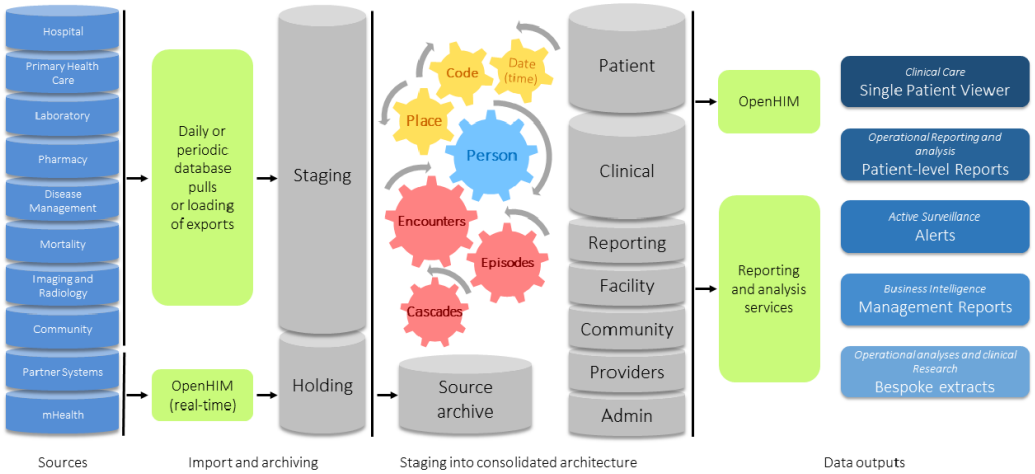


Figure 3.1. The architecture of the Western Cape Provincial Health Data Centre (10).

Routine Hospital Information System

RHIS (known as Clinicom (10) and Electronic Continuity of Care Record) is used in Western Cape hospitals to record patient demographics, admissions, discharge summaries, diagnostic codes (International Classification of Diseases 10th Revision [ICD-10]) and hospital administration data against unique identifiers (10). Reporting has improved incrementally since 2007 as hospitals became networked in the province (108). Currently each hospitalisation and the corresponding outcome (death, transfer to another facility or home discharge) is recorded.

3.2.1.1 Child Healthcare Problem Identification Programme

Child PIP was established in 2005 to audit all in-facility deaths in children (0-18 years) in South Africa and aims to improve healthcare provision (28,109) (Table 3.1). This mortality review process involves detailed steps in which i) the child death is reviewed within 24 hours, ii) a nurse and doctor present cases at weekly or monthly mortality meetings, and, iii) data management and analyses identify trends and makes recommendations to address modifiable factors within and outside of healthcare services (109). The cause of death is identified through a clinical audit process. As Child PIP is voluntary, uptake varies within the Western Cape, with 37 out of 43 hospitals (86%) currently participating and this coverage has increased since earlier years. Patient-level data are collected at the facility-level to review practices, and are reported into a national Child PIP database to inform policies nationally. Key social and

nutritional data are collected to describe the circumstances surrounding the death. Critical to the process is identifying potential modifiable factors with the purpose of identifying problems for prioritising and planning. Modifiable factors are divided into two categories: person (e.g., administrator, clinical personnel, caregiver) and place (e.g., ward, home, referring facility).

3.2.1.2 Death Notification Surveillance

The Western Cape Government Department of Health and Wellness (WCGHW) , City of Cape Town and South African Medical Research Council Burden of Disease Research Unit together developed a DN Surveillance system to monitor district and subdistrict mortality and causes of death (110) (Table 3.1), leveraging VR data reported to the South African Department of Home Affairs (DHA). Six district information offices collected copies of DN forms from the local DHA offices (110). Patient-level sociodemographic and cause of death information from the DN forms were captured, with data cleaning and mortality reports produced and provided to the province by the South African Medical Research Council. Cause of death data was shared with the WCGHW between 2010-2013. This system was discontinued from 2014 and the Western Cape no longer receives these data. These data linked to the WCPHDC may have been incomplete if children's South African identification numbers were not recorded or had incomplete name or date of birth data.

Table 3.1. Overview of data sources used for identifying infectious disease admissions and deaths in children under five years in the Western Cape.

	Sources utilised from the Western Cape Provincial Health Data Centre A single consolidated environment which houses individuated patient-level health data for the Western Cape.		
	Routine hospital information systems	*Child Healthcare Problem Identification Programme*	*Death Notification Surveillance*
Brief description	Routine hospital information systems in the Western Cape capturing key information for each admission, including the unique patient identifier, patient demographics and hospital administration data, and discharge codes and summaries.	A national audit programme of all in-hospital child (0-18 years) deaths in public health facilities that participate voluntarily.	All deaths, in- or out-of-facilities, occurring in the Western Cape were recorded once the DN forms had been captured by the DHA. These data were leveraged for DN with cause of death data being shared with the WCGHW.
Time period	01/01/2007-01/12/2021	23/05/2007-08/02/2021	01/01/2010-01/12/2013
Coverage	All public hospitals capturing in-facility deaths since the date when electronic admission and discharge data were networked into the WCPHDC.*	Selected public health facilities that voluntarily participate, thereby only capturing in-facility deaths in participating facilities.	All notified deaths in the province, in- or out-of-facilities. This study was restricted to in-facility deaths.
Source of death reporting	Admission ICD-10 coding (primary, subsidiary and secondary 1-10) from clinical records.	Cause of death as determined by clinical audit.	Cause of death as recorded on DN form.
Variables	Deaths: Date of death, ICD-10 codes recorded during admission (to determine proxy cause of death), and hospital admission date. Admissions: Birth, admission and discharge dates; ICD-10 codes for hospital admission cause, sex, admission ward, and place of residence.	Date of death, cause of death, and hospital admission date.	Date of death and cause of death.
Frequency of data source updates to the WCPHDC	Daily.	Approximately annually.	Annually, but no longer provided.

	Routine hospital information systems	*Child Healthcare Problem Identification Programme*	*Death Notification Surveillance*
Advantages	Complete and timeous recording of all deaths in facilities with electronic data capture as every separation (when a patient leaves hospital due to death, discharge, or is transferred) requires an entry.	Reports in depth information on child deaths, including modifiable factors. Reports are available timeously.	Includes all deaths (public and private health sector, and out-of-facility deaths) with associated causes.
Disadvantages	Only available for public health facilities and in-hospital deaths. The cause of death is not explicitly coded, but has to be inferred from the diagnostic code(s) for the admission during which the death occurred.	Not all public health facilities participate (voluntary). Private sector death information is not included.	Cannot be used for short/medium term planning due to the reporting delay (two years). Contributing or modifiable factors are not recorded. Deaths are underreported (not reported or form does not reach the DHA), incomplete or incorrect. Deaths are also not available for children who are foreign nationals without a South African identification number. Data are collated nationally and individual cause of death data is not provided to provincial health departments. Aggregate mortality data are only provided at the level of the province and not for smaller geographic areas (no longer receive individual-level data).

DHA: Department of Home Affairs, DN: Death Notification ICD-10: International Classification of Diseases 10th Revision, WCGHW: Western Cape Government Department of Health and Wellness, WCPHDC: Western Cape Provincial Health Data Centre.
*In-facility death reporting was achieved incrementally since 2007 as hospitals became networked in the province.

3.2.2 District health information system

The DHIS is an aggregate reporting system that collects data on specific variables (10), such as maternal mortality and immunisation data from the EPI. This currently includes childhood

vaccines for polio, TB, rotavirus, diphtheria, tetanus, pertussis, *Haemophilus influenzae* type B, hepatitis B, pneumococcus, rubella and human papillomavirus as well as influenza for high risk patient groups, and maternal pertussis and diphtheria vaccines (23,80,81).

3.2.3 Population estimates

The Western Cape population estimates used throughout this thesis are based on the 2022 mid-year estimates from Statistics South Africa at district-level, projected at subdistrict-level using the ratio method within the WCPHDC (6). The ratio method (111) predicts the population growth of subareas by utilising population projections for a larger overall population.

3.3 Data variables and calculations

Using the above-described data sources (section 3.2), I either extracted key variables or derived required data variables from existing variables. Detailed descriptions of the data variables and calculations can be found below and are summarised in Table 3.2.

3.3.1 Infectious diseases admissions

I drafted a list of ICD-10 codes to infer each infectious disease which was reviewed and finalised in consultation with clinicians including paediatric infectious disease specialists. The full list is available in Table S3.1 in section 10.1 in Chapter 10. The resulting comprehensive list enabled the identification of as many admissions as possible that could be due to an infectious disease. Using data available in the RHIS, I identified an infectious disease admission by the presence of any of these ICD-10 codes across any of the recorded fields (i.e. primary, subsidiary, or first ten recorded secondary codes). This was to account for potential differences in ICD-10 coding practices by clinicians or data clerks. Limiting to certain ICD-10 fields would potentially have resulted in underestimating infectious disease admissions if these diagnostics codes were recorded as subsidiary or secondary codes rather than primary codes. For example, if children are admitted with chronic conditions, such as HIV or cerebral palsy, these conditions may be captured as the primary code, potentially missing the associated infectious disease for that admission. Conversely, using all recorded fields for the cause of admission might have led to overestimating infectious disease admissions. For example, children who were primarily admitted (with an associated primary code) for other reasons, such as surgical procedures, and co-incidentally had an infectious disease that would not by itself justify admission, but would be diagnosed and recorded as subsidiary or secondary codes, would be classified as an infectious disease admission with this approach. In addition, children

with a recent history of infectious disease admissions may have this noted during their current admission, without it being the current admission cause.

When a child is transferred between wards or facilities, multiple records and ICD-10 codes may be associated with the admission or death, referred to by the WCPHDC as a "threaded admission". Threaded admissions, defined as those with <12 hours between discharge from one health facility/ward and re-admission to another, were treated as a single admission. These separate data entries for each of these admissions may contain different ICD-10 codes. To ensure no information surrounding the infectious disease admission was lost, all available ICD-10 codes were used to identify the presence or absence of an infectious disease. Once this was done, I collapsed all available information on the multiple separate records within a "threaded admission" into a single admission record.

3.3.2 Infectious disease deaths

As described in section 3.2.1, the WCPHDC includes three data sources which contain death related information: RHIS, Child PIP and DN Surveillance. I used data from each data source for the respective time periods for which data were available to determine a de-duplicated infectious disease cause of death per data source. Duplicates were identified in each data source using the unique identifier, date of death and cause of death. I dropped duplicates before the data sources were joined together using the unique identifier. The process to determine causes and dates of death is described in detail below.

3.3.2.1 Cause of death per data source

Routine Health Information System

The cause of in-facility deaths is not captured in RHIS, therefore, ICD-10 diagnosis codes identified during the admission were used as the source to determine the proxy cause of death. All admission entries were maintained and ordered by discharge date and time, irrespective of whether they were threaded, to determine the proxy cause of death. This approach was to ensure all information was obtained as some entries may have been associated with null or missing diagnosis codes, even at the time of discharge. Diagnosis codes could change during an admission, however, diagnoses codes at the time of final separation (death or discharge) are considered to be more reliable. Therefore, discharge or death diagnoses codes were used over admission diagnoses codes.

Using the three ICD-10 codes recorded closest to the date of death in RHIS, I identified a proxy cause of infectious disease death from the top three ranking diagnosis codes for an admission. If there was only one record for the child, the first three available diagnosis codes were used in whatever order available to identify if the death was due to an infectious cause. Primary ICD-10 codes outranked subsidiary and secondary codes. For children with "threaded admissions", the codes recorded closest to the death outranked those diagnosis codes recorded earlier.

Child Healthcare Problem Identification Programme

The cause of death is identified through a clinical audit process, as described above. I linked these deaths to the data available in the RHIS using the unique identifier.

Death notification Surveillance

The primary cause of death is identified per the DN form, as described above. I then linked the data with the RHIS and Child PIP through a unique identifier.

3.3.2.2 Coding of date and single cause of death across the three death data sources

Child's cause of death was used in Chapter 4 and 5 and in-facility deaths was used in Chapter 7. The dates of death were also compared across data sources. Data inconsistencies, possibly caused by incorrect data capturing or linkage errors resulting in the incorrect recording of deaths on one or more systems, made these data points unreliable. Therefore, if dates of death in two or more of the systems differed by more than 30 days or did not align to an admission date in RHIS, the child was dropped from the dataset. This was done because I was unable to confidently determine if the death occurred or if it was an error. If the admission or discharge dates were <30 days from the recorded date of death, then date of death from Child PIP or DN Surveillance was assumed to be correct.

Some dates of death were missing in the RHIS for children who were recorded in Child PIP. For these children, the date of death was assigned as the Child PIP date of death as this was assumed to be more accurate. The number of children/admissions dropped from the base dataset for this thesis, or with date of death re-coded, is detailed in data quality description in Section 3.4.

Where cause of death differed across the three death datasets, I applied the following hierarchy in attributing an overall cause of death to determine mortality estimates using the de-duplicated dataset: (1) Child PIP (most reliable) as causes of death are identified through an audit process;

(2) DN Surveillance ranked second as cause of death as identified by the attending clinician at the time of death, but without an audit process; and (3) RHIS ranked third as cause of death and was inferred from diagnosis codes.

3.3.3 Child's place of residence

Child's place of residence (district or subdistrict) was utilised in all analyses (Chapter 4-7). Location data for each facility in the Western Cape was accessible, which made it possible to associate hospitalisations with specific subdistricts and districts. Nevertheless, I made the decision to prioritise the child's residential location, available in RHIS, for all analyses. This choice was made to prevent potential data distortion caused by mapping admissions and deaths directly to the facility, as the location would be influenced by the distribution of hospitals across the province and the referral patterns for severe illnesses. For instance, most tertiary hospitals are situated within the City of Cape Town, which might mistakenly suggest a higher disease burden in that district when, in reality, it is largely a result of referral patterns. Some of the postal codes in the reference WCPHDC table that I utilised to assign location did not have subdistrict or district information, which necessitated acquiring and mapping these manually to ensure location data was as complete as possible. Postal codes were available in another table in the RHIS and I was able to impute missing subdistrict/district using this table. To safeguard patient anonymity, I mapped child's place of residence to subdistrict only and not lower, to more identifiable geographical levels.

3.3.4 COVID-19 cases and admissions

COVID-19 case and admission data were used in Chapter 5 and 6. COVID-19 cases and admissions were used as a proxy for service pressure. COVID-19 cases were defined as having a laboratory confirmed COVID-19 diagnosis (positive SARS-CoV-2 polymerase chain reaction [PCR] or antigen test), irrespective of symptoms. COVID-19 admissions were defined as a hospital admission occurring within 14 days before or after a laboratory-confirmed COVID-19 diagnosis. Neither clinical diagnosis of COVID-19, nor multisystem inflammatory syndrome in children, were counted as COVID-19 cases unless there was a corresponding positive SARS-CoV-2 test as these clinical data were not routinely available for all people with data in the WCPHDC. Testing coverage fluctuated throughout the period due to variations in laboratory capacity, facility practices, and guidelines aimed at prioritising COVID-19 testing for those requiring it most for clinical management purposes. COVID-19 cases and admissions included

the number of new diagnoses and whether these were first or subsequent infections. COVID-19 cases and admissions were calculated by the WCPHDC. I linked the COVID-19 test data to the base dataset created for each hospitalisation to determine if the child had confirmed COVID-19 or not during their admission.

3.3.5 Immunisation coverage

Immunisation coverage was used in Chapter 5 and 6. I coded proxy immunisation coverage quarterly by dividing the number of fully immunised children aged under one year, available from DHIS, by the previous years under one year population from the population estimates (to represent a proxy eligible cohort). The population estimate was adjusted for quarterly live births from the WCPHDC, which records live births in all public sector facilities.

3.3.6 Admissions rates, admission mortality rates and case fatality rates

I estimated infectious disease admission rates for each time period by dividing the total infectious disease admissions by 80% of the population estimates for children under five years of age (representing the proportion accessing public sector healthcare services). Rates are presented per 1,000 person months with 95% CIs.

I also estimated mortality rates with 95% CIs including: i) admission mortality rates per 100,000 live births (number of infectious disease in-facility deaths divided by the number of live births documented in the province) and ii) CFRs (number of infectious disease in-facility deaths divided by total infectious disease admissions).

These rates were either calculated for all specified infectious diseases or a specific infectious disease, depending on the objective, and is specified in each respective chapter.

3.3.7 HIV exposure and infection status

HIV exposure and infection status was used in Chapter 7 and determined at the time of each hospitalisation which was categorised as HIV positive, HIV exposed uninfected (HEU), HIV unexposed uninfected (HUU) or unknown using HIV-related data at the time of infectious disease admission (112). Children's HIV exposure and infection status may have changed if they previously had a negative HIV test, but subsequently had a positive HIV test during their current hospital admission. Children who could not be linked to mothers in the WCPHDC, whose mothers were diagnosed with HIV postnatally, or who had an unknown timing of HIV

acquisition relative to the hospital admission were classified as having unknown HIV exposure and infection status.

Table 3.2. Summary of key independent variables utilised across the four objectives as required.

Variable	Description	Data Source
Age	Age at the time of hospital admission or death categorised as <28 days, 28 days – 1 year, and >1 - <5 years for Chapters 4-6 and 0-3 months, 4-6 months, 7-11 months and 1 - <5 years in Chapter 7.	RHIS Child PIP DN Surveillance
Child's district	The district of the child's place of residence.	RHIS
Child's subdistrict	The subdistrict of the child's place of residence.	RHIS
COVID-19 infection	Total COVID-19 admissions and cases for the Western Cape to determine service pressure. Hospital admissions among children were also linked to COVID-19 outcomes for the relevant period.	RHIS
Date of birth	Date of birth.	RHIS Child PIP DN Surveillance
Date of death	Date of death.	RHIS Child PIP DN surveillance
Duration from admission to death	Difference between the date of hospital admission and date of death.	RHIS Child PIP DN surveillance
Facility	The facility a child is admitted to or died at.	RHIS Child PIP DN Surveillance
Facility district	The district of the facility a child is admitted to or died at.	RHIS Child PIP DN Surveillance
Facility subdistrict	The subdistrict of the facility a child is admitted to or died at.	RHIS Child PIP DN Surveillance
Intensive care unit (ICU) admissions	ICU admission during hospital stay.	RHIS
Infectious disease hospital admission	Hospital admissions for either LRTI, diarrhoea, meningitis and TBM as identified by the comprehensive list of ICD-10 codes.	RHIS
Infectious cause of death	Cause of death for either LRTI, diarrhoea, meningitis and TBM identified across different data sources. The single cause of death was ranked as follows: i) Child PIP, ii) DN surveillance and iii) RHIS.	RHIS Child PIP DN surveillance
HIV exposure and infection status	HIV exposure and infection status was determined at each hospitalisation and categorised as HIV positive, HEU, HUU or unknown.	RHIS
Length of stay	Difference between the hospital admission date and discharge date for children who are discharged alive.	RHIS

Variable	Description	Data Source
Severe acute malnutrition (SAM)	Children who are diagnosed with SAM during a hospital admission.	RHIS
Seasonality	Historic LRTI admission patterns were used to determine seasonality peaks and troughs and adjusted for in the model: January - March, April - June, July - September, and October – December. Seasonal surges were defined as March – June using historic data. Historic diarrhoea admission patterns were used to determine seasonality peaks and troughs: December – February, March – May, June – August, September – November. Seasonal surges were defined as November – May using historic data.	N/A
Sex	Categorised as male and female.	RHIS Child PIP DN Surveillance
Source of death	Source of death from RHIS, Child PIP or DN Surveillance used for data comparison.	RHIS Child PIP DN Surveillance
Time from admission to death	Difference between the hospital admission date and date of death for children who died during a hospital admission.	RHIS Child PIP DN Surveillance

Child PIP: Child Healthcare Problem Identification Programme, DN Surveillance: Death Notification Surveillance, HEU: HIV exposed uninfected, HUU: HIV unexposed uninfected, ICD-10: International Classification of Diseases 10th Revision, ICU: intensive care unit, LRTI: lower respiratory tract infection, RHIS: Routine Hospital Information System, SAM: severe acute malnutrition.

3.4 Data quality checks

I did several data quality checks on the data before it was finalised for data analyses to support data accuracy. Based on knowledge of the data, I established the following criteria for the data quality checks:

- Missing or indeterminate sex (n = 218 admissions).
- Missing admission or discharge dates (n = 262 admissions).
- Implausible birth, admission, discharge and death (if applicable) dates where it was implausible for one event to occur after another (e.g. birth after death) and the difference between these were ≥30 days (n= 3 admissions). If the difference was <30 days, the child was retained in the dataset and the events were assumed to occur on the same day.
- Admission duplicates defined by the same entry identified by a unique hospital admission number and unique identifier for the child (none).
- Death duplicates defined by the same date of death and unique identifier for the child (n= 50 admissions).

- Dates of death differed by more than 30 days or did not align to an admission date in RHIS given that dates of death were drawn from Child PIP and DN surveillance as well (as described in section 3.2.2.2) (n = 5 admissions/2 children).

If any of these data quality checks were violated, the child was dropped from the base dataset (538 total admissions). This final base dataset (217,871 admissions from 2007 to 2021) was used as the starting point for each of the analyses presented in this thesis. Each chapter describes the specific data requirements implemented for the corresponding analysis.

3.5 Data governance

The WCPHDC has multiple data governance practices to ensure data requests are responded to legally and ethically. It is mandatory to have all data requests arbitrated by a health official or external structure who then assesses the protocol and data permissions. This arbitration is done centrally at the WCPHDC, which ensures all data requests are managed i) identically, ii) without compromising patient confidentiality, and iii) in a manner that ensures all requirements are fulfilled prior to data access. A documented cycle is required for each data release and clearly states the legal compliance to the protection of and access to personal, identifiable information. To ensure patient confidentiality is not breached, standard procedures, and structural and procedural controls are in place. These controls include separating databases for patient and clinical data, making it possible that different analysts have access to identifiable data for patient matching and for clinical data extraction.

As multiple data systems are linked and consolidated at the WCPHDC, data requests and proposed analyses can be facilitated in a responsible manner. For all patient-level data I extracted a perturbed, unique study patient identifier, which was used rather than the unique identifier used in the WCPHDC for data linkage. All data was stored on a secure network housed at the WCPHDC and was password protected. The above-mentioned procedures were strictly adhered to for this research project.

3.6 Data management and analyses software

All data sources within the WCPHDC were accessed through the SQL database, where the bulk of the data management was done to create the base dataset for analyses for this thesis. After extraction of the linked WCPHDC data with perturbed patient identifier, I used R Studio (2022.12.0) for data linkage by location and time period (for data not available in the

WCPHDC), data aggregation, and selected data visualisation. Data were also analysed and visualised in either Excel or Stata 17.0 or Stata 18.0.

3.7 Use of this work currently in the Western Cape Provincial Health Data Centre

The coding of infectious disease episodes and deaths I performed as part of this thesis has been implemented into the child cascade in the WCPHDC and have been used in the province's Child Health Surge Season dashboard (Figure 3.2).

Figure 3.2. The Surge Season Dashboard, accessible through the Single Patient Viewer, developed by the Western Cape Provincial Health Data Centre which utilised the work from this thesis.

3.8 Ethics approval

This PhD research proposal study was approved by the Faculty of Health Sciences Human Research Ethics Committee (HREC) at the University of Cape Town (HREC REF 197/2021) (section 10.1 – Chapter 3 appendix). This research study was also registered on the National Health Research Database (reference number WC_202104_027). A separate ethics approval was not required for the University of Bristol as all data used in this thesis was from the Western Cape. Patients contributing data to the WCPHDC do not explicitly consent, as these data are utilised to directly support patient care. To ensure patient confidentiality and protect individuals, only de-identified data was used in this research study, except for date of birth, which was included in analyses which required the exact age for children under five years.

Chapter 4

Comparison of paediatric infectious disease deaths in public sector health facilities using different data sources in the Western Cape, South Africa (2007-2021)

4.1 Overview

As outlined in section 2.10 of Chapter 2, mortality data are frequently outdated, lacking useful disaggregation, and often have missing or poorly defined cause-of-death information. These limitations make it hard to assess the extent and impact of infectious disease mortality, limiting the ability to implement effective interventions to reduce childhood mortality. Therefore, this study aimed to address some of these limitations specifically for children under five years of age who died from infectious diseases in public sector facilities in the Western Cape, as outlined by Objective 1 in Chapter 1. The study, along with the subsequent ones, was uniquely positioned to assess this due to the data being accessible through the WCPHDC.

The content of this chapter has been published as a peer-reviewed manuscript in BMC Public Health. It has been revised and adjusted to align with the structure, format, style, numbering, and referencing conventions used in this thesis. The final published version is available in Chapter 4 appendix (section 10.2) with the following reference: *Kehoe K, Morden E, Jacobs T, Zinyakatira N, Smith M, Heekes A, Murray J, le Roux DM, Wessels T, Richards M, Eley B, Jones HE, Redaniel MT, Davies MA. Comparison of paediatric infectious disease deaths in public sector health facilities using different data sources in the Western Cape, South Africa (2007-2021). BMC Infect Dis. 2023 Feb 22;23(1):104.* This work was also presented as a poster presentation at 17th annual Public Health Association of South (PHASA) conference in September 2022 in Durban, South Africa.

I was responsible for the data management required to develop the dataset for this analysis, as described in Chapter 3. I conducted all data analyses, drafted the manuscript, incorporated feedback from co-authors, and completed the final version of the manuscript, submitting it for publication.

4.2 Introduction

Monitoring childhood mortality is important to assess factors related to child survival such as access to and quality of healthcare, safety, nutrition and protection (26,27). This closely aligns with the SDG 3 that by 2030 all countries should reduce U5MR to <25 deaths per 1,000 live births (3). Accurate monitoring of the contribution to mortality of infectious diseases, including

LRTIs, diarrhoea, meningitis, and TBM, is thus vital to monitor progress, as these preventable deaths are responsible for a substantial proportion of child mortality in resource-limited settings (5,49,55,113). Data for these infectious diseases are often outdated or scarce, especially at lower geographic levels within these settings, warranting the need to better understand the current burden.

Childhood mortality monitoring through DN systems may have several disadvantages including the limited use of these systems in many settings and that there may be up to two year delays in releasing these data, making them unhelpful for real-time use (5,114). In addition, not all child deaths may be registered (115), resulting in low completeness (113). Routinely collected health datasets may provide more rapid child mortality estimates and the limitations of the several different routine health data sources available can be reduced by integrating and comparing them (37).

I compared the completeness of death data for children recorded as dying from infectious diseases in the Western Cape, South Africa, using three death data sources as follows: i) RHIS data which captures key information for each admission, including the unique patient identifier, patient demographics and hospital administration data, and discharge codes and summaries (10); ii) Child PIP which is a child death audit review process of all in-hospital child (0-18 years) deaths in public health facilities that participate voluntarily (28,109); and iii) DN Surveillance which includes all deaths, in- or out-of-facility, recorded on DN forms (110). These three data sources are integrated and linked in the WCPHDC through a unique patient identifier that is used across public health services in the province (10). RHIS includes every electronically recorded in-facility child death but does not typically include cause of death, but rather diagnostic coding of the reason for admission during which the death occurred. In contrast, there may be under-reporting or missing data on all in-facility child deaths in DN Surveillance and Child PIP, but these systems capture recorded causes of death from notification forms and audits respectively, making their cause of death data more accurate. Child death audit review systems, used globally (116), define causes of death similarly to DN Surveillance, but also identify modifiable factors contributing to these deaths (28,109).

In addition to comparing completeness of the different death data sources, I assessed the accuracy of RHIS recorded diagnostic codes versus those in DN Surveillance and Child PIP. I

determined the admission mortality rates for in-facility infectious disease deaths in the public sector across the Western Cape province and by district or subdistrict.

4.3 Methods

Setting and study population

The Western Cape province consists of six districts: City of Cape Town, Cape Winelands, Central Karoo, Garden Route, Overberg, and West Coast. The province had an estimated seven million people in 2020 (15) of whom 8% (563,590) were children aged 0-4 years (16). About 80% of the child population utilise public sector services. The WCGHW manages 52 hospitals and 272 primary care clinics, and the City of Cape Town manages an additional 82 clinics (10). I included all children hospitalised under five years of age, including neonates, at a public health facility within the Western Cape province from 2007-2021, as described in Chapter 3.

Data comparison and analysis

Data were linked across the RHIS, Child PIP and DN Surveillance using the unique identifier, for the four infectious diseases of interest for the respective time periods that data were available (Table 3.1 in Chapter 3).

I compared data to determine the number of de-duplicated infectious diseases deaths across all sources. I determined the percentage of each of the infectious disease deaths present in Child PIP and DN Surveillance versus RHIS. To understand the accuracy of RHIS causes of death, the level of agreement between RHIS and each of Child PIP and DN Surveillance was determined. To test the level of agreement, I calculated the Kappa statistic for the four infectious diseases of interest, with the agreement for values of 0.81-1.00 being considered "almost perfect", 0.61-0.80 "substantial", 0.41-0.60 "moderate", 0.21-0.40 "fair" and 0.01-0.20 "none to slight" (117).

I calculated admission mortality rates for the province and each district/subdistrict (based on child's place of residence) over time using the de-duplicated, integrated dataset that included all sources (as described in Chapter 3). The calculation for admission mortality rates was previously outlined in section 3.3 of Chapter 3 and is now being defined within the specific context of this chapter. Admission mortality rate is defined as infectious disease deaths occurring in a healthcare facility divided by live birth population estimates, presented per 1,000 live births with 95% CIs. The population denominator was estimated from population estimates

as 80% of live births (118), i.e. the estimated proportion of the population using public sector services in the province or respective district/subdistrict. Since the number of live births per City of Cape Town subdistrict was not available, as births are mapped to Home Affairs Offices rather than place of residence, I estimated the subdistrict live births denominator based on the proportion of infants among the total population for that subdistrict. Live births from the population estimates were only available until 2020, so the comparison was limited to 2007-2020. For district and subdistrict comparisons, 2019 death and population data was used, as this was the last pre-pandemic year and data thereafter are confounded by several pandemic related factors (119).

Data were cleaned and coded in SQL and analysed using Excel and R Studio 2022.12.0.

4.4 Results

Using all three data sources, there were 217,899 admissions for one of the four infectious disease admissions among children under five years from 2007-2021 with a total of 1,947 deaths recorded among these children (~1% of hospital admissions among children under five years with an infectious disease diagnosis) (Table 4.1). A total of 1,661 children died (85% of all deaths) from one of the four infectious diseases included in this study. Of the remaining 286 deaths, most had either missing cause of death and missing ICD-10 code or were attributed to sepsis or perinatal factors such as low birthweight and prematurity. The highest proportion of infectious disease deaths was in children aged 28 days to one year (1,000 deaths, 60%) – the same age group where most (52%) of the infectious disease admissions occurred (5% among <28 days and 44% among >1 and <5 years). Most deaths occurred in the two large tertiary hospitals in the province which account for 39% of all infectious admissions (713 deaths [43% of infectious disease deaths] and 596 deaths [36% of infectious disease deaths] in these two hospitals respectively). The highest proportion of infectious disease admissions at any other hospital accounted for ≤4%. Most primary diagnosis codes (primary reason or condition for the hospital admission**)** for infectious disease deaths in RHIS were coded by a registrar or consultant (1,430 deaths, 86%), rather than a data clerk, whereas less than a third of subsidiary codes (a coexisting reason or condition for the hospital admission) were coded by a registrar or consultant (532 deaths, 32%).

Table 4.1. Summary of infectious disease deaths among 217,899 children admitted for an infectious disease in public sector facilities in the Western Cape, 2007-2021.

Variable	Total (%)
Total number of deaths	1,947 (~1% of infectious disease admissions)
Infectious disease deaths (LRTI, diarrhoea, TBM or meningitis)	1,661 (85% of total deaths)
Other causes of death (missing cause of death or ICD-10 code, sepsis, or perinatal factors [low birth weight or prematurity])	286 (15% of total deaths)
Age among infectious disease deaths	
<28 days	202 (12%)
28 days to 1 year	1,000 (60%)
>1 to <5 years	459 (28%)
Location	
Hospital A	713 (43% of infectious disease deaths)
Hospital B	596 (36% of infectious disease deaths)
Other hospitals	352 (21% of infectious disease deaths)
ICD-10 coding	
Primary diagnosis coding by registrar or consultant	1,430 (86% of infectious disease deaths)
Subsidiary diagnosis coding by registrar or consultant	532 (32% of infectious disease deaths)

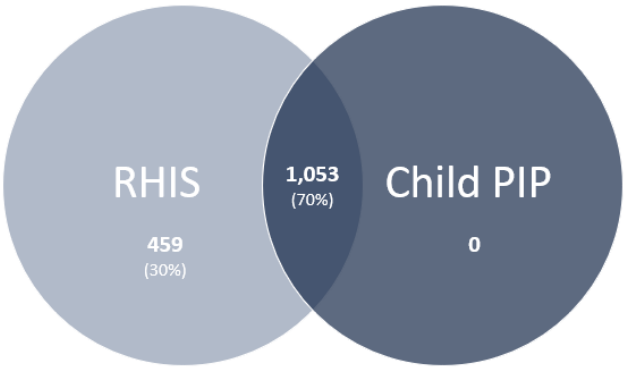
ICD-10: International Classification of Diseases 10th Revision, LRTI: lower respiratory tract infection, TBM: tuberculous meningitis.

