**UNIVERSITY OF THE WESTERN CAPE**

**Faculty of Community and Health Sciences**

**MINI-THESIS**

# Estimating the Impact of the COVID-19 pandemic on Tuberculosis in Cape Town, South Africa

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A mini-thesis submitted in partial fulfilment of the requirements for the degree of Masters of Public Health in the Department of Community and Health Sciences, School of Public Health, University of Western Cape.



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**Keywords/phrases**

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care cascade

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post-treatment loss

treatment success

routine health data

Cape Town

**Acronyms and Abbreviations**

| | |
|---|---|
| CCT | City of Cape Town Health Department |
| COVID-19 | Coronavirus disease of 2019 |
| DR-TB | Drug-resistant tuberculosis |
| DS-TB | Drug-susceptible tuberculosis |
| HIV | Human Immunodeficiency Virus |
| ILTF | Initial loss to follow-up |
| $IMPAC_{19}T_B$ | Epidemiological impact and intersection of the COVID-19 and tuberculosis pandemics in Brazil, Russia, India and South Africa |
| LF-LAM | Lateral flow urine lipoarabinomannan assay |
| LTF | Loss to follow-up |
| NDoH | National Department of Health |
| NICD | National Institute for Communicable Diseases |
| NHLS | National Health Laboratory Services |
| PHC | Primary health care |
| PHDC | Provincial Health Data Centre |
| PLHIV | People Living with HIV |
| PTL | Post-treatment loss |
| SARS-CoV-2 | Severe Acute Respiratory Syndrome Coronavirus 2 |
| TB | Tuberculosis |
| TUTT | Targeted Universal Testing for TB |
| UWC BMREC | University of the Western Cape Biomedical Research Ethics Committee |
| WCGH | Western Cape Government Health Department |
| WHO | World Health Organisation |

## Definition of key terms

### Drug-susceptible tuberculosis (DS-TB)

DS-TB is drug-susceptible TB (alternatively called drug-sensitive tuberculosis). It is tuberculosis which is bacteriologically or clinically diagnosed, and in which there is no evidence of infection with strains resistant to first line medication (such as rifampicin) (World Health Organization, 2022).

### Drug-resistant tuberculosis (DR-TB)

DR-TB is tuberculosis which has been found to be resistant to one or more of the first line medications (such as rifampicin) (World Health Organization, 2020a).

### Initial loss to follow-up (ILTF)

ILTF is the loss of people who are diagnosed with TB but for whom there is no evidence of having started TB treatment at a site of TB registration and notification. ILTF includes people who die between diagnosis and treatment, those who never access treatment at a notification site for other reasons, and those who access treatment, but are not recorded as having done so.

In Cape Town TB registration and notification takes place at designated treatment facilities at primary health care level and at 2 specialist TB hospitals, but not at other hospitals (Osman et al., 2021). This means that ILTF includes some people who may have had some treatment for TB at hospital level, but never linked to a registration and notification site.



In this mini-thesis the definition of ILTF was expanded from how others have defined "pre-treatment loss to follow-up" (MacPherson et al., 2014) and ILTF (Naidoo et al., 2017), with the important addition that individuals with clinically diagnosed TB were included due to the available data source (not only individuals with bacteriologically confirmed TB).

### Post-treatment loss (PTL)

PTL is the loss of people who initiate treatment but who do not successfully complete TB treatment. Similarly to the components of ILTF, PTL includes people who die between initiating treatment and treatment success, people who are lost from TB care for other reasons, and people

who successfully complete treatment, but are not recorded as having done so. In this mini-thesis, post-treatment loss was abbreviated to PTL.

**Abstract**

**Background**

Tuberculosis (TB) is responsible for major morbidity and mortality globally. Gains made to end TB in the decade 2010 to 2019 have been at a pace which is predicted to be insufficient to reach global 2035 TB targets. A new disease, Coronavirus Disease of 2019 (COVID-19), was declared a pandemic in 2020 and is impacting directly and indirectly on health, including TB, with fears and early evidence that it could significantly set back the efforts to end TB.

**Aim**

The aim of this study was to estimate losses along the TB care cascade pre- and during-COVID-19 in Cape Town, a metropolitan district in South Africa with high TB and COVID-19 disease burdens.

**Methodology**

This was a quantitative study comparing two retrospective virtual cohorts using routinely collected public health service data. The sample population was all individuals diagnosed with TB in Cape Town from 1 July 2018 to 31 December 2021 (n = 90 345), as consolidated in the Western Cape Provincial Health Data Centre (PHDC). DS-TB care cascades were constructed for two predefined 12-month periods: pre-COVID-19 (1 October 2018 - 31 September 2019, n = 27 481) and during-COVID-19 (1 April 2020 - 31 March 2021, n = 19 800). The cascades included three pillars: people diagnosed with TB (pillar one) who were notified and treated for TB (pillar two) and who were successfully treated (pillar three), as well as between-pillar losses of initial loss to follow-up (ILTF) and post-treatment loss (PTL). The pillars and between-pillar losses in the pre-and during-COVID-19 cascades were compared and the cascade outcomes were examined for association with age, sex, HIV status, category of TB, mode of diagnosis and health sub-district.

**Results**

In the pre-COVID-19 DS-TB cascade the number of people diagnosed with TB was 27 481, ILTF was 13.4%, PTL was 25.2% and treatment success was 64.8%. Treatment success was

associated with age, HIV status, category of TB, mode of diagnosis and sub-district, but not with sex.

There was a substantial drop in the number of people diagnosed with DS-TB in the annual period following the onset of the COVID-19 pandemic (from 27 481 to 19 800, a 28% drop). The losses in the DS-TB cascade increased in the annual period following the onset of the COVID-19 pandemic, with ILTF increasing by 1.8% to 15.2% and PTL increasing by 0.9% to 26.1%, resulting in an overall fall in treatment success from 64.8% to 62.7%.

**Conclusion**

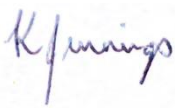
The DS-TB cascade revealed a very large burden of TB disease in Cape Town, as has been previously documented. Pre-existing substantial losses across the DS-TB cascades between diagnosis and treatment success increased following the advent of COVID-19. A data-informed response to mitigate the negative effects and strengthen possible positive effects of the COVID-19 pandemic on TB, building on prior work to end TB, could include improving the implementation of current interventions as well as developing new approaches to close gaps in the TB care cascade. Further research is needed, particularly to explain the large decrease in the number of people diagnosed with TB.

**Declaration**

I declare that ***Estimating the Impact of the COVID-19 pandemic on Tuberculosis in Cape Town, South Africa*** is my own work, that it has not been submitted for any degree or examination in any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

Full name: Karen Ann Jennings

Date: 20 March 2023

Signed: 

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- My loving and supportive family

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# Chapter 1: Introduction

This chapter gives some background to the TB and COVID-19 pandemics and the intersection of the two. It then describes the research problem, purpose, aims and objectives and overall outline of this mini-thesis.

## 1.1 Background

### 1.1.1 Tuberculosis

Tuberculosis (TB) is an infectious disease, caused by the bacterium *Mycobacterium tuberculosis*, which has long been responsible for major morbidity and mortality. In 2019 an estimated 10 million people developed TB and there were over 1 million deaths, predominantly in low and middle income countries (LMIC) (World Health Organization, 2020a).

Efforts to end TB have met with some success; there were global reductions in TB mortality and morbidity in the decade 2010 to 2019, but probably insufficient to be on track to reach the ambitious 2035 targets set in 2015 in the "End-TB strategy" (World Health Organization, 2014; Uplekar et al., 2015; Floyd et al., 2018; Strong et al., 2020). The momentum to achieve the End-TB targets was given further (political) support with commitment to action in a United Nations High Level Meeting to "end TB by 2030" (World Health Organization, 2018), echoing Sustainable Development Goal 3.3, to end the tuberculosis epidemic (as well as AIDS, malaria and neglected tropical diseases) by 2030 (United Nations, 2015).

South Africa is one of eight high-TB-burden countries which collectively account for two-thirds of the world's total of TB (World Health Organization, 2020a). To reach the 2035 End-TB incidence and mortality targets, of a 95% reduction in deaths and 90% reduction in incidence compared to the baseline of 2015, it is estimated that South Africa would need to decrease from an estimated annual TB incidence rate of 834 per 100 000 population and approximately 100 000 TB deaths in 2015 to an incidence rate of 83 per

100 000 population and 4 900 TB deaths (Naidoo et al., 2017). As interim and stepping stone targets, South Africa adopted Stop TB's targets of "90-90-90" in the National Strategic Plan for HIV, TB and STIs 2017–2022, i.e. aiming to diagnose and treat 90% of those with TB, including 90% of high-risk and vulnerable populations with TB, and successfully treat 90% of people with drug-sensitive TB (DS-TB) (South African National AIDS Council, 2017; Stop TB Partnership, 2017).

Previously identified challenges in reaching targets include gaps in biomedical interventions, such as the need for better TB diagnostics and shorter course treatment and preventive therapy for both DS and drug- resistant TB (DR-TB), and also health system issues such as poor and inequitable access to health care. In addition, social determinants of health such as poor living and working conditions, and risk factors for TB such as HIV infection, malnutrition, diabetes, smoking and alcohol abuse, fuel the epidemic (Reid et al., 2019; Chakaya, Harries & Marks, 2020). A new challenge is Coronavirus Disease of 2019 (COVID-19).

### 1.1.2 COVID-19

A new threat to ending TB is the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first identified in December 2019 (Huang et al., 2020). The subsequent escalation of COVID-19, the disease caused by SARS-CoV-2, was declared a pandemic by the World Health Organization (WHO) at a media briefing on 11 March 2020 (World Health Organization, 2020b). Globally, as of 11 November 2022, there have been 630 832 131 confirmed cases and 6 584 104 COVID-19 reported deaths (World Health Organization, n.d.).

In South Africa, the first case of COVID-19 was reported on 5 March 2020 and as of 5 November 2022 a total of 4 030 563 laboratory-confirmed COVID-19 cases have been reported (National Institute for Communicable Disease, 2020, 2022). An estimate of excess deaths from 5 May 2020 to 3 September 2022, based on expected deaths modelled from historical data, was 329 100 (Bradshaw et al., 2022). Previous reports put the proportion of excess deaths attributable to COVID-19 at 85 to 95%, with the balance

being due to “collateral” causes, such as the health service being overwhelmed during COVID-19 waves (Moultrie et al., 2021). Similarly to other countries which experienced the COVID-19 pandemic ahead of South Africa, a “level 5 lockdown” with “drastic measures to contain the spread of the virus and save lives” was implemented in South Africa, initially for 3 weeks from 26 March 2020, then extended until 1 May 2020, under a National State of Disaster (Presidency of the Republic of South Africa, 2020a,b). Level 5 lockdown included severe restrictions on people’s movement, such that “every person is confined to his or her place of residence, unless strictly for the purpose of performing an essential service, obtaining an essential good or service, collecting a social grant, pension or seeking emergency, life-saving, or chronic medical attention” (South African Government, 2021a). Subsequently, with extensions of the National State of Disaster and according to measured COVID-19 trends and health system capacity during the waves of COVID-19, the level of lockdown was adjusted amongst levels 4 to 1 of lockdown, until it was completely lifted on 5 April 2022 (South African Government, 2022a). Mask wearing in public became mandatory on 1 May 2020 and this regulation was in place until it was lifted on 22 June 2022 (South African Government, n.d.).

### 1.1.3 Intersection of TB and COVID-19

The WHO Director-General Dr Tedros Adhanom Ghebreyesus’ message in the annual Global TB Report 2020 was that, on top of pre-existing gaps in ending TB, the COVID-19 pandemic “threatens to unwind the gains made [in ending TB] over recent years” (World Health Organization, 2020a: v). This is true globally, but even more so in high-TB-burden countries such as South Africa, which will have tragic consequences for TB-related morbidity and mortality. In April 2021 the Premier of the Western Cape in South Africa, as co-chairperson of the multi-sector Provincial Council of AIDS & TB, launched an emergency response plan to address TB. The press release issued for the launch noted that routine Western Cape health data comparing April 2019 with April 2020 showed an over 50% decline in the number of TB tests done and the number of people diagnosed with TB, with mixed and partial recovery in TB screening, testing and diagnosis in subsequent months (South African Government, 2021b). More recently, at a national level, a “TB Recovery Plan” has been launched by the Department of Health and the TB

Think Tank (a "collective of experts, academics, researchers and civil society advocates who guide the country's TB response") (Bailey, 2022).

## 1.2 Problem statement

There were global and local reductions in TB mortality and morbidity in the years preceding the COVID-19 pandemic, but insufficient to reach targets to "end TB by 2030" (World Health Organization, 2018). It is feared that the effect of the COVID-19 pandemic on TB will have worsened this situation, for instance the number of people diagnosed with TB in 2020 vs. 2019 dropped globally by 18% and in South Africa by 26% (Dheda et al., 2022). The epidemiological impact of COVID-19 on TB at the population level has not been well documented, particularly at sub-national levels and there is a need to add empiric evidence (Sahu et al., 2021).

## 1.3 Purpose

The purpose of the study was to determine the impact of COVID-19 on TB in Cape Town. It was part of Objective 1 of a study entitled the "Epidemiological impact and intersection of the COVID-19 and tuberculosis pandemics in Brazil, Russia, India and South Africa ($IMPAC_{19}T_B$)", which aims to estimate in each country at the national level, and where possible the sub-national level, the "differential losses along the TB care cascade attributable to COVID-19" (Appendix 1). As part of Objective 1, this mini-thesis study aimed to estimate these losses in Cape Town, a metropolitan district in the Western Cape Province of South Africa, with high TB and COVID-19 disease burdens. The Western Cape has a data centre which, since 2015, has consolidated public sector health data from different sources using a unique patient identifier (Boulle et al., 2019), thus providing an opportunity for research enhanced by access to comprehensive data. Identifying how the TB care cascade has been impacted (which is feared to be negatively, but possibly also positively impacted in some ways) could help focus a health system data-informed response to the effects of the COVID-19 pandemic on TB.

## 1.4 Aim and objectives

The aim of the study was to describe the pattern of drug-sensitive tuberculosis **(**DS-TB) diagnosis, notification and treatment, and treatment success, and to compare the losses along this DS-TB care cascade in the public health sector in Cape Town, South Africa, prior to and during the COVID-19 pandemic. The objectives were:

1. To compile a pre-COVID-19 and a during COVID-19 DS-TB care cascade.
2. To conduct an analysis of losses along the DS-TB care cascades (pre-COVID-19 and during COVID-19) disaggregated by sex, age, HIV status, category of TB, mode of diagnosis and health sub-district.
3. To compare the DS-TB care cascade outcomes pre-COVID-19 to during COVID-19.

## 1.5 Outline of the mini-thesis

Chapter one has given some background to the TB and COVID-19 pandemics and the intersection of the two. It further outlined the research problem, purpose, aims and objectives. Chapter two is a literature review, providing international and national context to the research problem and elaborating the TB care cascade framework. Chapter three describes the research design and methodology, including the study setting and data collection, cleaning and analysis, as well as ethical considerations. The results of the study are presented in Chapter four and the study findings and strengths and limitations of the study are discussed in Chapter five. In the concluding chapter, chapter six, the study findings are summarised and recommendations are put forward for interventions, practice, policy and further research.

# Chapter 2: Literature Review

In this chapter, to locate this mini-thesis study within the arena of already published literature on the research topic, first the literature describing the theoretical epidemiological impact of COVID-19 on TB is reviewed, followed by sections on empirical evidence and strategies to mitigate the negative effects of COVID-19 on TB. Finally, the literature describing the TB care cascade conceptual tool, which informs the methodology of this study, is explored.