Data source comparison

During the time period for which RHIS and Child PIP data were both available (23/05/2007–08/02/2021), 1,512 infectious deaths were recorded across these two data sources (Figure 4.1a). All of these deaths were recorded in RHIS, and Child PIP was 70% complete (1,053 deaths).

When comparing infectious disease deaths across all available data sources for the period when all three sources where available (438 deaths from 2010-2013), DN Surveillance was 69% complete (303 deaths identified, of which 239 were also recorded in Child PIP while 64 were recorded in DN Surveillance and RHIS only) (Figure 4.1b). An additional 22% of deaths were identified in RHIS and Child PIP but not DN Surveillance (95 deaths), while the remaining 9% were in RHIS alone (40 deaths).

a)



b)

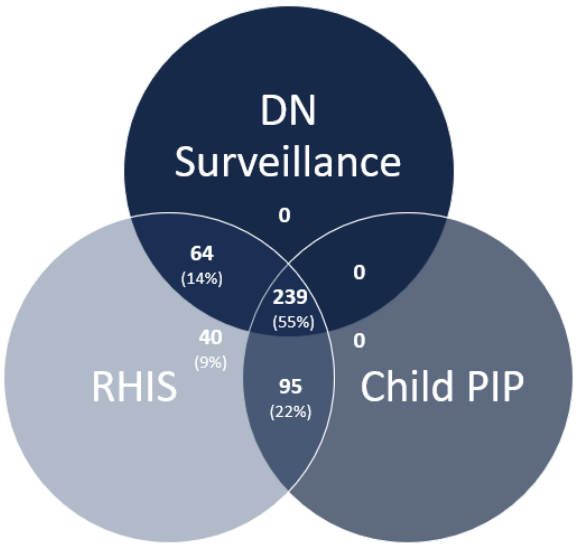


Figure 4.1. Venn diagrams comparing infectious disease deaths across data sources for the time periods that the data sources were available: a) Routine Health Information System and Child Healthcare Problem Identification Programme from 23/05/2007–08/02/2021 (1,512 deaths) and b) Routine Health Information System, Death Notification Surveillance and Child Healthcare Problem Identification Programme from 2010-2013 (438 deaths).

Child PIP: Child Healthcare Problem Identification Programme, DN Surveillance: Death Notification Surveillance, RHIS: Routine Health Information System.

Cause of death agreement

Of the 1,186 deaths recorded in Child PIP (considered most reliable for cause of death) from May 2007 – February 2021, 564 (48%) were due to one of the four infectious diseases of interest. Although all these deaths were recorded in RHIS, 3% (16 deaths) could not be identified as an infectious disease death based on RHIS alone. An additional 2% (10 deaths) were identified as an infectious disease death but not as being due to one of the four infectious diseases of study (Table 4.2). The concordance between Child PIP and RHIS was: diarrhoea (92%), LRTI (84%), meningitis (77%), and TBM (74%). The overall level of agreement for the four infectious diseases was “almost perfect” (Kappa statistic 0.810; 95% CI 0.766-0.855). For Child PIP causes of death, a greater proportion of mismatches were detected for meningitis and TBM, whereas a greater number of mismatches was detected for LRTI as this is more common; all due to the absence of the corresponding diagnostic code in RHIS. Given the small number of meningitis and TBM deaths, the data for these infectious diseases should be interpreted with caution.

Table 4.2. Comparison of Routine Health Information Systems and Child Healthcare Problem Identification Programme causes of death among children admitted for diarrhoea, lower respiratory tract infections, meningitis or tuberculous meningitis in the Western Cape (May 2007 – February 2021).

	RHIS cause of death						
Child PIP cause of death	**Diarrhoea**	**LRTI**	**Meningitis**	**TBM**	**Other infectious disease**	**Other condition**	**Total**
Diarrhoea	119 (92%)	6 (5%)	1 (1%)	0	0	3 (2%)	129 (100%)
LRTI	29 (9%)	285 (84%)	5 (1%)	0	9 (3%)	10 (3%)	338 (100%)
Meningitis	1 (2%)	7 (11%)	48 (77%)	3 (5%)	1 (2%)	2 (3%)	62 (100%)
TBM	2 (6%)	2 (6%)	4 (11%)	26 (74%)	0	1 (3%)	35 (100%)
Total	151	300	58	29	10	16	564

Child PIP: Child Healthcare Problem Identification Programme, LRTI: lower respiratory tract infections, RHIS: Routine Health Information Systems, TBM: tuberculous meningitis.
Table includes all deaths that were recorded as being due to diarrhoea, LRTI, meningitis or TBM in Child PIP. Row percentages are shown. Coloured cells are to highlight the level of agreement of each infectious disease, respectively.

Of the 542 deaths in DN Surveillance from 2010-2013, 132 (15%) were due to one of the four infectious diseases of interest. Of these, 128 (96%) were identified as being due to an infectious disease of interest in RHIS (Table 4.3). The overall level of agreement for the four infectious diseases was "moderate" (Kappa statistic 0.782; 95% CI 0.690-0.875). The best agreement between DN Surveillance and RHIS was for diarrhoea (98%) and LRTI (83%). TBM (45%) and meningitis (56%) agreement was lower mostly due to the absence of the corresponding diagnostic code in RHIS. Given the small number of meningitis and TBM deaths, the data for these infectious diseases should be interpreted with caution. Again, the greater number of mismatches was detected for LRTI cause of death in DN Surveillance.

Table 4.3. Comparison of Routine Health Information Systems and Death Notification Surveillance causes of death among children admitted for diarrhoea, lower respiratory tract infections, meningitis or tuberculous meningitis in the Western Cape (2010-2013).

	RHIS cause of death					
DN Surveillance cause of death	**Diarrhoea**	**LRTI**	**Meningitis**	**TBM**	**Other condition**	**Total**
Diarrhoea	52 (98%)	1 (2%)	0	0	0	53
LRTI	8 (14%)	49 (83%)	0	0	2 (3%)	59
Meningitis	0	3 (27%)	5 (45%)	2 (18%)	1 (9%)	11
TBM	1 (11%)	0	2 (22%)	5 (56%)	1 (11%)	9
Total	61	53	7	7	4	132

DN: Death Notification, LRTI: lower respiratory tract infections, RHIS: Routine Health Information Systems, TBM: tuberculous meningitis.
Table includes all deaths that were recorded as being due to diarrhoea, LRTI, meningitis or TBM in DN Surveillance. Row percentages are shown. Coloured are to highlight the level of agreement of each infectious disease, respectively.

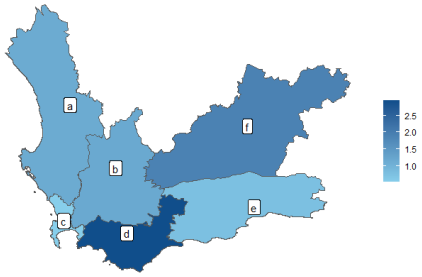
Admission mortality rates

Using the combined de-duplicated dataset, admission mortality rates for these infectious diseases in the Western Cape more than halved between 2007 and 2020 (1.60 [95% CI: 1.37-1.85)] deaths per 1,000 live births [2007] and 0.73 [95% CI: 0.56-0.93] deaths per 1,000 live births [2020]) (Figure 4.2a). Of the 1,661 infectious disease deaths from 2007-2021, 1,168 (70%) were in the City of Cape Town (Figure 4.2b). Admission mortality rates for the four infectious diseases of interest in City of Cape Town decreased by almost fourfold from 2.59 (95% CI: 2.20-3.03) deaths per 1,000 births [2007] to 0.76 (95% CI: 0.52-1.07) deaths per 1,000 live births [2020]. Only 2% (25 deaths) of infectious disease deaths could not be mapped to a child's place of residence in the province (either outside the province or missing).

Figure 4.2. Admission mortality rates per 1,000 live births mapped to child's residence, with 95% confidence intervals represented by the shaded areas for a) the Western Cape and b) the City of Cape Town and the total number of infectious disease deaths for c) the Western Cape and d) the City of Cape Town for all four infectious disease deaths combined using the de-duplicated dataset. Note: population estimates were only available until 2020, so the comparison was limited to 2007-2020.

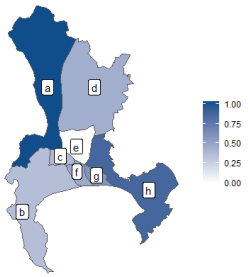
In 2019, the admission mortality rates were highest in Overberg and Central Karoo (Figure 4.3a). Admission mortality rates in the other four districts were around one or fewer deaths per 1,000 live births. For the City of Cape Town, where the highest number of deaths were recorded, the highest admission mortality rate was in the Western subdistrict with other subdistricts having below one death per 1,000 live births (Figure 4.3b).

a)



District	Admission mortality rate (95% CI)	Number of deaths
a. West Coast	1.15 (0.42-2.5)	6
b. Cape Winelands	1.19 (0.63-2.02)	13
c. City of Cape Town	0.52 (0.35-0.74)	29
d. Overberg	2.95 (1.48-5.28)	11
e. Garden Route	0.77 (0.28-1.67)	6
f. Central Karoo	1.91 (0.23-6.89)	2

b)



Sub-district	Admission mortality rate (95% CI)	Number of deaths
a. Western	1.03 (0.41-2.11)	7
b. Southern	0.35 (0.04-1.25)	2
c. Klipfontein	0.38 (0.05-1.36)	2
d. Northern	0.44 (0.05-1.58)	2
e. Tygerberg	0	0
f. Mitchells Plain	0.47 (0.13-1.19)	4
g. Khayelitsha	0.59 (0.16-1.51)	4
h. Eastern	0.87 (0.38-1.72)	8

Figure 4.3. Admission mortality rates per 1,000 live births (95% confidence interval) and number of deaths mapped to child's residence using the combined de-duplicated dataset and population estimates as the denominator for the four infectious disease deaths of interest in 2019 by a) all Western Cape districts and b) the City of Cape Town subdistricts. Note: 2019 death and population data were used, as this was the last pre-pandemic year and data thereafter are likely affected by several pandemic related factors.

4.5 Discussion

This is believed to be the first study to compare and synthesise routinely collected in-facility child death data in the public sector in South Africa. I was able to comprehensively evaluate the accuracy of in-facility diagnostic coding for children who die from infectious diseases and demonstrated that data linkage and consolidation across multiple sources improved the accuracy of in-facility infectious disease mortality estimates.

Completeness of Child PIP and DN Surveillance for the four infectious disease deaths recorded electronically in RHIS was approximately 70%. While causes of death in RHIS rely on inference from the diagnosis code for the relevant admission, the level of agreement for the infectious cause of death with more accurate sources was generally high, specifically between Child PIP and RHIS (≥74%) and for diarrhoea and LRTI in both Child PIP and DN Surveillance (>80%). The higher concordance may be because diagnoses of diarrhoea or LRTI can be made confidently based on symptoms only, whereas laboratory tests would usually be needed to confirm diagnoses of meningitis and TBM, and pathogen testing seldomly happens in this

setting. Lower level of agreement for meningitis and TBM may be driven by suboptimal diagnosis, infrequent pathogen testing and incorrect diagnosis coding. Despite these limitations, the level of agreement across data sources provide reassurance that RHIS has reasonable accuracy of diagnostic coding for children who die. It is thus a useful and timely source of child death data, since RHIS is updated daily, whereas audit data sources (Child PIP) are only provided and integrated into the WCPHDC periodically and DN data is very delayed, not available at district/subdistrict level and currently not available to health services, preventing linkage to other individual patient data. While low completeness of electronic ICD-10 coding was reported in a large tertiary hospital in the province (120), I found more accurate and complete diagnostic coding in patients who die, which has also been shown in other settings (114). These findings suggest that data comparison improves validity over using a single data source, which is consistent with other public health studies utilising triangulation or integration of routine health data sources, individual- or population-level, focusing on various health conditions (121–124).

The admission mortality rates for the four infectious diseases decreased significantly over the 14-year period, somewhat plateauing from 2014/15 onwards with a slight reduction noted from 2019. This downward trend has been observed across the province for the individual infectious diseases where data are available, including pneumonia (125) and diarrhoea (7). These declines may be due to: i) improved PVT for HIV and increased child ART coverage (4), ii) the introduction of pneumococcal conjugate and rotavirus vaccines in 2009 (82), resulting in better prognoses for sick children and decreased pressure on health services due to a reduction in admissions, thus resulting in better outcomes, and/or iii) the improvement of services by standardising clinical governance through systems like Child PIP and child death reviews (28,36,109). When comparing across districts within the Western Cape, childhood mortality is significantly higher in the Overberg and Central Karoo districts in 2019. Within the City of Cape Town, mortality varies across subdistricts likely driven mainly by socioeconomic inequities including access to healthcare. This geographic difference is consistent with nationally reported pneumonia mortality, which is made available annually (7,8,125).

Strengths and limitations

This study was strengthened by the availability of comprehensive individual-level electronic health data with known causes of death. These study outcomes should enable policy makers

and clinicians to better understand in-facility mortality due to infectious diseases over time and across geographies in the province using the de-duplicated, integrated dataset. In addition, the list of ICD-10 codes was comprehensive to ensure I was able to identify as many infectious disease hospitalisations and deaths as possible, allowing us to better understand the burden of disease in the community.

This study has several limitations. Firstly, only in-facility deaths were included based on the design and data availability. To understand the complete picture of child mortality, out-of-facility deaths would need to be included as well, however I did not have access to any data sources beyond DN Surveillance for out-of-facility deaths. Secondly, I do not know if any in-facility deaths are missing as I was fully reliant on electronic capture of admissions and deaths. It is believed that reporting of in-facility deaths may be more complete in recent years due to increases in networking of hospitals over time and the reduction in deaths is likely an underestimate, as a greater proportion of all deaths were reported electronically in more recent years. Thirdly, some errors in diagnostic coding are likely. However, this limitation was mitigated as most primary diagnoses were coded by a registrar or consultant rather than a data clerk. Fourthly, the ICD-10 codes entered electronically were not verified against the in-facility written patient folders. I believe the impact of this was limited given: i) diagnostic coding has been shown to be better in deceased children (114) and ii) there was a high level of agreement of cause of death, particularly for diarrhoea and LRTI, when compared to the Child PIP and DN Surveillance. Fifthly, I did not have Child PIP and DN Surveillance for the entire time period of the study, which may result in infectious diseases being missed in RHIS, if they were identified as infectious in Child PIP or DN Surveillance. However, it is believed this was mitigated by improved diagnostic coding in recent years and among children who die. Finally, the approach and results from comparing death data may not be generalisable beyond the Western Cape for several reasons: the Western Cape has different health information systems to other provinces and countries, many of which have not or only partially implemented a unique patient identifier. There may be differential practices for diagnostic coding and different case definitions across provinces for national reporting, and routinely collected data quality may be suboptimal.

4.6 Conclusion

This study demonstrated decreasing admission mortality rates across the province over time, with plateauing in recent years and good agreement of RHIS cause of death data with the more

accurate child death audit and DN data, particularly for LRTI and diarrhoea. This finding validates the use of routine data systems such as the RHIS data in the Western Cape to understand mortality on a regular cadence and highlights the importance of strengthening the collection and curation of this data. Nonetheless, routine health service data is strengthened by integrating with data from additional sources such as child death audit systems and DN Surveillance, emphasising the value of both VR and routine child death audits. Data on cause of death from death certificates including out-of-facility deaths should be made available to health services so that they can accurately monitor child health and the outcomes of the services they deliver. Additionally, this approach of using RHIS or similar data systems and integrating different sources of death data could be extensible to other infectious and/or non-infectious diseases and/or populations in the Western Cape or other settings where data are either already available or can be strengthened and integrated.

Chapter 5

Lower respiratory tract infection admissions and deaths among children under five years in public sector facilities in the Western Cape, South Africa, before and during the COVID-19 pandemic (2019-2021)

5.1 Overview

As described in section 2.9, Chapter 2, the COVID-19 pandemic resulted in the implementation of strict PHSM (including mobility restrictions, physical distancing, mask-wearing and hand hygiene), limitations on non-essential healthcare services, and public fear of COVID-19 infection, all of which potentially affected transmission and healthcare use for other diseases such as LRTIs. Therefore, to better understand these potential changes, this study aimed to describe the changes that occurred in LRTI admissions and in-facility deaths in relation to COVID-19 surges and PHSM, as outlined by Objective 2 in Chapter 1.

The content of this chapter has been published as a peer-reviewed manuscript in South African Medical Journal. It has been revised and adjusted to align with the structure, format, style, numbering, and referencing conventions used in this thesis. The final published version is available in Chapter 5 appendix (section 10.3) with the following reference: *Kehoe K, Morden E, Zinyakatira N, Heekes A, Jones HE, Walter SR, Jacobs T, Murray J, Buys H, Eley B, Redaniel MT, Davies MA. Lower respiratory tract infection admissions and deaths among children under 5 years in public sector facilities in the Western Cape Province, South Africa, before and during the COVID-19 pandemic (2019 - 2021). S Afr Med J. 2024 Mar 18;114(3):e1560.* This work was also presented as a poster presentation at 41st Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID) in May 2023 in Lisbon, Portugal.

I was responsible for the data management required to develop the dataset for this analysis, as described in Chapter 3. I conducted all data analyses, drafted the manuscript, incorporated feedback from co-authors, and completed the final version of the manuscript, submitting it for publication.

5.2 Introduction

The COVID-19 pandemic and subsequent responses by both the South African Government and the population resulted in many changes impacting disease transmission, access to healthcare services, and population mobility (102,103). Changes were driven by a combination of public fear of COVID-19 infection, restricted provision of non-essential health services and

the introduction of strict PHSM (103), aimed at curbing the spread of SARS-CoV-2 and ensuring sufficient hospital capacity for COVID-19 admissions.

Based on core indicators of COVID-19 burden such as case numbers and hospitalisations, PHSM, first introduced on 26 March 2020, were either relaxed or tightened nationally. PHSM included physical distancing, restrictions on non-essential services, remote working, and closures of schools and early childhood development centres (103). Additional practices such as mask-wearing, using of alcohol-based sanitisers and promotion of handwashing were implemented throughout the pandemic (103,126). The WCGHW kept primary healthcare services including childhood immunisation operational. However, they intentionally de-escalated certain healthcare services by postponing elective surgery, reducing routine clinic appointments and increasing duration of drugs dispensed to increase capacity to treat COVID-19 patients. All these factors, combined with the fear of acquiring COVID-19 at healthcare facilities, likely impacted both the transmission and healthcare service use for other infectious diseases such as non-COVID-19 LRTIs. To effectively plan for future pandemic responses, it is important to evaluate the impacts on LRTI morbidity and mortality which, prior to COVID-19, persisted across South Africa in children aged under five years with pronounced seasonality in the early winter months (March/April to June) (8,19).

I aimed to assess the changes in number and rates of LRTI hospital admissions and in-facility mortality among children aged under five years in relation to COVID-19 surges and associated measures, including PHSM, in public sector facilities in the Western Cape from January 2019 – November 2021.

5.3 Methods

Study population

The setting and study population has been described in section 4.3 of Chapter 4. For this analysis, I included data for all children aged under five years who were hospitalised or died from LRTIs at Western Cape public sector facilities from January 2019 to November 2021.

Data sources and variables

Detailed descriptions of the data sources and variables used in this analysis have been provided in Chapter 3, with the data limited to the study population defined above.

COVID-19 public health and social measures

The first PHSM implementation occurred shortly after the first imported COVID-19 case was identified in South Africa, when COVID-19 cases and admissions were still low. During subsequent COVID-19 waves, stricter PHSM were implemented at the onset of or during COVID-19 waves when the number of cases/admissions were highest nationally and/or healthcare services were under severe pressure. PHSM were relaxed during inter-wave periods. The PHSM and implementation dates are summarised in Table 5.1. Briefly, more stringent PHSM included restrictions of movement within and into the country; reduced social interactions through curfews, closures of schools, early childhood development centres and other institutions; and wearing of masks or face coverings (103). There was also wide-spread provision of alcohol-based sanitisers and promotion of hand-washing (103,126). These PHSM could have impacted the spread of COVID-19, as well as other infections.

The analysis period extends to November 2021, two months after the end of the final wave that caused major pressure on healthcare services. There was no further increase in stringency of PHSM thereafter. The analysis thus concluded at the last implementation (relaxation) of PHSM.

Table 5.1. Summary of COVID-19 public health and social measures implemented by the South African Government to curb the spread of COVID-19 (103).

Alert level	Public health and social measures implemented	Dates of implementation
Alert Level 5	- Every person was confined to their place of residence unless performing essentials services or obtaining essential goods. - Schools, early childhood development and higher education institutions were closed. - People were required to wear face masks/coverings in public spaces. - Inter-provincial and intra-provincial travel was prohibited and international borders were shut. - Retail shops and shopping malls were closed, except if they were providing essential goods. - The sale of alcohol and cigarettes and tobacco products was prohibited. - Limitations on the capacity and operating times for public transport.	26 March – 30 April 2020
Alert Level 4	- Every person was required to be in their place of residence from 21:00 – 04:00. Exceptions included essential services, attending to security or medical emergencies, and air travel arrivals. Fines were implemented for persons not adhering to the curfew. - Schools, early childhood development and higher education institutions were closed. - People were required to wear face masks/coverings in public spaces. - Inter-provincial and intra-provincial travel for leisure was prohibited and international boarders were shut. - Supermarkets, retail shops and shopping malls had limitations on capacity. - The sale of alcohol was prohibited. The ban on cigarettes and tobacco products was lifted in August 2020. - Limitations on the capacity of public transport. - Attendance of funerals and cremations was limited to 50 persons or less. All other social gatherings were prohibited.	1-31 May 2020 28 June – 15 July 2021
Alert Level 3	- Every person was required to be in their place of residence from 22:00 – 04:00. Exceptions included essential services, attending to security or medical emergencies, and air travel arrivals. Fines were implemented for persons not adhering to the curfew. - Schools and early childhood development open with physical distance measures in place. Higher education institutions also open with physical distance measures. - People were required to wear face masks/coverings in public spaces. - Inter-provincial travel was permitted. International borders were partially open for international air travel. - Supermarkets, retail shops and shopping malls were open with compliance to safety measures. - Alcohol ban was briefly lifted between January and June 2021, but was reintroduced in July 2021. The ban on cigarettes and tobacco products was lifted in August 2020. - Limitations on the capacity of public transport. - Limitations on gatherings.	1 June – 17 August 2020 29 December 2020 – 28 February 2021 16 June 2021 – 27 June 2021 26 July – 12 September 2021

Alert level	Public health and social measures implemented	Dates of implementation
Alert Level 2	- Every person was required to be in their place of residence from 23:00 – 04:00. Exceptions included essential services, attending to security or medical emergencies, and air travel arrivals. Fines were implemented for persons not adhering to the curfew. - Schools, early childhood development and higher education institutions were open with physical distance measures in place. - People were required to wear face masks/coverings in public spaces. - Inter-provincial travel was permitted. International borders were partially open for international air travel. - Supermarkets, retail shops and shopping malls were open with compliance to safety measures. - Limitations on the capacity of public transport. - Limitations on gatherings.	18 August – 20 September 2020 13-30 September 2021
Alert Level 1	- Schools, early childhood development and higher education institutions were open with physical distance measures in place. - People were required to wear face masks/coverings in public spaces. - No restrictions on travel. Travelers had to provide proof of COVID-19 vaccination or a negative COVID-19 test. - Supermarket, retail shops and shopping malls were open with compliance to safety measures. - Limitations on the capacity of public transport. - Proof of vaccination or a negative COVID-19 test was required for gatherings.	1 March – 30 May 2021 1 October 2021 – 4 April 2022

Data analysis

I described characteristics of children who were either admitted or died in-facilities due to LRTIs during different time periods: the entire study period (January 2019 – November 2021), pre-pandemic (January 2019 – March 2020) and COVID-19 pandemic (April 2020 – November 2021). Characteristics described included sex, age, admission severity and COVID-19 co-infection, as defined in section 3.3 of Chapter 3. Medians and interquartile ranges (IQR) were used for continuous variables and frequencies and proportions for categorical variables.

I described how LRTI admission rates, admission mortality rates and CFRs changed across time periods. These calculations are outlined in section 3.3 of Chapter 3 and are now being defined within the specific context of this chapter. LRTI admission rates were estimated for each time period by dividing LRTI admissions by 80% of the population estimates for children aged under five years (representing the estimated proportion accessing public sector healthcare services). Rates are presented per 1,000 person months with 95% CIs. I also estimated mortality rates with 95% CIs including: i) admission mortality rates per 100,000 live births (number of

LRTI in-facility deaths divided by the number of live births documented in the province) and ii) CFRs (number of LRTI in-facility deaths divided by total LRTI admissions).

To assess the association between COVID-19 surges and associated factors, including PHSM, and LRTI admissions more formally, I conducted an interrupted time series analysis (127) using negative binomial segmented regression applied to monthly-level data and allowing for both a level and trend change. I applied random effects for location to account for differences in access to healthcare across locations. Location was defined as the child's place of residence assigned to the district, except for the City of Cape Town (the metropolitan area), where it was further subdivided into subdistricts. Time was measured in calendar months and divided into pre-COVID-19 (January 2019 to March 2020) and COVID-19 (April 2020 to November 2021) periods. The COVID-19 period was further divided based on changes in PHSM, including alternating periods of stricter and eased measures: April to August 2020, September to December 2020, January to February 2021, March to June 2021, July to September 2021 and October to November 2021. A separate model was fitted to each pair of restriction periods to assess changes in LRTI related to each change in restriction level. IRRs and 95% CIs were reported for the step change, trend change and the post-interruption trend for each model comparison. The step change refers to the shift in LRTI admissions immediately post-PHSM introduction compared to immediately pre-PHSM. The trend change represents the ratio of the trend in LRTI admissions over time after PHSM implementation versus the trend before PHSM. The post-interruption trend is the trend per calendar month in LRTI admissions in the period after PHSM implementation.

The model adjusted for several aggregated variables deemed potential confounders (limited by data availability and described in section 3.3 of Chapter 3) including proportion male, median age of children with LRTI admissions, median duration of LRTI admissions, quarterly proxy immunisation coverage, COVID-19 confirmed admissions and seasonality (measured in quarters: January-March, April-June, July-September, October-December) to account for autocorrelation. Immunisation coverage was previously defined in section 3.3 of Chapter 3 and is now being defined within the context of this chapter. Proxy immunisation coverage was calculated quarterly by dividing the number of fully immunised children aged under one year by the previous years under one year population (to represent a proxy eligible cohort), adjusted for quarterly live births from the WCPHDC (records live births in all public sector facilities). I

conducted a sensitivity analysis excluding children co-infected with COVID-19 during LRTI admission to assess potential impact on LRTI admission rates.

To assess what would have happened to LRTI admission rates under the expected seasonality pattern had the pandemic and its associated factors not occurred, I also modelled the pre-COVID-19 period alone. I used the estimated relationship between covariates and outcome to forecast counterfactual LRTI admission rates for the pandemic period. This pre-pandemic period model included the same variables as the full model, except for COVID-19 cases and the interruption variable. Observed, model predicted and counterfactual LRTI admission rates per 1,000 person months were plotted.

Data cleaning and coding were performed in SQL, while data linkage and aggregation were done in R Studio 2022.12.0, and analysis in Stata 17.0.

5.4 Results

Characteristics of LRTI admissions and in-facility deaths in children

Of 36,277 children admitted for LRTIs for the entire study period, most were males (21,118, 58%) and aged 28 days – 1 year (18,496, 51%), with 2% (679) of LRTI admissions including a period in an ICU (Table 5.2). The distribution of these characteristics for LRTI hospital admissions were similar during the pre-COVID-19 and COVID-19 periods. Among children who died from LRTIs in-facility, the median age at death was 6.8 months (IQR 3.6-19.3 months) pre-COVID-19 and 5.6 months (IQR 1.9-16.1 months) during the pandemic period. The median time from admission to death was 6 days (IQR 1-16 days) pre-COVID-19 and 3.5 days (IQR 1-10 days) during COVID-19).

Table 5.2. Characteristics of children who were admitted for or died from a lower respiratory tract infection in a public sector facility in the Western Cape before and during COVID-19 (January 2019 – November 2021). Column percentages for the total admissions or deaths are shown per time period.

	Overall (January 2019 – November 2021)	**Pre-COVID-19** (January 2019 – March 2020)	**COVID-19** (April 2020 – November 2021)
LRTI admissions			
Total admissions	36,277	17,539	18,738
Male	21,118 (58%)	10,246 (58%)	10,872 (58%)
Female	15,169 (42%)	7,293 (42%)	7,866 (42%)
Age			
Median age (months, IQR)	9.6 (3.5 – 20.5)	9.7 (3.7 – 20.3)	9.5 (3.4 – 20.8)
<28 days	2,144 (6%)	967 (6%)	1,177 (6%)
28 days – 1 year	18,496 (51%)	9,037 (51%)	9,459 (51%)
>1 year – <5 years	15,637 (43%)	7,535 (43%)	8,102 (43%)
Admission severity			
ICU admissions	679 (2%)	299 (2%)	380 (2%)
Median length of stay (days, IQR)	2 (1 – 4)	2 (1 – 4)	2 (1 – 4)
COVID-19 coinfection*	N/A	0	320 (2%)
LRTI deaths			
Total deaths	111	49	62
Male	55 (50%)	22 (45%)	33 (53%)
Female	56 (50%)	27 (55%)	29 (47%)
Age			
Median age (months, IQR)	6.4 (2.5 – 17.5)	6.8 (3.6 – 19.3)	5.6 (1.9 – 16.1)
<28 days	18 (16%)	6 (12%)	12 (19%)
28 days – 1 year	54 (49%)	23 (47%)	30 (50%)
>1 year – <5 years	39 (35%)	20 (41%)	19 (31%)
Admissions severity			
ICU admissions	56 (50%)	24 (49%)	32 (52%)
Median time from admission to death (days, IQR)	4 (1 – 10)	6 (1 – 16)	3.5 (1 – 10)
COVID-19 co-infection	N/A	0	1 (2%)

ICU: intensive care unit, IQR: interquartile range, LRTI: lower respiratory tract infection.

* Testing coverage fluctuated throughout the period due to variations in laboratory capacity, facility practices, and guidelines aimed at prioritising COVID-19 testing for those requiring it most for clinical management purposes.

Daily LRTI admissions and COVID-19 cases

During stricter PHSM, which were implemented prior to the COVID-19 peaks, LRTI admission were at the lowest levels (Figure 5.1). The pre-pandemic early winter surge (April to June) in LRTI admissions shifted to later in the year after the onset of COVID-19 PHSM.

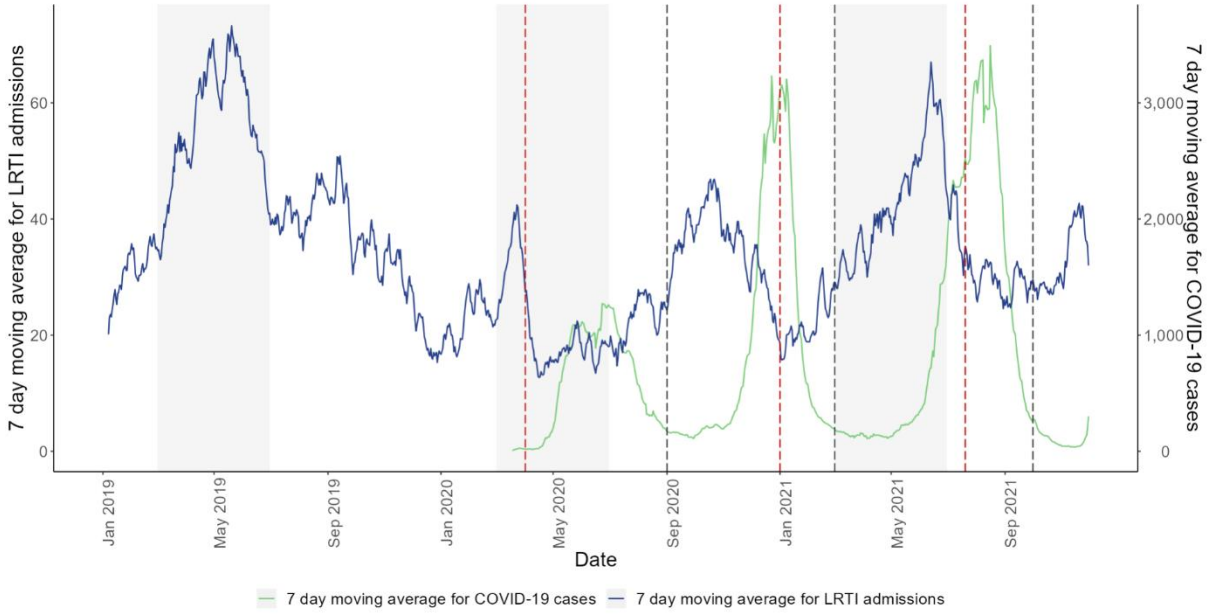


Figure 5.1. Daily lower respiratory tract infection admissions among children under five years (blue line) and all COVID-19 cases in the Western Cape (7 day moving average) (green line) from January 2019 to November 2021. The red dashed vertical lines indicate the stricter implementation of public health and social measures (PHSM), whereas the grey dashed vertical lines indicate the relaxation of PHSM. Stricter implementation of PHSM included restrictions on population mobility and closure of schools, early childhood development centres and other institutions. COVID-19 cases reflect both public and private sector recorded positive SARS-CoV-2 PCR and antigen tests, irrespective of symptoms. The expected seasonality peak period from November to May, based on historic trends, has been highlighted in light grey.

LRTI: lower respiratory tract infection, PCR: polymerase chain reaction, PHSM: public health and social measures.

Rates of LRTI admissions and in-facility deaths across PHSM periods

LRTI admission rates lowered from 13.20 LRTI admissions per 1,000 person months (95% CI: 13.01-13.39) pre-pandemic to 9.94 LRTI admissions per 1,000 person months (95% CI: 9.80-10.09) during COVID-19 overall (Table 5.3). During the first and strictest implementation of PHSM, the admission rate lowered from pre-COVID-19 to 6.48 LRTI admissions per 1,000 person months (95% CI: 6.25-6.72) (Table 5.3). During the period of PHSM relaxation, (second, and fourth implementation) the average LRTI admission rates were higher from the preceding period, except for the sixth implementation, where LRTI admission rates remained similar.

There was a slight decrease in LRTI admission mortality rates: 42.72 deaths per 100,000 live births (95% CI 31.60-56.47) in the pre-pandemic period to 38.79 deaths per 100,000 live births (95% CI 29.74-49.72) in the pandemic period overall (Table 5.3). The pattern of fluctuations in LRTI admission rates with PHSM was not observed in LRTI admission mortality rates. There was a decrease during the first (the strictest) and the fourth (a relaxation) implementation of PHSM. The CFRs followed a similar pattern to the admission mortality rates; however, the highest CFR (0.53%, 95% CI 0.21-1.01) was observed during the third implementation (tightening of restrictions) of PHSM.

Table 5.3. Admission rates, admission mortality rates and case fatality rates for children who were admitted due to lower respiratory tract infections in public sector facilities in the Western Cape pre-COVID-19 and during COVID-19 (January 2019 – November 2021).

Period	LRTI admissions	Admission rate per 1,000 person months (95% CI)	LRTI deaths	Admission mortality rate per 100,000 live births (95% CI)	Case fatality rate (95% CI)
Pre-COVID (January 2019 – March 2020)	17,539	13.20 (13.01-13.39)	49	42.72 (31.60-56.47)	0.28% (0.21-0.37)
COVID-19 (April 2020 – November 2021	18,738	9.94 (9.80-10.09)	62	38.79 (29.74-49.72)	0.33% (0.25-0.42)
First implementation of PHSM (April – August 2020)*	2,976	6.48 (6.25-6.72)	11	26.35 (13.15-47.14)	0.37% (0.18-0.66)
Second implementation of PHSM (September – December 2020)**	4,283	11.66 (11.31-12.01)	14	43.67 (23.88-73.26)	0.33% (0.18-0.55)
Third implementation of PHSM (January – February 2021)*	1,315	6.84 (6.48-7.21)	7	46.71 (18.78-96.22)	0.53% (0.21-1.01)
Fourth implementation of PHSM (March – June 2021)**	5,294	13.77 (13.40-14.14)	11	34.10 (17.02-61.01)	0.21% (0.10-0.37)
Fifth implementation of PHSM (July – September 2021)*	2,876	9.97 (9.61-10.34)	12	50.06 (25.87-87.43)	0.42% (0.22-0.73)
Sixth implementation of PHSM (October – November 2021)**	1,944	10.37 (9.92-10.83)	7	47.20 (18.98-97.23)	0.35% (0.14-0.72)

CI: confidence interval, LRTI: lower respiratory tract infection, PHSM: public health and social measures.
* Tightening of public health and social measures
** Relaxation of public health and social measures

Interrupted time series model: changes in LRTI admissions in relation to PHSM

After adjusting for potential confounders, it was estimated that the COVID-19 period was associated with a 13% (IRR 0.87, 95% CI 0.80-0.94) step reduction in LRTI admissions versus pre-COVID-19 (Table 5.4) followed by an increase in average trend of 2% per month (IRR 1.02, 95% CI 1.02-1.04). Analysing different periods of PHSM implementation revealed that the initial (strictest) implementation of PHSM was associated with the greatest step drop in LRTI admissions (IRR 0.62, 95% CI 0.52-0.73), followed by an 8% average increase per month (IRR 1.08, 95% CI 1.03-1.14). Generally, step increases were associated with PHSM easing. There was a diminishing step change effect over time, with no evidence of change for the last PHSM implementation. Similar step and trend changes were observed when COVID-19 co-infected cases were excluded from the analysis (Table S5.1 in section 10.3 of Chapter 10).

Table 5.4. Changes in lower respiratory tract infection admissions among children aged under five years after the implementation of different COVID-19 public health and social measures in public sector facilities in the Western Cape, South Africa (January 2019 – November 2021) overall (column headed "Entire period") and for the different restriction periods each relative to the previous period (subsequent columns). Bold values indicate point estimates with 95% confidence intervals that exclude the null value.

	Entire period	**Different restriction periods based on PHSM compared with the immediate preceding period**					
	COVID-19 versus pre-COVID-19	**First implementation of PHSM versus pre-COVID-19 ***	**Second versus first implementation of PHSM****	**Third versus second implementation of PHSM***	**Fourth versus third implementation of PHSM****	**Fifth versus fourth implementation of PHSM***	**Sixth versus fifth implementation of PHSM****
Interruptions							
Time period	Jan 2019 – Nov 2021	Jan 2019 – Aug 2020	Apr – Dec 2020	Sept 2020 – Feb 2021	Jan – June 2021	Mar – Aug 2021	Jul – Nov 2021
Interruption	Apr 2020	Apr 2020	Sept 2020	Jan 2021	Mar 2021	Jul 2021	Oct 2021
Model output							
Step change (IRR, 95% CI)	**0.87 (0.80-0.94)**	**0.62 (0.52-0.73)**	1.12 (0.95-1.30)	0.85 (0.73-1.01)	1.02 (0.72-1.46)	0.95 (0.70-1.29)	1.02 (0.88-1.19)
Trend change (IRR, 95% CI)	**1.03 (1.02-1.04)**	**1.10 (1.05-1.15)**	**0.85 (0.77-0.94)**	**1.36 (1.09-1.69)**	0.90 (0.62-1.30)	0.95 (0.83-1.07)	1.12 (0.96-1.30)
Average post-interruption trend (IRR per month, 95% CI)	**1.02 (1.01-1.02)**	**1.08 (1.03-1.14)**	0.92 (0.85-1.00)	1.17 (0.99-1.40)	1.08 (0.98-1.18)	0.96 (0.88-1.04)	1.08 (0.95-1.21)

CI = confidence intervals; IRR = incidence rate ratios; LRTI = lower respiratory tract infection; PHSM = public health and social measures.
* Tightening of public health and social measures
** Relaxation of public health and social measures

Counterfactual and estimated LRTI admission rates

Predicted counterfactual LRTI admission rates during the first PHSM implementation based on the assumption of no PHSM effect were higher than observed rates through the initial period following the first PHSM measures (Figure 5.2). Subsequently observed and counterfactual LRTI admission rates were similar at longer durations post-interruption.

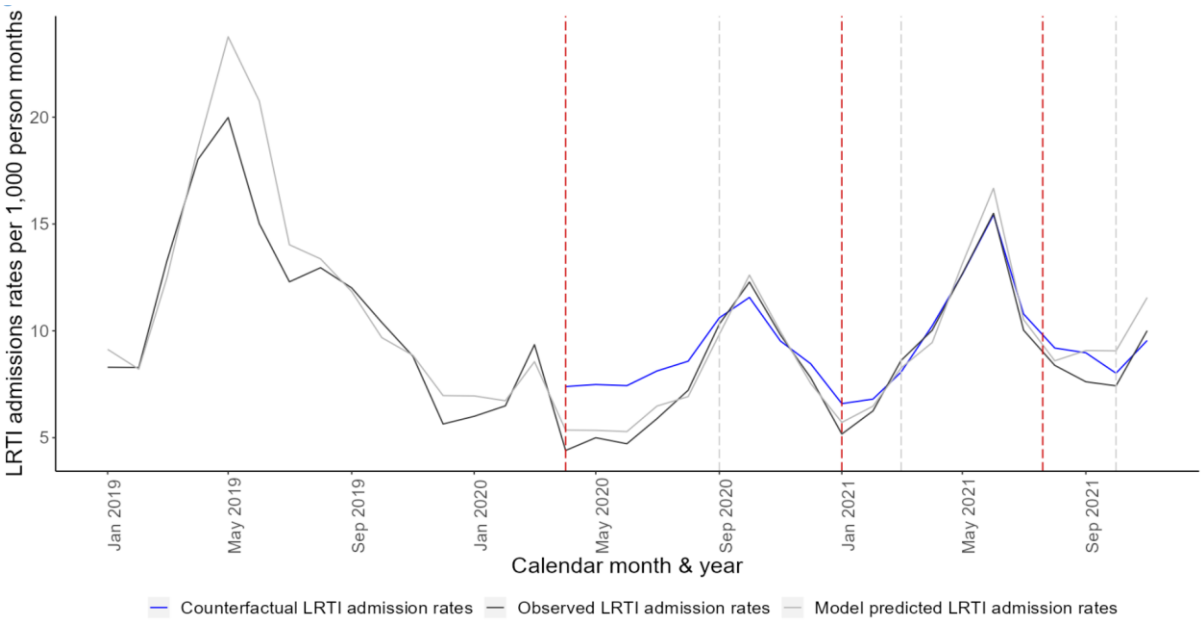


Figure 5.2. Counterfactual (blue line), observed (dark grey line) and model (light grey line) predicted rates of lower respiratory tract infection hospitalisations among children in the Western Cape (January 2019 – November 2021). The red dashed vertical lines indicate the stricter implementation of public health and social measures (PHSM), whereas the grey dashed vertical lines indicate the relaxation of PHSM. Stricter implementation of PHSM included restrictions on population mobility and closure of schools, early childhood development centres and other institutions.

5.5 Discussion

This study demonstrated how the effects of the COVID-19 pandemic, including PHSM co-occurring service de-escalation and fear of accessing healthcare services, impacted LRTI admissions and in-facility deaths in public healthcare facilities in the Western Cape, South Africa. Overall, the greatest reductions were associated with stricter PHSM, with greatest declines in LRTI admissions noted as PHSM were first introduced. Early on, in-facility LRTI admission mortality rates decreased when more stringent PHSM were in place. However,

increases in CFRs were observed with reductions of LRTI admissions, generally during stricter PHSM.

Previous studies in other low- and middle-income settings have reported similar findings (128,129), indicating PHSM changes impacted LRTI admissions rates among children, with the greatest reductions temporally associated with stricter PHSM. However, determining the extent to which these reductions were influenced by decreased transmission from school closures, physical distancing, improved hygiene practices, versus reduced healthcare use due to mobility restrictions and/or fear is difficult as these factors often occurred simultaneously. Nonetheless, because PHSM were implemented nationwide in South Africa, whereas the timing of the worst COVID-19 healthcare service admission pressure varied by province, I could examine the impact of PHSM independently from the effect of facilities being overburdened by COVID-19 admissions. The change in childhood LRTI admission patterns, preceding the COVID-19 admission peak and coinciding with the adjustment of PHSM stringency, suggests that reduced admissions were not due to reduced healthcare access driven by overburdened healthcare facilities. Rather, these findings indicate that PHSM and resulting behavioural shifts influenced disease transmission. Additionally, the interplay of PHSM and fear of contracting COVID-19 at healthcare facilities affected healthcare utilisation.

Behaviour changes due to COVID-19 PHSM (physical distancing, mask wearing, hand hygiene practices and healthcare use) disrupted the previously established seasonal pattern of an autumn/winter LRTI admission peak, potentially altering immunity to LRTI pathogens, with children being less exposed to LRTIs at younger ages. Similar shifts in seasonality for LRTI admissions have been observed in other settings (128–130).

Despite decreases in children aged under five years dying across South Africa during COVID-19, pneumonia remained one of the main causes of death (130,131). Children dying from LRTIs during COVID-19 were generally younger, with shorter admission-to-death time versus pre-pandemic. This suggests either only more severely ill children sought healthcare during the pandemic and/or there were challenges in accessing healthcare in the context of PHSM, leading to worsened illness severity upon presentation. Admission mortality rates were overall slightly lower in the pandemic versus pre-pandemic, consistent with findings in other South African facilities (128). While it is possible that the proportion of out-of-facility mortality increased during this time, I was unable to evaluate this as this study was limited to in-facility mortality.

I observed fluctuations in LRTI admission rates each time the PHSM were altered. The highest CFRs and admission mortality rates largely coincided with increased service pressure during COVID-19 waves as well as reductions in mobility due to tightening of PHSM and/or fear of transmission during COVID-19 waves. Caution should be exercised when interpreting these findings, as CFRs are sensitive to the number of admissions, and the lowest number of LRTI admissions occurred during this time.

Strengths and limitations

This study was strengthened by using individual-level data for the aggregation, allowing me to have linked admission and mortality outcomes of children, informed by data linkage within the WCPHDC (132). I had data for the entire Western Cape province for all time periods, increasing the generalisability of these findings. I used a comprehensive list of ICD-10 codes to identify LRTI admissions and in-facility deaths, ensuring thorough case identification. Mapping LRTI admissions and deaths to a child's residence helped identify the burden of severe illness in the community.

This study had several limitations. Aggregated monthly data sometimes grouped PHSM implementations in the same month, addressed by selecting the closest month for analysis. Out-of-facility death data were not available. Out-of-facility deaths may have increased due to healthcare access challenges in the context of PHSM. I relied solely on electronic health records, however, it is believed that electronic data completeness was high and, if anything, increased in more recent years and during the pandemic, which would have resulted in under-estimating the PHSM-associated reductions in LRTI admissions and deaths. I only had data on LRTI admissions, not all cases, hindering the understanding of the full impact of COVID-19 surges and the associated factors. I was only able to adjust for socioeconomic status using the subdistrict or district of the child's residence as a crude proxy. Data variables were limited by availability. Hospital data and population estimates reflected the child's residence, whereas immunisations, live births and COVID-19 data represented healthcare service locations. Population estimates, the denominator to calculate rates, were based on an assumption of the percentage of children reliant on public sector services. A different assumption may alter the rates themselves but would not impact estimated changes over time.

5.6 Conclusion

COVID-19 surges and changes in stringency of COVID-19 PHSM were associated with temporal reductions in LRTI admissions and deaths, albeit with impacts diminishing over time. This is likely due to a combination of physical distancing and hand hygiene measures directly impacting LRTI transmission as well as decreased population mobility and hesitancy/fear reducing access of healthcare services. The lowest levels of LRTI admissions coincided with the strictest PHSM, rather than with COVID-19 wave peaks. This suggests that the changing pattern of LRTI admissions was not due to the COVID-19 pandemic itself nor high COVID-19 service pressure crowding out paediatric LRTI admissions, but could be due to direct impacts of PHSM on respiratory pathogen transmission as well as reduced mobility and fear reducing healthcare access. These findings can be used to inform policies for responses to future pandemics.

Chapter 6

Diarrhoeal admissions among children under five years in public sector facilities in the Western Cape, South Africa, before and during the COVID-19 pandemic (2019-2021)

6.1 Overview

In Chapter 5, I described the changes that occurred in LRTI admissions and in-facility deaths in relation to PHSM changes and COVID-19 surges. The COVID-19 surges and their associated measures were linked to declining LRTI admissions and in-facility deaths, likely driven by a combination of reduced infectious disease transmission and reduced use of healthcare services, with effects diminishing over time. These findings may inform future pandemic response policies. Given the prevalence and ongoing morbidity of diarrhoea in the Western Cape province, it was important to also understand the impact that the pandemic had on diarrhoea admissions. Additionally, the Western Cape experiences increased cases of LRTI and diarrhoea during the surge season (November – May) annually and monitors these infectious diseases separately to ensure the correct interventions are implemented for both prevention and case management. COVID-19 cases also presented with LRTI and diarrhoea co-infections during the pandemic. The anticipated effects of certain interventions aimed at reducing COVID-19 spread were likely to differ between LRTI and diarrhoea. Since PHSM were primarily designed to curb COVID-19 transmission, which occurs through airborne or droplet spread, they were expected to have the most significant impact on LRTI admissions. Although some PHSM, such as handwashing promotion, provision of alcohol-based sanitisers, and the closure of early childhood development centres, may have also influenced diarrhoea admissions, the measures specifically targeting airborne or droplet transmission (e.g., mask-wearing, social distancing) were expected to have a limited effect on diarrhoea. Therefore, it was decided to investigate the changes in each of these diseases separately to provide up-to-date data to clinicians and healthcare workers, particularly those involved in the management of these two diseases. The study presented below aimed to describe the changes that occurred in diarrhoea admissions in relation to COVID-19 surges and PHSM, as outlined in Objective 4 in Chapter 1. The same methods were used as described in Chapter 5 and are briefly summarised here. Furthermore, the PHSM literature related to diarrhoea transmissions are highlighted below.

6.2 Introduction

As discussed in Chapter 5, the COVID-19 pandemic prompted significant changes in South Africa, influenced by restricted non-essential health services, implementation of PHSM, and fear of acquiring COVID-19. PHSM were implemented to manage SARS-CoV-2 transmission and to ensure sufficient hospital capacity for COVID-19 cases. These measures included mobility restrictions, physical distancing, wearing masks, and hand hygiene practices (102,103).

PHSM strategies resulted in significant behaviour change among individuals. Firstly, there was promotion of hand hygiene, emphasising hand washing with soap and water and the wide-spread provision of alcohol-based sanitisers (103), as highlighted in Table 5.1 in Chapter 5. Hand hygiene practices have been crucial in reducing the spread of other infectious diseases such as LRTIs, Ebola, influenza and gastroenteritis (133–135). Mobility restrictions such as curfews, physical distancing and closures of early childhood development centres and schools were also implemented (103). These behavioural changes due to PHSM and fear of acquiring COVID-19 likely influenced the transmission of other infectious diseases globally and in South Africa. Prior to the COVID-19 pandemic, diarrhoea cases and hospital admissions persisted among children younger than five years in South Africa with wide geographic variation, typically peaking in the summer season (November to May) (7,74). Understanding the changes in diarrhoea admissions in the context of PHSM, including the potential impact of these measures on healthcare access, is important to effectively plan for future pandemics as well as periods of expected increases in diarrhoea cases.

I examined fluctuations in the number and rates of diarrhoea hospital admissions in children aged under five years of age in relation to COVID-19 surges and associated measures, including PHSM, across Western Cape public sector facilities.

6.3 Methods

The methods have been described in detail in section 5.3, Chapter 5 and are briefly described here. Using data from the WCPHDC, as described in Chapter 3, the study included hospitalisation data for children aged under five years admitted due to diarrhoea from January 2019 to November 2021. The analysis involved examining characteristics such as sex, age, admission severity, and COVID-19 co-infection (defined in section 3.3 of Chapter 3). Crude observed diarrhoea admission rates were estimated for different time periods, as previously outlined in section 3.3 of Chapter 3, but will now be defined within the context of this chapter.

Diarrhoea admission rates were estimated for each time period by dividing diarrhoea admissions by 80% of the population estimates for children aged under five years (representing the estimated proportion accessing public sector healthcare services). Negative binomial segmented regression was applied in an interrupted time series analysis to assess the association between COVID-19 surges, PHSM, and diarrhoea admissions. The model was adjusted for proportion male, median age of children with diarrhoea admissions, median duration of diarrhoea admissions, quarterly proxy immunisation coverage, COVID-19 confirmed admissions (defined in section 3.3 of Chapter 3) and seasonality (measured in quarters: December – February, March – May, June – August, September – November) to account for autocorrelation.

6.4 Results

Characteristics of diarrhoea admissions

Over the study period, 17,204 children were admitted for diarrhoea, with the majority of admissions being in males (9,304, 54%), and almost half being in children aged under one year (8,286, 48%) (Table 6.1). The median age at diarrhoea admission was 12.5 months (IQR: 6.4-22.4 months) and the median length of stay was 2 days (IQR: 1-4 days). Of the recorded diarrhoeal admissions, 1% (204) were admitted to the ICU. These characteristics remained similar across the pre-pandemic and pandemic time periods. COVID-19 coinfection occurred in 1% of children admitted with diarrhoea (119) during the pandemic.

Table 6.1. Characteristics of children who were admitted for diarrhoea in a public sector facility in the Western Cape before and during the COVID-19 pandemic period (January 2019 – November 2021). Column percentages for the total admissions or deaths are shown per time period.

	Overall (January 2019 – November 2021)	**Pre-COVID-19** (January 2019 – March 2020)	**COVID-19** (April 2020 – November 2021)
Total admissions	17,204	8,490	8,714
Male admissions	9,304 (54%)	4,571 (54%)	4,733 (54%)
Female admissions	7,900 (46%)	3,919 (46%)	3,981 (46%)
Age			
Median age (months, IQR)	12.5 (6.4 – 22.4)	12.2 (6.4 – 22.2)	12.7 (6.4 – 22.6)
<28 days	511 (3%)	244 (3%)	267 (3%)
28 days – 1 year	7,775 (45%)	3,922 (46%)	3,853 (44%)
>1 year – <5 years	8,918 (52%)	4,324 (51%)	4,594 (53%)
Admission severity			
ICU admissions	204 (1%)	104 (1%)	100 (1%)
Median length of stay (days, IQR)	2 (1 – 4)	2 (1 – 4)	2 (1 – 4)
COVID-19 co-infection*	N/A	0	119 (1%)

ICU: intensive care unit, IQR: interquartile range.
* Testing coverage fluctuated throughout the period due to variations in laboratory capacity, facility practices, and guidelines aimed at prioritising COVID-19 testing for those requiring it most for clinical management purposes.

Daily diarrhoea admissions and COVID-19 cases

During periods of stricter PHSM, implemented prior to the COVID-19 peaks in wave one and three, diarrhoeal disease admissions were at the lowest levels (Figure 6.1). The inter-wave periods saw a steady increase in diarrhoea cases, which was minimally affected by the stricter implementation of PHSM during wave two. The summer surge (November to May) in diarrhoea cases observed annually pre-pandemic (highlighted in grey in Figure 6.1) was not observed in 2021 during the pandemic. Instead, diarrhoea admissions slowly increased until April 2021, with a peak in May – June 2021, when the surge period should be declining based on pre-pandemic data. This peak attenuated once stricter PHSM were introduced in mid-June 2021.

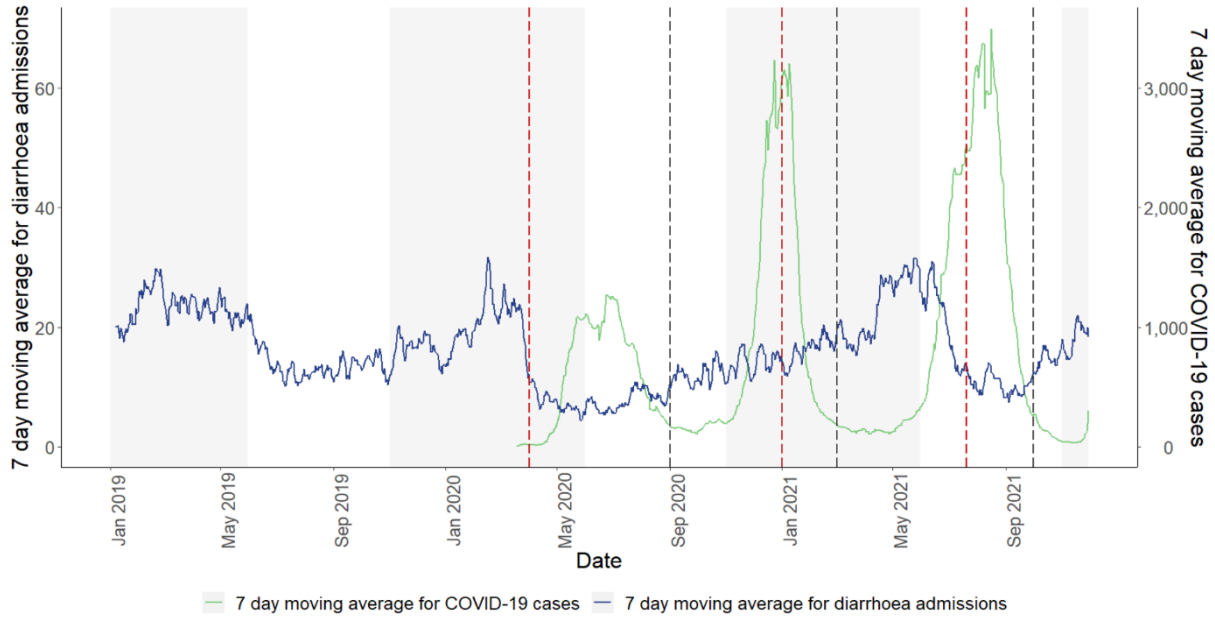


Figure 6.1. Daily diarrhoeal admissions among children aged under five years (blue line) and all COVID-19 cases in the Western Cape (7 day moving average) (green line) from January 2019 to November 2021. The red dashed vertical lines indicate the stricter implementation of public health and social measures (PHSM), whereas the dark grey dashed vertical lines indicate the relaxation of PHSM. Stricter implementation of PHSM included restrictions on population mobility and closure of schools, early childhood development centres and other institutions. COVID-19 cases reflect both public and private sector recorded positive SARS-CoV-2 PCR and antigen tests, irrespective of symptoms. The expected seasonality peak periods from November to May, based on historic trends, have been highlighted in light grey.

PCR: polymerase chain reaction, PHSM: public health and social measures.

Rates of diarrhoea admissions in across PHSM periods

Diarrhoea admission rates decreased from 6.39 admissions per 1,000 person months (95% CI: 6.25-6.53) pre-pandemic to 4.62 admissions per 1,000 person months (95% CI: 4.53-4.72) during COVID-19 overall (Table 6.2). Admissions rates were at their lowest during the first and strictest implementation of PHSM (2.55 admissions per 1,000 person months, 95% CI: 2.41-2.70) (Table 6.2). Following each instance of PHSM easing (second, fourth, and sixth implementation), diarrhoea admission rates were higher compared to the preceding time period.

Table 6.2. Crude observed admission rates in public sector facilities in the Western Cape pre-COVID-19 and during COVID-19 (January 2019 – November 2021).

Period	Diarrhoea admissions	Admission rate per 1,000 person months (95% CI)
Pre-COVID (January 2019 – March 2020)	8,490	6.39 (6.25 – 6.53)
COVID-19 (April 2020 – November 2021)	8,714	4.62 (4.53 – 4.72)
First implementation of PHSM (April – August 2020)*	1,172	2.55 (2.41 – 2.70)
Second implementation of PHSM (September – December 2020)**	1,614	4.39 (4.18 – 4.61)
Third implementation of PHSM (January – February 2021)*	972	5.06 (4.74 – 5.38)
Fourth implementation of PHSM (March – June 2021)**	2,919	7.59 (7.32 – 7.87)
Fifth implementation of PHSM (July – September 2021)*	1,021	3.54 (3.33 – 3.76)
Sixth implementation of PHSM (October – November 2021)**	1,016	5.28 (4.96 – 5.62)

CI: confidence interval, PHSM: public health and social measures.
* Tightening of public health and social measures
** Relaxation of public health and social measures

Interrupted time series model: changes in diarrhoea admissions in relation to PHSM

It was estimated that the pandemic period was associated with a 14% (IRR 0.76, 95% CI 0.69-0.84) step reduction in diarrhoea admissions compared to the pre-pandemic period (Table 6.3), adjusted for potential confounders. Comparing pre-pandemic and pandemic rates, I found a 2% average monthly increase in diarrhoea admissions during the pandemic period (IRR 1.02, 95% CI: 1.01-1.02), following the initial step reduction. In the models that assessed each PHSM period separately, it was estimated that there was an initial 50% step reduction in diarrhoea admissions during the strictest, initial implementation of PHSM (IRR 0.50, 95% CI: 0.43-.059), followed by an average increase of 17% per month (IRR 1.17, 95% CI: 1.11-1.23). Further step decreases were observed across the majority of subsequent time periods, except during the least strict PHSM periods (second and sixth implementation). Trend increases were observed early on (first and second PHSM implementation).

Table 6.3. Changes in diarrhoeal admission rates among children age under five years after the implementation of different COVID-19 public health and social measures in public sector facilities in the Western Cape, South Africa (January 2019 – November 2021) overall (column headed "Entire period") and for the different restriction periods each relative to the previous period (subsequent columns). Bold values indicate point estimates with 95% confidence intervals that exclude the null value.

	Entire period	**Different restriction periods based on PHSM compared with the immediate preceding period**					
	COVID-19 vs pre-COVID-19	**First implementation of PHSM vs pre-COVID-19 ***	**Second vs first implementation of PHSM****	**Third vs second implementation of PHSM***	**Fourth vs third implementation of PHSM****	**Fifth vs fourth implementation of PHSM***	**Sixth vs fifth implementation of PHSM****
Interruptions							
Time period	Jan 2019 – Nov 2021	Jan 2019 – Aug 2020	Apr – Dec 2020	Sept 2020 – Feb 2021	Jan – June 2021	Mar – Aug 2021	Jul – Nov 2021
Interruption	Apr 2020	Apr 2020	Sept 2020	Jan 2021	Mar 2021	Jul 2021	Oct 2021
Model output							
Step change (IRR, 95% CI)	**0.76 (0.69 – 0.84)**	**0.50 (0.43 – 0.59)**	1.00 (0.71- 1.43)	0.89 (0.75 – 1.07)	0.92 (0.59 – 1.41)	**0.49 (0.38 – 0.65)**	**1.42 (1.09 – 1.84)**
Trend change (IRR, 95% CI)	**1.02 (1.01 – 1.03)**	**1.17 (1.11– 1.24)**	1.03 (0.91 – 1.17)	**0.69 (0.53 – 0.89)**	1.01 (0.74 – 1.39)	0.78 (0.63 – 1.03)	1.02 (0.81 – 1.28)
Average post-interruption trend (IRR per month, 95% CI)	**1.02 (1.01 – 1.02)**	**1.17 (1.11 – 1.23)**	1.09 (1.00 – 1.18)	**0.74 (0.59 – 0.94)**	1.08 (1.00 – 1.17)	0.55 (0.71 – 1.02)	0.94 (0.81 – 1.09)

CI = confidence intervals; IRR = incidence rate ratios; PHSM = public health and social measures

* Tightening of public health and social measures

** Relaxation of public health and social measures

Counterfactual and estimated diarrhoea admission rates

Forecasted counterfactual diarrhoea admission rates during the initial PHSM implementation, assuming no effects from PHSM, were higher than the observed rates during the first period of PHSM implementation (Figure 6.2). Counterfactual diarrhoea admission rates remained slightly higher than the observed rates until the fourth implementation (relaxation); thereafter, counterfactual and observed rates were similar.