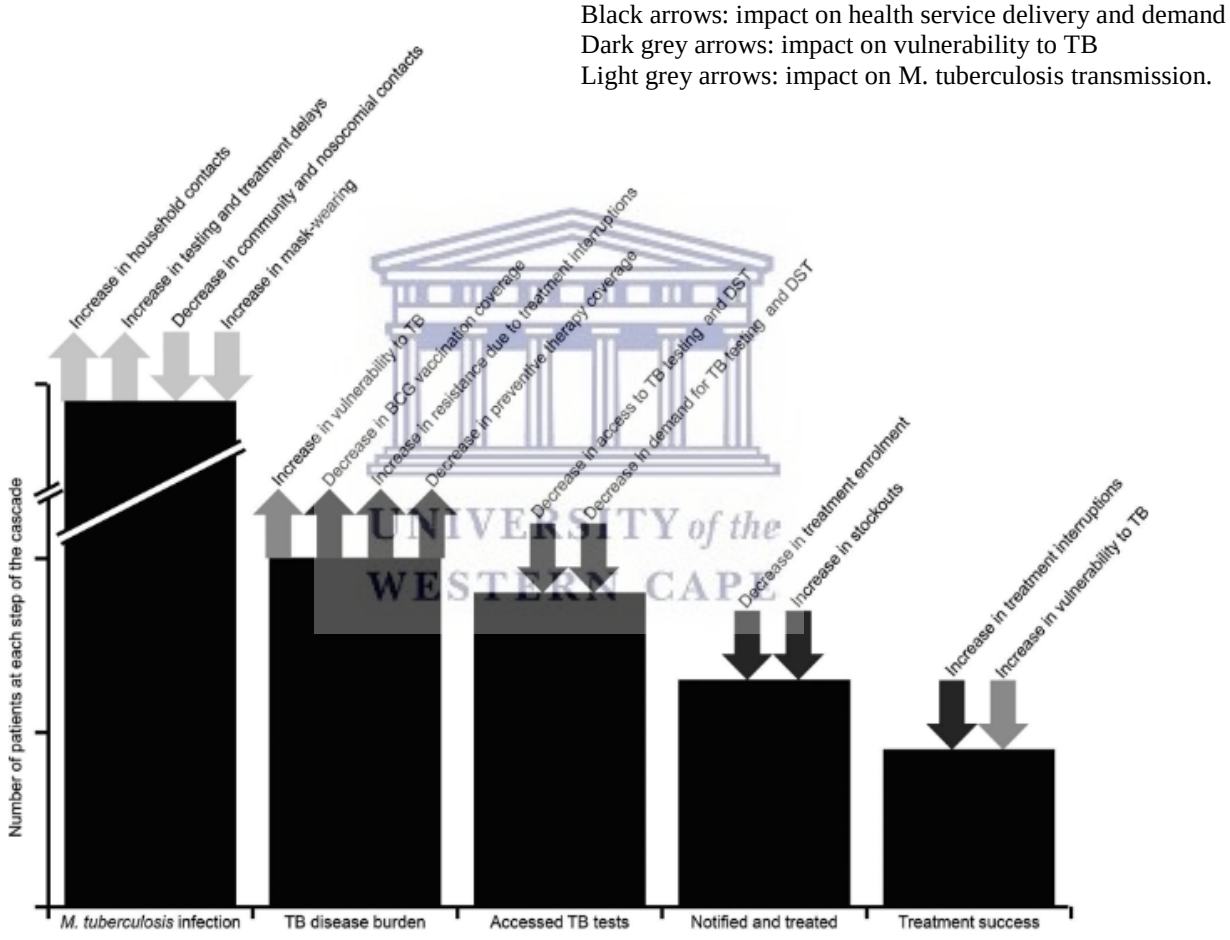
## 2.1 Theoretical epidemiological impact of COVID-19 on TB

As the COVID-19 pandemic spread across the globe in 2020 a number of publications highlighted potential for an overall negative impact on TB (Boffa et al., 2020; Togun et al., 2020). However, it was also argued that some aspects of TB prevention and care could be positively impacted. For instance, mask wearing to prevent COVID-19 transmission could decrease the transmission of TB (Van den Driessche et al., 2021). A letter to a journal editor to mark World TB Day pointed out the complexity of possible clinical and epidemiological interactions of COVID-19 with TB, including possible decreased transmission of TB due to COVID-19 related self-isolation and quarantine, but possible increased transmission of TB due to COVID-19 related respiratory symptoms (Wingfield et al., 2020). Similarly, a modelling study noted the complexity of possible beneficial effects on TB transmission of lockdowns and social distancing, but increased TB transmission if health system disruptions resulted in lower and slower TB case detection. The model predicted a decrease in global TB case detection of 25% over a period of 3 months with a 13% increase in TB deaths (Glaziou, in press). Another modelling study found that the potential benefit of social distancing on TB incidence may result in lower incidence in settings with low health service disruption, but that deaths would increase in all scenarios which had some health service disruption (McQuaid et al., 2020). WHO predicted that the acute drop in case detection would result in an increase in mortality in 2020 globally, including in South Africa, which would take a few years to reach pre-pandemic baselines and that there would be a rebound increase in tuberculosis incidence (World Health Organization, 2021a).

As depicted in Figure 1 below, McQuaid et al (2021) put forward a conceptual framework for the possible effects of the COVID-19 pandemic on the TB care cascade, categorising the effects into three groups: "disruption to TB health service delivery and changes in demand, alterations in vulnerability to TB... and opportunities for Mycobacterium tuberculosis transmission" (McQuaid et al., 2021: 437).

**Figure 1. Potential impact of COVID-19 on the TB care cascade.**

As depicted in McQuaid et al, 2021(McQuaid et al., 2021: 437).




While theoretically these effects would collectively lead to an increase in TB disease burden and decreased treatment success, a more mixed picture is described for the possible effect on TB infection with suggested increases (due to an increase in household

contacts and increased delay in testing and treatment) or decreases (due to a decrease in community contacts and increase in mask- wearing).

The overriding concern has been for possible negative effects on TB prevention and care due to likely decreased access to diagnostic and treatment services for TB in health systems under pressure from COVID-19 (Dheda et al., 2022).

## 2.2 Epidemiological impact of COVID-19 on TB globally and locally

Decreased testing to diagnose TB and decreased case finding has been reported from different settings across the globe. Early in the COVID-19 pandemic a study on TB case finding in China comparing January to May 2019 with January to May 2020 showed decreases of 24%, 39%, 25%, 15% and 13% for each of the months respectively (Chen & Zhang, 2020). In South Africa, data from the National Institute for Communicable Disease (NICD) showed a 48% reduction in diagnostic TB testing in the initial lockdown period of 30 March - 7 April 2020 (Ismail & Moultrie, 2020). A study from South Africa analysing routine health service data showed a reduction in access to public health services between March 2020 and December 2020, including a drop of 31% in the Western Cape in primary health care headcount compared to the same period in the previous year, which the authors concluded resulted in decreased TB screening and case finding (Pillay et al., 2021).

With a longer period of hindsight, in the first of three papers in a 2022 Lancet Series on tuberculosis in the time of COVID-19, it is estimated that tuberculosis case detection in 2020 vs. 2019 dropped globally by 18% and in South Africa by 26% (Dheda et al., 2022). In countries supported by the Global Fund to fight AIDS, Tuberculosis, and Malaria, which include South Africa, there was a year-on-year decline in 2020 in key TB programme indicators, which was unprecedented since the inauguration of the fund in 2002 (Global Fund, 2022). The 2020:2021 indicators relating to finding and treating people with TB show some recovery of this impact of the COVID-19 pandemic on TB,

for instance the number of people treated for TB was 5.5 million in 2019, 4.5 million in 2020 and 5.2 million in 2021 (Global Fund, 2022).

The South African NICD data shows acute reductions in TB testing which coincide with each "lockdown" in 2020, illustrating the causative factor of reduced health care access and utilisation, as any effect on transmission would take longer to manifest, but this does not exclude the possibility of an effect on incidence over a longer period of time (Dheda et al., 2022). At the recent 7th South African TB conference (Foundation for Professional Development Conference & Special Events Department, 2022), TB testing data was presented by Dr Harry Moultrie, senior medical epidemiologist for geospatial modelling at NICD, showing that, at a national level, testing levels from September 2020 to November 2021 recovered to within the forecasted levels and thereafter exceeded forecasted levels (with forecasting based on pre-COVID-19 levels) (Moultrie, 2022). However, despite the increased testing volume, and contrary to the prediction by WHO (World Health Organization, 2021a), the NICD data does not show any "rebound" increase in the number of positive tests, raising questions of what may account for the "missing" TB cases, i.e. if this is an ongoing gap in identifying people with TB or reduced TB incidence (Moultrie, 2022).



The impact of the COVID-19 pandemic on TB treatment outcomes (of people with TB who initiated TB treatment) is starting to be reported in the literature, lagging behind the testing and case finding data, in keeping with the 6 or more months usual treatment duration and reporting and publishing lags. In Zimbabwe an operational research study, comparing monthly TB treatment outcome data in an annual period after the onset of the COVID-19 pandemic with the preceding year, found that treatment success dropped from 80.9 % to 69.3% (Thekkur et al., 2021). In Cape Town operational data from some primary health care facilities showed a drop in TB treatment success with increased post-treatment loss (PTL) (personal communication with J Taylor, TB programme manager, CCT, 10 September 2021).

## 2.3 Mitigating the effect of COVID-19 on TB in South Africa

At a national level in South Africa, a "TB Recovery Plan" to address the negative impact of COVID-19 on TB was launched by the Department of Health and the TB Think Tank (Bailey, 2022). The TB Recovery Plan is a transitional plan that will lead into the updated National Strategic Plan on HIV, TB and STIs for the period 2023-2028, including interventions which were already being considered and piloted which are now identified for quicker implementation (South African Government, 2022b). It includes enhanced diagnostic capabilities using targeted universal testing for TB (TUTT), the lateral flow urine lipoarabinomannan assay (LF-LAM) and digital chest X-ray (dCXR) and a publically focussed TB screening application (app) for mobile phones and other digital platforms. It also seeks to improve linkage to care and retention in care, by NICD sending results by short message service (sms) directly to people with a confirmed lab diagnosis of TB and more patient-friendly treatment regimens and medicine collection options (USAID, 2021).

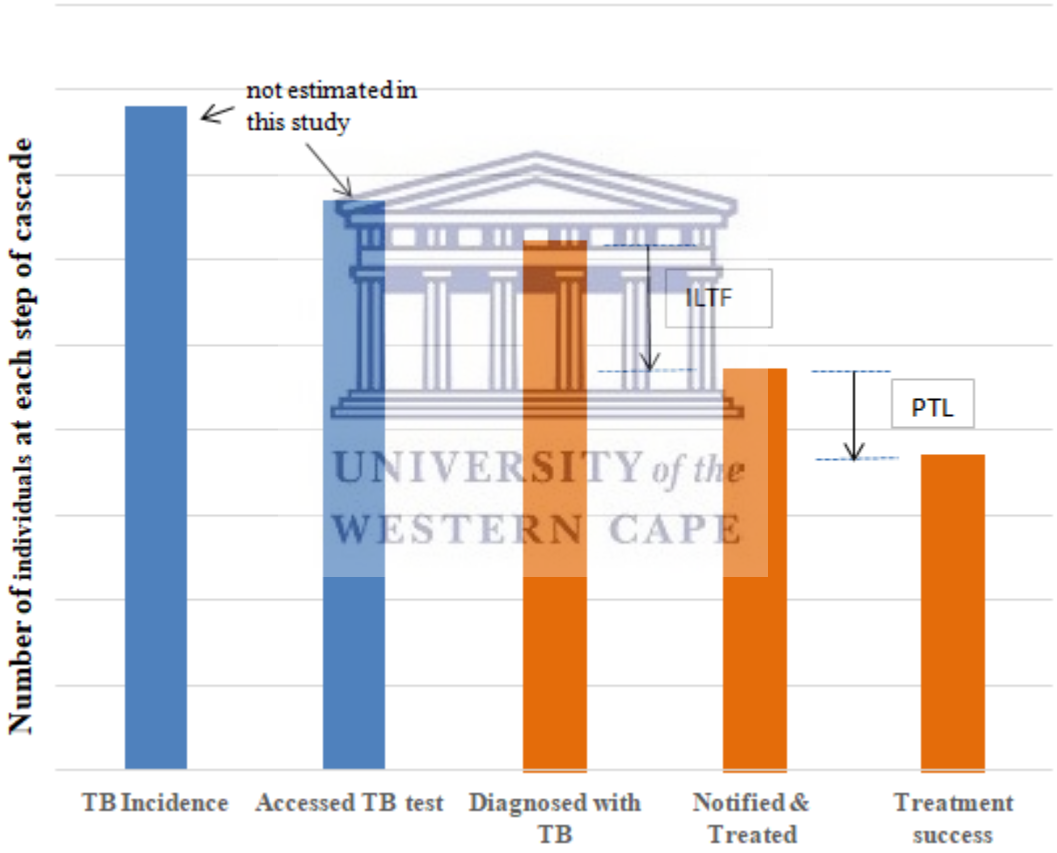
In the Western Cape the Provincial Council of AIDS & TB, a multi-sector body with a "whole of society" approach launched an emergency response plan to mitigate the negative impact of COVID-19 on TB (South African Government, 2021b). The expressed aim of the Western Cape Government Health Department of uninterrupted service delivery during COVID-19 for essential services such as TB and HIV was guided by a number of circulars, which also highlighted the potential for health system strengthening, such as by integrating screening for TB with COVID-19 (Western Cape Government Health, n.d.). However, as was experienced nationally (Pillay et al., 2021), decreased facility attendance headcounts in Cape Town were reported at primary care level at the onset of COVID-19, reducing the opportunity for identification of newly developed TB and usual TB care (personal communication with N Berkowitz, Epidemiologist, City of Cape Town Health Department, 6 July 2021).

## 2.4 TB care cascade: a conceptual tool

A care cascade is a conceptual tool which has been used to describe the continuum of care for a number of diseases, including TB, using routine health data and other secondary data to estimate pillars and losses in the cascade (Subbaraman et al., 2016, 2019; Naidoo et al., 2017; Lurie et al., 2020), as illustrated in Figure 2 below.

**Figure 2. TB care cascade: a conceptual tool.**

Adapted from Naidoo et al (2017) and Subbaraman et al (2019) (Naidoo et al., 2017; Subbaraman et al., 2019)






The first pillar of the TB care cascade is the number of individuals who develop TB in a specific population; the next pillar is the number of individuals who access TB testing; the next pillar is the number of individuals who are diagnosed; the next pillar is the number of individuals who are notified and treated; and the last pillar is the number of

individuals who are successfully treated. There are typically losses between each pillar, which represent individuals with suboptimal outcomes. The care cascade in a particular setting can inform programmatic efforts to close health system gaps to ultimately end TB (Naidoo et al., 2017; Subbaraman et al., 2019). The usual lens in national TB programmes of reporting treatment success of only individuals notified and treated for TB leads to under-recognition of the losses depicted in the preceding pillars of the cascade and across the whole cascade (Naidoo et al., 2017).

Naidoo et al's study on the TB care cascade in South Africa, analysing 2013 data, found that successful treatment of the estimated burden of TB of 532 005 (range 333 760 – 764 480) was only 53% (much lower than standard TB programme reporting), with losses at multiple points along the cascade (Naidoo et al., 2017). One of the methodological challenges in this study was estimating the burden of disease in the first pillar (resulting in a wide confidence interval), but subsequently the first South African national TB prevalence survey (in 2018), which showed a higher burden of pre-clinical TB than previously recognised, estimated a prevalence of 737 (95% CI 580-890) per 100 000 population (Moyo et al., 2021). Consequently, an updated TB care cascade in 2018 estimated the burden remaining at the high level of 390 000 (despite decreasing incidence in the preceding years). The biggest estimated loss was the "initial loss to follow- up" (ILTF) between diagnosis and starting treatment (76 247/311 899; 24.4%), while other losses were between estimated incidence and accessing TB testing (54 572/390 000; 14.0%), accessing a test and diagnosis (23 529/335 428; 7.0%) and treatment initiation and treatment success (49 649/235 652; 21.1%) (personal communication with Dr Pren Naidoo, consultant to the South African NDoH TB Think Tank, September 2021).

An operational research study between October 2018 and 31 March 2020 in two health sub districts in Cape Town (Khayelitsha and Tygerberg), using a care cascade approach, found an ILTF rate of 2 742/13 736; 20.0% for people diagnosed with DS-TB in hospital or at primary care level. Of all individuals who were ILTF 468/2 742; 17.1% had died, mostly within 30 days of diagnosis, and the majority (400/468; 85.5%) of these deaths occurred in patients diagnosed in hospital (Osman et al., 2021).

In conclusion, according to international and national literature there is evidence that pre-existing substantial gaps in the TB programme have increased during the COVID-19 pandemic. Using a conceptual tool, the TB care cascade, gaps can be quantified and visualised and inform programmatic efforts to close the gaps.

# Chapter 3: Research design and methodology

This chapter describes how the study's aims and objectives were achieved. It provides details of the study setting and design, as well as the sampling, data collection, cleaning and analysis. It also addresses validity and ethical considerations.

## 3.1 Study setting

Cape Town is the capital of the Western Cape Province, one of nine provinces in South Africa. Cape Town is one of six Western Cape districts (the Cape Metro District) and had an estimated population of 4.7 million people in 2021, which is 66% of the provincial total (Western Cape Government Health Chief Director: Strategy and Health Support, 2020). Public health care services are provided by the Western Cape Government Health Department (WCGH) at primary, secondary and tertiary care levels, and by the City of Cape Town (CCT) municipal government at primary care level (Western Cape Department of Health, 2018). According to the District Heath Plan 2018 – 2021, the medically uninsured population in 2018 was 76.76% and the population dependent on public sector services was 87.2% (Western Cape Department of Health, 2018). Services are provided free of charge to the user at primary health care level and on a sliding scale according to income at secondary and tertiary level. Most of the engagement around TB diagnosis and treatment is in the public health care sector, as TB disproportionately affects the socio-economically disadvantaged (Wood & Bekker, 2017).



The antenatal HIV prevalence was 20.7% in 2017 (Woldesenbet et al., 2019). HIV/AIDS/TB is the biggest contributor to premature mortality, accounting for nearly 1 in 5 years of life lost (YLL) in 2016 and although this was slightly down from 1 in 4 in 2009, most of the reduction was prior to 2013 (Davies et al., 2020). The disease burden of HIV/AIDS/TB is unequally spread across Cape Town's eight health sub-districts, reflecting socioeconomic disparities, with Khayelitsha and Eastern sub-districts having the highest YLL due to HIV/AIDS/TB (Davies et al., 2020).