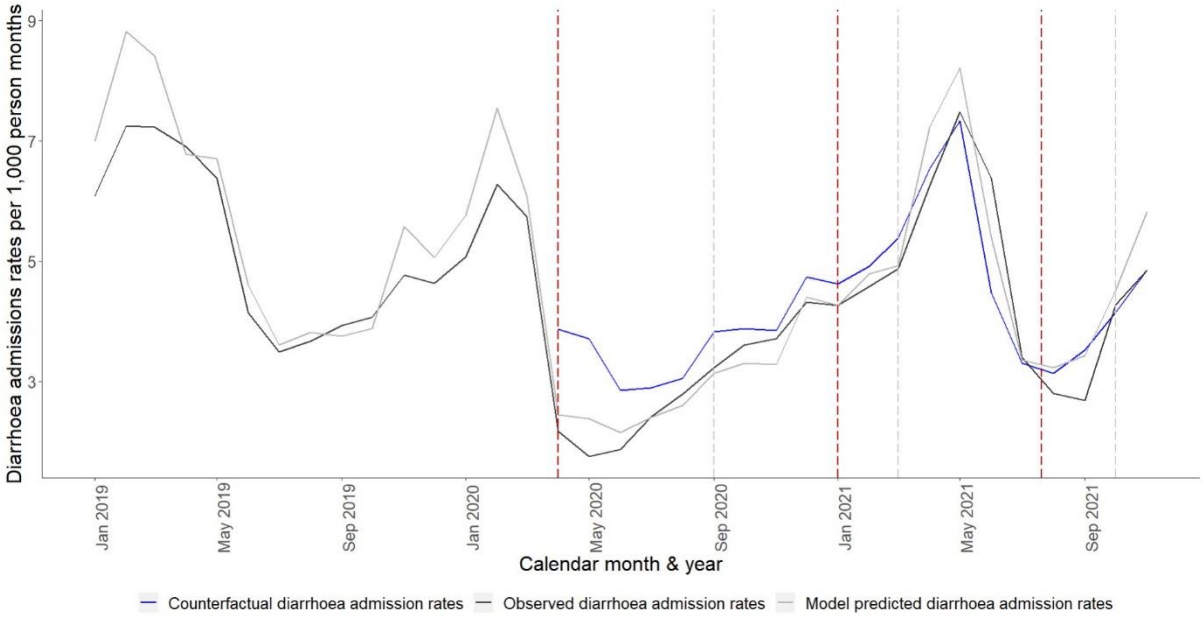


Figure 6.2. Counterfactual (blue line), observed (dark grey) and model (light grey) predicted rates of diarrhoeal hospitalisations among children in the Western Cape public sector (January 2019 – November 2021). The red dashed vertical lines indicate the times of stricter implementation of public health and social measures (PHSM), whereas the grey dashed vertical lines indicate the times of relaxation of PHSM. Stricter implementation of PHSM included restrictions on population mobility and closure of schools, early development centres and other institutions.

6.5 Discussion

This study found that the first and strictest implementation of PHSM was associated with substantial step reduction in diarrhoea hospital admissions in children aged under five years, followed by a small trend increase thereafter in public sector facilities in the Western Cape, South Africa. Similar but less pronounced step reductions in diarrhoea admissions followed subsequent tightening of PHSM during COVID-19 surges, with no evidence of a trend change thereafter.

Diarrhoea cases and related deaths declined among children during the pandemic in low- and middle-income settings (131,136–138), potentially due to hand hygiene and physical distancing PHSM, as well as reduced social contact among children due to closures of schools and early childhood development centres. In this study, changes in diarrhoea admission rates were associated with changes in PHSM, with reductions observed during stricter PHSM implementation. Despite decreased diarrhoea admission rates during stricter PHSM periods, the average post-interruption trend only increased for the first and strictest implementation of PHSM. Physical distancing and hand hygiene measures, affecting both children and caregivers, were consistently implemented during the pandemic and may have contributed to these observed step decreases in comparison to each preceding PHSM implementation. The simultaneous implementation of PHSM made it difficult to determine the extent to which each measure contributed to the observed changes. After the initial drop in childhood diarrhoea admissions when the strictest PHSM were first implemented, they steadily increased during both the first and second COVID-19 waves, peaking before the third wave. This suggests that PHSM and consequent behavioural changes altered disease transmission, and mobility restrictions together with a general fear of contracting COVID-19 at healthcare facilities further affected healthcare utilisation. The fact that the biggest reductions in diarrhoea admissions were co-incident with the stricter implementations of PHSM (March 2020 and July 2021) before the peaks of COVID-19 waves (when health services would have been busiest) suggests that admissions were reduced by reductions in transmission, mobility restrictions and fear of accessing health services, rather than being crowded out by overburdened services. A similar effect was observed with LRTI admissions (section 5.6 of Chapter 5).

Diarrhoea admissions peaked in May 2021in the observed data and the timing of this peak was predicted by the counterfactual scenario. There were similar increases in LRTIs in the Western Cape during this time (139). Historically, diarrhoeal surge season spans from November to May in the Western Cape, and during this time, tailored interventions are implemented to address the increased case load. The increases in diarrhoea admission incidence in May 2021 occurred before the third COVID-19 wave and overlapped with an increase in headcount at primary healthcare facilities and a PHSM relaxation, with the fewest restrictions and least school closures, potentially reversing some of the behaviour changes previously observed. Earlier in the year, the expected seasonal peak was disrupted in January 2021 and may be due to a combination of hand hygiene, extended school closures (the normal end of school holidays in mid-January was delayed to mid-February 2021) and mask wearing PHSM. Furthermore,

immunity to diarrhoea pathogens may have also been altered due to PHSM in 2020 and January 2021, so that by May 2021 younger children would have been less exposed than previously as they stayed home and had less social exposure, making them more vulnerable when PHSM were relaxed. Shortly after the May 2021 peak, diarrhoea admissions decreased to a similar number of cases observed at the start of the pandemic when PHSM were tightened just before the peak of cases in the 3rd COVID-19 wave.

Strengths and limitations

The strengths and limitations to this study have been described in Chapter 5 (139), and will also be outlined here, with emphasis on how these factors pertain to diarrhoea admissions as the outcome. Strengths included the use of an individual-level dataset for aggregation, linking admission outcomes for children (132). There was comprehensive data coverage of the Western Cape for all time periods, increasing study generalisability. I believe there was thorough case identification with a comprehensive list of ICD-10 codes for diarrhoea hospital admissions. Mapping diarrhoea admissions to a child's residence allowed for the assessment of the community burden of severe illness.

There were several limitations. Firstly, monthly data aggregation meant that the interruption analysis was at the closest month to the PHSM change, not on the exact date of implementation. Secondly, I was reliant on electronic health records, which may have limited the ability to assess impact of PHSM-related reductions in diarrhoea admissions. However, it is believed that the electronic data was reasonably complete, and this completeness increased over time with more complete data in more recent years. Thirdly, our analysis was limited to diarrhoea hospital admissions, considered severe cases, hindering a comprehensive understanding of COVID-19 surges and associated factors on mild diarrhoea cases in the community, which would only require outpatient or ambulatory care. Lastly, data variables, including rotavirus vaccination status, and socioeconomic status, were constrained by availability. Socioeconomic status was only adjusted for crudely using subdistrict or district of the child’s residence. Hospital data and population estimates reflect where children live, while immunisation, birth, and COVID-19 data pertain to healthcare locations. Population estimates, used for calculating rates, assume a certain percentage of children use public services, impacting rates but not estimated changes over time.

6.6 Conclusion

In conclusion, this study highlights the impact of PHSM on diarrhoea hospital admissions among children under five during the COVID-19 pandemic in the Western Cape, South Africa. There were substantial reductions in diarrhoea admissions coinciding with the implementation of stricter PHSM, suggesting combined effects of measures such as hand hygiene, physical distancing and healthcare access. Although subsequent relaxation of PHSM led to modest increases in diarrhoea admissions, the overall trend did not return to pre-pandemic levels. The disruption of the expected seasonal peak and the vulnerability of younger children to diarrhoea pathogens during periods of PHSM relaxation highlight the importance of continued monitoring in public health interventions to prevent diarrhoeal diseases and subsequent hospital admissions in this population.

Chapter 7

Repeat infectious disease hospitalisation in children with first infectious disease hospitalisation at less than six months of age in the Western Cape public sector (2017-2021)

7.1 Overview

There are several risk factors associated with infectious disease morbidity and mortality, as described in section 2.7, Chapter 2. Infectious disease cases are sometimes severe enough to result in hospitalisation, which provides an opportunity to implement interventions at an individual-level to prevent subsequent admissions. It is therefore important to understand which factors continue to contribute to infectious disease morbidity. Furthermore, understanding which factors are associated with an increased risk for re-admission at a population-level is important to allow for effective prevention strategies to be implemented. The study presented below aimed to describe characteristics associated with a repeat infectious disease admission based on characteristics at first infectious disease admission as outlined in Objective 4 in Chapter 1.

This work was also presented as a poster presentation at the 42nd Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID) in May 2024 in Copenhagen, Denmark.

7.2 Introduction

As discussed in Chapter 1 and 2, infectious diseases remain primary contributors to global morbidity and mortality among children aged under five years, significantly impacting their health outcomes. Common infectious causes of hospitalisation and mortality include LRTIs (including pneumonia), diarrhoea, malaria, meningitis and measles (6,140). Typically, the burden of these infectious diseases disproportionately affects low- and middle-income countries, including sub-Saharan Africa and South Africa (42,49,51,141).

A key contribution to the overall infectious disease burden in children, is those who experience recurrent infections, sometimes severe enough to require re-admission. Identifying children at high risk for infectious disease re-admission is vital as the first admission provides an opportunity for intervention to reduce their individual vulnerability to infection or severe disease and subsequent chronic illnesses, improve quality of care and to identify population-level interventions that could alleviate hospital admission burden (78,79). There is limited data

on factors associated with re-admission and, to my knowledge, no published studies for the Western Cape.

This study aimed to describe characteristics of children during their initial and first repeat (within two years) infectious disease hospitalisation, compare infectious disease causes at the initial and first re-admission, and identify characteristics associated with re-admission.

7.3 Methods

Data source and variables

Development of the consolidated dataset used in this chapter was described in Chapter 3. Briefly, I used data from RHIS (10), Child PIP (28,109) and DN Surveillance (110) to identify infectious disease admissions and deaths attributed to meningitis, LRTIs, and diarrhoea. Infectious disease admissions were determined from ICD-10 codes (section 10.1 of Chapter 10). A principal infectious disease admission cause was determined using the following hierarchy: i) meningitis, ii) LRTI and iii) diarrhoea. Thereafter, each infectious disease admission was categorised according to whether co-infection with one of the other infectious diseases of interest was present.

Eligibility criteria

I included children with a first admission for infectious diseases of interest (LRTIs, diarrhoea and meningitis other than TBM) between age >1 day and 6 months in any public sector hospital in the Western Cape from 1 January 2017 to 30 June 2021, and who were alive for at least seven days following discharge. Admissions at ≤1 day of age were considered as part of the child's birth admission and not included. These children were however included if they were subsequently admitted within six months of age, with the next admission being considered the first admission.

Outcome

The outcome of interest was the rate of first repeat infectious disease hospital admissions, defined as a re-admission resulting from an infectious disease starting ≥7 days after discharge for initial infectious disease admission, as re-admissions within six days of discharge were likely due to the first admission cause. Follow-up time thus started at seven days after date of discharge from the first infectious disease admission (i.e. survival time day zero). Follow-up was censored at the earliest of two years thereafter, date of death, or 31 December 2021.

Data analysis

I described characteristics (outlined in section 3.3 of Chapter 3) of children at first infectious disease admission overall, and among those with and without re-admission. Characteristics, described by frequencies and proportions, included attributes which remained consistent over time (such as sex, birthweight, child's district of residence). In addition, time-varying variables at each infectious disease admission were also described at children's first and repeat admission (including age, infectious disease admission cause, co-infection, length of stay, ICU admission, HIV exposure and infection status, SAM, and admission year). Characteristics with missing data were coded as unknown. For the children with re-admissions, infectious disease admission causes were compared between first and repeat hospitalisations, using a Chi-squared test.

I estimated Kaplan-Meier cumulative hazard probability (using the Nelson-Aalen estimator) of re-admission stratified by sex, infant birthweight, initial infectious disease admission cause, length of stay, ICU admission, and HIV exposure and infection status. I assessed characteristics associated with an infectious disease re-admission by adjusting for characteristics at first infectious disease admission (as listed in Table 7.1) with univariable and multivariable Cox Proportional Hazards models, accounting for death as a competing risk (142). I adjusted for child's district of residence and admission year in the multivariable analysis to account for potential geographic differences in healthcare access, improved electronic data in more recent years and the potential effect of annual changes in healthcare access (especially in 2020 and 2021 when COVID-19-related restrictions were in place). All covariates listed above were included based on plausibility of them being associated with an infectious disease re-admission and being routinely available in clinical data systems. Crude and adjusted hazard ratios (HR) with 95% CI were reported. Proportional hazards were assessed utilising Nelson-Aalen plots, log-log plots and proportional hazards test on the basis of the Schoenfeld residuals (142).

In a sensitivity analysis, the models were stratified by age group (0-3 and 4-6 months) to investigate if there were different associations for different age groups.

Data cleaning and coding were performed in SQL, and data were analysed in Stata 18.0.

7.4 Results

Childhood characteristics in first infectious disease admission and re-admission

Eligible children (26,729) admitted for a first-time infectious disease included in the analysis contributed 38,207 person years. These children were predominantly male (15,380, 58%) and first admitted for an LRTI (20,364, 76%) (Table 7.1). Most first admissions (18,454, 69%) occurred before three months of age and most children were admitted for four days or less (17,652 children, 66%). Small proportions of the cohort experienced co-infection (1,263, 5%), ICU admission (605, 3%) and SAM (119, 0.4%).

Table 7.1. Characteristics of infants at the time of first admission due to infectious diseases from January 2017 to June 2021 within their first six months of life: all first-time infectious disease admissions, non-re-admitted children, and re-admitted children.

Characteristic (n, %)	First-time admission (n = 26,729)	Non-re-admitted children (n = 20,999)	Re-admitted children (n = 5,730)
Sex			
Male	15,380 (58%)	11,895 (57%)	3,485 (61%)
Female	11,349 (42%)	9,104 (43%)	2,245 (39%)
Age			
0-3 months	18,454 (69%)	14,524 (69%)	3,930 (69%)
4-6 months	8,275 (31%)	6,475 (31%)	1,800 (31%)
Infant birthweight			
<1,500g	1,164 (4%)	751 (4%)	413 (7%)
1,500g – 2,499g	3,868 (14%)	2,865 (14%)	1,003 (17%)
2,500g – 3,999g	15,217 (57%)	12,126 (58%)	3,091 (54%)
≥4,000g	698 (3%)	567 (3%)	145 (3%)
Unknown	5,782 (22%)	4,690 (22%)	1,1092 (19%)
Infectious disease hospitalisation cause			
Lower respiratory tract infection	20,364 (76%)	15,749 (75%)	4,615 (81%)
Diarrhoea	5,271 (20%)	4,333 (21%)	938 (16%)
Meningitis	1,094 (4%)	917 (4%)	177 (3%)
Co-infection			
Yes	1,263 (5%)	981 (5%)	282 (5%)
Length of stay			
≤2 days	10,372 (39%)	8,364 (40%)	2,008 (35%)
3-4 days	7,280 (27%)	5,784 (27%)	1,496 (26%)
5-6 days	4,001 (15%)	3,122 (15%)	879 (15%)
≥7 days	5,076 (19%)	3,729 (18%)	1,347 (24%)
Intensive care unit admission			
Yes	605 (2%)	440 (2%)	165 (3%)
HIV exposure and infection status			
HIV positive	295 (1%)	192 (1%)	103 (2%)
HIV exposed uninfected	4,311 (16%)	3,372 (16%)	939 (16%)
HIV unexposed uninfected	16,978 (64%)	13,287 (63%)	3,691 (64%)
Unknown HIV status	5,145 (19%)	4,148 (20%)	997 (18%)
Severe acute malnutrition			
Yes	119 (0.5%)	88 (0.4%)	31 (0.5%)
Admission year			
2017	4,669 (18%)	3,471 (17%)	1,198 (21%)
2018	7,517 (28%)	5,738 (27%)	1,779 (31%)
2019	6,721 (25%)	5,262 (25%)	1,459 (25%)
2020	4,644 (17%)	3,806 (18%)	838 (15%)
2021*	3,178 (12%)	2,722 (13%)	456 (8%)
Child's district of residence			
Cape Winelands	3,938 (15%)	3,023 (14%)	915 (16%)
Central Karoo	394 (1%)	291 (1%)	103 (2%)
City of Cape Town	16,395 (61%)	13,068 (62%)	3,327 (58%)
Garden Route	2,369 (9%)	1,824 (9%)	545 (9%)
Overberg	1,509 (6%)	1,184 (6%)	325 (6%)
West Coast	1,882 (7%)	1,407 (7%)	475 (8%)
Unknown	242 (1%)	202 (1%)	40 (1%)

*Only includes 1 January to 30 June for the first admission, with follow-up occurring from 1 July to 31 December.

Of the 26,729 children admitted for an infectious disease, within two years 21.4% (5,730) were re-admitted, 0.5% (122) died more than seven days after discharge and 78.1% (20,860) were censored (mostly at two years of follow-up). The incidence rate for first infectious disease re-admission within two years of first admissions was 150 children per 1,000 person-years. The median time from the start of follow-up to re-admission was 130 days (IQR: 48-292). The majority of re-admissions occurred after seven months of age (3,145, 55%), were mostly due to LRTIs (4,321, 75%) with shorter lengths of stay than first admission (≤2 days 2,867, 50% versus 39% for first admission) (Table 7.2). The proportion of re-admitted children who were co-infected (227, 4%) or admitted to ICU (86 children, 2%) remained low during re-admission. However, the proportion of re-admissions with SAM was twice as high when compared to the first infectious disease admission (73, 1%), although it remained low overall.

Table 7.2. Characteristics of re-admitted children at the time of their first infectious disease re-admission, occurring at least 7 days after their discharge from their initial infectious disease admission between 2017 and 2021.

Characteristic (n, %)	Re-admitted children (n = 5,730)
Age	
0-3 months	1,013 (18%)
4-6 months	1,572 (27%)
7-11 months	1,708 (30%)
1- <5 years	1,437 (25%)
Infectious disease hospitalisation cause	
Lower respiratory tract infection	4,321 (75%)
Diarrhoea	1,312 (23%)
Meningitis	97 (2%)
Co-infection	
Yes	227 (4%)
Length of stay	
≤2 days	2,867 (50%)
3-4 days	1,424 (25%)
5-6 days	582 (10%)
≥7 days	857 (15%)
Intensive care unit admission	
Yes	86 (2%)
HIV exposure and infection status	
HIV positive	130 (2%)
HIV exposed uninfected	926 (16%)
HIV unexposed uninfected	3,687 (65%)
Unknown HIV status	987 (17%)
Severe acute malnutrition	
Yes	73 (1%)
Admission year	
2017	551 (10%)
2018	1,588 (28%)
2019	1,652 (29%)
2020	930 (16%)
2021*	1,009 (17%)

*Only includes 1 January to 30 June for the first admission, with follow-up occurring from 1 July to 31 December.

First admission cause was associated with the repeat infectious disease admission cause ($p<0.001$, Chi-squared test). Children initially hospitalised for meningitis or an LRTI were predominantly re-admitted for an LRTI (Table 7.3). In contrast, those initially admitted for diarrhoea showed equal proportions of re-admissions for either diarrhoea or an LRTI.

Table 7.3. Causes of infectious disease hospital admissions for children who experience a repeat infectious disease admission from January 2017 to June 2021. Row percentages are shown.

First infectious disease admission cause	Repeat infectious disease admission cause			Total
	Meningitis	Lower respiratory tract infection	Diarrhoea	
Meningitis	17 (10%)	118 (66%)	42 (24%)	177 (100%)
Lower respiratory tract infection	59 (1%)	3,741 (81%)	815 (18%)	4,615 (100%)
Diarrhoea	21 (2%)	462 (49%)	455 (49%)	938 (100%)

Characteristics associated with an infectious disease re-admission: univariable and multivariable models

The following characteristics at first admission were associated with increased risk of a re-admission in the univariable analysis: male sex, lower birthweight, LRTI admission, longer length of stay, and having HIV (Figure 7.1 and Table 7.4).

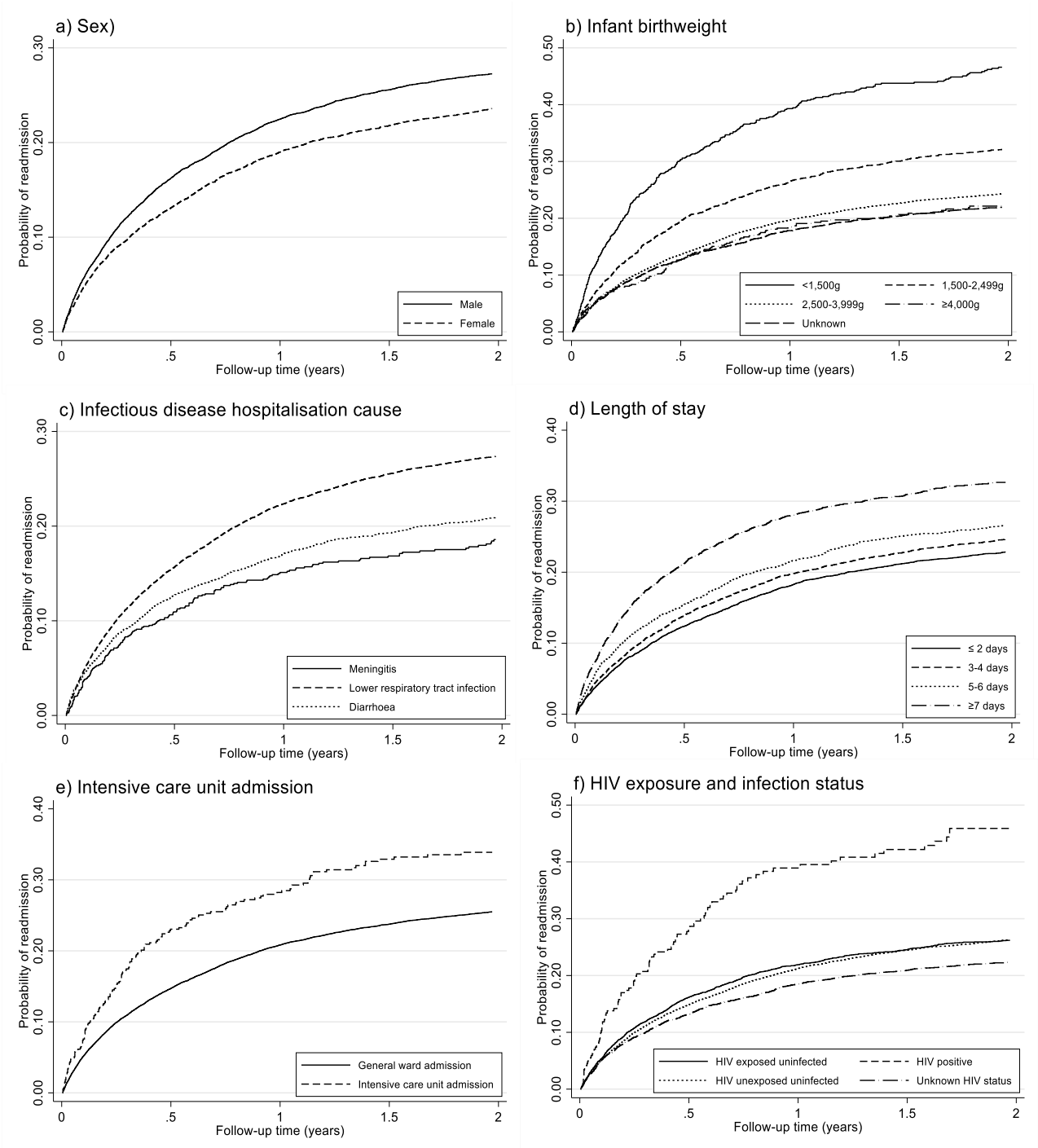


Figure 7.1. Kaplan Meier curves using the Nelson-Aalen estimator depicting the probability of re-admission for an infectious disease among children (n=26,729) following their initial infectious disease admission over a two-year follow-up period. The characteristics assessed from the initial infectious disease admission were a) sex, b) infant birthweight, c) cause of initial infectious disease admission, d) length of stay, e) admission to intensive care, and f) HIV exposure and infection status at admission.

In the multivariable analysis, several associations persisted. Male children were at higher risk of re-admission (adjusted hazard ratio [aHR] 1.19, 95% CI 1.13-1.25) (Table 7.4). Children with very low birthweight (<1,500g) were approximately two times more likely to be re-admitted compared with children with normal birthweight (2,500g – 3,999g) (aHR 1.77, 95% CI 1.59-1.97). Compared to children whose initial admission was for meningitis, those with diarrhoea (aHR 1.30, 95% CI 1.11-1.54) and LRTI (aHR 1.61, 95% CI 1.39-1.88) had a higher risk of re-admission. Longer length of first stay was also associated with infectious disease re-admission, with those whose initial hospital stay was ≥7 days having the highest risk versus those with initial length of stay ≤2 days (aHR 1.44, 95% CI 1.33-1.56). The association between re-admission and initial ICU admission (compared to only general ward admission), was attenuated after adjustment (aHR 1.07, 95% CI 0.91-1.26). Children living with HIV at their initial infectious disease admission had approximately a 50% higher risk of re-admission than those without HIV (aHR 1.55, 95% CI 1.26-1.90). There was no evidence to reject the proportional hazards assumption (Figure S7.1 and Table S7.1 in section 10.4 of Chapter 10).

Table 7.4. Crude and adjusted hazard ratios* to assess the association between repeat infectious disease admissions and characteristics at first infectious disease admission among children (n=26,729) admitted within six months of life from January 2017 to June 2021, while accounting for death as a competing risk. Hazard ratios and 95% confidence intervals bolded do not include the null value. Note: as missing variables were coded as unknown, all children included in the study were included in the model.

	Univariable model hazard ratio (95% CI)	Multivariable model adjusted hazard ratio (95% CI)
Sex		
Female	1.0	1.0
Male	**1.17 (1.11-1.23)**	**1.19 (1.13-1.25)**
Age		
0-3 months	1.0	1.0
4-6 months	1.04 (0.98-1.09)	**1.11 (1.04-1.17)**
Infant birthweight		
<1,500g	**1.96 (1.77-2.18)**	**1.77 (1.59-1.97)**
1,500g – 2,499g	**1.33 (1.24-1.43)**	**1.27 (1.18-1.37)**
2,500g – 3,999g	1.0	1.0
≥4,000g	0.92 (0.77-1.10)	0.92 (0.77-1.10)
Unknown	**0.91 (0.85-0.97)**	0.90 (0.78-1.03)
Infectious disease hospitalisation cause		
Meningitis	1.0	1.0
Lower respiratory tract infection	**1.47 (1.27-1.71)**	**1.61 (1.39-1.88)**
Diarrhoea	1.13 (0.96-1.33)	**1.30 (1.11-1.54)**
Co-infection		
No	1.0	1.0
Yes	1.07 (0.94-1.20)	1.02 (0.91-1.16)
Length of stay		
≤2 days	1.0	1.0
3-4 days	**1.08 (1.01-1.16)**	**1.09 (1.02-1.17)**
5-6 days	**1.18 (1.09-1.27)**	**1.19 (1.01-1.29)**
≥7 days	**1.48 (1.31-1.50)**	**1.44 (1.33-1.56)**
Intensive care unit admission		
No	1.0	1.0
Yes	**1.35 (1.16-1.58)**	1.07 (0.91-1.26)
HIV exposure and infection status		
HIV exposed uninfected	1.01 (0.94-1.09)	1.00 (0.93-1.08)
HIV positive	**1.78 (1.46-2.17)**	**1.55 (1.26-1.90)**
HIV unexposed uninfected	1.0	1.0
Unknown HIV status	**0.86 (0.80-0.92)**	0.96 (0.83-1.12)
Severe acuate malnutrition		
No	1.0	1.0
Yes	1.26 (0.89-1.79)	1.04 (0.73-1.48)

*Adjusted for: sex, age, infant birthweight, infectious disease hospitalisation, co-infection, length of stay, intensive care unit admission, HIV exposure and infection status, severe acute malnutrition, child's district of residence, and admission year.

Characteristics associated with an infectious disease re-admission: sensitivity analyses

In a sensitivity analysis for each age group, there were similar associations across age groups, except for HIV exposure and infection status (Table S7.2 in section 10.4 of Chapter 10).

Younger children (0-3 months) living with HIV were more likely to be re-admitted in both the univariable (HR 2.07, 95% CI 1.60-2.67) and multivariable (aHR 1.61, 95% CI 1.25-2.09) models. However, the association with HIV infection in older children (4-6 months) was attenuated after adjustment (aHR 1.36, 95% CI 0.96-1.93).

7.5 Discussion

To my knowledge, this is the first study to assess characteristics associated with a repeat infectious disease admission across the Western Cape. About a fifth of children who experienced an infectious disease hospital admission in the first six months of life were re-admitted for a subsequent infectious disease within two years. Children who were male, had lower birthweight, whose first admission was due to LRTI or diarrhoea, had longer initial lengths of stay, or were living with HIV were more likely to be re-admitted for an infectious disease.

These results could enable clinicians and healthcare providers to identify children most at risk of re-admission during their first infectious disease admission, allowing an opportunity to target interventions known to prevent infections such as promoting extended breastfeeding, optimising nutrition, vaccination, supplements such as vitamin A and zinc (49,50) and social support. The main cause of first admission impacted risk of re-admission, with an approximate 60% higher association of re-admissions in those whose first admission was due to LRTI. LRTIs continue to be a primary contributor to infectious disease morbidity and mortality (42), and other studies have shown an increased risk of re-admission among children for bronchiolitis and pneumonia (78,143). Diarrhoea admissions were also associated with re-admission in the multivariable analysis, driven by the adjustment for length of stay. The majority of diarrhoeal admissions were of shorter length of stay (≤2 days), primarily to rehydrate children. Length of admission was associated with re-admission, particularly among children hospitalised for ≥7 days, corresponding with findings from other studies (78,144). Longer length of stay may indicate more severe disease at the time of admission, or quality of care/hospital efficiency issues. Admission to ICU was only associated with re-admission in the univariable model, suggesting that factors associated with severe disease (requiring ICU) at first admission also make these children more vulnerable to re-admission. Male children had a higher risk of re-admission, as previously reported for pneumonia and LRTIs in other settings (78,143,144). Children who were older at first admission (4-6 months) had a slightly higher risk of re-admission, which may be due to increased exposure to pathogens later in life due to

changes in caregivers and/or attending childcare facilities. Although under-ascertainment of re-admissions cannot be excluded in those first admitted at a younger age, who are more likely to either have unascertained mortality or migrate out of the province, compared to those whose first admission occurs at an older age. This finding may also have been influenced by birthweight. Low birthweight has previously been associated with infectious disease morbidity, particularly for LRTIs (66,145,146) and diarrhoea (49). Low birthweight babies may require extended hospital stays after birth until they gain sufficient weight or recover from neonatal illnesses, resulting in their first infectious disease admission, outside of their birth admission, occurring at older ages.

Comorbidities which are amenable to intervention at an individual-level were also associated with re-admission and the first admission provides an opportunity for diagnosis and optimising management. Children living with HIV had a 50% greater likelihood of experiencing infectious disease re-admission, consistent with previous research showing a higher risk of hospital re-admission among individuals with HIV (147,148). In South Africa, increased re-admissions have not been previously reported for HEU children (64), which has been corroborated by these study findings. Importantly, among children living with HIV who were older at first admission (4-6 months), there was no increased risk of re-admission. It is possible that children who are admitted with HIV at older ages are on ART and/or may have less rapidly progressive HIV disease than those whose first admission with HIV occurs at less than 4 months of age, attenuating the effect of HIV on risk of subsequent admissions. During admissions, it would thus be important to ensure that children are tested for HIV, that those with HIV are optimally treated, and that children HEU are provided post-exposure prophylaxis if eligible and their mothers are on suppressive ART. There was no significant association between SAM and re-admission, likely as the proportion of children with SAM in these data was very small and SAM may have been under-ascertained as it was based on recorded ICD-10 codes only, which may not be captured despite children meeting SAM diagnosis criteria. Considering the higher prevalence of SAM during re-admissions and the risk that SAM poses for increased morbidity and mortality (149), this is another co-morbidity that should be identified and adequately addressed at first admission.

There were several associations with infectious disease re-admission which are amenable to population-level interventions to reduce infectious disease admission and re-admission burden among children. Firstly, HIV infections among mothers should be reduced through effective prevention programmes and vertical HIV transmission prevented by through maternal

suppressive ART. Children with HIV should be diagnosed as early as possible and effectively treated. Secondly, social support for children and their parents/caregivers can protect them from socioeconomic vulnerabilities and health risks. This includes ensuring the nutritional well-being of at-risk children and their parents through referral to the Integrated Nutrition Supplemental Programme and ensuring that their mothers receive Child Support Grants to reduce food insecurity. Thirdly, promoting and enhancing complete vaccinations through the national EPI programme, which includes vaccinations against pneumonia and diarrhoea, is essential. Lastly, low birthweight births could be reduced by ensuring mothers receive optimal antenatal care and social support.

Strengths and limitations

This study was strengthened by the comprehensive individual-level, longitudinal data accessed through the WCPHDC with provincial-wide coverage, allowing inclusion of a large sample size and follow-up of children up to two years after first admission. A comprehensive ICD-10 code list was used to ensure thorough case identification of infectious disease admissions (Table S3.1 in section 10.1 of Chapter 10).

There are several limitations to the interpretation of these study results. Firstly, assessment of potentially critical characteristics such as gestational age, vaccination status at admission, and socioeconomic factors was not possible. Furthermore, variables like birthweight and HIV exposure and infection status were only available for children who were born in the province and some children had missing residence data. South Africa does not currently implement a national health electronic record and therefore these data could not be obtained elsewhere for mothers who sought antenatal care outside of the province or who gave birth outside of the province (approximately 20% of children admitted for infectious diseases in the Westen Cape). The primary model showed older children having a higher risk of re-admission, however, this may not be plausible. The association between age at first admission and risk of re-admission could be biased due to missing data for deaths occurring outside of facilities and under-ascertainment of admissions in children admitted at younger ages who may be in the province temporarily (for their delivery and first few months of life) and then move to other provinces where their caregiver permanently resides or if their caregiver changes. Only admissions in the Western Cape could be ascertained. Secondly, infectious diseases included were limited to LRTIs, diarrhoea and meningitis. These diseases were selected due to their high prevalence within the Western Cape (7,19,23). Pulmonary TB is also prevalent in the Western Cape (23),

however it was not included as provincial algorithms used to infer pulmonary TB in children are not well developed at present. Thirdly, I exclusively utilised electronic data from hospitals. It is hypothesised that the data completeness improved over the study period due to the increasing networking of hospitals, particularly in recent years. Fourthly, this study was limited to the public sector, which may have resulted in an underestimation of re-admissions. However, as approximately 80% of children access public healthcare and are likely to access public healthcare or re-admission if their first admission was in the public sector, most children are likely included in this analysis with minimal re-admission under-ascertainment, if they continue to reside in the province. Fifthly, death data was only available for children who died in facilities. Most child deaths occur outside of facilities and therefore death was under-ascertained. Furthermore, younger children are more likely to die, potentially underestimating the association of young age at first admission with infectious disease re-admission. Sixthly, these findings may not be generalisable to other parts of South Africa as evidence suggests better healthcare access in the Western Cape (23). However, these findings may be generalisable to other settings with similar healthcare access patterns and infectious disease burden. Lastly, data analysed was solely dependent on available data in RHIS, resulting in some children having an unknown birthweight or HIV status at the time of their first infectious disease admission. The models showed that these children generally have a lower risk of infectious disease re-admission, which is likely not plausible. Rather, this could indicate that these children have either left the province, receive healthcare in the private sector or died outside of facilities. Therefore, there is likely substantial under-ascertainment of outcomes in these children in the Western Cape public sector, indicating these associations should be disregarded.

7.6 Conclusion

In conclusion, this study represents the first comprehensive investigation into characteristics associated with repeat infectious disease admissions across the Western Cape, South Africa. These findings highlight the importance of targeted interventions to mitigate repeat infectious disease admissions within vulnerable groups for children. Enhanced healthcare delivery strategies and interventions are crucial to optimise outcomes for children in the Western Cape and similar settings globally.

Chapter 8

Discussion

8.1 Introduction

The aim of this study was to quantify and describe factors impacting or associated with the burden of infectious disease hospital admissions and mortality due to specific conditions (LRTIs, diarrhoea, meningitis, and TBM where applicable) in children under five years, using data from the WCPHDC in South Africa. This chapter brings together findings from the component analyses related to child infectious disease admission incidence, risk factors and implications for practice. Discussion points raised in previous chapters will not be repeated in this section, but instead it will focus on the points that arise when considering the entirety of the thesis, focusing on infectious diseases and child health in the Western Cape. Recommendations for future research and policy will also be outlined.

8.2 Synopsis of key findings

The combined results from this thesis provide novel data highlighting the ongoing morbidity and mortality of infectious diseases among children under five years in the Western Cape province of South Africa. This study was limited to infectious diseases that remain prevalent among children in the Western Cape, as described in Chapter 2.

Objective 1, outlined in Chapter 4, focused on identifying proxy causes of infectious disease deaths from RHIS through comparison with recorded causes of death from the more detailed Child PIP and DN Surveillance. Routinely collected data from RHIS could reliably be used to identify proxy causes of deaths, particularly for LRTIs and diarrhoea. This finding is valuable considering the time lag that often occurs in mortality reporting into VR systems and in more detailed mortality reporting systems, such as Child PIP. This chapter also highlighted the strength of leveraging multiple data sources to assess causes of child deaths most accurately and overcome the concerns often associated with the data quality for any single data source.

Objectives 2 and 3, outlined in Chapters 5 and 6 respectively, investigated the changes in LRTI and diarrhoea hospitalisations relative to implementation of PHSM and COVID-19 surges. Early in the COVID-19 pandemic, there was a decline in LRTI and diarrhoea admissions, likely due to a combination of factors related to the implementation of PHSM and their effects including reduced infectious disease transmission, reduced healthcare usage, and increases in prevention behaviours such as hand washing, physical distancing and mask wearing. LRTI admissions among children under five years peaked before COVID-19 waves, after the initial

reduction in admissions that occurred due to the implementation of the strictest PHSM. On the other hand, after the start of each COVID-19 wave and implementation of stricter PHSM, there was an initial reduction in diarrhoea admissions, which steadily increased across the wave. Despite these slight variations for each infectious disease, the association between LRTI and diarrhoea admission rates and COVID-19 surges and PHSM diminished over time.

Objective 4, outlined in Chapter 7, aimed to quantify the burden and identify risk factors for infectious disease re-admissions for children with an initial infectious disease admission before six months of age. This study identified several characteristics associated with repeat infectious disease admissions including: male sex, lower birthweight, initial LRTI or diarrhoea admission (versus meningitis), longer length of stay for initial admission, and children living with HIV. These data did not show an increased risk of infectious disease re-admission for children who were first admitted with SAM or to ICU. However, there was an increase in the proportion with SAM among children re-admitted (versus among first admissions), which is important to consider given that this was potentially under-ascertained due to reliance on diagnostic coding. Based on these results, it may be possible to identify children at risk of repeat admissions, implement a comprehensive package of care for these children using the first admission as a window of opportunity, as well as identify population-level interventions to reduce overall risk of infectious diseases and subsequent admissions.

The WCPHDC team has used the data management and comparison work done in this thesis as a baseline to develop a Surge Season dashboard which can be accessed by health professionals to monitor changes in LRTIs, diarrhoea and SAM (Figure 3.2 in section 3.7 of Chapter 3). The forums set up to manage surge seasons convene regularly with access to these data for review. This real-time access empowers them to trigger responses required to deal with changes in access and demand.

Overall, these research results were able to determine proxy causes of death through data comparison and enumerate the ongoing infectious disease burden in the Western Cape, where data have previously been sparse and/or not available for specific conditions and lower levels of geography other than provincial. Based on the findings across all objectives, there are several key areas to highlight in reference to the impact of these study findings.

8.3 Comprehensively understanding of childhood mortality

As 2030 approaches, it is important to closely monitor progress towards and guide interventions to achieve the 3rd SDG (good health and well-being) (3). Effective monitoring of this progress necessitates reliable mortality estimates, accurate causes of death, timely data access/release, disaggregation by geography, and comprehensive coverage of all deaths, both in- and out-of-facilities. However, there are currently several limitations associated with mortality data that make this challenging.

Although overall trends tend to be consistent across data sources, reported estimates (numbers and rates of deaths) often vary in South Africa. For example, a higher number of deaths was consistently reported in the 2011 census compared to the VR system across the majority of South African provinces (5). This may be due to use of different data sources, reflecting in- or out-of-facility deaths or both, different methodologies used to obtain estimates, and/or under- or over-reporting into different systems (4,5).

Cause of death data may also vary across data sources, which may result in under-reporting for certain causes of death or deaths being captured as ill-defined due to the delay in investigation of the deaths. Recorded causes of death may also differ due to differences in case definitions and ranking of primary or secondary causes. Missing or ill-defined causes of death are not useful in determining factors associated with mortality or diseases that need to be addressed by the healthcare system (37) and beyond.

Mortality data sources are often outdated, rendering them impractical for short- and medium-term planning (5). For example, the VR estimates, available nationally, are released publicly at least two years after they are reported to the DHA (5), with no cause of death provided to provinces. This necessitates the strengthening of systems collecting provincial- and district-level U5MRs to ensure comprehensive, accurate and timely data availability.

In addition, the disaggregation of provincial and district mortality rates from national estimates is vital to inform appropriate and tailored service delivery for child health within a given context or at a particular level of healthcare services (5,26). This is particularly important in South Africa, given the disparities in healthcare service delivery, health status and sociodemographic differences within and between the provinces (26), as discussed in section 1.2 of Chapter 1.

There is often under-ascertainment in mortality estimates. In South Africa, many hospital-based child death data sources only capture public health facility data (10,28), with private sector

deaths not included. Notably, out-of-facility deaths account for the majority of child deaths in South Africa (20,36–38), and this is probably higher in other provinces or other countries with fewer resources. The burden of out-of-facility deaths is therefore not always well understood as these are often excluded from U5MR estimates or CFRs, due to the CFR definition which has been described in section 2.2 of Chapter 2. To overcome this limitation, additional data sources have recently been developed to capture out-of-facility deaths in South Africa (36). The CDR is a multiagency process and has created a process in the Western Cape to improve the accuracy of reporting and allow for in-depth investigation to ascertain causes of child deaths, specifically out-of-facility deaths, or deaths where the attending clinician is not comfortable to declare the death due to natural causes on the death certificate. The aim of the CDR is to understand and ascertain causes of death in children to ultimately promote and improve child health and well-being (35,150).

The research presented in Chapter 4 was able to overcome some of these challenges pertaining to mortality data as well as fill some of the current knowledge gaps highlighted in Chapter 2. Firstly, access was obtained to several data sources reporting in-facility deaths, which were leveraged to reliably ascertain causes of death from Child PIP and DN Surveillance and subsequently determine proxy causes of death using routinely collected data in RHIS. A hierarchy of evidence on the cause of death across various data sources was proposed, which produced unified estimates of the number of deaths based on all available evidence. Secondly, the WCPHDC is updated routinely across all incorporated data sources which allowed determination of infectious disease mortality burden more timeously, an issue persisting with many data sources currently. These data enabled estimations of infectious disease mortality rates for the province. Thirdly, the WCPHDC includes all public healthcare facilities in the province allowing ascertainment of mortality rates at a more granular level than is reported by death registration. This is important as the burden of infectious disease mortality varies across geographies. These strengths collectively enhance the understanding of infectious disease mortality within the province.

However, the issue of comprehensively understanding mortality rates and associated factors persists. Despite combining evidence from three data sources, most childhood deaths continue to occur outside of health facilities. I did not have access to these CDR data and therefore, the research was unable to assess burden and causes of death outside of health facilities across any of the analyses. Despite systems being developed to monitor out-of-facility deaths in the Western Cape, access to these data is limited and the WCPHDC currently does not receive it

routinely. It would be beneficial to have data in the same consolidated environment as a child's medical history using their unique identifier. However, there are potential challenges with having access to these data, as it is argued that sharing these data may compromise the outcome of legal proceedings pertaining to children or clinicians/health professionals may have access to potentially stigmatising information. However, data on out-of-facility deaths are essential for comprehensive healthcare service planning. It is recommended that the WCGHW urgently address the absence of out-of-facility data, including causes and trends, in the WCPHDC to promote better health outcomes for children. Balancing access and the level of access will remain important to ensure private confidentiality while providing the best possible healthcare.

8.4 The impact of health policy on infectious disease morbidity and mortality

Over time, there have been several health policies in South Africa that have been implemented to improve child health and well-being. For example, the implementation of the pneumococcal and rotavirus vaccinations for pneumonia and diarrhoea respectively (4) and access to HIV prevention (151) and treatment for infants and mothers (152). There have been several assessments of the effects of these specific policies and their associated health outcomes (83,91,153). However, the COVID-19 pandemic resulted in the introduction of unique policies, focusing on health, but included several other components beyond health. Despite being aimed at reducing COVID-19 transmission and ensuring the effective management of COVID-19 cases and admissions (103), there were far reaching implications socially and across other health conditions. This wider focus and its implications differed from other health policies that have been previously introduced, and thus were important to quantify and understand for future pandemics and periods of increased infections or outbreaks.

The effect of COVID-19 interventions and PHSM can be observed across all analyses in this thesis, demonstrating the impact these changes had on health conditions extending beyond COVID-19. Among children under five years, in-facility deaths and mortality rates for infectious diseases included in this thesis decreased during 2020 and 2021, as shown in Chapter 4 and 5. Similarly, these infectious disease admissions and admission rates also declined, particularly when the initial PHSM were implemented, as shown in Chapter 5 and 6. These findings are important to understand how these measures had wider impacts on both protecting and ensuring adequate capacity of healthcare services during a time period of altered demand. It could be useful to assess these data for future events that may impact healthcare services. Changes worth monitoring could include: i) outbreaks and/or pandemics as seen during the annual Western Cape diarrhoeal and respiratory surge seasons and the COVID-19 pandemic

(154), ii) climate changes causing droughts (74) or storms affecting power and water supplies (155) or iii) fiscal changes resulting in significant budget cuts (156,157).

The Western Cape health services have historically been responsive to altering healthcare services as case loads increase and/or alter from previously established patterns. Examples include the management of COVID-19, case management for drought associated diseases, and seasonal increases in pneumonia and diarrhoea (74,154). Annually, during the paediatric surge seasons for LRTIs and diarrhoea, there are increased public health campaigns, provision of more beds in facilities, training opportunities for healthcare workers and increased surveillance with frequent data reviews (74). Given that these activities were already well established, healthcare services were able to both continue and adapt this approach in the landscape of an ever-changing health context particularly during the COVID-19 pandemic and periods of serious drought (74,154). The findings from this thesis suggest that the WCGHW continued to ensure healthcare capacity for children during the pandemic, potentially driven by lessons learnt from surge seasons. This is illustrated in Chapters 5 and 6 where LRTI and diarrhoeas admissions peaked before COVD-19 waves, suggesting that reduced paediatric admissions were not due to reduced healthcare access driven by overburdened healthcare facilities.

Additionally, one of the major gaps identified in Chapter 2 was the lack of accurate and up-to-date data on infectious disease morbidity and mortality. The analyses conducted for Chapters 4-7 successfully generated updated results for the infectious diseases of interest. This was made possible by the algorithms developed to identify proxy causes of death and infectious disease admission using all evidences, as described in Chapter 3. Furthermore, these results could be used to assess the impact of current health policies and/or introduce and evaluate new ones with associated interventions that would be helpful in effectively reducing infectious disease morbidity and mortality. Examples of this could include monitoring surge season, assessing infectious disease burden in relation to immunisations and guiding new policies on the introduction of new interventions.

In conclusion, the analyses presented in this thesis provide meaningful insights into the effects of health policies on infectious disease morbidity and mortality. Moreover, the impact of the COVID-19 pandemic underscores the need for comprehensive assessment and understanding of policy implications for future healthcare service disruptions. By leveraging these insights, policymakers can better tailor interventions to effectively reduce infectious disease burden and improve child health outcomes in South Africa.

8.5 Comprehensive strategies addressing social determinants of health to reduce re-admissions and promote child health

By using the more accurate data on infectious disease morbidity and mortality derived in earlier chapters, associations with infectious disease re-admission were identified. The results from Chapter 7 identified factors amenable to intervention at both the individual- and population-level. These findings provide valuable insights for policymakers and healthcare workers as they could be used to support the development of strategies to address the social determinants of health and to guide the healthcare interventions themselves, such as the implementation of new vaccines for mothers and infants. For example, the pertussis outbreak in 2022/23 across South Africa led to the introduction of the maternal pertussis vaccination as well as boosters for children aged 6-12 years (81).

Addressing re-admission risk necessitates a comprehensive approach, integrating clinical interventions targeting individual-level risk factors with population-level strategies aimed at broader social and health system determinants. Reducing infectious disease re-admissions is vital not only for improving individuals' health trajectories but also for alleviating the burden on healthcare services (78,79), ensuring capacity for other conditions. It could also play a significant role in reducing antimicrobial use and the associated risk of resistance spread (158), particularly in hospitals that are less crowded with children suffering from infectious diseases.

In addition to individual-level interventions, community involvement plays a crucial role in addressing the complexities of infectious disease re-admissions among children. Communities serve as key sources of social support, promoters of healthy practices, and facilitators of healthcare access (159). Examples of this in the Western Cape include Community-Oriented Primary Care (COPC) and the First 1000 Days Initiative. The Western Cape implemented COPC due to the need to address a substantial quadruple burden of disease amid increasing budget constraints (160). COPC integrates both primary healthcare and public health to address the health needs of defined communities through a continuous and systematic approach, optimising resource use, engaging communities, and improving health outcomes by focusing on prevention, treatment, and the social determinants of health, while also providing a favourable return on investment. COPC focuses on all health needs of the surrounding community including HIV and TB, maternal and child health, diabetes and hypertension. The role of communities in the First 1000 Days Initiative is crucial as it involves focusing on the social determinants of health by involving all components of society, including individuals, civil society/community, and the government. It is a whole of society approach which aims to

improve child wellness including nutrition and health; care and support to the family, home and community; and safety and protection. This approach emphasises the importance of addressing social disparities and health inequalities, promoting a broader societal responsibility in supporting early childhood development (161). By engaging communities, interventions can be more effectively tailored to local needs and challenges, fostering sustainable improvements in health outcomes. These community-based programs could greatly benefit from the data presented in this thesis, which underscores the persistent morbidity and mortality from infectious diseases among children. This information could be used to strengthen prevention initiatives like immunisation, enhance health education, or help guide interventions for the remaining healthcare gaps.

Moreover, addressing healthcare access is crucial in reducing re-admissions and promoting child health. Limited access to healthcare services, including primary/community healthcare services, exacerbates the risk of re-admission among vulnerable populations. Ensuring equitable access to quality healthcare is essential to promote health and well-being (8), which is also important in mitigating the burden of infectious diseases on children and their families. By enhancing healthcare infrastructure, improving health service delivery, and implementing policies that prioritise access for underserved communities, a more resilient healthcare system capable of effectively managing infectious diseases and reducing re-admission rates can be built. It is important to remain cognisant of inequalities across and within provinces, ensuring healthcare and child health services, such as vaccinations, are implemented effectively in each province (4,5).

In summary, adopting a multifaceted approach that integrates clinical interventions, community engagement, and improvements in healthcare access can effectively address the social determinants of health and reduce infectious disease re-admissions, ultimately promoting better child health outcomes.

8.6 Study limitations summary

This research project has contributed significantly to an improved understanding of the infectious disease morbidity and mortality in children under five years in the Western Cape. Nonetheless, these findings should be considered in the light of several limitations. Each results chapter has included specific limitations and are summarised here before specifying recommendations to try to address these outstanding limitations.

One significant limitation across this thesis is the inclusion of only in-facility deaths, excluding out-of-facility deaths leading to an incomplete picture of child mortality. Given the under-ascertainment of deaths, the mortality rates are likely underestimated.

These results may not be applicable beyond the Western Cape due to different health information systems, diagnostic coding practices, and healthcare access patterns in other provinces across South Africa. The focus on the public sector might also underestimate in-facility deaths and admissions, including re-admissions, as it excludes data from the private sector, though most children use public services.

Potential biases in the data present further challenges. Missing data for children who move between provinces or are temporarily in the province could lead to biases in analysing re-admission risks. While data completeness is hypothesised to have improved over time in the WCPHDC, this was not verified, potentially affecting the assessment of admissions and deaths rates. The reliance on electronic health records is another limitation. While recent improvements in electronic reporting may mitigate some issues, there is still the potential for missing data. Additionally, the accuracy of ICD-10 diagnostic coding, which was not verified against written patient records, might affect the reliability of the data.

Data limitations and availability also may have also affected study results. Certain variables such as socioeconomic status, individual-level vaccination status, birthweight, and HIV status and modifiable factors collected in death audits were not available and/or accessible for all or some children. Furthermore, some health conditions and key characteristics (potential confounders), like gestational age and vaccination status at admission, were not assessed due to data unavailability. The models used in the relevant chapters did not produce causal estimates, however this was not the intention given that this work relied on routinely collected data, largely driven by the above-mentioned data availability. Despite this, the estimates produced will be helpful in understanding the true burden of disease and the identified associations with repeat admissions can be used routinely in healthcare settings to improve health outcomes.

8.7 Recommendations for research and practice

Based on the results of this thesis, there are strong emerging themes around the critical role that data plays in healthcare. Therefore, the recommendations from this research will focus on four key areas to improve: 1) data availability, 2) data quality, 3) data access and 4) data use to support decision-making.

Data availability

As described above and across several chapters, mortality data are not always available in a useful manner, whether that be for more recent time periods, for specific locations or for specific health outcomes. Based on the findings of this research, there are several recommendations to overcome these challenges, particularly for the Western Cape. Firstly, I would recommend investing in the strengthening of existing systems to accurately capture all deaths in the province to ensure that all key details are captured including accurate cause and date of death. Secondly, I would advocate making aggregated data reports and dashboards (to ensure data privacy and confidentiality) available regularly to relevant and key stakeholders including healthcare workers and policy makers. This is particularly important for out-of-facility deaths, where the majority deaths occur (20,36–38) and data are not readily available at present. Given the availability of the unique identifier in the WCPHDC, it would be possible to link out-of-facility deaths with other data available in the WCPHDC. This would provide insight into the full burden and causes of childhood mortality in the province which is crucial for implementing interventions and policies aimed at preventing deaths. Thirdly, I suggest utilising all accessible data sources to aid a thorough understanding of mortality rates and causes of death, using the approach described in Chapter 4. I would also recommend extending the work done for this thesis using routine data to determine a proxy cause of death to other infectious diseases as well as other causes of death. This could easily be done by the WCPHDC, providing these causes were available in Child PIP and DN surveillance to enable the initial comparison work that is required. Extending this work would offer the advantage of providing healthcare workers and policymakers with more frequent access to data spanning various causes of death. This enhanced accessibility would facilitate a more real-time understanding of the contributors to mortality within the province. Across all these recommendations, it is important to consider privacy protection of patients. Data availability could result in misuse of the information, legal consequences, psychological and social harm, and unauthorised access to confidential information. South Africa has implemented the Protection of Personal Information Act which establishes minimum standards for retrieving and processing personal information, defining “processing” as activities including collecting, receiving, recording, organising, retrieving, using, distributing, or sharing such information (162). It is therefore important to carefully manage data availability and patient privacy, and the WCPHDC has implemented data governance structures to ensure this, as described in section 3.5 of Chapter 3. In combination, having access to data with the appropriate level of detail and robust

governance would allow clinicians and policymakers to determine potential interventions that can be implemented immediately in parallel to health systems strengthening activities, without compromising patient privacy.

Data quality

Ensuring high data quality is crucial for instilling confidence in the data being utilised and obtaining an accurate representation of health-related events. This underscores the significance of thorough accuracy and completeness assessment when working with any data source/s. The WCPHDC relies on routinely collected operational health services data, emphasising the necessity for accuracy, reliability, completeness, and real-time updates in source data. Good data quality can be ensured in two ways: i) ongoing enhancement of source data quality, and ii) thorough data interrogation during data processing and management. Source data provided to the WCPHDC has progressively increased across all healthcare facilities, with improved coding practices shown over time in the public sector (highlighted in Chapter 5 and 6). The quality of coding has typically been better in higher resourced settings, such as the private sector in South Africa, which has dedicator coders, particularly for the purpose of medical costing (163). Despite coding improving over time in the public sector, there may still be issues with accuracy and completeness. To overcome this challenge, the WCPHDC uses multiple evidences beyond diagnostic coding to identify health service contact points and condition (10).

Based on this, I would suggest implementing a comprehensive approach to ensure data quality by enhancing source data quality with more attention given to improving the accuracy and consistency of cause of death classification and disease coding by clinicians. Regular clinician training focused on improving coding practices could be implemented with subsequent monitoring to determine if there have been improvements. Thorough assessments of data quality, as outlined in Chapter 3, are crucial for instilling confidence in the data and ensuring data integrity and reliability which can inform healthcare decision-making and policy formulation, ultimately improving overall health outcomes.

Data access

Once high quality data are available, it is essential that these are made readily available and presented in ways that are tailored to data users need. In doing so, it is important ensure strong data governance to maintain patient privacy and confidentiality. In the Western Cape, a platform called Single Patient Viewer, allows clinicians and healthcare workers to routinely access data reports, dashboards, and individual patient histories seamlessly (10). Data access

is carefully governed with only the required access provided to users. This platform is beneficial in ensuring the most up-to-date data are readily accessible to support enhanced patient care. It is also important to have these data safely accessible for research, such as was done for this thesis. The work done for this thesis involved data wrangling, analysis, and derivation of variables from the available data in ways not previously done, establishing a lasting contribution to the WCPHDC, and producing insights that further motivate the need for data access, both for clinical care and research.

Data use to support decision-making

Lastly, once the above three components are in place, data should routinely be used for decision-making at the individual- and population-level to improve health outcomes. In the Western Cape specifically, this can be done by further leveraging available data to develop reports and dashboards across health conditions, as done for example with the Surge Season dashboard and the public facing TB dashboard (164).

Beyond what was used for this study, there are several additional data sources that collect data on deaths, such as Child PIP and CDR. This thesis did not access the Child PIP data on modifiable factors, but I would recommend that these data are made available routinely to the WCPHDC, clinicians and policymakers to better assess the factors contributing to deaths and poor health outcomes. Furthermore, understanding which modifiable factors consistently contribute to childhood mortality could be more formally assessed through research to better understand where interventions to reduce mortality can best be implemented.

The findings from this thesis which identified associations with infectious disease re-admission from Chapter 7, alongside a broader understanding of factors influencing health outcomes, highlight that the social determinants leading to adverse health outcomes and mortality extend beyond healthcare and the healthcare system. It is important to promote strong intersectoral collaboration to effectively address these social determinants of health. The COVID-19 pandemic accelerated and relied on strong intersectoral collaboration to ensure that PHSM were effectively implemented, healthcare services were protected and EPI and COVID-19 vaccinations were provided to people, irrespective of their healthcare access. Assessments from the Western Cape on intersectoral collaboration (focusing on COVID-19 and First 1000 Days Initiative on child health) has shown that it is possible, but requires a shared understanding on what intersectoral collaboration means, defining the desired outcome, ensuring early engagement, and drawing on existing relationships (161,165).

The findings presented in this thesis can be further utilised to enhance data-driven decision-making. First, the data from Chapter 7 could be used to develop a risk-scoring algorithm for hospital admissions, ensuring that appropriate interventions are implemented during a child's first infectious disease admission, with the aim of reducing the likelihood of severe disease and poor outcomes. Second, the data from Chapters 5 and 6 underscore the importance of routinely monitoring hospital admission data, particularly during catastrophic events such as pandemics or climate change. The analyses provided offer an effective method for understanding changes in rates and trends in response to healthcare and societal interventions, which can be invaluable when close monitoring is required. This approach can be extended to assess the impact interventions, such as the introduction of new vaccines like RSV once approved for use in South Africa.

8.8 Conclusion

This thesis has analysed infectious disease (LRTIs, diarrhoea and meningitis) morbidity and mortality in children under five years in the Western Cape, South Africa. It firstly reviewed morbidity, including both infectious disease incidence and hospitalisation incidence, and mortality, for children under five years for these infectious diseases prevalent in the Western Cape (Chapter 2). The thesis also reviewed common risk factors for infectious diseases, considering re-admissions, and prevention strategies, such as vaccinations. Lastly, it reviewed the implications of the COVID-19 pandemic on infection disease patterns, prevention, and treatment in children under five years.

The first significant contribution of this work was creating a de-duplicated dataset for infectious disease mortality, identifying causes of death through comparisons of several mortality data sources. This dataset enabled the analysis of infectious disease mortality burden and rates across the province and by more granular geographies, including district and subdistrict. More rural districts consistently report higher infectious disease mortality when compared to the City of Cape Town, highlighting the need for ongoing monitoring and tailoring of interventions by different geographies.

The second significant contribution was enumerating admission totals and admission rates for infectious diseases, providing more up-to-date estimates as well as quantifying the changes that occurred in relation to COVID-19, a major disruption to healthcare services. This was made possible using the de-duplicated dataset which relied on all available data to identify infectious disease cases.

The third significant contribution was that this work leveraged the de-duplicated and comprehensive infectious disease admissions dataset to determine associations with infectious disease re-admission. This has allowed the identification of factors associated with infectious disease re-admission, including male sex, lower birthweight, initial LRTI or diarrhoea admission (versus meningitis), longer length of stay for initial admission, and living with HIV, which are amenable to interventions, both at the individual- and population-level.

In conclusion, this thesis provides up-to-date and comprehensive infectious disease mortality and morbidity data for children under five years in the Western Cape. It shows that there remains persistent infectious disease morbidity and mortality and highlights geographic differences, particularly for infectious disease deaths. Using these findings, it would be important to address the existing gaps identified by this work to improve data quality and comprehensiveness, and healthcare and health outcomes for children under five years.

Chapter 9

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Chapter 10

Appendices

10.1 Chapter 3 appendix

Table S3.1. List of International Classification of Diseases 10th Revision (ICD-10) codes used for infectious disease coding (132).