In 2011 South Africa replaced sputum smear microscopy with Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) as the initial diagnostic test for TB (Churchyard et al., 2015). Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) is a diagnostic test based on nucleic acid amplification test that uses a disposable cartridge with the GeneXpert System (Cepheid, n.d.) and simultaneously detects Mycobacterium tuberculosis and resistance to rifampacin, one of the first line drugs in TB treatment (Centers for Disease Control and Prevention (CDC), 2016). TB testing is done by the National Health Laboratory Services (NHLS) and is available via all primary, secondary and tertiary health care facilities, while TB treatment may be initiated at any level of care and ongoing treatment is provided at most primary health care facilities as well as TB hospitals. Public sector TB diagnosis and treatment is also available at Department of Correctional Services (DCS) and South African National Defence Force (SANDF) facilities.

In Cape Town from 2018 to 2021 in the public sector, TB was diagnosed at over 100 facilities, mostly (about 70%) in PHC, with a sizeable proportion diagnosed at district and regional hospitals (about 20%) as well as tertiary hospitals (about 10%). A very small proportion (less than 1%) was diagnosed at facilities not under the authority of Departments of Health, including DCS and SANDF facilities. Most ongoing TB treatment was provided in PHC, while two dedicated TB hospitals provided treatment for complicated TB. (Personal communication with Ms Mariette Smith, PHDC senior data scientist, October 2022).



According to a routine TB case-finding report of the 2019 treatment cohort in Cape Town, DS-TB accounted for the majority of TB (24 293/25 281; 96%), of which 76.7 % was new and 5% was recurrent TB (but could be much higher as there was a high proportion of missing data: 18.3%), while DR-TB accounted for 988/ 25 281; 4% (personal communication with Judy Taylor, TB programme manager, City of Cape Town Health Department, 10 Sept 2021). The annual District Health Barometer (DHB) reported a DS-TB treatment success rate of 76.3% in the 2018 cohort, well below the 90% target of the National Strategic Plan on HIV, TB and STIs 2017–2022 (South African National AIDS Council, 2017) (Massyn et al., 2020). The biggest gaps in reaching the target were

the large “loss to follow-up” (LTF) rate between treatment initiation and treatment outcome of 19.5% and “died while on treatment” rate of 3.5% (personal communication with J Taylor, TB programme manager, CCT, 10 Sept 2021).

## 3.2 Study design

This was a quantitative observational study (Varkevisser, Pathmanathan & Brownlee, 2003) comparing retrospective virtual cohorts. Retrospective studies have the advantage that the data has already been collected (Mann, 2003). Routine health data was used to construct TB care cascades for two pre-defined time periods. This study design has been used in similar studies both internationally and locally (Subbaraman et al., 2016, 2019; Naidoo et al., 2017; Lurie et al., 2020). Previous studies started with two pillars which were not included in this study: the estimated TB burden and an estimate of the number of individuals who accessed TB tests, as shown in Figure 2 above (Subbaraman et al., 2016, 2019; Naidoo et al., 2017). This mini-thesis study started with the pillar depicting the number of individuals diagnosed with TB and included the two subsequent pillars, i.e. the pillar of the number of individuals notified and treated for TB and the pillar of the number of individuals with TB treatment success. This allowed the use of routinely collected health information to construct the cascade. (The pillars which were not included use modelling assumptions in the computation, which was beyond the scope of this study.)



## 3.3 Study population & sampling

The study population included all individuals diagnosed with TB in Cape Town from 1 July 2018 to 31 December 2021, as consolidated in the Western Cape Provincial Health Data Centre (PHDC). It included children and adults. As an individual can develop TB more than once, individuals who developed TB more than once in the sample period could appear more than once in the data set. The sample size was 90 435.

As will be further detailed in section 3.6, individuals with DR-TB (4 804/90 435; 5.3%) were excluded, as the treatment timeline for DR-TB is generally longer than for DS-TB

and treatment outcomes would not have been available for the study period. As there is currently no private sector TB data included in PHDC, the study population excluded individuals diagnosed by private sector services. The study population could have inadvertently excluded individuals who had been diagnosed with TB in the public sector, but for whom no evidence of TB existed in PHDC. It also excluded individuals who died with TB before diagnosis and individuals with TB disease but not yet diagnosed with TB (the latter group represented on a pillar of the TB care cascade preceding the first pillar of this mini-thesis study).

## 3.4 Data collection

The source of data was PHDC, which is housed within WCGH. The sources of this data include programme specific sources of TB and HIV related treatment, such as the electronic TB register (ETR.net), electronic DR-TB register (EDRWeb) and electronic HIV and TB database, in the so-called Three Interlinked Electronic Register (Tier.net). The sources also include general health care information systems which contain TB screening and visit data and more recently also contain HIV and TB register data, replacing ETR.net and Tier.net, i.e. WCGH Primary Health Care Information System (PHCIS) and the City of Cape Town's Patient Record and Health Management Information System (PREHMIS). Other sources of data include the Clinical hospital information system (Clinicom), laboratory data from NLHS, drug dispensing information from pharmacy systems and patient hospital discharge summaries with clinical coding. In PHDC the various sources of data are linked using a unique patient identifier (which is the patient folder number at all levels of care), augmented by other identifiers, which provides a more complete data set than any individual data source (Boulle et al., 2021).

In PHDC a "TB episode", which spans the period from diagnosis to outcome, is considered to be an acute health condition (i.e. it can occur multiple times in a lifetime, with variable duration and have an outcome) and is inferred from a number of different TB "evidences", using multiple data sources (described above). Typical evidences are laboratory test results (such as XPert MTB/RIF, line probe assay, smear microscopy and culture); ICD10 diagnosis coding from primary care TB treatment register data as well as

hospital admissions; and TB treatment drug dispensing. Each episode is assigned a quantitative confidence score between 0 and 1, depending on the strength of the various evidences. For TB, a confidence score of ≥ 0.6 is considered "high confidence". The sample for this study included only individuals diagnosed with TB with a high confidence score. In PHDC an episode becomes part of an individual's electronic medical record and includes evidences, service utilisation, outcomes and co-morbidities and can be used by clinicians for individual patient management and can be aggregated for cohort management. (Personal communication with Ms Mariette Smith, PHDC senior data scientist, September 2022.)

A senior data scientist working for WCGH extracted the data from PHDC for this study according to the data elements in a data extraction tool (Appendix 2) which were known by the researcher to be available in PHDC and could be used to construct the pillars of the TB care cascade as well as the independent variables of age; sex; HIV status; category of TB; mode of diagnosis; and sub-district.

The pillars and the losses between the pillars which were constructed in this study and the independent variables were defined as described in Tables 1 and 2 below.

**Table 1. Definitions of the pillars & losses of the DS-TB care cascade.**

| Pillars & Losses | Definition |
|---|---|
| Diagnosed with DS-TB | Individuals diagnosed with DS-TB, including with bacteriologically confirmed and clinically diagnosed TB; pulmonary and extra-pulmonary TB; new and recurrent TB; at hospital and primary care level; excluding those who have been found to have DR-TB. Only diagnoses based on high confidence evidence of TB in PHDC were included. |
| Notified and Treated | Individuals diagnosed with DS-TB for whom there was evidence of TB treatment initiation at a site of TB registration and notification (i.e. a primary health care facility or TB-hospital, which in South Africa have been the TB registration and notification sites and custodians of TB treatment registers). Some initial TB treatment may have been given at other levels of hospital care. |
| Treatment success | Individuals diagnosed with DS-TB with evidence of TB cure or TB treatment completion by 6 months post diagnosis. The data was extracted more than a year post the periods of comparative analysis, obviating the potential problem of missing data relating to reporting lags. |
| Initial loss to follow-up (ILTF) | Individuals diagnosed with DS-TB for whom there was no evidence of having started TB treatment at a site of TB registration and notification. |
| Post-treatment loss (PTL) | Individuals with DS-TB for whom there was evidence of TB treatment initiation at a site of TB registration and notification but without TB treatment success. Abbreviated in this study to PTL. |

**Table 2. Definitions of the independent variables.**

| Variable | Definition |
|---|---|
| Age | Age in years at the date of first evidence of TB as calculated in PHDC from date of birth, and for purposes of analysis, dichotomised into adult (≥15) and child (0-14). If the age was unknown it was treated as missing data in analysis. |
| Sex | Sex as recorded in PHDC: male or female. If the sex was unknown it was treated as missing data in analysis. |
| HIV status | HIV status during TB as recorded in PHDC : HIV positive or HIV negative, inferred from a number of different evidences occurring at any time during the TB episode, including a window of 2 weeks before and 1 month after a TB episode. If the HIV status was unknown it was treated as missing data in analysis. |
| Category of TB | Category of TB as recorded in PHDC: new (i.e. first episode of TB) or recurrent (i.e. had any number of previous TB episodes). (There was no missing data for this variable as the data extract from PHDC was for TB episodes in the specified time period, so all individuals had to have 1 or more episodes.) |
| Mode of diagnosis | Mode of diagnosis as recorded in PHDC; bacteriologically confirmed (based on the results of at least one positive test of XPert MTB/RIF, line probe assay (LPA) and microscopy and culture), in the absence of which all TB episodes were assumed to be clinically diagnosed based on non-laboratory information such as chest X-ray. (There was therefore not any missing data.) |

| | |
|---|---|
| Sub-district | One of the eight health sub districts in Cape Town (Eastern, Khayelitsha, Klipfontein, Mitchells Plain, Northern, Southern, Tygerberg, Western) as well as a ninth "outside Cape Town" category (for individuals diagnosed in Cape Town, but allocated to a sub-district outside of Cape Town), according to "TB allocated treatment sub-district" in PHDC. The "TB allocated treatment sub-district" is inferred in PHDC using an algorithm based on the last TB treatment facility visited, or TB treatment facility referred to, or TB treatment facility diagnosed at, or other TB register information, or manual (re)allocation by a health care worker of an individual diagnosed with TB. If the sub-district was unknown it was treated as missing data in analysis. |

## 3.5 Data cleaning

The PHDC undertook de-duplication of the data, using the unique patient identifier. To confirm that there were indeed no duplicates the dataset was checked in Excel ("Microsoft Excel Spreadsheet Software | Microsoft 365", n.d.). An outlier of age (114) was considered, but PHDC review of the episode revealed credible data for this episode. However the age in 2 episodes was recorded as -1; these were re-coded as "age unknown". Further plausibility checks were done using Excel Logic functions, which identified 53 episodes in which the date of death was recorded as occurring before the TB episode; in these instances the date of death was re-coded as missing. In terms of missing data, 46 episodes had the "TB allocated treatment sub-district" field missing, but data was available for the "TB allocated treatment facility", so these were manually recoded to the appropriate sub-district. Other missing data that could not be corrected in this secondary data set was excluded from bivariate analysis and is detailed for each variable in Table 2 above.

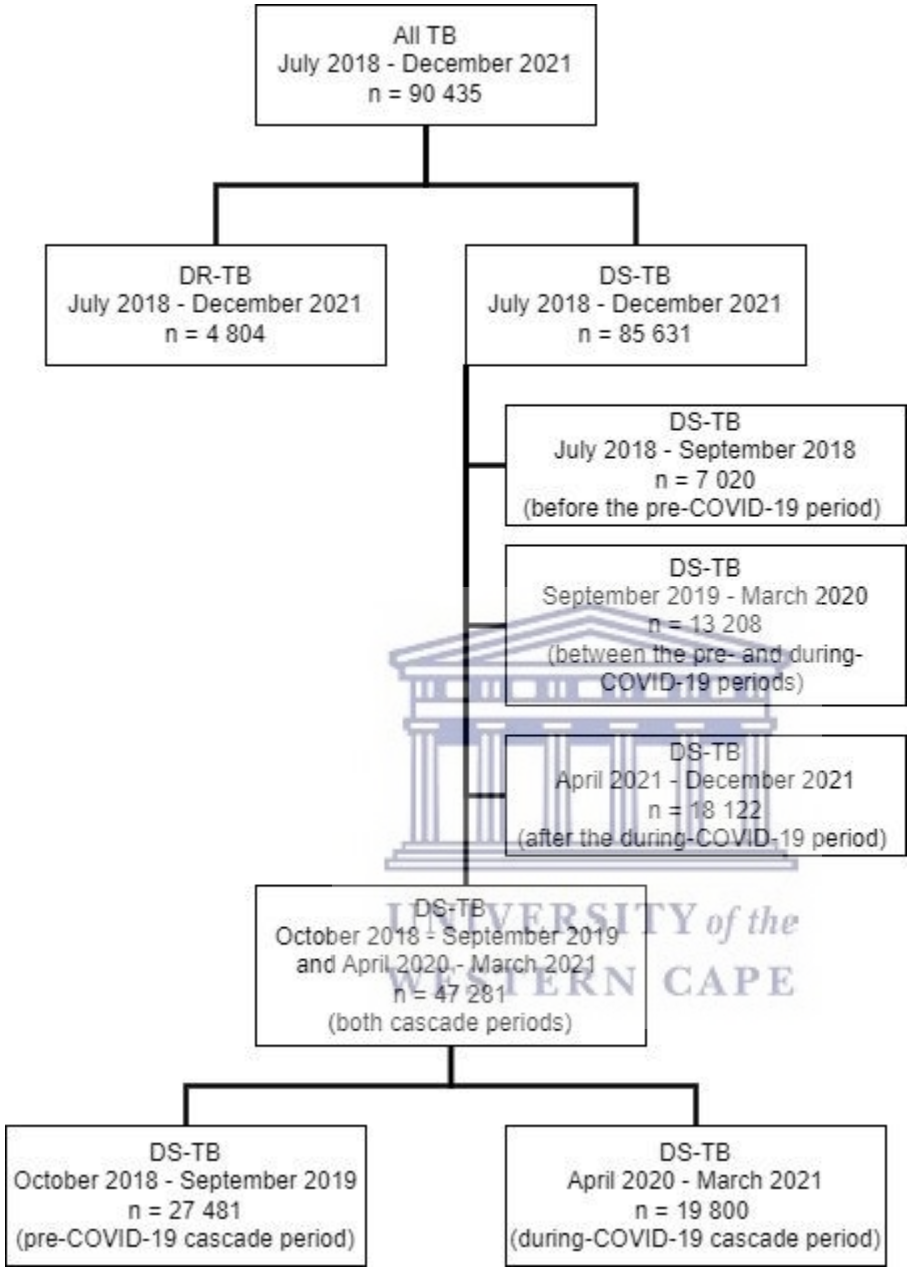
## 3.6 Data analysis

The entire data set received from PHDC included data relating to all individuals diagnosed with TB (DS-TB and DR-TB) from 1 July 2018 to 31 December 2021. The data set was split to allow analysis according to DS-TB that occurred in the pre-defined pre-COVID-19 period (1 October 2018 to 30 September 2019) and the during-COVID-19 period (1 April 2020 to 31 March 2021). Each period was chosen to be a 12 month period as there is some seasonal variation in TB. The pre-COVID-19 period was chosen as the most recent period possible, yet allowing for 6 month TB treatment outcomes to occur before the start of the during-COVID-19 period. The start date of the during-COVID-19 period was pragmatically defined as 1 April 2020, following the onset of the first lockdown on 26 March 2020 (Presidency of the Republic of South Africa, 2020a). These periods are illustrated in Appendix 3. The split of the data set is shown as a flow diagram in Figure 3 below.

A descriptive analysis was done to illustrate as a line graph the number of people diagnosed with DS-TB per month from July 2018 to December 2021. The sample population characteristics of the annual pre- and during-COVID-19 DS-TB cascades were calculated as proportions for the categorical variables sex, age, HIV status, category of TB, mode of diagnosis and sub-district. Pre- and during-COVID 19 DS-TB cascades were constructed as frequency tables including the pillars for the dependent variables Diagnosed with DS-TB; Notified and Treated; and Treatment success and the between-pillar losses of ILTF and PTL were calculated. For each cascade bivariate analysis (Chi square test) was conducted for ILTF, PTL and treatment success, testing for association with the independent variables. Chi square test was also used to test for association between the pre- and during-COVID-19 DS-TB cascades for the pillars and losses and the independent variables.

The open-source web tool OpenEpi was used to calculate the 95% confidence limits for proportions (Dean, Sullivan & Soe, n.d.) and all other analyses were conducted using the SPSS 29 software package (“IBM® SPSS® Statistics”, n.d.).

**Figure 3. Flow diagram of people diagnosed with TB: pre- & during-COVID-19 12-month cascade periods within the entire data set July 2018 - December 2021**






## 3.7 Validity

All episodes used only 6 month treatment outcomes so that equivalent time periods for follow-up were analysed. Standardised definitions for data elements in PHDC ensured

reliability in this setting, but may be hard to reproduce in settings without access to a consolidated source of data. The study findings may be generalisable to other similar settings.

## 3.8 Ethical considerations

The data was supplied in a de-identified format by PHDC to protect the identities of individuals. The PHDC provided the data as a password protected data set, which only the researcher of this study and the researchers of the larger IMPAC$_{19}$T$_B$ study had access to. The sample size was very large, which means that, even in the disaggregated data, analysis did not allow for re-identification of individuals. Data was securely stored electronically on a personal computer with back up on an external hard drive using password-protected documents. The study setting has not been anonymised, however it is thought to be unlikely that this would result in harm to the citizens of Cape Town or district and sub-district health care managers, and that any possible harm is outweighed by the possible benefits such as contribution to the improvement of public health (Piasecki et al., 2021).

Ethics approval for this study was obtained from the University of the Western Cape Biomedical Research Ethics Committee (UWC BMREC). A waiver of informed consent was sought and granted, as this was a retrospective review of routinely collected health service data and it was not feasible to obtain individual consent from individuals. Approval to perform the study was obtained from the Western Cape Government Health and City Health Departments, including access to the data from PHDC (Appendix 4).

As highlighted by the Stop TB Partnership in a recently updated publication, “words matter”, therefore this mini-thesis refers for instance to efforts to “end TB” not to “achieve TB control” and to “individuals with TB”, not “TB cases”, except when “cases” is used in a shorthand way to communicate research and clinical concepts (Stop TB Partnership, 2022).

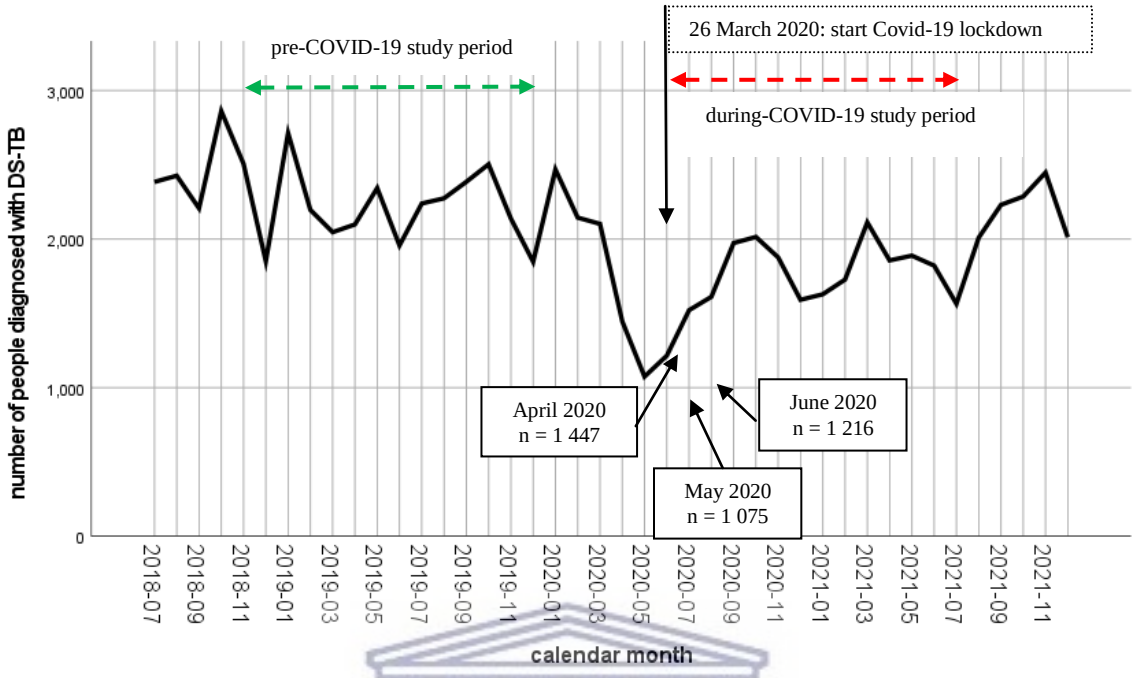
# Chapter 4: Results

In this chapter, first the context of the total number of people diagnosed with DS-TB in the entire 42 month period of July 2018 to December 2021 is described. This is followed by presentation and statistical analysis of the pre- and during-COVID-19 DS-TB cascades (which were selected annual cascades within the entire period), disaggregated by the independent variables. Lastly, the DS-TB cascades for the pre-COVID-19 and the during-COVID-19 periods are compared.

## 4.1 People diagnosed with DS-TB: July 2018 to December 2021

Figure 4 below shows the number of people diagnosed with DS-TB per month from July 2018 to December 2021, with the pre-COVID-19 period of October 2018 to September 2019 shown with a green dotted arrow and the during-COVID-19 period of April 2020 to March 2021 shown with a red dotted arrow. Up until, and including, March 2020 the number of people diagnosed with DS-TB was mostly above 2 000 per month (the range was from 1 848 to 2 862 per month), dipping below 2 000 only at end-of-calendar-year periods (1 852 in December 2018 and 1 848 in December 2019) and in June 2018 (1 958). However, a very big drop in the number of people diagnosed with DS-TB is evident from April 2020 (1 447, 1 075 and 1 216 in April, May and June 2020 respectively). Thereafter, the number of people diagnosed with DS-TB remained below 2 000 per month, except for in March 2021 (when this was 2 113), until more than a year later when this was once again more than 2 000 per month, in the August to December 2021 period (when it ranged between 2 010 and 2 448, in August and November 2021 respectively).

**Figure 4. Number of people diagnosed with DS-TB per month in Cape Town: July 2018 - December 2021.**




## 4.2 The pre-COVID-19 and during-COVID-19 DS-TB cascades

The two cascade 12-month periods were a pre-COVID-19 period of October 2018 to September 2019 and a during-COVID-19 period of April 2020 to March 2021.

### 4.2.1 Sample population characteristics

The sample population characteristics per independent variable in the pre- and during-COVID-19 periods are shown in Table 3 below. In both the pre- and during-COVID-19 periods the majority of individuals were male (15 581/27 481; 56.7% pre-COVID-19 and 11 310/19 800; 57.1% during-COVID-19), adult (24 891/27 481; 90.6% pre-COVID-19 and 18 131/19 800; 91.6% during-COVID-19), had TB for the first time (21 220/27 481; 77.2% pre-COVID-19 and 14 946/19 800; 75.5% during-COVID-19) and had a bacteriologically confirmed diagnosis (19 541/27 481; 71.1% pre-COVID-19 and 14 503/19 800; 73.2% during-COVID-19). The proportion of individuals with TB who were HIV-positive was 11 781/27 481; 42.9% pre-COVID-19 and 8 509/19 800; 43.0% during-COVID-19, but there was with a fairly large proportion with HIV status unknown:

4 414/27 481; 16.1% and 2 613/ 19 800; 13.2% in the pre-COVID-19 and post-COVID-19 periods respectively. People diagnosed with TB were disproportionately spread across Cape Town's sub-districts, with Northern having the lowest proportion (2 220/ 27 481; 8.1% and 1 655/19 800; 8.4%) and Khayelitsha the highest proportion (4 374/27 481; 15.9% and 2 964/19 800; 15.0%) in the pre-COVID-19 and during-COVID-19 periods respectively.

**Table 3. Sample population characteristics in the pre- & during-COVID-19 periods.**

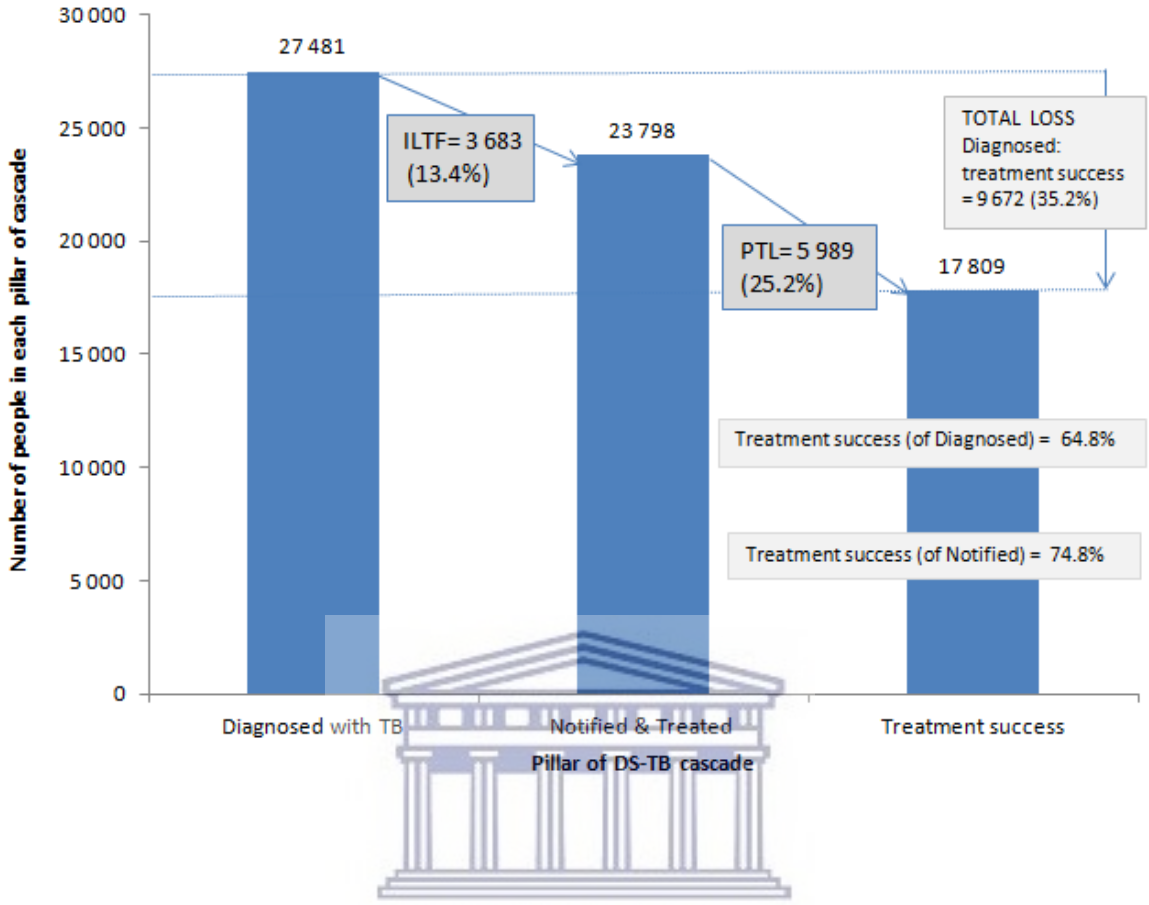
| **Variable** | | **COVID-19 PERIOD** | | | |
|---|---|---|---|---|---|
| | | **pre-COVID-19** | | **during-COVID-19** | |
| | | n | % | n | % |
| **Total DS-TB episodes** | | **27 481** | **100.0%** | **19 800** | **100%** |
| **Sex** | female | 11 849 | 43.1% | 8 445 | 42.7% |
| | male | 15 581 | 56.7% | 11 310 | 57.1% |
| | unknown | 51 | 0.2% | 45 | 0.2% |
| **Age** | child | 2 589 | 9.4% | 1 663 | 8.4% |
| | adult | 24 891 | 90.6% | 18 131 | 91.6% |
| | unknown | 1 | 0.0% | 6 | 0.0% |
| **HIV status** | negative | 11 286 | 41.1% | 8 678 | 43.8% |
| | positive | 11 781 | 42.9% | 8 509 | 43.0% |
| | unknown | 4 414 | 16.1% | 2 613 | 13.2% |
| **Category of TB** | new | 21 220 | 77.2% | 14 946 | 75.5% |
| | recurrent | 6 261 | 22.8% | 4 854 | 24.5% |
| **Mode of diagnosis** | bacteriological | 19 541 | 71.1% | 14 503 | 73.2% |
| | clinical | 7 940 | 28.9% | 5 297 | 26.8% |
| **Sub-district** | Eastern | 3 928 | 14.3% | 2 955 | 14.9% |
| | Khayelitsha | 4 374 | 15.9% | 2 964 | 15.0% |
| | Klipfontein | 3 037 | 11.1% | 2 244 | 11.3% |
| | Mitchells Plain | 3 879 | 14.1% | 2 743 | 13.9% |
| | Northern | 2 220 | 8.1% | 1 655 | 8.4% |
| | Southern | 2 369 | 8.6% | 1 673 | 8.4% |
| | Tygerberg | 4 037 | 14.7% | 2 824 | 14.3% |
| | Western | 3 156 | 11.5% | 2 443 | 12.3% |
| | outside Cape Town* | 481 | 1.8% | 299 | 1.5% |

* some individuals in the Western Cape who live and usually access care outside of Cape Town, hence are allocated by PHDC to a sub-district outside of Cape Town for treatment, are diagnosed at a facility in Cape Town, for instance as occurs with some tertiary level diagnoses, as the only tertiary level hospitals in the whole Province are in Cape Town

### 4.2.2 The pre-COVID-19 DS-TB cascade

The pre-COVID-19 DS-TB cascade (October 2018 to September 2019) is shown in Figure 5 below. The first pillar, representing the number of DS-TB episodes in the 12 month pre-COVID-19 period, was 27 481, the second pillar, the number notified and treated, was 23 798, and the last pillar, the number successfully treated was 17 809. The calculated losses between the first and second pillars, ILTF, was thus 3 683/27 481; 13.4% and between the second and third pillars, PTL, was 5 989/23 798; 25.2%. The losses between the first and third pillars of the cascade were thus collectively 9 672/27 481; 35.2%, resulting in a treatment success rate of 17 809/27 481; 64.8% (of individuals diagnosed with TB). Treatment success, if the denominator was considered to be individuals notified and treated, was 17 809/23 798; 74.8%.

**Figure 5. DS-TB cascade pre-COVID-19 (October 2018 - September 2019).**




The losses between the pillars of the cascade and the resultant treatment success varied by independent variable. There was a statistically significant association (at the 95% confidence level) between ILTF, PTL and treatment success for each of age, HIV status, category of TB and mode of diagnosis, and while this was also the case for sex and ILTF and PTL, no association between sex and treatment success was found, as further described and shown in Tables 4 and 5 below.

Males had slightly lower ILTF, but slightly higher PTL than females. For males ILTF was 2 032/15 581; 13.0% while for females it was 1 648/11 849; 13.9%, $X^2$ (1, n = 27 430) = 4.35, p = 0.037. For males PTL was 3 494/13 549; 25.8% while for females it was 2 484/10 201; 24.4%, $X^2$ (1, n = 23 750) = 6.38, p = 0.012. The combined effect of these losses was that treatment success for males was 10 055/15 581; 64.5%, while for females it was 7 717/11 849; 65.1%, $X^2$ (1, n = 27 430) = 1.04, p = 0.307.

Children had higher ILTF (491/2 589; 19%) than adults (3 192/24 891; 12.8%), $X^2$ (1, n = 27 480) = 76.19, p < 0.001, but PTL was lower in children (369/ 2098; 17.6%) than in adults (5 619/21 699; 25.9%), $X^2$ (1, n = 23 797) =70.1, p < 0.001. The combined effect of these losses was that children had higher treatment success (1 729/2 589; 66.8%) than adults (16 080/24 891; 64.6%), $X^2$ (1, n = 27 480) = 4.89, p = 0.027.

HIV-positive individuals had higher ILTF (1 692/ 11 781; 14.4%), than HIV-negative individuals (820/11 286; 7.3%), $X^2$ (1, n = 23 067) = 299.13, p < 0.001 and higher PTL (2 916/10 089; 28.9%) than HIV-negative individuals, (2 329/10 466; 22.3%), $X^2$ (1, n = 20 555) = 119.52, p < 0.001. The combined effect of these losses was that treatment success for HIV-positive individuals (7 173/11 781; 60.9%), was lower than for HIV-negative individuals (8 137/11 286; 72.1%), $X^2$ (1, n = 23 067) = 324.64, p < 0.001.

Individuals with recurrent TB had higher ILTF (910/6 261; 14.5%) than individuals with new TB (2 773/21 220; 13.1%, $X^2$ (1, n =27 481) = 8.96, p = 0.003 and higher PTL (1 526/ 5 351; 28.5%) than individuals with new TB (4 463/18 447; 24.2%), $X^2$ (1, n = 23 798) = 41.19, p < 0.001. The combined effect of these losses was that individuals with recurrent TB had poorer treatment success (3 825/6 261; 61.1%) than individuals with new TB (13 984/21 220; 65.9%), $X^2$ (1, n =27 481) = 48.99, p < 0.001.



Individuals with a bacteriologically confirmed diagnosis had higher ILTF (2 728/19 541; 14.0%) than those who were diagnosed clinically (955/7 940; 12.0%), $X^2$ (1, n = 27 481) = 18.17, p < 0.001 as well as higher PTL (4 434/16 813; 26.4%) than those who were diagnosed clinically (1 555/6 985; 22.3%), $X^2$ (1, n = 23 798) = 44.27, p < 0.001. The combined effect of these losses was that individuals with a bacteriologically confirmed diagnosis had poorer treatment success (12 379/19 541; 63.3%) than those who were diagnosed clinically (5 430/7 940; 68.4%), $X^2$ (1, n = 27 481) = 62.86, p < 0.001.