ICD-10 code	Description
Lower respiratory tract infections	
B01.2	Varicella pneumonia (J17.1*)
B20.6	HIV disease resulting in Pneumocystis jirovecii pneumonia
B25.0	Cytomegaloviral pneumonitis (J17.1*)
B59	Pneumocystosis (J17.3*)
J05	Acute obstructive laryngitis [croup] and epiglottitis
J05.0	Acute obstructive laryngitis [croup]
J05.1	Acute epiglottitis
J05.X	Acute obstructive laryngitis [croup] and epiglottitis
J09	Influenza due to identified zoonotic or pandemic influenza virus
J09.X	Influenza due to certain identified influenza virus
J10	Influenza with other manifestations, other influenza virus identified
J10.0	Influenza with pneumonia, other influenza virus identified
J10.1	Influenza with other respiratory manifestations, other influenza virus identified
J10.8	Influenza with other manifestations, other influenza virus identified
J10.X	Influenza due to other identified influenza virus
J11	Influenza, virus not identified
J11.0	Influenza with pneumonia, virus not identified
J11.1	Influenza with other respiratory manifestations, virus not identified
J11.8	Influenza with other manifestations, virus not identified
J11.X	Influenza, virus not identified
J12	Viral pneumonia, not elsewhere classified
J12.0	Adenoviral pneumonia
J12.1	Respiratory syncytial virus pneumonia
J12.2	Parainfluenza virus pneumonia
J12.3	Human metapneumovirus pneumonia
J12.8	Other viral pneumonia
J12.9	Viral pneumonia, unspecified
J12.X	Viral pneumonia, not elsewhere classified
J13	Pneumonia due to Streptococcus pneumoniae
J13.X	Pneumonia due to Streptococcus pneumoniae
J14	Pneumonia due to Haemophilus influenzae
J14.X	Pneumonia due to Haemophilus influenzae
J15	Bacterial pneumonia, not elsewhere classified
J15.0	Pneumonia due to Klebsiella pneumoniae
J15.1	Pneumonia due to Pseudomonas
J15.2	Pneumonia due to Staphylococcus
J15.3	Pneumonia due to Streptococcus, Group B

ICD-10 code	Description
Lower respiratory tract infections	
J15.4	Pneumonia due to other streptococci
J15.5	Pneumonia due to Escherichia coli
J15.6	Pneumonia due to other aerobic Gram-negative bacteria
J15.7	Pneumonia due to Mycoplasma pneumoniae
J15.8	Other bacterial pneumonia
J15.9	Bacterial pneumonia, unspecified
J15.X	Bacterial pneumonia, not elsewhere classified
J16	Pneumonia due to other infectious organisms, not elsewhere classified
J16.0	Chlamydial pneumonia
J16.8	Pneumonia due to other specified infectious organisms
J16.X	Pneumonia due to other infectious organisms, not elsewhere classified
J17	Pneumonia in diseases classified elsewhere
J17.0	Pneumonia in bacterial diseases classified elsewhere
J17.1	Pneumonia in viral diseases classified elsewhere
J17.2	Pneumonia in mycoses
J17.3	Pneumonia in parasitic diseases
J17.8	Pneumonia in other diseases classified elsewhere
J17.X	Pneumonia in diseases classified elsewhere
J18	Pneumonia, organism unspecified
J18.0	Bronchopneumonia, unspecified
J18.1	Lobar pneumonia, unspecified
J18.2	Hypostatic pneumonia, unspecified
J18.8	Other pneumonia, organism unspecified
J18.9	Pneumonia, unspecified
J18.X	Pneumonia, organism unspecified
J20	Acute bronchitis
J20.0	Acute bronchitis due to Mycoplasma pneumoniae
J20.1	Acute bronchitis due to Haemophilus influenzae
J20.2	Acute bronchitis due to streptococcus
J20.3	Acute bronchitis due to coxsackievirus
J20.4	Acute bronchitis due to parainfluenza virus
J20.5	Acute bronchitis due to respiratory syncytial virus
J20.6	Acute bronchitis due to rhinovirus
J20.7	Acute bronchitis due to echovirus
J20.8	Acute bronchitis due to other specified organisms
J20.9	Acute bronchitis, unspecified
J20.X	Acute bronchitis
J21	Acute bronchiolitis
J21.0	Acute bronchiolitis due to respiratory syncytial virus
J21.1	Acute bronchiolitis due to human metapneumovirus
J21.8	Acute bronchiolitis due to other specified organisms
J21.9	Acute bronchiolitis, unspecified
J21.X	Acute bronchiolitis
J22	Unspecified acute lower respiratory infection

ICD-10 code	Description
Lower respiratory tract infections	
J22.X	Unspecified acute lower respiratory infection
P23	Congenital pneumonia
P23.0	Congenital pneumonia due to viral agent
P23.1	Congenital pneumonia due to Chlamydia
P23.2	Congenital pneumonia due to staphylococcus
P23.3	Congenital pneumonia due to Streptococcus, Group B
P23.4	Congenital pneumonia due to Escherichia coli
P23.5	Congenital pneumonia due to Pseudomonas
P23.6	Congenital pneumonia due to other bacterial agents
P23.8	Congenital pneumonia due to other organisms
P23.9	Congenital pneumonia, unspecified
Diarrhoea	
A00.9	Cholera, unspecified
A01	Typhoid and paratyphoid fevers
A01.0	Typhoid fever
A01.1	Paratyphoid fever A
A01.2	Paratyphoid fever B
A01.3	Paratyphoid fever C
A01.4	Paratyphoid fever, unspecified
A01.X	Typhoid and paratyphoid fevers
A02	Other salmonella infections
A02.0	Salmonella enteritis
A02.2	Localized salmonella infections
A02.8	Other specified salmonella infections
A02.9	Salmonella infection, unspecified
A03	Shigellosis
A03.0	Shigellosis due to Shigella dysenteriae
A03.1	Shigellosis due to Shigella flexneri
A03.2	Shigellosis due to Shigella boydii
A03.3	Shigellosis due to Shigella sonnei
A03.8	Other Shigellosis
A03.9	Shigellosis, unspecified
A03.X	Shigellosis
A04	Other bacterial intestinal infections
A04.0	Enteropathogenic Escherichia coli infection
A04.1	Enterotoxigenic Escherichia coli infection
A04.2	Enteroinvasive Escherichia coli infection
A04.3	Enterohaemorrhagic Escherichia coli infection
A04.4	Other intestinal Escherichia coli infections
A04.5	Campylobacter enteritis
A04.6	Enteritis due to Yersinia enterocolitica
A04.7	Enterocolitis due to Clostridium difficile
A04.8	Other specified bacterial intestinal infections
A04.9	Bacterial intestinal infection, unspecified

ICD-10 code	Description
Diarrhoea	
A05	Other bacterial foodborne intoxications, not elsewhere classified
A05.0	Foodborne staphylococcal intoxication
A05.1	Botulism
A05.2	Foodborne Clostridium perfringens [Clostridium welchii] intoxication
A05.3	Foodborne Vibrio parahaemolyticus intoxication
A05.4	Foodborne Bacillus cereus intoxication
A05.8	Other specified bacterial foodborne intoxications
A05.9	Bacterial foodborne intoxication, unspecified
A06	Amoebiasis
A06.0	Acute amoebic dysentery
A06.1	Chronic intestinal amoebiasis
A06.9	Amoebiasis, unspecified
A07	Other protozoal intestinal diseases
A07.0	Balantidiasis
A07.1	Giardiasis [lambliasis]
A07.2	Cryptosporidiosis
A07.3	Isosporiasis
A07.8	Other specified protozoal intestinal diseases
A07.9	Protozoal intestinal disease, unspecified
A08	Viral and other specified intestinal infections
A08.0	Rotaviral enteritis
A08.1	Acute gastroenteropathy due to Norwalk agent
A08.2	Adenoviral enteritis
A08.3	Other viral enteritis
A08.4	Viral intestinal infection, unspecified
A08.5	Other specified intestinal infections
A08.X	Viral and other specified intestinal infections
A09	Other gastroenteritis and colitis of infectious and unspecified origin
A09.0	Other and unspecified gastroenteritis and colitis of infectious origin
A09.9	Gastroenteritis and colitis of unspecified origin
A09.X	Other gastroenteritis and colitis of infectious and unspecified origin
K52.3	Indeterminate colitis
R19.7	Diarrhoea, unspecified
Meningitis	
Bacterial meningitis	
A20.3	Plague meningitis
A32.1	Listerial meningitis and meningoencephalitis
A39.0	Meningococcal meningitis (G01*)
G00	Bacterial meningitis, not elsewhere classified
G00.0	Haemophilus meningitis
G00.1	Pneumococcal meningitis
G00.2	Streptococcal meningitis
G00.3	Staphylococcal meningitis
G00.8	Other bacterial meningitis

ICD-10 code	Description
Bacterial meningitis	
G00.9	Bacterial meningitis, unspecified
G00.X	Bacterial meningitis, not elsewhere classified
G01	Meningitis in bacterial diseases classified elsewhere
G01.X	Meningitis in bacterial diseases classified elsewhere
Viral meningitis	
A87	Viral meningitis
A87.0	Enteroviral meningitis (G02.0*)
A87.1	Adenoviral meningitis (G02.0*)
A87.2	Lymphocytic choriomeningitis
A87.8	Other viral meningitis
A87.9	Viral meningitis, unspecified
A87.X	Viral meningitis
B00.3	Herpesviral meningitis (G02.0*)
B01.0	Varicella meningitis (G02.0*)
B02.1	Zoster meningitis (G02.0*)
B26.1	Mumps meningitis (G02.0*)
G02.0	Meningitis in viral diseases classified elsewhere
G03.0	Nonpyogenic meningitis
G03.2	Benign recurrent meningitis [Mollaret]
Fungal meningitis	
B37.5	Candidal meningitis (G02.1*)
B38.4	Coccidioidomycosis meningitis (G02.1*)
G02.1	Meningitis in mycoses
Other meningitis	
G02	Meningitis in other infectious and parasitic diseases classified elsewhere
G02.8	Meningitis in other specified infectious and parasitic diseases classified elsewhere
G03	Meningitis due to other and unspecified causes
G03.1	Chronic meningitis
G03.8	Meningitis due to other specified causes
G03.9	Meningitis, unspecified
G03.X	Meningitis due to other and unspecified causes
Tuberculous meningitis	
A17	Tuberculosis of nervous system
A17.1	Meningeal tuberculoma (G07*)
A17.8	Other tuberculosis of nervous system
A17.9	Tuberculosis of nervous system, unspecified (G99.8*)
A17.X	Tuberculosis of nervous system
Other infectious diseases	
B23.8	HIV disease resulting in other specified conditions
D64.9	Anaemia, unspecified
E86	Volume depletion
G41.9	Status epilepticus, unspecified
P28.1	Other and unspecified atelectasis of newborn
R11	Nausea and vomiting

Faculty of Health Sciences Human Research Ethics Committee at the University of Cape Town Ethics Approval.

UNIVERSITY OF CAPE TOWN
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12 April 2021

HREC REF: 197/2021

Prof M Davies
CIDER
Fairland House, Salt River
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Dear Prof Davies

PROJECT TITLE: BURDEN AND CAUSES OF ONGOING PAEDIATRIC INFECTIOUS DISEASE MORBIDITY AND MORTALITY IN THE WESTERN CAPE PROVINCE OF SOUTH AFRICA (PHD CANDIDATE: MS KATHLEEN KEHOE)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.

Approval is granted for one year until the 30 April 2022.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: - Ms Kathleen Kehoe will also be involved in this study.

Please quote the HREC REF 197/2021 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC/REF 197/2021sa

10.2 Chapter 4 appendix

Comparison of paediatric infectious disease deaths in public sector health facilities using different data sources in the Western Cape, South Africa (2007-2021).

BMC Infectious Diseases

RESEARCH

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Comparison of paediatric infectious disease deaths in public sector health facilities using different data sources in the Western Cape, South Africa (2007–2021)

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Abstract

Background Routinely collected population-wide health data are often used to understand mortality trends including child mortality, as these data are often available more readily or quickly and for lower geographic levels than population-wide mortality data. However, understanding the completeness and accuracy of routine health data sources is essential for their appropriate interpretation and use. This study aims to assess the accuracy of diagnostic coding for public sector in-facility childhood (age < 5 years) infectious disease deaths (lower respiratory tract infections [LRTI], diarrhoea, meningitis, and tuberculous meningitis [TBM]) in routine hospital information systems (RHIS) through comparison with causes of death identified in a child death audit system (Child Healthcare Problem Identification Programme [Child PIP]) and the vital registration system (Death Notification [DN] Surveillance) in the Western Cape, South Africa and to calculate admission mortality rates (number of deaths in admitted patients per 1000 live births) using the best available data from all sources.

Methods The three data sources: RHIS, Child PIP, and DN Surveillance are integrated and linked by the Western Cape Provincial Health Data Centre using a unique patient identifier. We calculated the deduplicated total number of infectious disease deaths and estimated admission mortality rates using all three data sources. We determined the completeness of Child PIP and DN Surveillance in identifying deaths recorded in RHIS and the level of agreement for causes of death between data sources.

Results Completeness of recorded in-facility infectious disease deaths in Child PIP (23/05/2007–08/02/2021) and DN Surveillance (2010–2013) was 70% and 69% respectively. The greatest agreement in infectious causes of death were for diarrhoea and LRTI: 92% and 84% respectively between RHIS and Child PIP, and 98% and 83% respectively between RHIS and DN Surveillance. In-facility infectious disease admission mortality rates decreased significantly for the province: 1.60 (95% CI: 1.37–1.85) to 0.73 (95% CI: 0.56–0.93) deaths per 1000 live births from 2007 to 2020.

Conclusion RHIS had accurate causes of death amongst children dying from infectious diseases, particularly for diarrhoea and LRTI, with declining in-facility admission mortality rates over time. We recommend integrating data sources to ensure the most accurate assessment of child deaths.

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Keywords Paediatric infectious disease deaths, Data comparison, Data completeness, South Africa

Introduction

Monitoring childhood mortality is important to assess factors related to child survival such as access to and quality of healthcare, safety, nutrition and protection [1, 2]. This closely aligns with the third Sustainable Development Goal that by 2030 all countries should reduce under-five mortality rate to < 25 deaths/1000 live births [3]. Accurate monitoring of the contribution to mortality of infectious diseases, including lower respiratory infections (LRTI), diarrhoea, meningitis, and tuberculous meningitis (TBM), is thus vital to monitor progress, as these preventable deaths are responsible for a substantial proportion of child mortality in resource-limited settings [4–7]. Data for these infectious diseases are often outdated or scarce, especially at lower geographic levels within these settings, warranting the need to better understand the current burden.

Childhood mortality monitoring through death notification systems may have several disadvantages including the limited use of these systems in many settings and that there may be up to 2 year delays in releasing these data, making them unhelpful for real-time use [5, 8]. In addition, not all child deaths may be registered [9], resulting in low completeness [4]. Routinely collected health datasets may provide more rapid child mortality estimates and the limitations of the several different routine health data sources available can be reduced by integrating and comparing them [10].

We compared the completeness of death data for children recorded as dying from infectious diseases in the Western Cape, South Africa, using three death data sources as follows: (i) routine health information systems (RHIS) data which captures key information for each admission, including the unique patient identifier, patient demographics and hospital administration data, and discharge codes and summaries [11]; (ii) Child Healthcare Problem Identification Programme (Child PIP) which is a child death audit review process of all in-hospital child (0–18 years) deaths in public health facilities that participate voluntarily [12, 13]; and (iii) Death Notification (DN) Surveillance which includes all deaths, in- or out-of-hospital, recorded on DN forms [14]. These three data sources are integrated and linked in the Western Cape Provincial Health Data Centre (WCPHDC) through a unique patient identifier that is used across public health services in the province [11]. RHIS includes every electronically recorded in-facility child death but does not typically include cause of death, but rather diagnostic coding of the reason for admission during which the death occurred. In contrast, there may be under-reporting or missing data on all in-facility child deaths in DN Surveillance and Child PIP, but these capture recorded causes of death from notification forms and audits respectively, making their cause of death data more accurate. Child death audit review systems, used globally [15], define causes of death similarly to DN, but also identify modifiable factors contributing to these deaths [12, 13].

In addition to comparing completeness of the different death data sources, we assessed the accuracy of RHIS recorded diagnostic codes vs. those in DN Surveillance and Child PIP. We determined the admission mortality rates for in-facility infectious disease deaths in the public sector across the Western Cape province and by district/sub-district.

Methods

Setting study population

The Western Cape province consists of six districts: Cape Town Metro, Cape Winelands, Central Karoo, Garden Route, Overberg, and West Coast. The province had an estimated seven million people in 2020 [16] of whom 8% (563,590) were children aged 0–4 years [17]. About 80% of the child population utilise public-sector services. The Western Cape Department of Health manages 52 hospitals and 272 primary care clinics, and the City of Cape Town manages an additional 82 clinics [11]. We included all children hospitalised at age < 5 years, including neonates, at a public health facility within the Western Cape province from 2007 to 2021.

Data sources

We use the following data sources that are consolidated within the WCPHDC (Table 1): RHIS, Child PIP, and DN Surveillance data. The following infectious disease death categories were identified and used in the analysis: LRTI, diarrhoea, meningitis, and TBM (Additional file 1: Table S1). Unless otherwise stated, all totals reported in the results are related to these four infectious diseases only. We also identified an 'other infectious disease' category when looking at cause of death coding (Additional file 1: Table S1). This was utilised in the concordance analysis to determine if the diagnostic coding in the RHIS would detect an infectious disease e.g. HIV, even if an International Classification of Diseases 10th Revision (ICD-10) for the four infectious

Table 1 Overview of data sources used for comparing infectious disease deaths in children under five years

	Sources utilised from the Western Cape Provincial Health Data Centre **A single consolidated environment which houses individuated patient-level health data for the Western Cape**		
	Routine hospital information systems	**Child Healthcare Problem Identification Programme**	**Death Notification (DN) Surveillance**
Brief description	Routine hospital information systems in the province capturing key information for each admission, including the unique patient identifier, patient demographics and hospital administration data, and discharge codes and summaries	An audit process of all in-hospital child (0–18 years) deaths in public health facilities that participate voluntarily	All deaths, in- or out-of-hospital, are recorded once the DN forms have been captured by the DHA. These data were leveraged for DN with cause of death data being shared with the DoH
Time period	01/01/2007–01/12/2021	23/05/2007–08/02/2021	01/01/2010–01/12/2013
Coverage	All public hospitals capturing in-facility deaths since the date when electronic admission and discharge data were networked into the WCPHDC.*	Selected public health facilities that voluntarily participate, thereby only capturing in-facility deaths in participating facilities	All notified deaths in the province, in- or out-of-hospital. For this study, we restricted to in-facility deaths
Source of death reporting	Admission ICD-10 coding (primary, subsidiary and secondary 1–10) from clinical records	Cause of death as determined by clinical audit	Cause of death as recorded on DN form
Variables	Date of death, ICD-10 codes (to determine proxy cause of death), and hospital admission date	Date of death, cause of death, and hospital admission date	Date of death and cause of death
Frequency of data source updates to the WCPHDC	Daily	Approximately annually	No longer provided
Advantages	Complete and timeous recording of all deaths in facilities with electronic data capture as every separation requires an entry	Reports in depth information on child deaths, including modifiable factors. Reports are available timeously	Includes all deaths (public and private health sector, and out-of-hospital deaths) associated causes
Disadvantages	Only available for public health facilities and in-hospital deaths. The cause of death is not explicitly coded, but has to be inferred from the diagnostic code for the admission during which the death occurred	Not all public health facilities participate (voluntary). Private sector death information is not included	Cannot be used for short/medium term planning due to the reporting delay (2 years) Contributing or modifiable factors are not recorded Deaths are underreported (not reported or form does not reach the DHA), incomplete or incorrect. Deaths are also not available for foreign nationals without a South African identification number. Data are collated nationally and individual cause of death data is not provided to provincial health departments. Aggregate mortality data are only provided at the level of the province and not for smaller geographic areas

DHA Department of Home Affairs, *DoH* Department of Health, *DN* Death Notification, *ICD-10* International Classification of Diseases 10th Revision

*In-facility death reporting was achieved incrementally since 2007 as hospitals became networked in the province

diseases was absent. The list of ICD-10 codes for inferring each infectious disease were determined in consultation with clinicians including paediatric infectious disease specialists.

Western Cape Provincial Health Data Centre (WCPHDC)

The WCPHDC is a single consolidated environment that links individuated patient-level health data from different health information systems using a unique identifier available in all patient administration systems in public health facilities in the Western Cape, South Africa [11]. Data sources include hospitals (both inpatient and outpatient visits), primary healthcare facilities (outpatient visits), diagnostic laboratories, pharmacies, disease management systems, community data, partner systems, and mobile health systems [11].

The primary focus of the WCPHDC is to provide data for service delivery and support clinical care. Using these data, encounters (health service contacts e.g., outpatient visits or admissions) and health conditions e.g., HIV, tuberculosis, pregnancy and cascades (health care utilisation and outcomes of health conditions) are identified. Health conditions are inferred with different levels of certainty using multiple data sources (e.g. diagnostic or disease specific laboratory tests, medication, disease management system data and diagnostic [ICD10] codes). Most of these data are updated and linked daily with other sources, which are updated weekly, monthly, quarterly, or periodically depending on the data source [11]. Integration of this data improves the data quality, reducing the concerns regarding a single data source.

Routine hospital information systems (RHIS)

RHIS (known as Clinicom [11] and Electronic Continuity of Care Record [ECCR]) are used in hospitals in the province to record patient demographics, admissions, discharge summaries, diagnosis codes and hospital administration data against each unique identifier [11]. Reporting was achieved incrementally since 2007 as hospitals became networked in the province [18]. Each hospitalisation and the corresponding outcome (death, transfer to another facility or home discharge) is recorded. We identified an infectious disease by the presence of a relevant ICD-10 code across any of the recorded fields (i.e. primary, subsidiary, or first ten recorded secondary codes). For in-facility deaths, the cause of death is not specifically captured, and so we used ICD-10 diagnosis codes identified during the admission as the proxy cause of death (Table 1). In a child who is transferred between wards or facilities, there may be several records related to the admission when death occurred with multiple ICD-10 codes captured across these records. Using the three infectious disease ICD-10 codes closest to the event, a single proxy cause of death was identified with primary causes in turn outranking subsidiary or secondary causes and then codes recorded closest to the event outranking those recorded earlier.

Child Healthcare Problem Identification Programme (Child PIP)

Child PIP was established in 2005 to audit all in-facility deaths in children (0–18 years) in South Africa and improve healthcare provision [12, 13] (Table 1). The mortality review process involves detailed steps in which (i) the child death is reviewed within 24 h, (ii) a nurse and doctor present cases at weekly or monthly mortality meetings, and, (iii) data management and analysis identifies trends and makes recommendations [13]. The cause of death is identified through a clinical audit process. As Child PIP is voluntary, uptake varies within the Western Cape, with 37 out of 43 hospitals (86%) currently participating. The individual patient-level data are collected at facility level to review practices, and reported into a national Child PIP database to inform policies nationally. Key social and nutritional data are collected to describe the circumstances surrounding the death. Critical to the process is identifying potential modifiable factors, divided into two categories: person (e.g., administrator, clinical personnel, caregiver) and place (e.g., ward, home, referring facility).

Death notification (DN) surveillance

The Western Cape Department of Health (DoH), City of Cape Town and South African Medical Research Council Burden of Disease Research Unit together developed a Death Notification (DN) Surveillance system to monitor district and subdistrict mortality and causes of death [14] (Table 1), leveraging vital registration data reported to the South African Department of Home Affairs (DHA). Six district information offices collected copies of DN forms from the local DHA offices [14]. Sociodemographic and cause of death information from the DN was captured with data cleaning and mortality reports for the province produced. Patient-level cause of death data was shared with the Western Cape DoH between 2010 and 2013. This system was discontinued from 2014.

Data comparison and analysis

Data were linked across the RHIS, Child PIP and DN Surveillance data using the unique identifier, for the four infectious diseases of interest for the respective time periods that data were available. If dates of death differed by more than 30 days between datasets or did not align to an admission date in RHIS, the child was dropped from the dataset (three children). Where cause of death differed across datasets, we applied the following hierarchy in attributing an overall cause of death to determine

mortality estimates: (1) Child PIP (most reliable) as causes of death are identified through an audit process; (2) DN ranked second as cause of death is identified by the attending clinician at the time of death, but without an audit process; and (3) RHIS ranked third as cause of death had to be inferred from admission diagnosis codes.

We compared data to determine the number of de-duplicated infectious diseases deaths across all sources. We determined the percentage of each of the infectious disease deaths present in Child PIP and DN Surveillance vs. RHIS. To understand the accuracy of RHIS causes of death, we determined the level of agreement between RHIS and each of Child PIP and DN Surveillance. To test the level of agreement, we calculated the Kappa statistic for the four infectious diseases of interest, with the agreement for values of 0.81–1.00 being considered "almost perfect", 0.61–0.80 "substantial", 0.41–0.60 "moderate", 0.21–0.40 "fair" and 0.01–0.20 "none to slight" [19].

We calculated admission mortality rates for the province and each district/subdistrict (based on child's place of residence) over time using the de-duplicated, integrated dataset that included all sources. Admission mortality rate is defined as infectious disease deaths occurring in a health facility divided by live birth population estimates, presented per 1000 live births with 95% confidence intervals. The population denominator was estimated from population estimates as 80% of live births [20], i.e. the estimated proportion of the population using public sector services in the province or respective district/sub-district. Since the number of live births per Cape Town Metro sub-district was not available, as births are mapped to Home Affairs Offices rather than place of residence, we estimated the sub-district live births denominator based on the proportion of infants among the total population for that sub-district. Live births from the population estimates were only available until 2020, so the comparison was limited to 2007–2020. For district and sub-district comparisons, 2019 death and population data was used, as this was the last pre-pandemic year and data thereafter are confounded by several pandemic related factors [21].

Data were cleaned and coded in SQL and analysed using Excel and R Studio.

Ethics

This study was approved by the Human Research Ethics Committee in the Faculty of Health Sciences at the University of Cape Town (HREC REF 197/2021).

Results

Using all three data sources, there were 217,899 admissions for one of the four infectious disease admissions among children under 5 years from 2007 to 2021 with a total of 1947 deaths recorded among these children (~ 1% of hospital admissions among children under five years with an infectious disease diagnosis) (Table 2). Around 1661 children died (85% of all deaths) from one of the four infectious diseases included in this study. Of the remaining 286 deaths, most had either missing cause of death and missing ICD-10 code or were attributed to sepsis or perinatal factors such as low birth weight and prematurity. The highest proportion of

Table 2 Summary of infectious disease deaths among 217,899 children admitted for an infectious disease in public sector facilities in the Western Cape, 2007–2021

Variable	Total (%)
Total number of deaths	1947 (~ 1% of infectious disease admissions)
Infectious disease deaths (LRTI, diarrhoea, TBM or meningitis)	1661 (85% of total deaths)
Other causes of death (missing cause of death or ICD-10 code, sepsis, or perinatal factors [low birth weight or prematurity])	286 (15% of total deaths)
Age among infectious disease deaths	
< 28 days	202 (12%)
28 days to 1 year	1000 (60%)
> 1 to < 5 years	459 (28%)
Location	
Hospital A	713 (43% of infectious disease deaths)
Hospital B	596 (36% of infectious disease deaths)
Other hospitals	352 (21% of infectious disease deaths)
ICD-10 coding	
Primary diagnosis coding by registrar or consultant	1430 (86% of infectious disease deaths)
Subsidiary diagnosis coding by registrar or consultant	532 (32% of infectious disease deaths)

infectious disease deaths was in children aged 28 days to one year (1000 deaths, 60%). Most deaths occurred in the two large tertiary hospitals in the province which account for 39% of all infectious admissions (713 deaths [43% of infectious disease deaths] and 596 deaths [36% of infectious disease deaths] in these two hospital respectively). The highest proportion of infectious disease admissions at any other hospital accounted for ≤ 4%. Most primary diagnosis codes for infectious disease deaths in RHIS were coded by a registrar or consultant (1430 deaths, 86%), rather than a data clerk, whereas less than a third of subsidiary codes were coded by a registrar or consultant (532 deaths, 32%).

Data source comparison

During the time period for which RHIS and Child PIP data were both available (23/05/2007–08/02/2021), 1512 infectious deaths were recorded across these two data sources (Fig. 1a). All of these were recorded in RHIS, and Child PIP was 70% complete (1053 deaths).

When comparing infectious disease deaths across all available data sources for the period when all three sources where available (438 deaths from 2010 to 2013), DN Surveillance was 69% complete (303 deaths identified, of which 239 were also recorded in Child PIP while 64 were recorded in DN Surveillance and RHIS only) (Fig. 1b). An additional 22% of deaths were identified in RHIS and Child PIP but not DN Surveillance (95 deaths), while the remaining 9% were in RHIS alone (40 deaths).

Cause of death agreement

Of the 1186 deaths recorded in Child PIP (considered most reliable for cause of death) from May 2007–February 2021, 564 (48%) were due to one of the four infectious diseases of interest. Although all of these deaths were recorded in RHIS, 3% (16 deaths) could not be identified as an infectious disease death based on RHIS alone. An additional 2% (10 deaths) were identified as an infectious disease death but not as being due to one of the four infectious diseases of study (Table 3). The concordance between Child PIP and RHIS: diarrhoea (92%), LRTI (84%), meningitis (77%), and TBM (74%). The overall level of agreement for the four infectious diseases was almost perfect (Kappa statistic 0.810; 95% CI 0.766–0.855). For Child PIP causes of death, a greater proportion of mismatches were detected for meningitis and TBM, whereas a greater number of mismatches was detected for LRTI as this is more common; all due to the absence of the corresponding diagnostic code in RHIS.

Of the 542 deaths in DN Surveillance from 2010 to 2013, 132 (15%) were due to one of the four infectious diseases of interest. Of these, 128 (96%) were identified as being due to an infectious disease of interest in RHIS (Table 4). The overall level of agreement for the four infectious diseases was moderate (Kappa statistic 0.782; 95% CI 0.690–0.875). The best agreement between DN Surveillance and RHIS was for diarrhoea (98%) and LRTI (83%). TBM (45%) and meningitis (56%) agreement was lower mostly due to the absence of the corresponding diagnostic code in RHIS. Again, the greater number of mismatches was detected for LRTI cause of death in DN Surveillance.

Admission mortality rates

Using the combined de-duplicated dataset, admission mortality rates for these infectious diseases in the Western Cape more than halved between 2007 and 2020 (1.60 [95% CI: 1.37–1.85)] deaths per 1000 live births [2007] and 0.73 [95% CI: 0.56–0.93] deaths per 1000 live births [2020]) (Fig. 2a). Of the 1661 infectious disease deaths from 2007–2021,

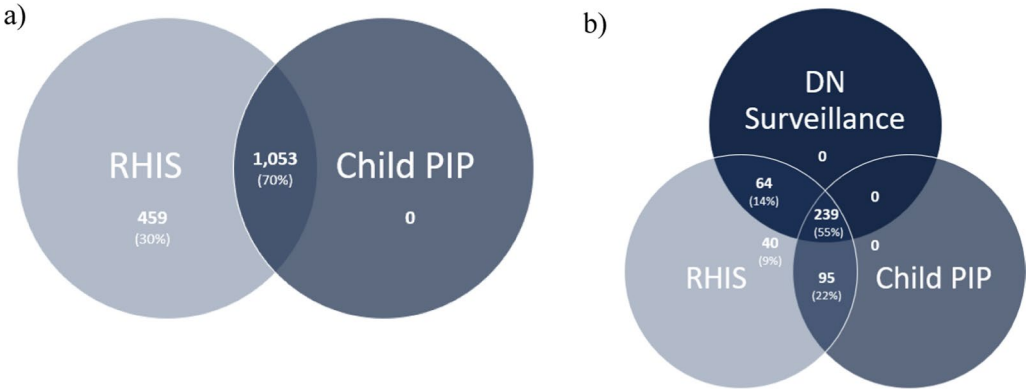


Fig. 1 Venn diagrams triangulating infectious disease deaths across data sources for the time periods that the data sources were available: **a** RHIS and Child PIP from 23/05/2007–08/02/2021 (1512 deaths) and **b** RHIS, DN Surveillance and Child PIP from 2010 to 2013 (438 deaths)

Table 3 Comparison of Routine Health Information Systems and Child Healthcare Problem Identification Programme causes of death among children admitted for diarrhoea, lower respiratory tract infections, meningitis or tuberculous meningitis in the Western Cape (May 2007–February 2021)

Child PIP cause of death	RHIS cause of death						
	Diarrhoea	LRTI	Meningitis	TBM	Other infectious disease	Other condition	Total
Diarrhoea	**119 (92%)**	6 (5%)	1 (1%)	0	0	3 (2%)	129 (100%)
LRTI	29 (9%)	**285 (84%)**	5 (1%)	0	9 (3%)	10 (3%)	338 (100%)
Meningitis	1 (2%)	7 (11%)	**48 (77%)**	3 (5%)	1 (2%)	2 (3%)	62 (100%)
TBM	2 (6%)	2 (6%)	4 (11%)	**26 (74%)**	0	1 (3%)	35 (100%)
Total	151	300	58	29	10	16	564

Table includes all deaths that were recorded as being due to diarrhoea, LRTI, meningitis or TBM in Child PIP. Row percentages are shown. Bold values are to highlight the level of agreement of each infectious disease, respectively

Child PIP Child Healthcare Problem Identification Programme, *LRTI* lower respiratory tract infections, *RHIS* Routine Health Information Systems, *TBM* tuberculous meningitis

Table 4 Comparison of Routine Health Information Systems and Death Notification Surveillance causes of death among children admitted for diarrhoea, lower respiratory tract infections, meningitis or tuberculous meningitis in the Western Cape (2010–2013)

DN Surveillance cause of death	RHIS cause of death					
	Diarrhoea	LRTI	Meningitis	TBM	Other condition	Total
Diarrhoea	**52 (98%)**	1 (2%)	0	0	0	53
LRTI	8 (14%)	**49 (83%)**	0	0	2 (3%)	59
Meningitis	0	3 (27%)	**5 (45%)**	2 (18%)	1 (9%)	11
TBM	1 (11%)	0	2 (22%)	**5 (56%)**	1 (11%)	9
Total	61	53	7	7	4	132

Table includes all deaths that were recorded as being due to diarrhoea, LRTI, meningitis or TBM in DN Surveillance. Row percentages are shown. Bold values are to highlight the level of agreement of each infectious disease, respectively

DN Death Notification, *LRTI* lower respiratory tract infections, *RHIS* Routine Health Information Systems, *TBM* tuberculous meningitis

1168 (70%) were in the Cape Town Metro (Fig. 2b). Admission mortality rates for the four infectious diseases of interest in Cape Town Metro decreased by almost fourfold from 2.59 (95% CI: 2.20–3.03deaths per 1000 births [2007] to 0.76 (95% CI: 0.52–1.07) deaths per 1000 live births [2020]. Only 2% (25 deaths) of infectious disease deaths could not be mapped to a child's place of residence in the province (either outside the province or missing).

In 2019, the admission mortality rates were highest in Overberg and Central Karoo (Fig. 3a). Admission mortality rates in the other four districts were around one or lower death per 1000 live births. For the City of Cape Town, where the highest number of deaths were recorded, the highest admission mortality rate was in the Western sub-district with other sub-districts below one death per 1000 live births (Fig. 3b).

Discussion

We believe this is the first study to compare and synthesize routinely collected in-facility child death data in the public sector in South Africa. We were able to comprehensively evaluate the accuracy of in-facility diagnostic coding for children who die from infectious diseases and demonstrated that data linkage and consolidation across multiple sources improved the accuracy of in-facility infectious disease mortality estimates.