**Table 4**. **DS-TB cascade pre-COVID-19: pillars & losses by independent variable.**

| | | Diagnosed with TB | ILTF n (%) | Notified & Treated | PTL n (%) | Treatment success | Treatment success rate (of those diagnosed) |
|---|---|---|---|---|---|---|---|
| **Total** | | **27 481** | **3683 (13.4%)** | **23 798** | **5989 (25.2%)** | **17 809** | **64.8%** |
| **sex** | female | 11 849 | 1648 (13.9%) | 10 201 | 2484 (24.4%) | 7 717 | 65.1% |
| | male | 15 581 | 2032 (13.0%) | 13 549 | 3494 (25.8%) | 10 055 | 64.5% |
| **age** | child | 2 589 | 491 (19.0%) | 2 098 | 369 (17.6%) | 1 729 | 66.8% |
| | adult | 24 891 | 3192 (12.8%) | 21 699 | 5619 (25.9%) | 16 080 | 64.6% |
| **HIV status** | HIV negative | 11 286 | 820 (7.3%) | 10 466 | 2329 (22.3%) | 8 137 | 72.1% |
| | HIV positive | 11 781 | 1692 (14.4%) | 10 089 | 2916 (28.9%) | 7 173 | 60.9% |
| **category of TB** | new | 21 220 | 2773 (13.1%) | 18 447 | 4463 (24.2%) | 13 984 | 65.9% |
| | recurrent | 6 261 | 910 (14.5%) | 5 351 | 1526 (28.5%) | 3 825 | 61.1% |
| **mode of diagnosis** | bacteriological | 19 541 | 2728 (14.0%) | 16 813 | 4434 (26.4%) | 12 379 | 63.3% |
| | clinical | 7 940 | 955 (12.0%) | 6 985 | 1555 (22.3%) | 5 430 | 68.4% |

**Table 5. DS-TB cascade pre-COVID-19: comparing losses (ILTF & PTL) & treatment success by independent variable.**

| Variable | | ILTF rate (loss pillar 1 to 2) | Chi-Square statistic | p value | PTL rate (loss pillar 2 to 3) | Chi-Square statistic | p value | Treatment success rate (pillar 3 of 1) | Chi-Square statistic | p value |
|---|---|---|---|---|---|---|---|---|---|---|
| **total** | | 13.4% | | | 25.2% | | | 64.8% | | |
| **sex** | female | 13.9% | 4.35 | **0.037** | 24.4% | 6.38 | **0.012** | 65.1% | 1.04 | 0.307 |
| | male | 13.0% | | | 25.8% | | | 64.5% | | |
| **age** | child | 19.0% | 76.19 | **<0.001** | 17.6% | 70.1 | **<0.001** | 66.8% | 4.89 | **0.027** |
| | adult | 12.8% | | | 25.9% | | | 64.6% | | |
| **HIV status** | HIV negative | 7.3% | 299.13 | **<0.001** | 22.3% | 119.52 | **<0.001** | 72.1% | 324.64 | **<0.001** |
| | HIV positive | 14.4% | | | 28.9% | | | 60.9% | | |
| **category of TB** | new | 13.1% | 8.96 | **0.003** | 24.2% | 41.19 | **<0.001** | 65.9% | 48.99 | **<0.001** |
| | recurrent | 14.5% | | | 28.5% | | | 61.1% | | |
| **mode of diagnosis** | bacteriological | 14.0% | 18.17 | **<0.001** | 26.4% | 44.27 | **<0.001** | 63.3% | 62.86 | **<0.001** |
| | clinical | 12.0% | | | 22.3% | | | 68.4% | | |

Disaggregating the cascade data by sub-district revealed variation between the sub-districts. Of Cape Town's 8 sub-districts, Southern had the highest ILTF (408/2 369; 17.2%), while Khayelitsha had the lowest ILTF (418/4 374; 9.6%). Southern also had the highest PTL (743/1 961; 37.9%), while Mitchells Plain had the lowest PTL (603/3 497; 17.2%). In contrast to having the lowest ILTF, Khayelitsha had the second highest PTL (1 050/3 956; 26.5%). Of individuals diagnosed with DS-TB, Mitchells Plain had the highest treatment success (2 894/3 879; 74.6%), while Southern had the lowest (1 218/2 369; 51.4%). The results for all of Cape Town's sub-districts are shown in Table 6 below. ILTF was associated with sub-district: $X^2$ (7, n = 27 000) = 141.47, $p < 0.001$, as was PTL: $X^2$ (7, n = 23 497) = 324.68, $p < 0.001$, and treatment success: $X^2$ (7, n = 27 000) = 378.66, $p < 0.001$.

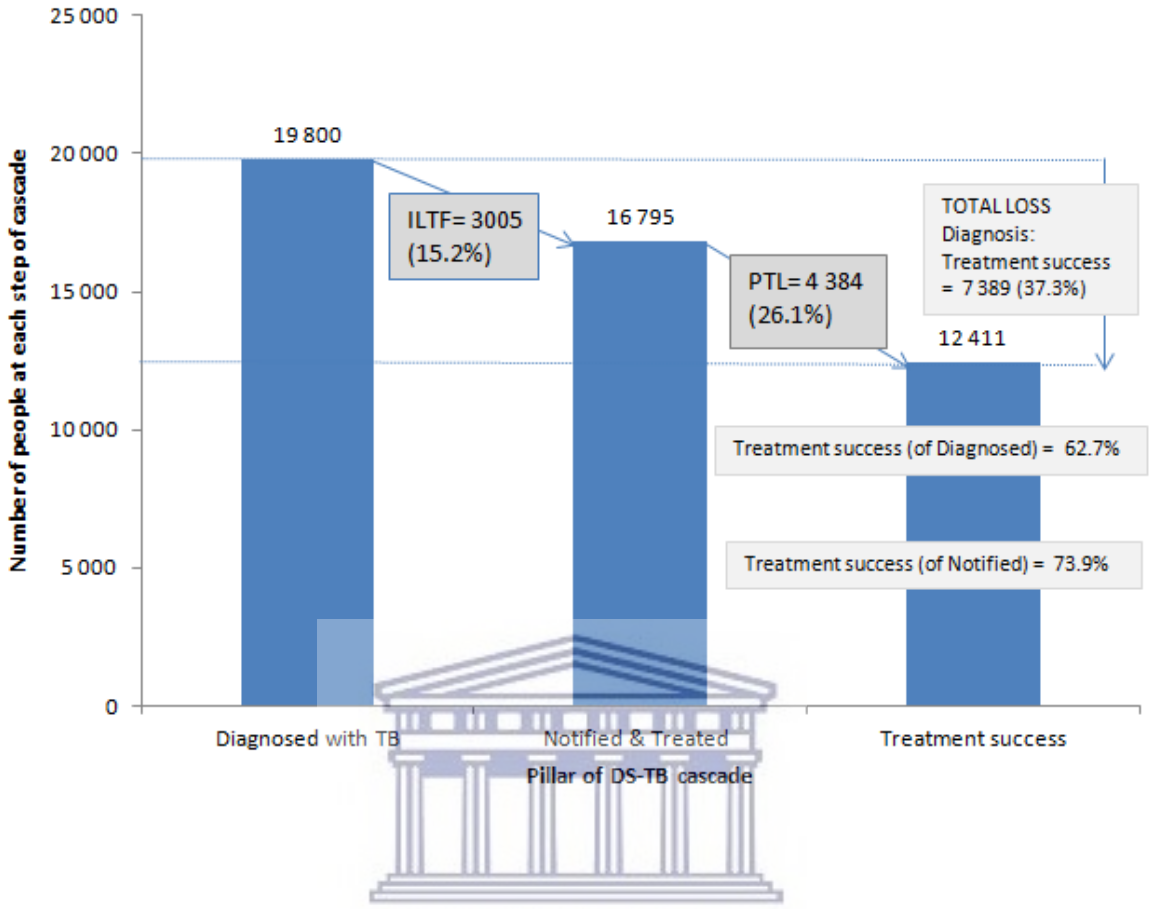
**Table 6. DS-TB cascade pre-COVID-19: pillars, losses & treatment success by sub-district.**

| Sub-district | Diagnosed with TB (pillar 1) | ILTF rate (pillar 1 to 2) | Notified & Treated (pillar 2) | PTL rate (pillar 2 to 3) | Treatment success (pillar 3) | Total losses (pillar 1 to 3) | Treatment success rate (of those diagnosed) |
|---|---|---|---|---|---|---|---|
| Eastern | 3 928 | 14.8% | 3 347 | 26.1% | 2 474 | 1 454 | 63.0% |
| Khayelitsha | 4 374 | 9.6% | 3 956 | 26.5% | 2 906 | 1 468 | 66.4% |
| Klipfontein | 3 037 | 13.7% | 2 620 | 20.7% | 2 078 | 959 | 68.4% |
| Mitchells Plain | 3 879 | 9.8% | 3 497 | 17.2% | 2 894 | 985 | 74.6% |
| Northern | 2 220 | 13.9% | 1 911 | 25.9% | 1 417 | 803 | 63.8% |
| Southern | 2 369 | 17.2% | 1 961 | 37.9% | 1 218 | 1 151 | 51.4% |
| Tygerberg | 4 037 | 12.9% | 3 518 | 26.1% | 2 599 | 1 438 | 64.4% |
| Western | 3 156 | 14.9% | 2 687 | 23.8% | 2 048 | 1 108 | 64.9% |

### 4.2.3 The during-COVID-19 DS-TB cascade

The during-COVID-19 DS-TB cascade is shown in Figure 6 below. The number of individuals diagnosed with DS-TB in the 12 month during-COVID-19 period was 19 800, the number notified and treated was 16 795, and the number successfully treated was 12 411. The calculated losses between the first and second pillars, the ILTF, was thus 3 005/19 800; 15.2% and between the second and third pillars, the PTL, was 4 384/16 795; 26.1%. The losses between the first and third pillars of the cascade were thus collectively 7 389/19 800; 37.3%, resulting in a treatment success rate of 12 411/19 800; 62.7% (of people diagnosed with TB). The treatment success rate, if the denominator was considered to be individuals notified and treated, was 12 411/16 795; 73.9%.

**Figure 6. DS-TB cascade during-COVID-19 (April 2020 - March 2021).**




As was the case with the pre-COVID-19 DS-TB cascade, the losses between the pillars of the cascade and the resultant treatment success varied by independent variable, as described in Tables 7 and 8 below. There was a statistically significant association (at the 95% confidence level) between ILTF, PTL and treatment success for HIV status as well as between PTL and treatment success for the category of TB and no association between ILTF, PTL and treatment success for sex. While there was a statistically significant association between ILTF and PTL for age and mode of diagnosis, there was no association for treatment success for these two variables: children were more likely to be ILTF, but less likely to be PTL and individuals with a bacteriological diagnosis of TB were less likely to be ILTF, but more likely to be PTL.

**Table 7. DS-TB cascade during-COVID-19: pillars & losses by independent variable.**

| | | Diagnosed with TB | ILTF n (%) | Notified & Treated | PTL n (%) | Treatment success | Treatment success rate (of those diagnosed) |
|---|---|---|---|---|---|---|---|
| **Total** | | 19 800 | 3005 (15.2%) | 16 795 | 4384 (26.1%) | 12 411 | 62.7% |
| **sex** | female | 8 445 | 1309 (15.5%) | 7 136 | 1806 (25.3%) | 5 330 | 63.1% |
| | male | 11 310 | 1690 (14.9%) | 9 620 | 2568 (26.7% | 7 052 | 62.4% |
| **age** | child | 1 663 | 372 (22.4%) | 1 291 | 250 (19.4% | 1 041 | 62.6% |
| | adult | 18 131 | 2633 (14.5%) | 15 498 | 4132 (26.7%) | 11 366 | 62.7% |
| **HIV status** | HIV negative | 8 678 | 701 (8.1%) | 7 977 | 1894 (23.7%) | 6 083 | 70.1% |
| | HIV positive | 8 509 | 1493 (17.5% | 7 016 | 2091 (29.8%) | 4 925 | 57.9% |
| **category of TB** | new | 14 946 | 2268 (15.2%) | 12 678 | 3159 (24.9%) | 9 519 | 63.7% |
| | recurrent | 4 854 | 737 (15.2%) | 4 117 | 1225 (29.8%) | 2 892 | 59.6% |
| **mode of diagnosis** | bacteriological | 14 503 | 2127 (14.7%) | 12 376 | 3336 (27.0%) | 9 040 | 62.3% |
| | clinical | 5 297 | 878 (16.6%) | 4 419 | 1048 (23.7%) | 3 371 | 63.6% |

**Table 8. DS-TB cascade during-COVID-19: comparing losses (ILTF & PTL) & treatment success by independent variable.**

| Variable | | ILTF rate (loss pillar 1 to 2) | Chi-Square statistic | p value | PTL rate (loss pillar 2 to 3) | Chi-Square statistic | p value | Treatment success rate (pillar 3 of 1) | Chi-Square statistic | p value |
|---|---|---|---|---|---|---|---|---|---|---|
| **total** | | 15.2% | | | 26.1% | | | 62.7% | | |
| **sex** | female | 15.5% | 1.17 | 0.280 | 25.3% | 4.08 | **0.043** | 63.1% | 1.20 | 0.273 |
| | male | 14.9% | | | 26.7% | | | 62.4% | | |
| **age** | child | 22.4% | 72.85 | **<0.001** | 19.4% | 32.90 | **<0.001** | 62.6% | 0.01 | 0.942 |
| | adult | 14.5% | | | 26.7% | | | 62.7% | | |
| **HIV status** | HIV negative | 8.1% | 345.87 | **<0.001** | 23.7% | 70.25 | **<0.001** | 70.1% | 278.48 | **<0.001** |
| | HIV positive | 17.5% | | | 29.8% | | | 57.9% | | |
| **category of TB** | new | 15.2% | 0.00 | 0.988 | 24.9% | 37.70 | **<0.001** | 63.7% | 26.45 | **<0.001** |
| | recurrent | 15.2% | | | 29.8% | | | 59.6% | | |
| **mode of diagnosis** | bacteriological | 14.7% | 10.99 | <**0.001** | 27.0% | 17.71 | <**0.001** | 62.3% | 2.84 | 0.092 |
| | clinical | 16.6% | | | 23.7% | | | 63.6% | | |

As was the case with the pre-COVID-19 DS-TB cascade, disaggregating the cascade data by sub-district revealed variation between the sub-districts. Southern had the highest ILTF (290/1 673; 17.3%) and Klipfontein had the highest PTL (341/2 244; 33.6%), while Mitchells Plain had both the lowest ILTF (346/2 743; 12.6%) and PTL (435/2 397; 18.1%). Of individuals diagnosed with DS-TB, Mitchells Plain had the highest treatment success (1 962/2 743; 71.5%), while Southern had the lowest (920/1 673; 55.0%). The results for all of Cape Town's sub-districts are shown in Table 9 below. ILTF was associated with sub-district: $X^2$ (7, n = 19 501) = 38.20, p < 0.001, as was PTL: $X^2$ (7, n = 16 621) = 184.24, p < 0.001, and treatment success: $X^2$ (7, n = 19 501) = 196.74, p < 0.001.

**Table 9. DS-TB cascade during-COVID-19: pillars, losses & treatment success by sub-district.**

| Sub-district | Diagnosed with TB pillar 1) | ILTF rate (pillar 1 to 2) | Notified & Treated (pillar 2) | PTL rate (pillar 2 to 3) | Treatment success (pillar 3) | Total losses | Treatment success rate (of those diagnosed) |
|---|---|---|---|---|---|---|---|
| Eastern | 2 955 | 14.2% | 2 534 | 24.5% | 1 914 | 1 041 | 64.8% |
| Khayelitsha | 2 964 | 12.8% | 2 586 | 24.0% | 1 965 | 999 | 66.3% |
| Klipfontein | 2 244 | 15.2% | 1 903 | 33.6% | 1 263 | 981 | 56.3% |
| Mitchells Plain | 2 743 | 12.6% | 2 397 | 18.1% | 1 962 | 781 | 71.5% |
| Northern | 1 655 | 15.4% | 1 400 | 27.0% | 1 022 | 633 | 61.8% |
| Southern | 1 673 | 17.3% | 1 383 | 33.5% | 920 | 753 | 55.0% |
| Tygerberg | 2 824 | 15.8% | 2 379 | 26.5% | 1 749 | 1 075 | 61.9% |
| Western | 2 443 | 16.5% | 2 039 | 25.8% | 1 512 | 931 | 61.9% |

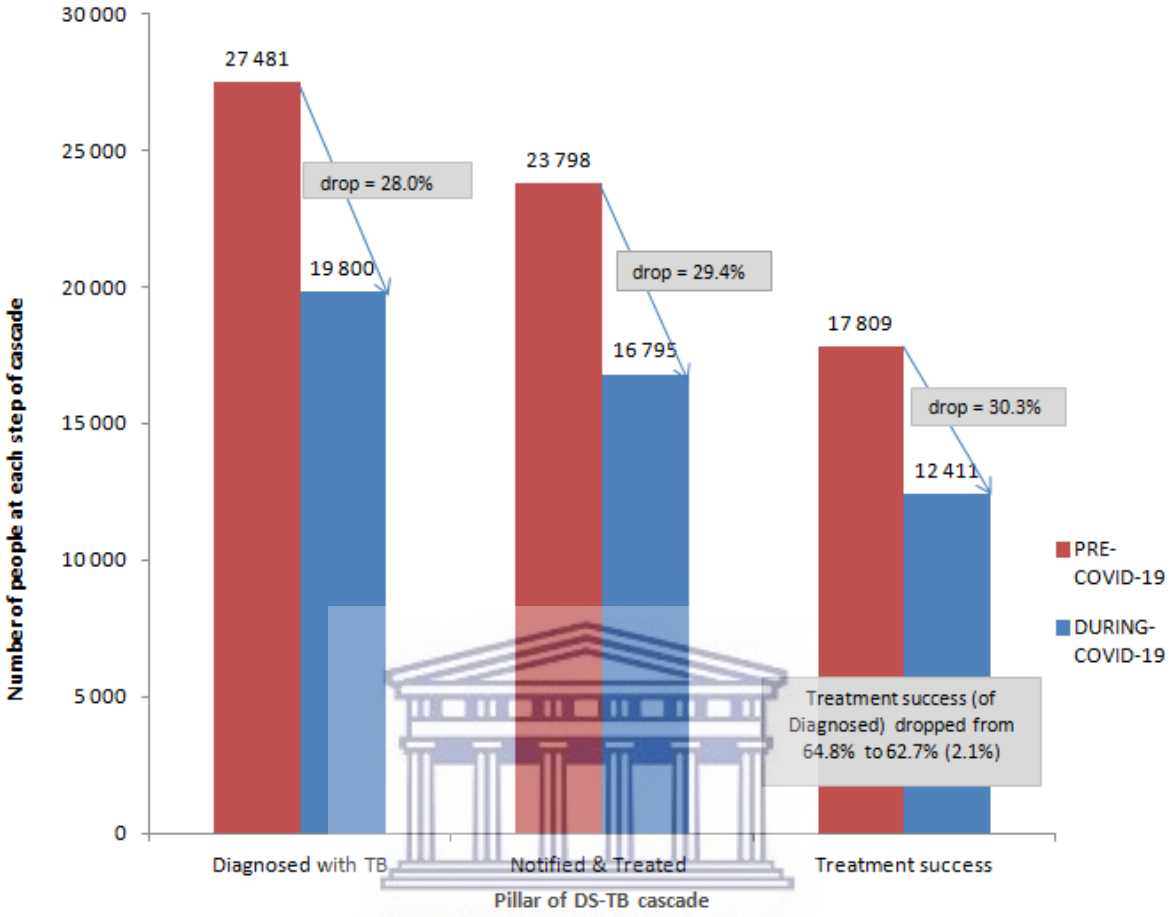
### 4.2.4 Comparing the pre- and during-COVID-19 DS-TB cascades

As illustrated in Figure 7 below, the number of individuals diagnosed with DS-TB (the first pillar of the cascade), dropped from 27 481 in the pre-COVID-19 period to 19 800 in the during-COVID-19 period, representing a decrease of 7 781, which is 7 781/27 481; 28.0% (95% CI [27.4% - 28.5%]).



ILTF increased in the during-COVID-19 period compared to the pre-COVID-19 period by 1.8%, from 13.4% to 15.2%. The Chi-Square test for association between categorical variables showed a statistically significant association at the 95% confidence level between COVID-19 period and the proportion of ILTF: $X^2$ (1, n = 47 281) = 29.88, p < 0.001. PTL increased slightly, by 0.9%, from 25.2% to 26.1%, just achieving statistical significance at the 95% confidence level: $X^2$ (1, n = 40 593) = 4.54, p = 0.033. The treatment success rate (of individuals diagnosed with TB) fell by 2.1%, from 64.8% to 62.7%: $X^2$ (1, n = 47 281) = 22.49, p < 0.001. The treatment success rate of individuals notified and treated fell by 0.9% from 74.8% to 73.9%: $X^2$ (1, n = 40 593) = 4.54, p = 0.033.

**Figure 7. Comparing the pre- & during-COVID-19 DS-TB cascades.**






The Chi-Square test results comparing the proportions of ILTF and PTL in the during-COVID-19 period to the pre-COVID-19 period for the dichotomous variables sex, age, HIV status, category of TB and mode of diagnosis, are shown in Table 10 below, with statistically significant results in bold font. No association was found for any of these dichotomous variables between PTL and COVID-19 period. However, for ILTF the proportion of males ILTF increased from 13.0% in the pre-COVID-19 period to 14.9% in the during-COVID-19 period: $X^2$ (1, n = 26 891) = 19.86, $p < 0.001$; the proportion of children ILTF increased from 19.0 % in the pre-COVID-19 period to 22.4% in the during-COVID-19 period: $X^2$ (1, n = 4 252) = 7.25, p = 0.007; and the proportion of HIV positive individuals ILTF increased from 14.4% in the pre-COVID-19 period to 17.5% in the during-COVID-19 period: $X^2$ (1, n = 20 290) = 37.85, $p < 0.001$.

**Table 10. Comparing the pre- & during-COVID-19 DS-TB cascades: ILTF & PTL by dichotomous independent variable.**

| Variable | | Loss between pillars | Pre-COVID-19 | During-COVID-19 | Chi-Square statistic | p value |
|---|---|---|---|---|---|---|
| total | total | ILTF | 13.4% | 15.2% | 29.88 | **<0.001** |
| | | PTL | 25.2% | 26.1% | 4.54 | **<0.033** |
| sex (male female) | male | ILTF | 13.0% | 14.9% | 19.86 | **<0.001** |
| | | PTL | 25.8% | 26.7% | 2.39 | 0.122 |
| age (child/adult) | child | ILTF | 19.0% | 22.4% | 7.25 | **0.007** |
| | | PTL | 17.6% | 19.4% | 1.69 | 0.194 |
| HIV status (positive/negative) | HIV positive | ILTF | 14.4% | 17.5% | 37.85 | **<0.001** |
| | | PTL | 28.9% | 29.8% | 1.62 | 0.203 |
| category of TB (new/recurrent) | recurrent | ILTF | 14.5% | 15.2% | 0.912 | 0.34 |
| | | PTL | 28.5% | 29.8% | 1.73 | 0.189 |
| mode diagnosis (bacteriological/clinical) | bacteriological | ILTF | 14.0% | 14.7% | 3.39 | 0.066 |
| | | PTL | 26.4% | 27.0% | 1.24 | 0.265 |

While nearly all of Cape Town's sub-districts had small increases in ILTF and PTL in the during-COVID-19 period compared to the pre-COVID-19 period, Klipfontein had a particularly large increase in PTL (from 20.7% in the pre-COVID-19 period to 33.6% in the during-COVID-19 period). Southern had a lower PTL (33.5%), in the during-COVID-19 period, albeit a reduction from a high PTL (37.9%) in the pre-COVID-19 period. ILTF and PTL pre- and during-COVID-19, per sub-district, are shown in Table 11 below.

**Table 11. DS-TB cascades pre- & during-COVID-19: ILTF & PTL by sub-district**.

| Sub-district | ILTF | | PTL | |
|---|---|---|---|---|
| | pre COVID-19 | during COVID-19 | pre COVID-19 | during COVID-19 |
| Eastern | 14.8% | 14.2% | 26.1% | 24.5% |
| Khayelitsha | 9.6% | 12.8% | 26.5% | 24.0% |
| Klipfontein | 13.7% | 15.2% | **20.7%** | **33.6%** |
| Mitchells Plain | 9.8% | 12.6% | 17.2% | 18.1% |
| Northern | 13.9% | 15.4% | 25.9% | 27.0% |
| Southern | 17.2% | 17.3% | **37.9%** | **33.5%** |
| Tygerberg | 12.9% | 15.8% | 26.1% | 26.5% |
| Western | 14.9% | 16.5% | 23.8% | 25.8% |

# Chapter 5: Discussion

This chapter discusses the findings of the study, drawing on the literature to contextualise these findings.

The first section reflects on the number of individuals diagnosed with DS-TB per month from July 2018 to December 2021, during which period the two pre-defined 12-month pre- and during-COVID-19 DS-TB cascades were constructed. This is followed by discussion of the DS-TB cascade in the pre-COVID-19 period, disaggregated by the independent variables, detailing the first pillar (individuals diagnosed with DS-TB), and then the losses (ILTF and PTL) and the consequent TB treatment success rate. In the next section, the changes in the DS-TB cascade from the pre-COVID-19 period to the during-COVID-19 period are discussed, focusing on key changes. Lastly, the strengths and limitations of the study are considered.

## 5.1 Pattern of the number of people diagnosed with DS-TB monthly before and after the onset of the COVID-19 pandemic: July 2018 - December 2021

There was month to month variation in the number of individuals diagnosed with DS-TB, which up until March 2020 mostly ranged above 2 000 per month. Some of the factors accounting for this variation may be the previously reported seasonal variation (Tedijanto et al., 2018), with fewer diagnoses in mid-winter months, and patient health-seeking behaviour which reduces health service utilisation during the month of December.

On top of this pattern of monthly variation in the number of individuals diagnosed with DS-TB, the most prominent feature of the period July 2018 to December 2021 was the big drop in the number of individuals diagnosed with DS-TB in April, May and June 2020. This is similar to the pattern seen across the world (World Health Organization, 2021b), as well as in South Africa, where it has been attributed to an abrupt decline in TB

testing as a result of a variety of factors, primarily lockdown related limitations of population mobility and therefore reduced access to health services, as well as probable changes in health seeking behaviour due to fear of being exposed to COVID-19 at health facilities (Ismail & Moultrie, 2020). It was theorised that reduced laboratory testing capacity may have a negative influence on testing, but in South Africa COVID-19 testing did not replace Xpert MTB/RIF TB testing and TB testing capacity was not reduced (Ismail & Moultrie, 2020). Other researchers found that, although the intention was to keep the provision of essential services intact, there were reductions in staffing levels as a result of health care worker COVID-19 infection as well as some facility temporary closures, resulting in a reduction in access to routine health services, including for HIV and TB testing (Pillay et al., 2021).

## 5.2 The pre-COVID-19 DS-TB cascade: pillars and losses

### 5.2.1 Pre-COVID-19 DS-TB cascade: individuals diagnosed with DS-TB

One of the main features of the October 2018 to September 2019 (pre-COVID-19) cascade is the large number of people diagnosed with DS-TB. This is in keeping with published literature, including a 100-year review of TB in Cape Town between 1910 and 2010, which concluded that TB rates in Cape Town remain among the highest in the world (Wood & Bekker, 2017).



### 5.2.2 Pre-COVID-19 DS-TB cascade: individuals diagnosed with DS-TB by independent variables

The male preponderance found in this study (56.7%) echoes published literature (Yates & Atkinson, 2017).

While the majority (90.6%) of individuals diagnosed with DS-TB were adults, children (<15) accounted for a notable 9.4%. A study of TB in Cape Town found that TB notification peaks in the age groups 0-5, 20-24 and 45- 49 (Wood et al, 2011 in Blaser et al., 2016). The reason for this age pattern is unclear, although a modelling study

concluded it can be explained by "the protective effect of a first latent infection on subsequent infections and the faster progression to disease among previously treated patients" (Blaser et al., 2016: 60).

There was a high TB-HIV co-infection rate found in this study (42.9%), which could be even higher in the population, as the HIV status was unknown in 16.1% of people diagnosed with DS-TB. Published research estimated the HIV-associated TB burden in Cape Town in 1999 to be 50% (Wood & Bekker, 2017).

There was a high proportion of individuals (22.8%) with DS-TB who had previously had TB. A high proportion of recurrent TB (26%) was also found in a study describing the 2009 burden of tuberculosis (TB) in Cape Town and is thought to be due to ongoing TB transmission, not previous inadequate treatment (Wood et al., 2011).

The diagnosis in individuals with DS-TB was predominantly bacteriologically confirmed (71.1%), with the balance being diagnosed clinically. This is higher than was found in the previously quoted 2009 Cape Town study, in which 56% of TB diagnoses were bacteriologically confirmed (Wood et al., 2011). This could be explained by the national rollout from 2011 of TB testing using Xpert MTB/RIF, with a higher sensitivity than previous laboratory testing methods (Meyer-Rath et al., 2012).



The number of people with TB was unevenly split across the sub-districts, reflecting the high HIV disease burden and poor socioeconomic status in the most affected sub-districts of Khayelitsha, Tygerberg, Mitchells Plain and Eastern, as has been previously described (Davies et al., 2020).

### 5.2.3 Pre-COVID-19 DS-TB cascade: losses and treatment success

Substantial losses across the 3 pillars of the cascade were found, of 13.4% ILTF and 25.2% PTL. A study on the TB care cascade in South Africa (Naidoo et al., 2017), which was recently updated using 2018 data, also found high rates of ILTF (24.4%) and PTL

(21.1%) (personal communication with Dr Pren Naidoo, consultant to the South African NDoH TB Think Tank, September 2021). Osman et al (2021), in a Cape Town based study, reported a higher ILTF than was found in this mini-thesis study, of 20.0% for individuals diagnosed with DS-TB in hospital or at primary care level in Khayelitsha and Tygerberg between October 2018 and 31 March 2020 (Osman et al., 2021). In that study ILTF was measured at 30 days post diagnosis, which may account for the different results which were found in that study and this mini-thesis study.

The resultant treatment success rate was 64.8% (TB treatment success of individuals diagnosed with TB). Even in the way the TB programme usually reports success rate (TB treatment success of individuals who were notified and treated), which was a success rate of 74.8%, this is far short of global, national and local targets, such as the third 90 of the UNAIDS 90-90-90 targets, i.e. to successfully treat 90% of individuals diagnosed with TB (South African National AIDS Council, 2017).

A high proportion of children were found to be ILTF (19.0%). In Cape Town it has been found that a higher proportion of children than adults are diagnosed at hospital level (Dudley, L et al, 2018 in du Preez et al., 2020), and the linkage to primary care notifying and treatment services can be delayed and incomplete (du Preez et al, 2018 in du Preez et al., 2020). This is true at the international level as well, particularly for young children. A study found a large gap between TB disease and TB notifications, with an estimated 64.8% and 48.9% undiagnosed (or unreported) in the 0-4 age and 5-14 age groups respectively, versus 25.2% undiagnosed (or unreported) in the over 15 (adult) age group (Marais et al., 2021). However, in this mini-thesis study children ultimately had a higher treatment success rate than adults (children 66.8% and adults 64.6%) as PTL was lower in children than in adults (17.6% and 25.9% respectively).

HIV-positive individuals had higher ILTF and PTL, consequently a lower treatment success rate (ILTF 14.4%, PTL 28.9% and treatment success 60.9%), than HIV-negative individuals (ILTF 7.3%, PTL 22.3% and treatment success 72.1%). Individuals in their second or subsequent episode of TB had higher losses (ILTF 14.5% and PTL 28.5%) and

poorer outcomes (treatment success 61.1%) than those having TB for the first time (ILTF 13.1%, PTL 24.2% and treatment success 65.9%). Similar findings have been reported in the literature; in a study on adolescents and young adults in Cape Town, risk factors for loss from TB care included being TB/HIV co-infected and previously treated for TB (Mulongeni et al., 2019). In the Mulongeni et al study (2019) being male was also a risk factor for loss from TB care, however in this mini-thesis study males had slightly lower ILTF compared to females (13.0% and 13.9% respectively), although slightly higher PTL than females (25.8% and 24.4% respectively), with resultant treatment success of 64.5% in males and 65.1% in females (which was not a statistically significant difference).

Khayelitsha, the sub-district with the highest number of TB episodes, had the lowest ILTF of all the sub-districts, at 9.6%. From 2018 to 2020 Khayelitsha was one of the locations for an operational research study entitled LINKEDin, aiming to reduce ILTF between hospital level and primary care levels, which may have positively impacted ILTF (Osman et al., 2021; Vanqa et al., 2021; Viljoen et al., 2022). However, due to having one of the highest PTL (26.5%), the success rate in Khayelitsha (66.4%) was not the highest of all sub-districts: this was in Mitchells Plain, where it was 74.6%.

## 5.3 Comparing the during- and pre-COVID-19 DS-TB cascades: pillars and losses



### 5.3.1 Comparing the during- and pre-COVID 19 DS-TB cascades: Diagnosed with TB

The biggest change comparing the pre-COVID-19 period with the during-COVID-19 period was the large decrease (28%) in the number of individuals diagnosed with DS-TB. This echoes the estimates of a drop in tuberculosis case detection in 2020 vs. 2019 globally by 18% and in South Africa by 26% (Dheda et al., 2022). Evidence suggests this occurred across age groups, for instance paediatric TB diagnoses at two large hospitals in Johannesburg, South Africa, fell significantly in a 6 month period following the onset of the COVID-19 pandemic compared to the previous 27 months (Lebina et al., 2020).

While there appears to be growing consensus that the sudden drop in the number of individuals diagnosed with TB following the onset of the COVID-9 pandemic was due to reduced health care access, what is still unclear is why TB diagnoses have still not recovered to the pre-COVID levels, or shown rebound increases, as was predicted. The sudden reduction suggests reduced access, but "does not exclude or confirm the effect of reduced transmission" (Dheda et al., 2022: 605). A review published in August 2022 noted that although in most situations an increase in TB notification followed the decreases in TB notification, the increase fell short of the pre-COVID-19 levels (Trajman et al., 2022). One early suggestion was that the drop could be due to delays in reporting caused by disrupted health systems (McQuaid et al., 2021). However, this does not explain the ongoing findings, which may represent actual reduced transmission of the disease, or an insufficient recovery program to detect the "missing" people with TB. A modelling study had predicted that social distancing may result in lower TB incidence, but only in settings with low health service disruption; (McQuaid et al., 2020).