Completeness of Child PIP and DN Surveillance for the four infectious disease deaths recorded electronically in RHIS was approximately 70%. While causes of death in RHIS rely on inference from the diagnosis code for the relevant admission, the level of agreement for the infectious cause of death with more accurate sources was generally high, specifically between Child PIP and RHIS ($\geq$74%) and for diarrhoea and LRTI in both Child PIP and DN Surveillance (>80%). The higher concordance may be because diagnoses of diarrhoea or LRTI can be made confidently based on symptoms only, whereas laboratory tests would usually be needed to confirm diagnoses of meningitis and TBM, and pathogen testing seldomly happens in this setting. Lower level of agreement for meningitis and TBM may be driven by suboptimal diagnosis, infrequent pathogen testing and incorrect

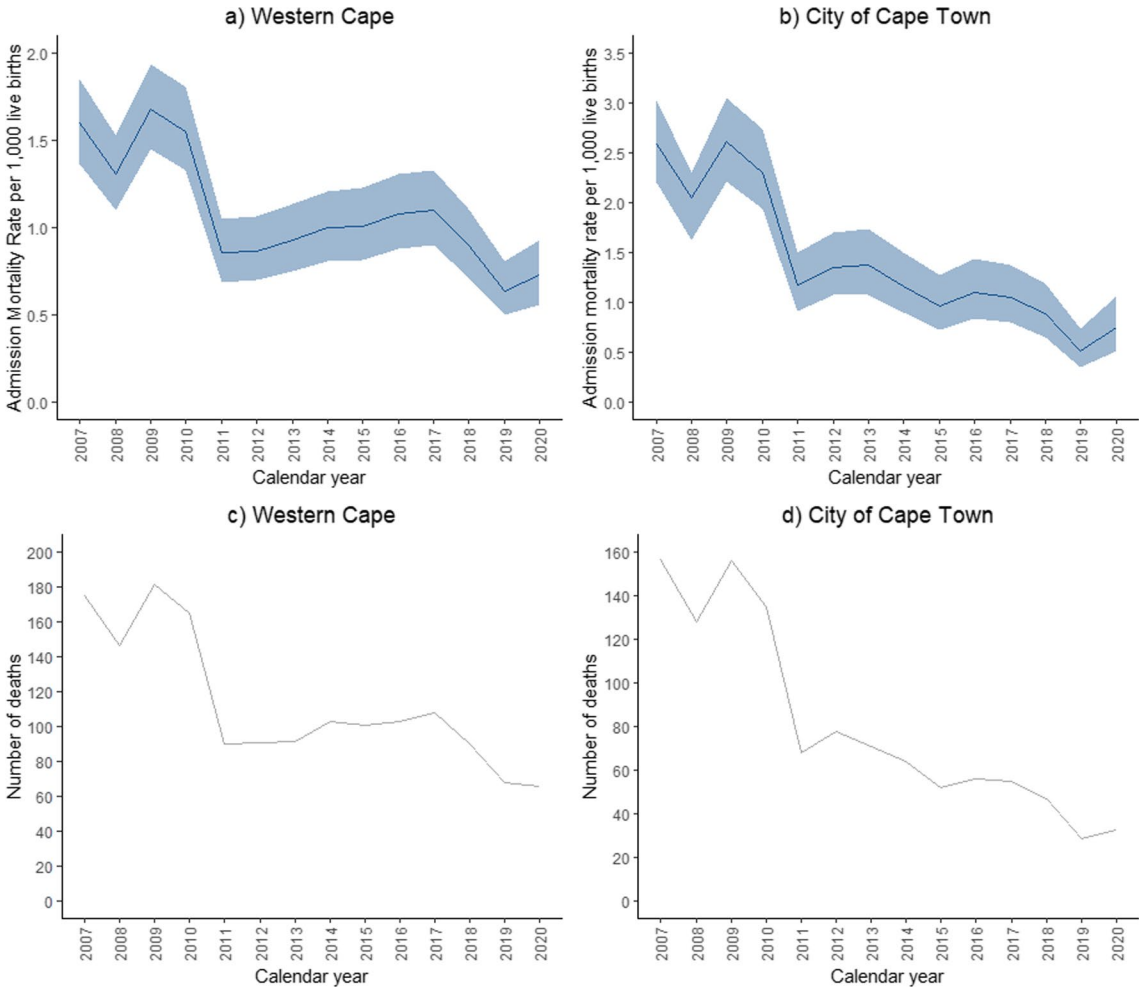
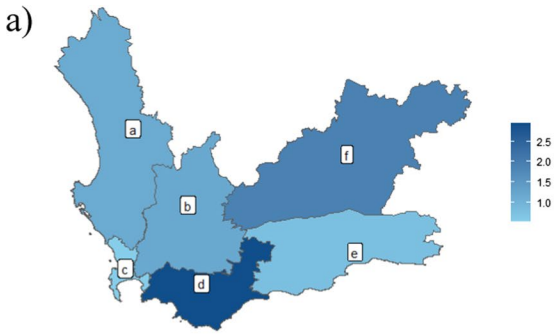


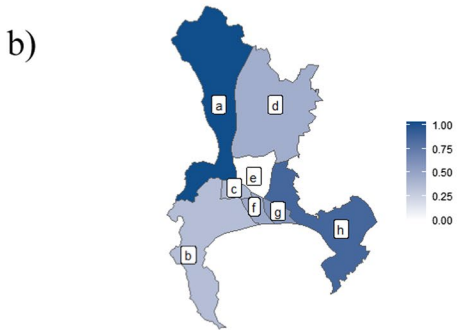
Fig. 2 Admission mortality rates per 1000 live births mapped to child's residence, with 95% confidence intervals represented by the shaded areas for **a** the Western Cape and **b** the City of Cape Town and the total number of infectious disease deaths for **c** the Western Cape and **d** the City of Cape Town for all four infectious disease deaths combined using the de-duplicated dataset. Population estimates were only available until 2020, so the comparison was limited to 2007–2020

diagnosis coding. Despite these limitations, the level of agreement across data sources provide reassurance that RHIS has reasonable accuracy of diagnostic coding for children who die. It is thus a useful and timely source of child death data, since RHIS is updated daily, whereas audit data sources (Child PIP) are only provided and integrated into the WCPHDC periodically and DN data is very delayed, not available at district/sub-district level and currently not available to health services, preventing linkage to other individual patient data. While low completeness of electronic ICD-10 coding was reported in a large tertiary hospital in the province [22], we found more accurate and complete diagnostic coding in patients who die, which has also been shown in other settings [8]. Our findings suggest that data comparison improves validity over using a single data source, which is consistent with other public health studies utilising triangulation or integration of routine health data sources, individual- or population-level, focusing on various health conditions [23–26].

The admission mortality rates for the four infectious diseases decreased significantly over the 14-year period, somewhat plateauing from 2014/15 with a slight reduction noted from 2019. This downward trend has been observed across the province for the individual infectious diseases where data are available, including pneumonia [27] and diarrhoea [28]. These declines may be due to: (i) improved prevention of HIV from mother-to-child and increased antiretroviral therapy coverage [29], (ii) the introduction of pneumococcal conjugate and rotavirus vaccines in 2009 [30], resulting in better prognoses for sick children and decreased pressure on health services



District	Admission mortality rate (95% CI)	Number of deaths
a. West Coast	1.15 (0.42-2.5)	6
b. Cape Winelands	1.19 (0.63-2.02)	13
c. City of Cape Town	0.52 (0.35-0.74)	29
d. Overberg	2.95 (1.48-5.28)	11
e. Garden Route	0.77 (0.28-1.67)	6
f. Central Karoo	1.91 (0.23-6.89)	2



Sub-district	Admission mortality rate (95% CI)	Number of deaths
a. Western	1.03 (0.41-2.11)	7
b. Southern	0.35 (0.04-1.25)	2
c. Klipfontein	0.38 (0.05-1.36)	2
d. Northern	0.44 (0.05-1.58)	2
e. Tygerberg	0	0
f. Mitchells Plain	0.47 (0.13-1.19)	4
g. Khayelitsha	0.59 (0.16-1.51)	4
h. Eastern	0.87 (0.38-1.72)	8

Fig. 3 Admission mortality rates per 1000 live births (95% confidence interval) and number of deaths mapped to child's residence using the combined de-duplicated dataset and population estimates as the denominator for the four infectious disease deaths of interest in 2019 by **a** all Western Cape districts and **b** the City of Cape Town sub-districts. 2019 death and population data were used, as this was the last pre-pandemic year and data thereafter are confounded by several pandemic related factors

due to a reduction in admissions, thus resulting in better outcomes, and/or iii) the improvement of services by standardising clinical governance through systems like Child PIP and child death reviews [12, 13, 31]. When comparing across districts within the Western Cape, childhood mortality is significantly higher in the Overberg and Central Karoo districts in 2019. Within the City of Cape Town, mortality varies across sub-districts likely driven mainly by socioeconomic inequities including access to health care. This geographic difference is consistent with nationally reported pneumonia mortality, which is made available annually [27, 28, 32].

Strengths and limitations

This study was strengthened by the availability of comprehensive individual-level electronic health data with known causes of death. These study outcomes should enable policy makers and clinicians to better understand in-facility mortality due to infectious diseases over time and across geographies in the province using the de-duplicated, integrated dataset. In addition, the list of ICD-10 codes was comprehensive to ensure we were able to identify as many infectious disease hospitalisations and deaths as possible, allowing us to better understand the burden of disease in the community.

This study has several limitations. Firstly, only in-facility deaths were included based on the design and data availability. To understand the complete picture of child mortality, out-of-facility deaths would need to be included as well, however we did not have access to any data sources beyond DN for out-of-facility deaths. Secondly, we do not know if any in-facility deaths are missing as we were fully reliant on electronic capture of admissions and deaths. We believe that reporting of in-facility deaths may be more complete in recent years due to increases in networking of hospitals over time and the reduction in deaths is an underestimate, as a greater proportion of all deaths were reported electronically in more recent years. Thirdly, some errors in diagnostic coding are likely. However, this was mitigated as most primary diagnoses were coded by a registrar or consultant rather than a data clerk. Fourthly, the ICD-10 codes entered electronically were not verified against the in-facility written patient folders. We believe the impact of this was limited given: (i) diagnostic coding has been shown to be better in deceased children [8] and (ii) there was a high level of agreement of cause of death, particularly for diarrhoea and LRTI, when compared to the Child PIP and DN Surveillance. Fifthly, we did not have Child PIP and DN Surveillance

for the entire time period of the study, which may result in infectious diseases being missed in RHIS, if they were identified as infectious in Child PIP or DN Surveillance. However, we believe this was mitigated by improved diagnostic coding in recent years and among children who die. Finally, the approach and results from comparing death data may not be generalisable beyond the Western Cape for several reasons: the Western Cape has different health information systems to other provinces and countries, many of which have not or only partially implemented a unique patient identifier. There may be differential practices for diagnostic coding and different case definitions across provinces for national reporting, and routinely collected data quality may be suboptimal.

Conclusion

Our study demonstrated decreasing admission mortality rates across the province over time, with plateauing in recent years and good agreement of RHIS cause of death data with the more accurate child death audit and DN data, particularly for LRTI and diarrhoea. This validates the use of routine data systems such as the RHIS data in the Western Cape to understand mortality on a regular cadence, and highlights the importance of strengthening the collection and curation of this data. Nonetheless, routine health service data is strengthened by integrating with data from additional sources such as child death audit systems and DNs, emphasizing the value of both vital registration and routine child death audits. Data on cause of death from death certificates including out-of-facility deaths should be made available to health services so that they can accurately monitor child health and the outcomes of the services they deliver. Additionally, this approach of using RHIS or similar data systems and integrating different sources of death data could be extensible to other infectious and/or non-infectious diseases and/or populations in the Western Cape or other settings where data are either already available or can be strengthened and integrated.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-023-08012-6.

Additional file 1: Table S1. List of International Classification of Diseases 10th Revision (ICD-10) codes used for infectious disease coding.

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Author contributions
KK, MAD, MTR, BE and HEJ conceptualized the research study. KK was responsible for the data management with assistance from NZ and AH. KK was responsible for data cleaning, statistical analyses and the initial draft manuscript. All authors reviewed, revised, read and approved the final manuscript.

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Availability of data and materials
The data that support the findings of this study are available from the Western Cape Provincial Health Data Centre, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available, however, from the corresponding author upon reasonable request and with permission of the Western Cape Provincial Health Data Centre.

Declarations

Ethics approval and consent to participate
This study was approved and conducted using all relevant guidelines and regulations by the Human Research Ethics Committee in the Faculty of Health Sciences at the University of Cape Town (HREC REF 197/2021). Patients contributing data to the Western Cape Provincial Health Data Centre do not explicitly consent, as these data are utilised to directly support patient care. For this research project, informed consent was waived by the Human Research Ethics Committee in the Faculty of Health Sciences at the University of Cape Town as only anonymised data was utilised to protect individuals.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Publisher's Note

10.3 Chapter 5 appendix

Lower respiratory tract infection admissions and deaths among children under 5 years in public sector facilities in the Western Cape Province, South Africa, before and during the COVID-19 pandemic (2019 – 2021).

Lower respiratory tract infection admissions and deaths among children under 5 years in public sector facilities in the Western Cape Province, South Africa, before and during the COVID-19 pandemic (2019 - 2021)

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Background. The COVID-19 pandemic resulted in the implementation of strict public health and social measures (PHSMs) (including mobility restrictions, social distancing, mask-wearing and hand hygiene), limitations on non-essential healthcare services, and public fear of COVID-19 infection, all of which potentially affected transmission and healthcare use for other diseases such as lower respiratory tract infections (LRTIs).
Objective. To determine changes in LRTI hospital admissions and in-facility mortality in children aged <5 years in the Western Cape Province during the pandemic.
Methods. We conducted a retrospective analysis of LRTI admissions and in-facility deaths from January 2019 to November 2021. We estimated changes in rates and trends of LRTI admissions during the pandemic compared with pre-pandemic period using interrupted time series analysis, adjusting for key characteristics.
Results. There were 36 277 children admitted for LRTIs during the study period, of whom 58% were male and 51% were aged 28 days - 1 year. COVID-19 restrictions were associated with a 13% step reduction in LRTI admissions compared with the pre-COVID-19 period (incidence rate ratio (IRR) 0.87, 95% confidence interval (CI)) 0.80 - 0.94). The average LRTI admission trend increased on average by 2% per month during the pandemic (IRR 1.02, 95% CI 1.02 - 1.04).
Conclusions. The COVID-19 surges and their associated measures were linked to declining LRTI admissions and in-facility deaths, likely driven by a combination of reduced infectious disease transmission and reduced use of healthcare services, with effects diminishing over time. These findings may inform future pandemic response policies.

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The COVID-19 pandemic and subsequent responses by both the South African (SA) government and the population resulted in many changes impacting disease transmission, access to healthcare services, and population mobility.[1,2] Changes were driven by a combination of public fear of COVID-19 infection, restricted provision of non-essential health services and the introduction of strict public health and social measures (PHSMs),[2] aimed at curbing the spread of SARS-CoV-2 and ensuring sufficient hospital capacity for COVID-19 admissions.

Based on core indicators of COVID-19 burden such as case numbers and hospitalisations, PHSMs, first introduced on 26 March 2020, were either relaxed or tightened nationally. PHSMs included physical distancing, restrictions on non-essential services, remote working and closures of schools and early childhood development centres.[2] Additional practices such as mask-wearing, using of alcohol-based sanitisers and promotion of handwashing were implemented throughout the pandemic.[2,3] The Western Cape Government Department of Health and Wellness (WCGHW) kept primary healthcare services, including childhood immunisation, operational. However, they intentionally de-escalated certain healthcare services by postponing elective surgery, reducing routine clinic appointments and increasing duration of drugs dispensed to increase capacity to treat COVID-19 patients. All of these factors, combined with the fear of acquiring COVID-19 at healthcare facilities, likely impacted both the transmission and healthcare service use for other infectious diseases such as non-COVID-19 lower respiratory tract infections

(LRTIs). To effectively plan for future pandemic responses, it is important to evaluate the impacts on LRTI morbidity and mortality that, prior to COVID-19, persisted across SA in children aged <5 years with pronounced seasonality in the early winter months (March/April - June).[4,5]

We aimed to assess the changes in number and rates of LRTI hospital admissions and in-facility mortality among children aged <5 years in relation to COVID-19 surges and associated measures, including PHSMs, in public sector facilities in the Western Cape Province from January 2019 to November 2021.

Methods

Setting and study population

The mid-year population estimate for the Western Cape Province in 2022 was ~7.2 million, of which ~8% (586 201) were children aged <5 years.[6] About 75% of the population access public sector healthcare, but this proportion among children <5 years is likely higher (around 80%).[7] We included hospitalisation data for all children aged <5 years who were hospitalised or died from LRTIs at Western Cape public sector facilities from January 2019 to November 2021.

Data sources and variables

We developed a consolidated dataset from the data sources described below, aggregating data by location and calendar month. Within the Western Cape, the public sector healthcare services are geographically distributed into one metropolitan and five rural districts. The metropolitan district services ~66% of the population,[6] and for this analysis we further grouped data into the eight health subdistricts.

LRTI hospital admissions and in-facility deaths

We identified LRTI hospital admissions and in-facility deaths using a dataset derived from three data sources available in the Western Cape Provincial Health Data Centre (WCPHDC): routine health information systems (RHIS);[7] Child Problem Identification Programme (Child PIP);[8,9] and Death Notification (DN) Surveillance.[10] This dataset is described in detail elsewhere.[11] Briefly, the dataset leveraged all available International Classification of Diseases 10th Revision (ICD-10) codes at discharge to identify LRTI hospital admissions. ICD-10 coding practices improved during the pandemic, with higher completeness when compared with pre-pandemic. The cause of in-facility LRTI deaths was determined using the cause of death recorded in Child PIP or DN Surveillance if available, or a proxy cause of death from RHIS based on ICD-10 admission code.

Population estimates

The Western Cape population estimates are based on the 2022 mid-year estimates from Statistics South Africa at district level, projected at subdistrict level using the ratio method.[6]

COVID-19 PHSMs

The first PHSM implementation occurred shortly after the first imported COVID-19 case was identified in SA, when COVID-19 cases and admissions were still low. During subsequent COVID-19 waves, stricter PHSMs were implemented at the onset of or during COVID-19 waves when the number of cases/admissions were highest nationally and/or healthcare services were under severe pressure. PHSMs were relaxed during inter-wave periods. The PHSMs and implementation dates are summarised in Table S1 (appendix https://www.samedical.org/file/2172). Briefly, more stringent PHSMs included restrictions of movement within and into the country; reduced social interactions through curfews, closures of schools, early childhood development centres and other institutions, and wearing of masks and face coverings.[2] There was also widespread provision of alcohol-based sanitisers and promotion of hand-washing.[2,3] These PHSMs could have impacted the spread of COVID-19, as well as other infections.

The analysis period extends to November 2021, 2 months after the end of the final wave that caused major pressure on healthcare services. There was no further increase in stringency of PHSMs thereafter. The analysis thus concluded at the last implementation (relaxation) of PHSMs.

Data analysis

We described characteristics of children who were either admitted or died in facilities due to LRTIs during different time periods: the entire study period (January 2019 - November 2021), pre-pandemic (January 2019 - March 2020) and COVID-19 pandemic (April 2020 - November 2021). Characteristics described included sex, age, admission severity and COVID-19 coinfection. Medians and interquartile ranges (IQRs) were used for continuous variables, and frequencies and proportions for categorical variables.

We described how LRTI admission rates, admission mortality rates and case fatality rates (CFRs) changed across time periods. LRTI admission rates were estimated for each time period by dividing LRTI admissions by 80% of the population estimates for children <5 years (representing the estimated proportion accessing public sector healthcare services). Rates are presented per 1 000 person months with 95% confidence intervals (CIs). We also estimated mortality rates with 95% CIs including: (*i*) admission mortality rates per 100 000 live births (number of LRTI in-facility deaths divided by the number of live births documented in the province) and (*ii*) CFRs (number of LRTI in-facility deaths divided by total LRTI admissions).

To assess the association between COVID-19 surges and associated factors, including PHSMs, and LRTI admissions more formally, we conducted an interrupted time series analysis[12] using negative binomial segmented regression applied to monthly level data and allowing for both a level and trend change. We applied random effects for location to account for differences in access to healthcare across locations. Time was measured in calendar months and divided into pre-COVID-19 (January 2019 - March 2020) and COVID-19 (April 2020 - November 2021) periods. The COVID-19 period was further divided based on changes in PHSMs, including alternating periods of stricter and eased measures: April - August 2020, September - December 2020, January - February 2021, March - June 2021, July - September 2021 and October - November 2021. A separate model was fitted to each pair of restriction periods to assess changes in LRTI related to each change in restriction level. Incidence rate ratios (IRRs) and 95% CIs were reported for the step change, trend change and the post-interruption trend for each model comparison. The step change refers to the shift in LRTI admissions immediately post-PHSM introduction compared to immediately pre-PHSM. The trend change represents the ratio of the trend in LRTI admissions over time after PHSM implementation v. the trend before PHSM. The post-interruption trend is the trend per calendar month in LRTI admissions in the period after PHSM implementation.

The model adjusted for several aggregated variables deemed potential confounders (limited by data availability), including proportion male, median age of LRTI admission, median duration of LRTI admission, quarterly proxy immunisation coverage, COVID-19 confirmed admissions and seasonality (measured in quarters: January - March, April - June, July - September, October - December) to account for autocorrelation. Proxy immunisation coverage was calculated quarterly by dividing the number of fully immunised children aged <1 year by the previous year's <1 year population (to represent a

proxy eligible cohort), adjusted for quarterly live births from the WCPHDC (which records live births in all public sector facilities). The number of children fully immunised with the expanded programme of immunisation (EPI) vaccines was extracted from the District Health Information System (January 2019 - December 2021).[7] Vaccines included in the EPI are polio, tuberculosis, rotavirus, diphtheria, tetanus, pertussis, *Haemophilus influenzae* type B, hepatitis B and pneumococcus.[5] COVID-19 cases and admissions were used to as a proxy for service pressure measured by people with a laboratory-confirmed COVID-19 diagnosis (positive SARS-CoV-2 PCR or antigen test), irrespective of symptoms. We did not consider COVID-19 cases based on clinical diagnosis only, nor on multisystem inflammatory syndrome in children unless there was a corresponding positive SARS-CoV-2 test. COVID-19 cases and admissions included the number of new diagnoses, irrespective of whether these were first or subsequent infections. We conducted a sensitivity analysis excluding children co-infected with COVID-19 during LRTI admission to assess potential impact on LRTI admission rates.

To assess what would have happened to LRTI admission rates under the expected seasonality pattern had the pandemic and its associated factors not occurred, we also modelled the pre-COVID-19 period alone. We used the estimated relationship between covariates and outcome to forecast counterfactual LRTI admission rates for the pandemic period. This pre-pandemic period model included the same variables as the full model, with the exception of COVID-19 cases and the interruption variable. Observed, model-predicted and counterfactual LRTI admission rates per 1 000 person months were plotted.

Data cleaning and coding were performed in SQL (ISO/IEC JTC 1, Switzerland), while data linkage and aggregation were done in R Studio 2022.12.0 (Rstudio, USA), and analysis in Stata 17.0 (StataCorp, USA).

Ethical approval

This study was approved by the Human Research Ethics Committee in the Faculty of Health Sciences at the University of Cape Town (ref. no. HREC REF 197/2021).

Results

Characteristics of LRTI admissions and in-facility deaths in children

Of 36 277 children admitted for LRTIs for the entire study period, most were male (*n*=21 118, 58%) and aged 28 days - 1 year (*n*=18 496, 51%), with 2% (*n*=679) of LRTI admissions including a period in an intensive care unit (ICU) (Table 1). The distribution of these characteristics for LRTI hospital admissions were similar during the pre-COVID-19 and COVID-19 periods. Among children who died from LRTIs in facility, the median age at death was 6.8 months (IQR 3.6 - 19.3 months) pre COVID-19 and 5.6 months (IQR 1.9 - 16.1 months) during the pandemic period. The median time from admission to death was 6 days (IQR 1 - 16 days) pre-COVID-19 and 3.5 days (IQR 1 - 10 days) during COVID-19.

Daily LRTI admissions and COVID-19 cases

During stricter PHSMs, which were implemented prior to the COVID-19 peaks, LRTI admissions were at the lowest levels (Fig. 1). The pre-pandemic early-winter surge (April - June) in LRTI admissions shifted to later in the year after the onset of COVID-19 PHSMs.

Rates of LRTI admissions and in-facility deaths across PHSM periods

LRTI admission rates lowered from 13.20 LRTI admissions per 1 000 person months (95% CI 13.01 - 13.39) pre-pandemic to 9.94 LRTI admissions per 1 000 person months (95% CI 9.80 - 10.09) during COVID-19 overall (Table 2). During the first and strictest implementation of PHSMs, the admission rate lowered from pre-COVID-19 to 6.48 LRTI admissions per 1 000 person months (95% CI 6.25 - 6.72) (Table 2). During the period of PHSMs relaxation, (second and fourth implementation) the average LRTI admission rates were higher than the preceding period, except for the sixth implementation, where LRTI admission rates remained similar.

There was a slight decrease in LRTI admission mortality rates: 42.72 deaths per 100 000 live births (95% CI 31.60 - 56.47) in the pre-pandemic period to 38.79 deaths per 100 000 live births (95% CI 29.74 - 49.72) in the pandemic period overall (Table 2). The pattern of fluctuations in LRTI admission rates with PHSMs was not observed in LRTI admission mortality rates. There was a decrease during the first (the strictest) and the fourth (a relaxation) implementation of PHSMs. The CFRs followed a similar pattern to the admission mortality rates; however, the highest CFR (0.53%, 95% CI 0.21 - 1.01) was observed during the third implementation (tightening of restrictions) of PHSMs.

Interrupted time series model: Changes in LRTI admissions in relation to PHSMs

After adjusting for potential confounders, we estimated that the COVID-19 period was associated with a 13% (IRR 0.87, 95% CI 0.80 - 0.94) step reduction in LRTI admissions v. pre-COVID-19 (Table 3), followed by an increase in average trend of 2% per month (IRR 1.02, 95% CI 1.02 - 1.04). Analysing different periods of PHSM implementation revealed that the initial (strictest) implementation of PHSMs was associated with the greatest step drop in LRTI admissions (IRR 0.62, 95% CI 0.52 - 0.73), followed by an 8% average increase per month (IRR 1.08, 95% CI 1.03 - 1.14). Generally, step increases were associated with PHSM easing. There was a diminishing step change effect over time, with no evidence of change for the last PHSM implementation. Similar step and trend changes were observed when COVID-19 co-infected cases were excluded from the analysis (appendix Table S2).

Counterfactual and estimated LRTI admission rates

Predicted counterfactual LRTI admission rates during the first PHSM implementation based on the assumption of no PHSM effect were higher than observed rates through the initial period following the first PHSM measures (Fig. 2). Subsequently, observed and counterfactual LRTI admission rates were similar at longer durations post interruption.

Discussion

Our study demonstrated how the effects of the COVID-19 pandemic, including PHSMs co-occurring service de-escalation and fear of accessing healthcare services, impacted LRTI admissions and in-facility deaths in public healthcare facilities in the Western Cape, SA. Overall, the greatest reductions were associated with stricter PHSMs, with greatest declines in LRTI admissions noted as PHSMs were first introduced. Early on, in-facility LRTI admission mortality rates decreased when more stringent PHSMs were in place. However, increases in CFRs were observed with reductions of LRTI admissions, generally during stricter PHSMs.

Previous studies in other low- and middle-income settings have reported similar findings,[13,14] indicating that PHSM changes impacted LRTI admission rates among children, with the greatest reductions temporally associated with stricter PHSMs. However, determining the extent to which these reductions were influenced by decreased transmission from school closures, social distancing and improved hygiene practices v. reduced healthcare use due to mobility restrictions and/or fear is difficult, as these factors often occurred simultaneously. Nonetheless, because PHSMs were implemented nationwide in

Table 1. Characteristics of children who were admitted for or died from a lower respiratory tract infection in a public sector facility in the Western Cape Province before and during COVID-19 (January 2019 - November 2021)

Characteristic	Overall (January 2019 - November 2021)	Pre-COVID-19 (January 2019 - March 2020)	COVID-19 (April 2020 - November 2021)
LRTI admissions			
Total admissions	36 277	17 539	18 738
Male, *n* (%)	21 118 (58)	10 246 (58)	10 872 (58)
Female, *n* (%)	15 169 (42)	7 293 (42)	7 866 (42)
Age			
Median age (months, IQR)	9.6 (3.5 - 20.5)	9.7 (3.7 - 20.3)	9.5 (3.4 - 20.8)
<28 days, *n* (%)	2 144 (6)	967 (6)	1 177 (6)
28 days - 1 year, *n* (%)	18 496 (51)	9 037 (51)	9 459 (51)
>1 year - <5 years, *n* (%)	15 637 (43)	7 535 (43)	8 102 (43)
Admission severity			
ICU admissions, *n* (%)	679 (2)	299 (2)	380 (2)
Median length of stay (days, IQR)	2 (1 - 4)	2 (1 - 4)	2 (1 - 4)
COVID-19 coinfection, *n* (%)	n/a	0	320 (2)
LRTI deaths			
Total deaths	111	49	62
Male, *n* (%)	55 (50)	22 (45)	33 (53)
Female, *n* (%)	56 (50)	27 (55)	29 (47)
Age			
Median age (months, IQR)	6.4 (2.5 - 17.5)	6.8 (3.6 - 19.3)	5.6 (1.9 - 16.1)
<28 days, *n* (%)	18 (16)	6 (12)	12 (19)
28 days - 1 year, *n* (%)	54 (49)	23 (47)	30 (50)
>1 year - <5 years, *n* (%)	39 (35)	20 (41)	19 (31)
Admissions severity			
ICU admissions, *n* (%)	56 (50)	24 (49)	32 (52)
Median time from admission to death (days, IQR)	4 (1 - 10)	6 (1 - 16)	3.5 (1 - 10)
COVID-19 coinfection, *n* (%)	N/A	0	1 (2)

LRTI = lower respiratory tract infection; IQR = interquartile range; ICU = intensive care unit.

Table 2. Admission rates, admission mortality rates and case fatality rates for children who were admitted owing to LRTIs in public sector facilities in the Western Cape Province pre-COVID-19 and during COVID-19 (January 2019 - November 2021)

Period	LRTI admissions, *n*	Admission rate per 1 000 person months (95% CI)	LRTI deaths	Admission mortality rate per 100 000 live births (95% CI)	Case fatality rate (95% CI)
Pre-COVID (January 2019 - March 2020)	17 539	13.20 (13.01 - 13.39)	49	42.72 (31.60 - 56.47)	0.28 (0.21 - 0.37)
COVID-19 (April 2020 - November 2021	18 738	9.94 (9.80 - 10.09)	62	38.79 (29.74 - 49.72)	0.33 (0.25 - 0.42)
First implementation of PHSMs (April - August 2020)*	2 976	6.48 (6.25 - 6.72)	11	26.35 (13.15 - 47.14)	0.37 (0.18 - 0.66)
Second implementation of PHSMs (September - December 2020)†	4 283	11.66 (11.31 - 12.01)	14	43.67(23.88 - 73.26)	0.33 (0.18 - 0.55)
Third implementation of PHSMs (January - February 2021)*	1 315	6.84 (6.48 - 7.21)	7	46.71 (18.78 - 96.22)	0.53 (0.21 - 1.01)
Fourth implementation of PHSMs (March - June 2021)†	5 294	13.77 (13.40 - 14.14)	11	34.10 (17.02 - 61.01)	0.21 (0.10 - 0.37)
Fifth implementation of PHSMs (July - September 2021)*	2 876	9.97 (9.61 - 10.34)	12	50.06 (25.87 - 87.43)	0.42 (0.22 - 0.73)
Sixth implementation of PHSMs (October - November 2021)†	1 944	10.37 (9.92 - 10.83)	7	47.20 (18.98 - 97.23)	0.35 (0.14 - 0.72)

LRTI = lower respiratory tract infection; CI = confidence interval; PHSMs = public health and social measures.
*Tightening of PHSMs.
†Relaxation of PHSMs.