National public sector TB testing data presented at the 7th South African TB conference held in September 2022 (Foundation for Professional Development Conference & Special Events Department, 2022) showed that, despite recent increases in Xpert MTB/RIF TB testing above predicted levels of testing against a pre-COVID-19 baseline, there had not been increases in the number of positive tests or test positivity above predicted levels. Although it is possible that this was due, at least in part, to low TB prevalent groups being targeted for testing, another possibility is that interventions to prevent COVID-19 transmission (such as social distancing and mask wearing) reduced TB transmission (Moultrie, 2022). However, as there are lags between exposure to TB, infection and development of disease, an increase in the burden of TB at the population level may not have declared itself yet (Benade et al., 2022).

### 5.3.2 Comparing the during- and pre-COVID 19 DS-TB cascades: losses (ILTF & PTL) and treatment success

Both ILTF and PTL increased from the pre-COVID-19 period to the during-COVID-19 period: ILTF by 1.8%, from 13.4% to 15.2% and PTL by 0.9%, from 25.2% to 26.1%.

Treatment success (of individuals diagnosed with TB) fell by 2.1%, from 64.8% to 62.7%. A drop in TB treatment success has been reported from Zimbabwe, although in that setting in a period from March 2020 to February 2021 the drop was larger, from 80.9% to 69.3% (Thekkur et al., 2021).

Comparing the proportions of ILTF and PTL in the during-COVID-19 period to the pre-COVID-19 period for the dichotomous variables sex, age, HIV status, sex, category of TB and mode of diagnosis, no association was found between PTL and COVID-19 period. However, for ILTF the proportion of males ILTF increased from 13.0% in the pre-COVID-19 period to 14.9% in the during-COVID-19 period, the proportion of children ILTF increased from 19.0% in the pre-COVID-19 period to 22.4% in the during-COVID-19 period and the proportion of HIV positive individuals ILTF increased from 14.4% in the pre-COVID-19 period to 17.5% in the during-COVID-19 period. No comparative published literature could be found of the impact of the COVID-19 epidemic on the TB care cascade for these sub-groups of individuals diagnosed with TB. However, in literature related to access to health care in general children and males have been shown in some settings to have poorer access and it is plausible that COVID-19 exacerbated this problem. In addition, mortality related to COVID-19 may have contributed to the increased losses for males and HIV positive individuals, both of which sub-groups had a higher risk of mortality due to COVID-19 (Boulle et al., 2021).



In terms of the changes in losses and treatment success at sub-district level, Klipfontein had the biggest change, with PTL increasing from 20.7% in the pre-COVID-19 period to 33.6% in the during-COVID-19 period and treatment success falling from 68.4% to 56.3%. It is not apparent why the TB care cascade in Klipfontein was impacted more than in other sub-districts.

## 5.4 Strengths and Limitations

One of the main strengths of the study was the use of PHDC data (instead of data from stand-alone routine TB programmatic reporting systems). This allowed the inclusion of TB diagnoses made on clinical grounds and obviated modelling, as was done by Naidoo

et al (2017), to estimate the Diagnosed with TB pillar (Naidoo et al., 2017). Using PHDC data also allowed a cohort-based approach to the cascade, with the same individuals followed across each pillar, as has been recommended in constructing TB care cascades, to minimise risk of bias (Subbaraman et al., 2019).

Using PHDC data, which comprises data collected routinely in health services in the various source systems of PHDC, brought probable quality and completeness of data problems. However, using PHDC triangulated data (over an individual health information data set used in routine TB programmatic reporting) is likely to have mitigated this limitation to some extent. The completeness of data elements related to mortality in PHDC may be particularly negatively affected, as mortality is not always known to health services and population register data is not currently being routinely received by PHDC (Boulle et al., 2019). However, in the context of this study, which did not investigate what the various components of the losses were, the overall losses in ILTF and PTL would not have been affected by this problem.

Another limitation is that this study used data from the public sector. While the vast majority of TB diagnosis and treatment is in the public sector (Naidoo et al., 2017), possible changes in sector use during the study period may be a confounder which could not be ascertained.



A further limitation is that TB incidence rates (i.e. the number of people diagnosed with TB in an annual period per 100 000 population) were not calculated in this study. Population size changes could theoretically have contributed to changes which were observed in the number of people diagnosed with TB in the two cascade periods. However, according to WCGH population estimates, the population in Cape Town has been increasing year-on-year (Western Cape Government Health Chief Director: Strategy and Health Support, 2020) which, if all else was equal, would translate to an increase in the number of people with TB, not a decrease, as was found in this study comparing the during-COVID-19 period with the pre-COVID-19 period.

A major limitation of the study was that it described a limited cascade of just 3 pillars, those for which routine data could be used, while the pillars of “TB burden” (at a population level) and “Accessed TB tests” (Naidoo et al., 2017; Subbaraman et al., 2019) were outside the scope of this study. Also outside of the scope of this study was evaluation of observed changes in the DS-TB care cascade in the context of preceding trends in the DS-TB care cascade before the study period.

As this was a retrospective epidemiological study there was no control group, so caution must be exhibited in attributing any of the changes to the effect of COVID-19, as other factors could be responsible for any of the observed differences between the pre- and during-COVID-19 DS-TB cascades.

# Chapter 6: Conclusion and Recommendations

In this final chapter the main findings are summarised and recommendations are put forward for interventions, practice, policy and further research.

## 6.1 Conclusion

The DS-TB cascades revealed a very large burden of TB disease in Cape Town, as has been previously documented and substantial losses across the DS-TB cascades between diagnosis and treatment success, resulting in far-from target treatment success rates.

In the pre-COVID-19 DS-TB cascade the number of people diagnosed with TB was 27 481, ILTF was 3 683/27481; 13.4%, PTL was 5 989/23 798; 25.2% and treatment success was 17 809/ 27 481; 64.8%. Adults (compared to children <15); individuals who were HIV-positive (compared to those who were HIV-negative); individuals with recurrent TB (compared to those who had TB for the first time); and individuals with bacteriologically confirmed TB (compared to those in whom a diagnosis was made clinically) had poorer treatment success. There was no association between treatment success and sex.



In the during-COVID-19 DS-TB cascade the number of people diagnosed with TB was 19 800, ILTF was 3 005/19 800; 15.2%, PTL was 4 384/16 795; 26.1% and treatment success was 12 411/19 800; 62.7%. As with the pre-COVID-19 DS-TB cascade, individuals who were HIV-positive (compared to those who were HIV-negative) and individuals with recurrent TB (compared to those who had TB for the first time) had poorer treatment success, and there was no association between treatment success and sex. However in the during-COVID-19 DS-TB cascade, differing from the pre-COVID-19 DS-TB cascade, there was also no association between age and mode of diagnosis.

There was a substantial drop in the number of people diagnosed with DS-TB in the annual period following the onset of the COVID-19 pandemic (from 27 481 to 19 800, a 28% drop), which was most pronounced in the first few months. The losses in the DS-TB

cascade increased in the annual period following the onset of the COVID-19 pandemic, with ILTF increasing by 1.8% to 15.2% and PTL increasing by 0.9% to 26.1%, resulting in an overall fall in treatment success from 64.8% to 62.7%. These changes were not equivalent across the evaluated categories, with males (compared to females), children <15 (compared to adults), and HIV positive individuals (compared to those who were HIV-negative) having larger increases in ILTF.

Variation was also observed between the sub-districts in ILTF, PTL and treatment success in the pre-COVID-19 DS-TB cascade and in the changes in ILTF, PTL and treatment success between the pre- and during-COVID-19 DS-TB periods.

## 6.2 Recommendations

The theme of the 7th South African TB conference held in September 2022 was "Working together to get TB back on track", which succinctly captures what is needed to address gaps in programmatic response to the TB epidemic which pre-dated, but have been eroded by COVID-19 (Foundation for Professional Development Conference & Special Events Department, 2022).

### 6.2.1 Practice



Ongoing surveillance of TB care cascade pillars and losses is imperative, to track if efforts to close gaps in the cascade are effective. Wider use in other settings of a unique patient identifier to link relevant data, such as is done in the PHDC, would increase availability of comprehensive data to inform such surveillance.

Mask wearing to prevent TB transmission has historically had poor uptake, but the increased access to masks and acceptance of mask-wearing which occurred during COVID-19 may provide a "silver lining" for TB programme efforts (Van den Driessche et al., 2021).

### 6.2.2 Interventions

Interventions are needed to close gaps in the TB care cascade, which could include improving the implementation of existing tools and current interventions as well as developing new approaches. Interventions need to go beyond the biomedical, to include health promotion and addressing the underlying social determinants of health. As South African National AIDS Council CEO Thembisile Xulu said at the 7th South African TB conference, we also need to "work together to end TB stigma and discrimination because these continue to be barriers against TB management"(Spotlight, 2022).

Sub-populations less likely to have a successful treatment could warrant specially targeted interventions; in this mini-thesis study these were people diagnosed with TB who were HIV/TB co-infected and people experiencing their second or subsequent episode of TB. TUTT, one of the key interventions in the South African NDoH TB Recovery Plan, involves testing of people who are asymptomatic but at risk for TB, including people living with HIV (PLHIV) and individuals with previous TB (Bailey, 2022). This strategy seeks to reduce the pool of undiagnosed TB and find "missing cases" (Martinson et al., 2022), but may also reduce ILTF and PTL if TB is diagnosed at an early stage of disease in asymptomatic individuals. Another intervention in the TB Recovery Plan which could address some of the TB cascade gaps in the HIV/TB co-infected sub-population is urine LF-LAM, which increases diagnostic yield in HIV/TB co-infected individuals with low CD4 counts who are at high risk of mortality (Bailey, 2022).

In the particular setting of this study, exploring the reasons for better performance in sub-districts such as Khayelitsha with lower ILTF, as well as a focus on sub-districts with poorer outcomes, such as Southern, could be of value.

### 6.2.3 Policy

As was shown in this study, ILTF is a large component of losses across the TB care cascade; however, it is not routinely reported. Reporting TB treatment success which

takes into account all individuals diagnosed with TB (as was done in this study), not only those initiated on treatment, could highlight this gap.

### 6.2.4 Further research

While this mini-thesis study documented the DS-TB care cascade in a pre-COVID-19 time period and changes in the cascade in a during-COVID-19 time period in a high-TB-burden setting (Cape Town) as per the study objectives, there are many unanswered questions about the impact of COVID-19 on TB.

Further studies using similar methodology could lead to more insights, such as extending the focus to include DR-TB, further sub-dividing the age categories and examining time delays between the pillars of the TB care cascade. The study reported overall losses in the DS-TB care cascade, but did not quantify various components of the losses, such as mortality. Investigating this would be of value, given mortality caused by COVID-19 in the general population and literature which documents an increased risk of death from COVID-19 in individuals with current or previous TB (Boulle et al., 2021). A time-trend analysis examining TB programme indicators further back than the pre-COVID-19 period of this study could shed further light.



From a qualitative research perspective, building on previous research to understand why there are losses along the TB care cascade, studies are needed to explore if and how COVID-19 affected these underlying determinants.

It was beyond the scope of this study, but it is critical to understand what the impact of COVID-19 has been on TB transmission, TB incidence and TB prevalence. If the observed drop in the number of people diagnosed with TB was due (at least in part) to reduced transmission and incidence, this would be a step forward in ending TB. It would also spur us on to uncover what interventions could maintain and strengthen the positive effect. However, if the drop in the number of people diagnosed with TB was due to a large increase in undiagnosed TB, it would be a step backwards in ending TB. TB

prevalence surveys, while costly, could uncover which of these scenarios, or what balance of these scenarios is the case.

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# Appendices

## Appendix 1: IMPAC$_{19}$T$_{B}$ study outline

## Appendix 2: Data extraction tool

## Appendix 3: Cascades timeline

## Appendix 4: Ethics and data access approvals

4a: UWC BMREC ethics approval

4b: WCGH approval

4c: CCT approval

4d: PHDC data access approval

**APPENDIX 1**

## $\underline{IMPAC_{19}T_B}$ - Epidemiological impact and intersection of the COVID-19 and tuberculosis pandemics in Brazil, Russia, India and South Africa

Overall study aim: Using a multidisciplinary research approach, we aim to investigate the epidemiological impact and intersection of the COVID-19 and TB pandemics at the patient and the population level in the four project countries: South Africa, India, Russia, and Brazil. Towards this aim, the **overall project has 5 key objectives**, with each of the country teams leading collaboration in specific domains. **The South African collaborative group will implement research activities in 3 of the 5 overall project objectives**:

- **Objective 1: To estimate differential losses along the TB care cascade attributable to COVID-19**
- Objective 4: To determine programme and other in-country response measures to mitigate the negative impacts of COVID-19 on TB healthcare services
- Objective 5: To use mathematical modelling to estimate the impact of COVID-19 and COVID-19 response measures on TB incidence and TB-associated mortality, and model the impact of recovery measures

This document provides information specific to our **request for approval to collect data in the Western Cape Province for Objective 1 and 4.** Objective 5 will use the data collected in objective 1 and 4.

**Western Cape Province (WCP)**

**Objective 1: Estimating the impact of COVID-19 and response measures on the TB care cascade**

This objective will use routine data collected programmatically for the construction of a TB care cascade. In South Africa this will allow for an updated TB care cascade nationally.

Within the Western Cape Province, our intention is to construct a TB care cascade for the City of Cape Town district. This will assist with program evaluation and identifying gaps in the quality of TB care for the City of Cape Town District. The use of the Western Cape Government: Provincial Health Data Centre TB Cascade will allow the opportunity to report on the TB care cascade for identified sub-populations, such as children, the elderly and people living with HIV. **The work on the TB indicators will be driven by a supervised MPH student (Dr Karen Jennings)** who will focus on the TB care cascade. For this we request the de-identified, de-duplicated TB patient cascade for the City of Cape Town District (defined as any TB evidence occurring at a facility in the City of Cape Town District) for the period July 2018 to December 2021.

**Objective 4: To determine programme and other in-country response measures to mitigate the negative impacts of COVID-19 on TB healthcare services**

This objective will provide a rich understanding across contexts of how COVID-19 has impacted on TB services from the perspective and using the personal experiences of healthcare workers, TB patients and caregivers of child TB patients. We intend to learn lessons from the COVID-19 response (both successes and mis-steps) that can inform the TB programme going forward. This is the first time that this has been explored across the BRICS countries.

This objective has 2 components:

1. *Component 1*: Electronic Surveys of TB Care, Treatment and Services
2. *Component 2*: In-depth qualitative work

For both these components we will collect data in the Western Cape Province.

*Component 1* comprises of

- A self-administered online survey amongst health workers across the Western Cape Province. This is a very brief questionnaire (estimated to take 8-10mins to complete) which captures health workers lessons from the COVID-19 response for the TB programme. The online survey will be shared via an electronic tool (REDCap) inviting health workers to participate in the study. The intention is to include as many health workers as possible across the entire WCP. To provide easy access to the survey, we will recruit potential health workers by; sharing the survey with relevant managers within the health system who can then share with health workers across all locations and in both the public and private sectors and using existing platforms e.g., TB Clinical forum (monthly meeting of TB health workers and TB academics). Further details can be found in the protocol document and the survey questions can be found in the relevant annexure to this application.
- An interviewer administered 'consumer satisfaction'-style survey with TB patients (≥15 years; n= ~50) and caregivers of child TB patients < 15 years (n = ~50) within the City of Cape Town Metro District. For patients and caregivers, we will use purposive sampling to approach clients of TB screening, adherence support and contact management strategies at preselected health facilities within the City of Cape Town Metro District. We will select between 4 and 6 health facilities with high TB burdens across the district. Selection of specific facilities will be done in consultation with management at the Provincial Department of Health and with City Health management, as we anticipate that we will include both provincial and City facilities. Approximately 10 TB patients (≥15 years) and 10 caregivers of child TB patients (<15 years) will be enrolled from each health facility. We will purposively sample to ensure that the final sample is balanced by location, gender, and age category. We will approach ~75% of study participants whilst they are at TB sections of health facilities. Trained research assistants (RAs) will visit each selected health facility and approach people sitting in the TB section to recruit to the study. To ensure that the perspectives of patients who are not at the facility and have had gaps in their care continuity are included, we will also approach ~25% of study participants from phone numbers listed in their electronic health records or patient folders (these participants will be asked to complete the questionnaire on the telephone). Further details can be found in the protocol document and the survey questions can be found in the relevant annexure to this application.

**Note: We are requesting to do surveys in the facility, but also use patient data to phone patients who may not be coming for care. We kindly request that this is made explicit in the approval letter, to assist us at facility level.**

*Component 2* comprises targeted semi-structured in-depth interviews with:

- TB programme managers (n = ~6) and healthcare workers (n = ~10), including nurses, doctors, and community workers across the WCP. TB programme managers will be purposively sampled by seniority of position within the district and provincial TB programme. For example, in the Western Cape South Africa, the HAST Director for the Western Cape or TB manager for the City of Cape Town will be approached for recruitment to the study. These participants will be approached by the researcher, either directly via email

or via other appropriate routine mechanisms. Health workers will be approached via their clinic managers and will be interviewed at a time and place convenient to them, to reduce the impact on their work. Eligibility criteria for health workers are aged ≥18 years; providing care at a health facility; able to provide consent and agree to being audio recorded. Although cross sectional, these interviews will detail health workers' experiences providing TB treatment and care, as well as provide insights into the potential barriers and facilitators to overcoming the challenges posed by COVID-19. We will adopt the maximal variation sampling strategy to maximize diversity in health worker experience (home context, age, experience in healthcare and cadre of staff, etc.). Each interview will last approximately 45-60 minutes. All interviews will be conducted and recorded in participants' preferred language and at a time and place convenient to participants. When possible, we are happy to conduct these discussions using phone or a virtual platform. As far as possible, we will ensure privacy and confidentiality whilst conducting the interviews. Participants will be reimbursed for their time, in the form of light refreshments, if interviews are face-to-face.