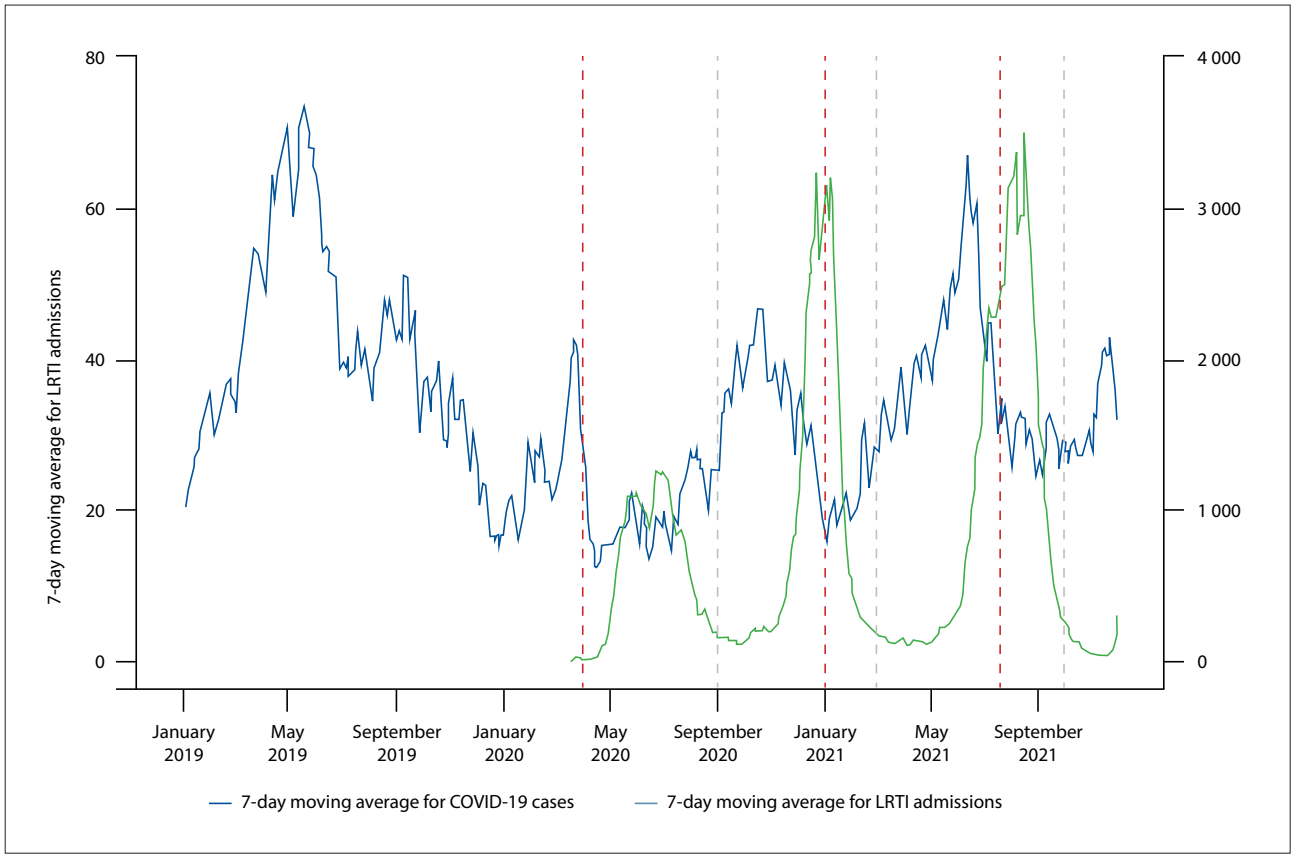

Fig. 1. Daily lower respiratory tract infection (LRTI) admissions among children <5 years and all COVID-19 cases (7-day moving average) from January 2019 to November 2021. The red lines indicate the stricter implementation of public health and social measures (PHSMs), whereas the grey lines indicate the relaxation of PSHMs. Stricter implementation of PHSMs included restrictions on population mobility and closure of schools, early childhood development centres and other institutions. COVID-19 cases reflect both public and private sector recorded positive SARS-CoV-2 PCR and antigen tests, irrespective of symptoms.

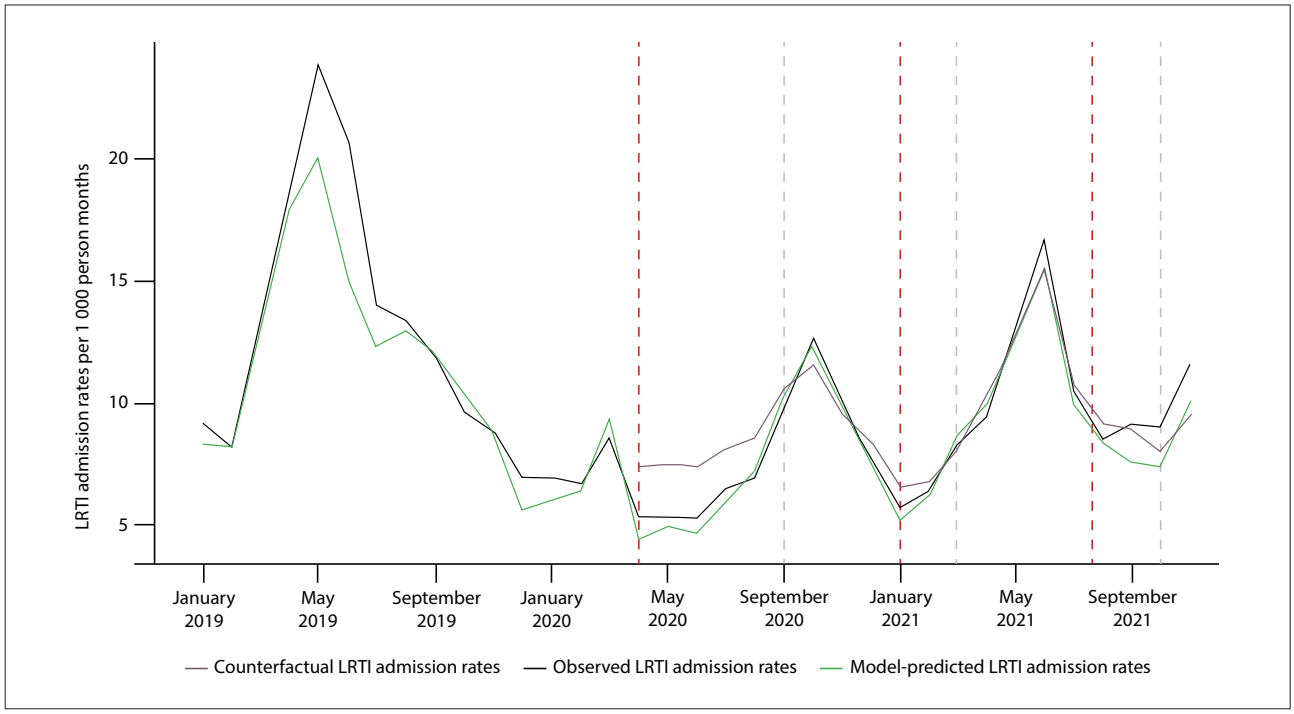

Fig. 2. Counterfactual, observed and model-predicted rates of lower respiratory tract infection (LRTI) hospitalisations among children in the Western Cape (January 2019 - November 2021). The red lines indicate the stricter implementation of public health and social measures (PHSMs), whereas the grey lines indicate the relaxation of PHSMs. Stricter implementation of PHSMs included restrictions on population mobility and closure of schools, early childhood development centres and other institutions.

Table 3. Changes in LRTI admissions among children <5 years after the implementation of different COVID-19 public health and social measures in public sector facilities in the Western Cape Province, South Africa (January 2019 - November 2021) overall and for the different restriction periods each relative to the previous period

	Entire period	Different restriction periods based on PHSMs compared with the immediate preceding period					
Characteristic	COVID-19 vs pre-COVID-19	First implementation of PHSM v. pre-COVID-19*	Second v. first implementation of PHSMs†	Third v. second implementation of PHSMs*	Fourth v. third implementation of PHSMs†	Fifth v. fourth implementation of PHSMs*	Sixth v. fifth implementation of PHSMs†
Interruption							
Time period	January 2019 - November 2021	January 2019 - August 2020	April - December 2020	September 2020 - February 2021	January - June 2021	March - August 2021	July - November 2021
Interruption	April 2020	April 2020	September 2020	January 2021	March 2021	July 2021	October 2021
Model output							
Step change (IRR, 95% CI)	0.87 (0.80 - 0.94)	0.62 (0.52 - 0.73)	1.12 (0.95 - 1.30)	0.85 (0.73 - 1.01)	1.02 (0.72 - 1.46)	0.95 (0.70 - 1.29)	1.02 (0.88 - 1.19)
Trend change (IRR, 95% CI)	1.03 (1.02 - 1.04)	1.10 (1.05 - 1.15)	0.85 (0.77 - 0.94)	1.36 (1.09 - 1.69)	0.90 (0.62 - 1.30)	0.95 (0.83 - 1.07)	1.12 (0.96 - 1.30)
Average post-interruption trend (IRR per month, 95% CI)	1.02 (1.01 - 1.02)	1.08 (1.03 - 1.14)	0.92 (0.85 - 1.00)	1.17 (0.99 - 1.40)	1.08 (0.98 - 1.18)	0.96 (0.88 - 1.04)	1.08 (0.95 - 1.21)

LRTI = lower respiratory tract infection; PHSMs = public health and social measures; IRR = incidence rate ratio; CI = confidence interval.
* Tightening of public health and social measures
† Relaxation of public health and social measures

SA, whereas the timing of the worst COVID-19 healthcare service admission pressure varied by province, we could examine the impact of PHSMs independently from the effect of facilities being overburdened by COVID-19 admissions. The change in childhood LRTI admission patterns, preceding the COVID-19 admission peak and coinciding with the adjustment of PHSM stringency, suggests that reduced admissions were not due to reduced healthcare access driven by overburdened healthcare facilities. Rather, our findings indicate that PHSMs and resulting behavioural shifts influenced disease transmission. Additionally, the interplay of PHSMs and fear of contracting COVID-19 at healthcare facilities affected healthcare utilisation.

Behaviour changes due to COVID-19 PHSMs (social distancing, mask wearing, hand hygiene practices and healthcare use) disrupted the previously established seasonal pattern of an autumn/winter LRTI admission peak, potentially altering immunity to LRTI pathogens, with children being less exposed to LRTIs at younger ages. Similar shifts in seasonality for LRTI admissions have been observed in other settings.[13-15]

Despite decreases in children <5 years dying across SA during COVID-19, pneumonia remained one of the main causes of death.[15,16] Children dying from LRTIs during COVID-19 were generally younger, with shorter admission-to-death time v. pre-pandemic. This suggests that either more severely ill children sought healthcare during the pandemic, or there were challenges in accessing healthcare in the context of PHSMs, potentially leading to worsened illness severity upon presentation. Admission mortality rates were overall slightly lower in the pandemic v. pre-pandemic, consistent with findings in other SA facilities.[13] It is possible that the proportion of out-of-facility mortality increased during this time, but we were unable to evaluate this as our study was limited to in-facility mortality. We observed fluctuations in LRTI admission rates each time the PHSMs were altered. The highest CFRs and admission mortality rates largely coincided with increased service pressure during COVID-19 waves as well as reductions in mobility due to tightening of PHSMs and/or fear of transmission during COVID-19 waves. Caution should be exercised when interpreting these findings, as CFRs are sensitive to the number of admissions, and the lowest number of LRTI admissions occurred during this time.

This study was strengthened by using individual-level data for the aggregation, allowing us to have linked admission and mortality outcomes of children, informed by data linkage within the WCPHDC.[11] We had data for the entire Western Cape Province for both time periods, increasing the generalisability of these findings. We used a comprehensive list of ICD-10 codes to identify LRTI admissions and in-facility deaths, ensuring thorough case identification. Mapping LRTI admissions and deaths to a child's residence helped identify the burden of severe illness in the community.

This study had several limitations. Aggregated monthly data sometimes grouped PHSM implementations in the same month, addressed by selecting the closest month for analysis. Out-of-facility deaths were inaccessible, which may have increased owing to healthcare access challenges in the context of PHSMs. We relied solely on electronic health records; however, we believe that electronic data completeness was high and, if anything, increased in more recent years and during the pandemic, which would have resulted in underestimating the PHSM-associated reductions in LRTI admissions and deaths. We only had LRTI admissions, not all cases, hindering our understanding of the full impact of COVID-19 surges and the associated factors. We were only able to adjust for socioeconomic status using the subdistrict or district of the child's residence as a crude proxy. Data variables were limited by availability.

Hospital data and population estimates reflected the child's residence, whereas immunisations, live births and COVID-19 data represented healthcare service locations. Population estimates, the denominator to calculate rates, are based on an assumption of the percentage of children reliant on public sector services. A different assumption may alter the rates themselves, but would not impact estimated changes over time.

Conclusion

COVID-19 surges and changes in stringency of COVID-19 PHSMs were associated with temporal reductions in LRTI admissions and deaths, albeit with impacts diminishing over time. This is likely due to a combination of social distancing and hand hygiene measures directly impacting LRTI transmission, as well as decreased population mobility and hesitancy/fear reducing access to healthcare services. The lowest levels of LRTI admissions coincided with the strictest PHSMs, rather than with COVID-19 wave peaks. This suggests that the changing pattern of LRTI admissions was not due to the COVID-19 pandemic nor high COVID-19 service pressure crowding out paediatric LRTI admissions, but could be due to direct impacts of PHSMs on respiratory pathogen transmission, as well as reduced mobility and fear reducing healthcare access. These findings can be used to inform policies for responses to future pandemics.

Declaration. This study will form part of KK's PhD.

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Author contributions. KK conceptualised the research study with guidance from MAD, MTR, SRW, HEJ and BE. KK was responsible for the data management with assistance from NZ and AH. KK was responsible for data cleaning, statistical analyses and the initial draft manuscript. SRW, HEJ, BE, MAD and MTR supervised data analysis. All authors (KK, EM, TJ, NZ, AH, JRM, HB, SRW, BE, HEJ, MTR and MAD) reviewed, revised and approved the final manuscript.

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Conflicts of interest. None.

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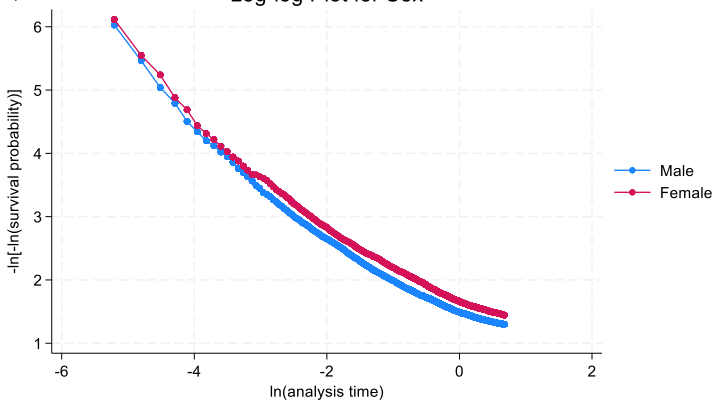
Table S5.1. Changes in lower respiratory tract infection admissions among children aged under five years after the implementation of different COVID-19 public health and social measures in public sector facilities in the Western Cape, South Africa (January 2019 – November 2021) overall (column headed "Entire period") and for the different restriction periods each relative to the previous period (subsequent columns) among children who were not co-infected with COVID-19 during their LRTI admission. Bold values indicate point estimates with 95% confidence intervals that exclude the null value.

	Entire period	**Different restriction periods based on PHSM compared with the immediate preceding period**					
	COVID-19 versus pre-COVID-19	**First implementation of PHSM versus pre-COVID-19 ***	**Second versus first implementation of PHSM****	**Third versus second implementation of PHSM***	**Fourth versus third implementation of PHSM****	**Fifth versus fourth implementation of PHSM***	**Sixth versus fifth implementation of PHSM****
Interruptions							
Time period	Jan 2019 – Nov 2021	Jan 2019 – Aug 2020	Apr – Dec 2020	Sept 2020 – Feb 2021	Jan – June 2021	Mar – Aug 2021	Jul – Nov 2021
Interruption	Apr 2020	Apr 2020	Sept 2020	Jan 2021	Mar 2021	Jul 2021	Oct 2021
Model output							
Step change (IRR, 95% CI)	**0.86 (0.79-0.94)**	**0.62 (0.52-0.73)**	1.12 (0.96-1.32)	0.85 (0.72-1.00)	0.99 (0.69-1.41)	0.92 (0.68-1.25)	1.02 (0.87-1.19)
Trend change (IRR, 95% CI)	**1.03 (1.02-1.04)**	**1.10 (1.05-1.16)**	**0.85 (0.76-0.94)**	**1.41 (1.13-1.76)**	0.86 (0.59-1.25)	0.95 (0.84-1.08)	1.13 (0.97-1.31)
Average post-interruption trend (IRR, 95% CI)	**1.02 (1.01-1.02)**	**1.09 (1.03-1.14)**	0.92 (0.85-1.00)	**1.21 (1.02-1.44)**	1.07 (0.97-1.17)	0.97 (0.89-1.05)	1.08 (0.96-1.22)

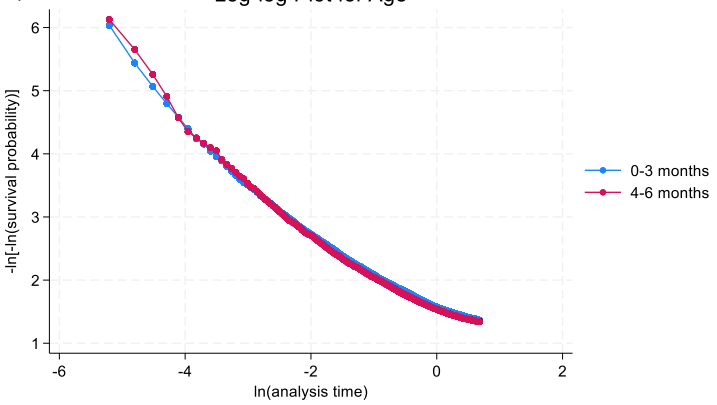
CI: confidence intervals; IRR: incidence rate ratios; LRTI: lower respiratory tract infection; PHSM: public health and social measures.
* Tightening of public health and social measures
** Relaxation of public health and social measures

10.4 Chapter 7 appendix

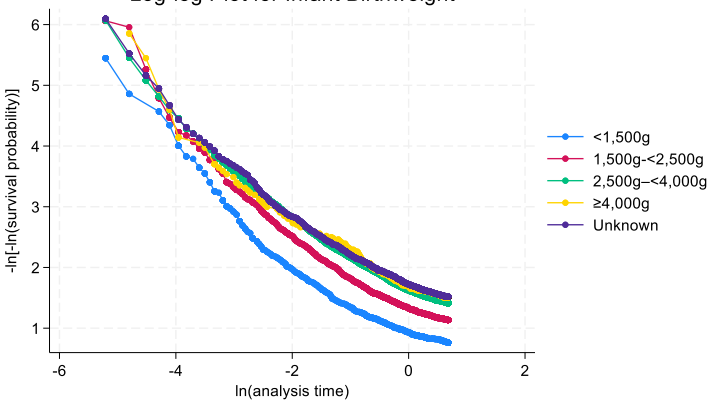
a)



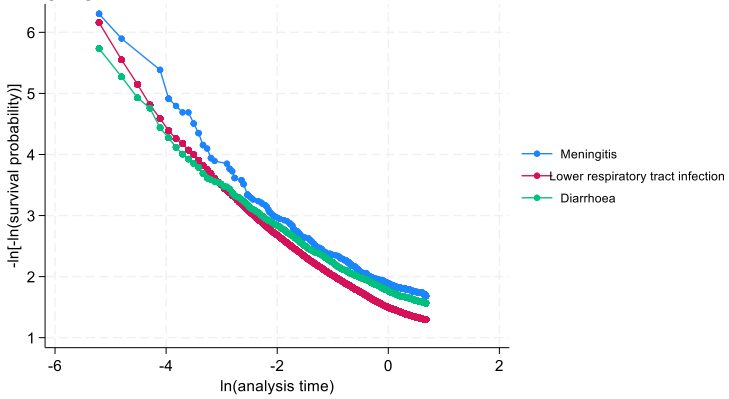
b)



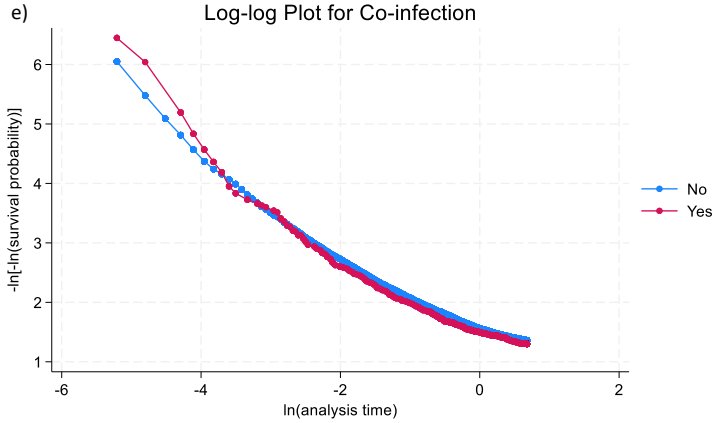
c)



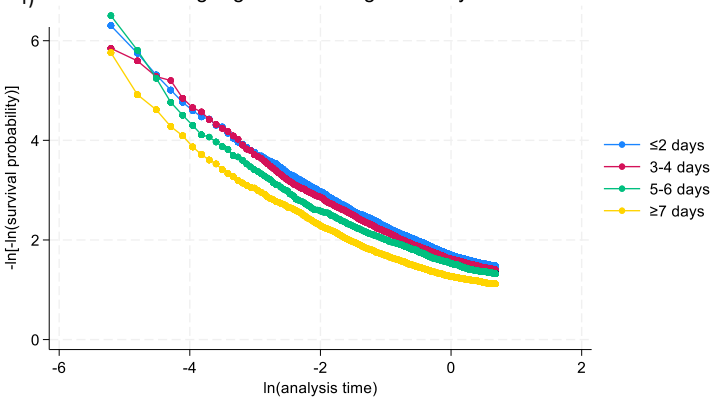
d)



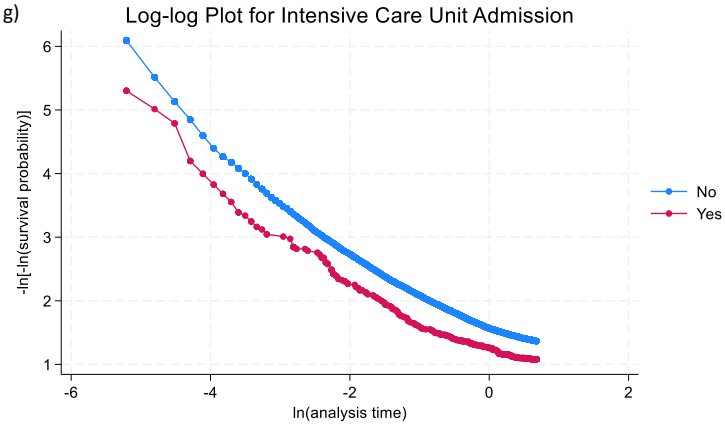
e)



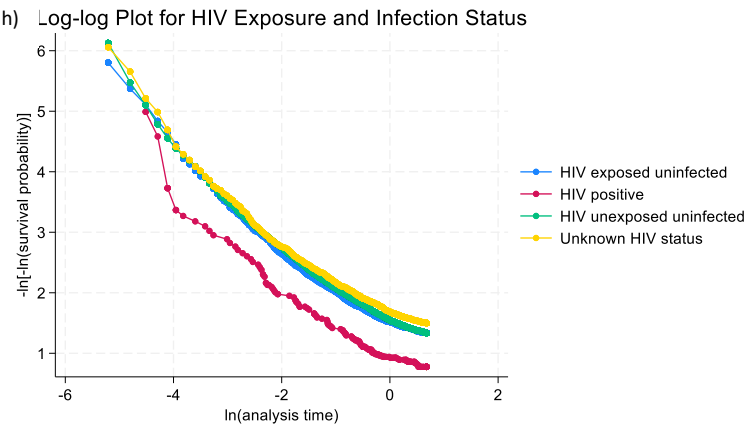
f)



g)



h)



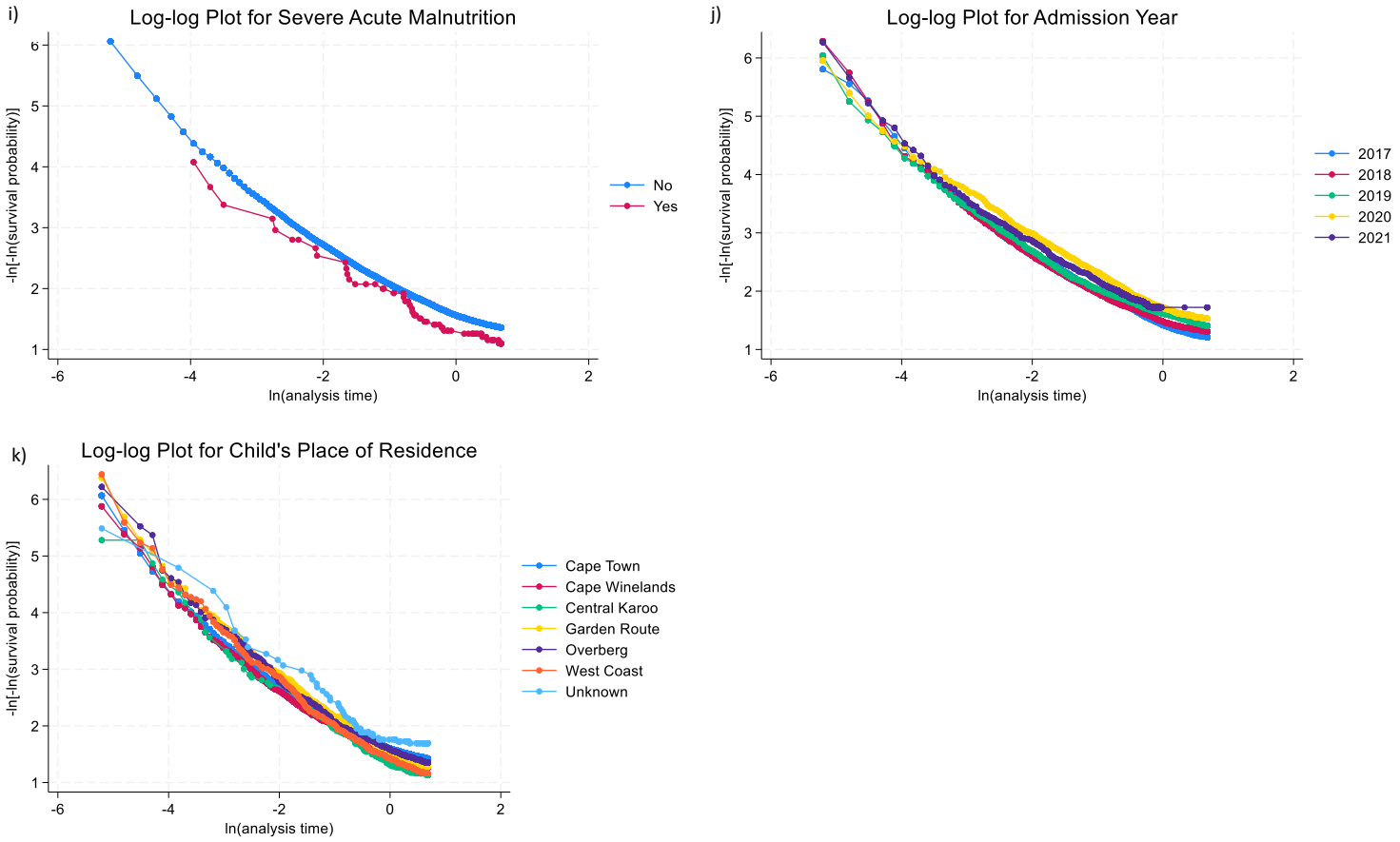


Figure S7.1. Log-log plots for all covariates included in the Cox Proportional Hazards model: a) sex, b) age, c) infant birthweight, d) infectious disease hospitalisation, e) co-infection, f) length of stay, g) intensive care unit admission, h) HIV exposure and infection status, i) severe acute malnutrition, j) child's district of residence, and k) admission year.

Table S7.1. Schoenfield residuals for all covariates included in the Cox Proportional Hazards model.

		Rho	Chi^2	Degrees of freedom	Probability > Chi^2
Sex	Male	-0.03299	6.25	1	0.0124
	Female	.	.	1	.
Age	0-3 months	.	.	1	.
	4-6 months	-0.02733	4.42	1	0.0356
Infant birthweight	<1,500g	-0.02066	2.49	1	0.1147
	1,500g – 2,499g	-0.01436	1.2	1	0.2743
	2,500g – 3,999g	.	.	1	.
	≥4,000g	-0.00375	0.08	1	0.7765
	Unknown	0.02128	3.02	1	0.082
Infectious disease hospitalisation cause	Meningitis	.	.	1	.
	Lower respiratory tract infection	-0.01069	0.65	1	0.4209
	Diarrhoea	-0.0172	1.68	1	0.1951
Co-infection	Yes	0.00487	0.14	1	0.7132
Length of stay	≤2 days	.	.	1	.
	3-4 days	-0.01185	0.81	1	0.3683
	5-6 days	-0.03624	7.54	1	0.0061
	≥7 days	-0.07551	34.33	1	0
Intensive care unit admission	Yes	-0.00545	0.17	1	0.6782
HIV exposure and infection status	HIV exposed uninfected	-0.02163	2.67	1	0.1021
	HIV positive	-0.00195	0.02	1	0.8821
	HIV unexposed uninfected	.	.	1	.
	Unknown HIV status	-0.03501	8.15	1	0.0043
Severe acute malnutrition	Yes	0.01842	1.95	1	0.1622
Admission year	2017	0.01657	1.56	1	0.211
	2018	-0.01328	1.01	1	0.3145
	2019	-0.00717	0.29	1	0.5871
	2020	0.01267	0.92	1	0.3373
	2021	.	.	1	.

		Rho	Chi²	Degrees of freedom	Probability > Chi²
Child's district of residence	Cape Winelands	0.01299	0.97	1	0.3257
	Central Karoo	0.01729	1.71	1	0.1907
	City of Cape Town	0.02042	2.39	1	0.1221
	Garden Route	0.02979	5.09	1	0.0241
	Overberg	0.02126	2.59	1	0.1076
	West Coast	0.02781	4.43	1	0.0354
	Unknown	.	.	1	.
	Global test		**122.87**	**27**	**0**

Table S7.2. Crude and adjusted hazard ratios* stratified by age to assess the association between repeat infectious disease admissions and characteristics at first infectious disease admission among children admitted within six months of life from January 2017 to June 2021, accounting for death as a competing risk. Hazard ratios and 95% confidence intervals bolded do not include the null value.

	0-3 months		4-6 months	
	Univariable model hazard ratio (95% CI)	**Multivariable model adjusted hazard ratio (95% CI)**	**Univariable model hazard ratio (95% CI)**	**Multivariable model adjusted hazard ratio (95% CI)**
Sex				
Female	1.0	1.0	1.0	1.0
Male	**1.18 (1.11-1.26)**	**1.21 (1.13-1.29)**	**1.13 (1.03-1.24)**	**1.14 (1.04-1.26)**
Infant birthweight				
<1,500g	**1.77 (1.55-2.02)**	**1.62 (1.41-1.86)**	**2.35 (1.99-2.80)**	**2.06 (1.73-2.45)**
1,500g – 2,499g	**1.31 (1.20-1.43)**	**1.26 (1.15-1.37)**	**1.39 (1.22-1.58)**	**1.30 (1.15-1.49)**
2,500g – 3,999g	1.0	1.0	1.0	1.0
≥4,000g	0.91 (0.74-1.13)	0.92 (0.74-1.13)	0.94 (0.69-1.28)	0.93 (0.69-1.26)
Unknown	**0.88 (0.81-0.96)**	0.84 (0.71-1.00)	0.95(0.84-1.07)	1.05 (0.83-1.32)
Infectious disease hospitalisation cause				
Meningitis	1.0	1.0	1.0	1.0
Lower respiratory tract infection	**1.40 (1.18-1.65)**	**1.54 (1.30-1.82)**	**1.73 (1.22-2.45)**	**1.83 (1.30-2.60)**
Diarrhoea	**1.23 (1.03-1.48)**	**1.44 (1.19-1.73)**	1.04 (0.72-1.49)	1.17 (0.81-1.68)
Co-infection				
No	1.0	1.0	1.0	1.0
Yes	1.04 (0.89-1.21)	1.05 (0.90-1.22)	1.11 (0.91-1.35)	0.97 (0.79-1.19)
Length of stay				
≤2 days	1.0	1.0	1.0	1.0
3-4 days	1.04 (0.96-1.14)	**1.05 (0.97-1.14)**	**1.17 (1.05-1.31)**	**1.15 (1.03-1.29)**
5-6 days	**1.16 (1.05-1.27)**	**1.16 (1.05-1.27)**	**1.26 (1.07-1.48)**	**1.21 (1.03-1.43)**
≥7 days	**1.40 (1.29-1.52)**	**1.36 (1.24-1.49)**	**1.80 (1.58-2.05)**	**1.70 (1.47-1.96)**
Intensive care unit admission				
No	1.0	1.0	1.0	1.0
Yes	**1.33 (1.12-1.58)**	1.08 (0.90-1.29)	**1.52 (1.04-2.21)**	1.17 (0.79-1.74)
HIV exposure and infection status				
HIV exposed uninfected	**1.19 (1.07-1.33)**	1.02 (0.94-1.11)	1.15 (0.98-1.35)	0.96 (0.84-1.09)
HIV positive	**2.07 (1.60-2.67)**	**1.61 (1.25-2.09)**	**2.08 (1.48-2.93)**	1.36 (0.96-1.93)
HIV unexposed uninfected	1.0	1.0	1.0	1.0
Unknown HIV status	**1.15 (1.06-1.26)**	1.04 (0.87-1.24)	**1.20 (1.07-1.36)**	0.82 (0.64-1.05)
Severe acuate malnutrition				
No	1.0	1.0	1.0	1.0
Yes	1.56 (0.89-2.75)	1.29 (0.72-2.29)	1.08 (0.69-1.70)	0.84 (0.53-1.34)

*Adjusted for: sex, age, infant birthweight, infectious disease hospitalisation, co-infection, length of stay, intensive care unit admission, HIV exposure and infection status, severe acute malnutrition, child's district of residence, and admission year.