- TB patients (n = ~12) and caregivers of children with TB (n = ~20). These participants will be sampled from those who completed the survey as above. We will not require any further input from health services to enrol these participants to be interviewed.

Further details around the qualitative work can be found in the protocol document and the discussions guides can be found in the relevant annexures to this application (two separate discussion guides for TB programme managers/healthcare workers and TB patients/caregivers).

**Ethical Considerations**

This study has received ethical approval from the Stellenbosch University Health Research Ethics Committee (N21/05/013_COVID-19).

For Objective 1: We have been granted a waiver of consent from the Stellenbosch University HREC (Approval attached to this application). All data collected for objective 1 will be aggregated data for each indicator. In addition, we have also requested a TB care cascade, which will be de-identified. We are NOT requesting any patient identifiable data.

For Objective 4: All participants enrolled in the study will provide informed consent prior to participating. All participation will be entirely voluntary. This research poses no more than minimal risk to participants. The chief risk is possible loss of anonymity in objective 4; however, all available means will be taken to protect participants' privacy and confidentiality. Speaking with participants about TB and other health-related issues may lead to some discomfort or distress. Where researchers deem it necessary, or participants request additional psycho-social support, participants will be referred to local clinics for counselling with a psychologist, counsellor, or social worker. The study will adhere to the ethical and safety guidelines laid out in the Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants and the WHO Guidance on ethical considerations in planning and reviewing research studies on sexual and reproductive health in adolescents. Details around ethical considerations are included in the protocol. All informed consent documents are included as additional documentation in this submission.

This study will not negatively impact on health facilities or staff in health facilities. We do not require any specific space or equipment/consumables to collect data. We do not require staff to assist us in enrolling potential participants. Our only request would be for the relevant person in the TB room to assist us with contact details of TB patients who have not returned for care. Our aim is to enrol TB patients and caregivers of child TB patients in the consumer satisfaction'-style survey, to ensure that we include their perspectives as well as those who remain in care.

**TB data extraction tool** **APPENDIX 2**

| variable | row # | age in years | sex | hiv status | TB first evidence date | TB evidences lab confirmed | DR-TB | TB allocated treatment facility name | TB allocated treatment sub-district | phc treatment (notified) | patient category | successful treatment outcome | date of death |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| categories | | 0-115 | M/F | Neg/Pos | yyyy/mm/dd | Y/N | Y/N | according to all TB treating facilities named in PHDC | Eastern<br>Khayelitsha<br>Klipfontein<br>Mitchells Plain<br>Northern<br>Southern<br>Tygerberg<br>Western<br>non-Metro | Y/N | New/ Retreatment according to episode number = 1 or ≥2 | Y/N (Y = Cured / Completed) N = LTF/ Failure/ Died/ Moved out/ develop DR) | yyyy/mm/dd |
| data | 1 | | | | | | | | | | | | |
| | 2 | | | | | | | | | | | | |
| | 3 | | | | | | | | | | | | |
| | 4 | | | | | | | | | | | | |
| | 5 | | | | | | | | | | | | |
| | 6 | | | | | | | | | | | | |
| | 7 | | | | | | | | | | | | |
| | 8 | | | | | | | | | | | | |
| | 9 | | | | | | | | | | | | |
| | 10 | | | | | | | | | | | | |
| | 11 | | | | | | | | | | | | |
| | 12 | | | | | | | | | | | | |
| | etc. | | | | | | | | | | | | |

**CASCADES TIMELINE** **APPENDIX 3**

| 2018 | | | | | | 2019 | | | | | | | | | | | | 2020 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Jul | Aug | Sep | Oct | Nov | Dec | Jan | Feb | Mar | Apr | May | Jun | Jul | Aug | Sep | Oct | Nov | Dec | Jan | Feb | Mar |
| | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 1 | 2 | 3 | 4 | 5 | 6 |
| | | | | | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | |

| 2021 | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Apr | May | Jun | Jul | Aug | Sep | Oct | Nov | Dec | Jan | Feb | Mar | Apr | May | Jun | Jul | Aug | Sep | Oct | Nov | Dec |
| | | | | | | | | | | | | | | | | | | | | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 1 | 2 | 3 | 4 | 5 | 6 | | | |
| | | | | | | | | | | | | | | | | | | | | |

**TB diagnosis (12 month period)**

1 to 12 pre-Covid -19 period

1 to 12 during Covid-19 period

**TB outcomes (which are beyond the period of TB diagnosis)**

**1 to 6 pre-Covid -19 period**

1 to 6 during Covid-19 period

PHDC data extract (July 2018 to Dec 2021)

UNIVERSITY of the WESTERN CAPE

60 YEARS of hope, action & knowledge

29 November 2021

Dr K Jennings
School of Public Health
**Faculty of Community and Health Sciences**

**Ethics Reference Number:** BM21/10/19

**Project Title:** Estimating the Impact of the Covid-19 pandemic on Tuberculosis in Cape Town, South Africa

**Approval Period:** **19 November 2021 – 19 November 2024**

I hereby certify that the Biomedical Science Research Ethics Committee of the University of the Western Cape approved the scientific methodology and ethics of the above mentioned research project and the requested amendment to the project.

Any further amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.

**Please remember to submit a progress report annually by 30 November for the duration of the project.**

For permission to conduct research using student and/or staff data or to distribute research surveys/questionnaires please apply via:
https://sites.google.com/uwc.ac.za/permissionresearch/home

*The permission letter must then be submitted to BMREC for record keeping purposes.*

The Committee must be informed of any serious adverse event and/or termination of the study.

*Ms Patricia Josias*
*Research Ethics Committee Officer*
*University of the Western Cape*

*NHREC Registration Number: BMREC-130416-050*

Western Cape Government
Health

**STRATEGY & HEALTH SUPPORT**
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REFERENCE: WC_202107_037
ENQUIRIES: Dr Sabela Petros

**Francie van Zijl Drive**
**Tygerberg**
**7505**
**Cape Town**
**South Africa**

For attention: DR Muhammad Osman, PROF Anneke Hesseling, DR Sue-Ann Meehan, DR Karen du Preez, MR Graeme Hoddinott, DR Rory Dunbar, DR Florian Marx, PROF Andrew Boulle, DR Harry Moultrie, DR Farzana Ismail, DR Kavindhran Velen, PROF Mary-Ann Davies, DR Karen Jennings

**Re: Epidemiological impact and intersection of the COVID-19 and tuberculosis pandemics in Brazil, Russia, India and South Africa (IMPAC19TB)**

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department finds you study feasible and has provisionally granted you approval for your research. This is subject to the custodian of the datasets ability to process your request. Please note that you are not guaranteed any datasets.

Please contact the following people to assist you with any further enquiries in accessing or obtaining the requested datasets:

| | | |
|---|---|---|
| **Provincial Health Data Centre** | **Mary- Ann Davies** | **021 483 0883** |
| | **Andrew Boulle** | **andrew.boulle@uct.ac.za** |

*Where planned analyses overlap substantially with analytic work already being undertaken internally by WCGH based on routine data held by WCGH, WCGH may propose collaboration on the ongoing analyses in preference to dataset provision. This will depend on the operative circumstances at the project stage.*

Kindly ensure that the following are adhered to:

1. Researchers, in accessing provincial health facilities or datasets, are expressing consent to provide the department with an electronic copy of the final feedback (**Annexure 9**) within six months of completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).
2. In the event where the research project goes beyond the *estimated completion* date which was submitted, researchers are expected to complete and submit a progress report (**Annexure 8**) to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).
3. The reference number above should be quoted in all future correspondence.

Yours sincerely

**DR M MOODLEY**
**DIRECTOR: HEALTH INTELLIGENCE**
**DATE: 09/11/2021**
**CC**

**Approval for City Health's own staff initiated research**

**Name: Karen Jennings**
**Staff number: 10027343**
**Title and MARS number: IMPAC19TB - Epidemiological impact and intersection of the COVID-19 and tuberculosis pandemics in Brazil, Russia, India and South Africa 9453**
**Within 9453, as a local part of Objective 1, and in fulfilment of a UWC MPH mini-thesis: Estimating the Impact of the Covid-19 pandemic on Tuberculosis in Cape Town, South Africa**

**(Attach summary of research proposal)**

| Guiding Criteria | Yes/No | Additional Comments |
|---|---|---|
| Research topic/title is sound? | Yes | |
| Research has clear aim and objectives? | Yes | |
| Research questions are sound and aligned to the stated objectives? | Yes | |
| Research methodology is sound? | Yes | |
| Research aim and objectives aligned to one or more of the CCT's 11 Priority Objectives? | Yes | IDP 2017 – 2022: Excellence in basic service delivery |
| Research aim and objectives aligned to one or more of the CCT's Strategic Focus Areas? | Yes | IDP 2017 – 2022: Caring City (3.1.a Excellence in service delivery), Inclusive City (4.3f: PHC), Well-run City (5.1.d Evidence-led decision-making programme) |
| Research outputs/deliverables are clearly defined? | Yes | |
| Research demonstrates value for money/resource input? | Yes | No CCT resource needed other than the researcher's time (to be managed within usual time and attendance parameters) |
| Research poses any potential risks to the CCT? | No | |

**Approval:**

1. **Line manager**

Signature Natacha Berkowitz Digitally signed by Natacha Berkowitz Date: 2021.12.23 15:40:47 +02'00' Acting Specialised Health Manager
Name .....
Date .....
Comments (e.g. time allocation during work hours and inclusion in WSP)

MPH (which includes this mini-thesis) appears on PDP. Time allocation is to be managed within usual time and attendance parameters (expectation is for minimal impact during usual working hours; there may need to be some flexitime requests accommodated for mini-thesis supervision).
.....
.....

2. **Area/Branch Manager**

Signature Natacha Berkowitz Digitally signed by Natacha Berkowitz Date: 2021.12.23 15:41:01 +02'00' Acting Specialised Health Manager
Name .....
Date .....

Comments
.....
.....
.....
.....
.....



**3. Director City Health**

Signature
Dr Paul Nkurunziza Soraya Elloker Digitally signed by Soraya Elloker Date: 2021.12.23 20:40:14 +02'00' Acting Director
Date .....

Comments Research supported
.....
.....
.....
.....
.....

Annexure A

## APPLICATION FOR ACCESS TO HEALTH DATASETS

The following application form is to be completed by all person/persons/organisations/groups who wish to access to health-related datasets from Western Cape Department of Health and is to be completed in accordance with the Departments' *Guidelines on requests for access to patient datasets from the Department of Health*. Please note that application for use of data does not guarantee that the data request will be approved. If the intended purpose for data access is altered or extended in anyway, a new agreement must be entered into.

**Applicant details:** *(Refers to the detail of the person requesting the change.)*

| | | | |
|---|---|---|---|
| **Name:** | Sue-Ann | **Surname:** | Meehan |
| **Designation / Rank:** | Senior Researcher | **Date:** | 06/08/2021 |
| **Organisation:** | Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University | | |
| **Email:** | sueannm@sun.ac.za | **Tel/Cell:** | 0726220711 |

*Please supply the contact detail of the person to whom the processed application must be returned.*

**Details of Data Request:** (please append any additional information where necessary)

| **Type of Data Requested :** (please tick appropriate option) | Aggregated data - **YES** for request 2 (see below) | Non-identified individualised data - **YES** for request 1 (see below) | Identified individualised data |
|---|---|---|---|

**Please provide a short description of the data requested. Please attach a list/attach a list of the variables required.**

Our request is twofold:

1) We request the de-identified, de-duplicated **TB patient cascade** for the City of Cape Town District (defined as first evidence of any TB episode occurring at a facility in the City of Cape Town District) for the period January 2017 to December 2022. We request the cascade be provided in two extracts, one immediately (which will not contain the end part of the period) and one after the period is completed.
   For this data set we request that a check for mortality among those patients with an unknown outcome is done against the South African population register before providing the data set.

**2)** We request aggregated data for TB, TB Prevention, TB/HIV and COVID-19 indicators from the PHDC for the City of Cape Town District. Specifics for each set of indicators is set out below. We request these indicators by month, age and sex for the period January 2017 to December 2022, provided in two extracts, one immediately (which will not contain the end part of the period) and one after the period is completed.



TB Indicators:

- Screened for TB
- Investigated for TB (sputum/non-sputum specimens)
  - Type of specimen
- Sputum (and non-sputum) specimens with a positive TB result
- Sputum specimens with a positive TB result that had smear microscopy
- Smear grade of sputum specimens with a positive TB result that had smear microscopy
- Positive sputum (and non-sputum) specimens with DST
  - DST results that were drug-susceptible
  - DST results that were RIF-resistant
- TB cases notified/reported (all patients)
- Number of previous TB episodes of TB cases notified/reported (all patients)
- TB cases initiated on TB treatment
- TB cases in reporting cohort
- TB cases with treatment success
  - Cure
  - Treatment complete
- Loss to follow up
- Transfer out
- Not evaluated
- Dead (death due to any cause during the TB episode)

- Treatment failure

TB prevention indicators:

- Started on TPT
  - Regimen used
  - Duration
- Completed TPT
- Developed TB on TPT
- Lost to follow-up on TPT
- Died on TPT and/or other severe adverse events
- TPT indication/at-risk group
  - child contact (0-5 years of age)
  - adult or adolescent (≥15 years old) household contact
  - People living with HIV (adults and children)
  - drug susceptible contact
  - drug resistant contact

TB/HIV Indicators:

- Notified/reported TB cases tested for HIV
- TB cases tested for HIV that were reported as HIV-positive
- Date of CD4 count and CD4 result of HIV-positive TB patients not receiving ART at the start of TB treatment (within a window of 12 months before the start of TB treatment and 2 months after)
- HIV-positive TB patients receiving ART at the start of TB treatment
- HIV-positive TB patients started on ART during TB treatment

COVID Indicators:

- Number vaccinated

| | | |
|---|---|---|
| **Do you have a National Health Research Database ref no.?** | Yes X No | Number: WC_202107_037 |
| **Time period the data should cover:** | Start date: 01/01/2017 | End date: 31/12/2022 |
| **Frequency of Access:** (please tick appropriate option) | Once-off | Periodically: two time periods |
| **If periodically, please specify time frames for access:**<br>**First extract:** Early 2022<br>**Second extract:** 28 February 2023 | | |
| **Is the data to be used for research purposes?** | Yes XX | No |
| **Please provide a brief motivation for this request, highlighting the purpose for which the data will be used**<br>IMPAC19TB - Overall project aim: Using a multidisciplinary research approach, we aim to investigate the epidemiological impact and intersection of the COVID-19 and TB pandemics at the patient and the population level in the four project countries: South Africa, India, Russia, and Brazil. To achieve this aim, we have 5 project objectives, which are detailed in the protocol. This data request is specifically to address objective 1; To estimate differential losses along the TB care cascade attributable to COVID-19. We will use the data requested to address this objective for the City of Cape Town district specifically.<br>**Study funded by:** SAMRC | | |
| **Do you have a security protocol for handling the data (attach detail if necessary)?** | Yes XX – we have a data management plan detailed in our study protocol (attached) | No |

| | | |
|---|---|---|
| **PHDC Manager- Technical assessment and comments:**<br>Components of this data set are feasible to obtain (extensively commented and corresponded by Arne von Delft) | | ■Feasible<br>*Where relevant:*<br>■Protocol cover<br>■Ethics<br>□ Consent docs |
| **Assigned PHDC analyst:**<br>Jonathan.Euvrard@westerncape.gov.za<br>Florence.Phelanyane@westerncape.gov.za | **PHDC Manager Signature:**<br>**Adam Loff**<br>*Deputy Director: Business Intelligence / Manager: Provincial Health Data Centre (PHDC)* | **Date: 19 May 2022** |

**Outcome of Application:** (To be completed by the Designated Health Authority)

| | | | |
|---|---|---|---|
| **Name:** | Dr M Moodley, Director: Health Intelligence | **Surname:** | |
| **Designation / Rank:** | | **Signed:** |  |
| **Application Approved:** | Yes X / No | **Date:** | dd/mm/yyyy |

## TERMS OF AGREEMENT FOR ACCESS TO HEALTH DATASETS

The Western Cape Department of Health is committed to ensuring availability of data that supports the provision of health care and other essential services to authorised Users. This agreement aims to ensure the authorisation, maintenance of confidentiality and appropriate use of datasets provided to Users.

This agreement is between:

The Western Cape Government: Department of Health, hereafter "the Department"

AND

Dr Muhammad Osman, hereafter "the User"

1. Application for use of data must be made through the channels identified in the "*Guidelines on requests for access to patient data and patient information systems*" document.
2. This agreement sets forth the terms and conditions to which the Department will disclose certain confidential health information in the form of a Dataset(s).
3. The User agrees that the Department is the owner of the Dataset(s).
4. Permitted Uses and Disclosures:

4.1. Except as otherwise specified herein, the User may make all uses and disclosures of the **two datasets listed above**, Dataset(s) necessary to conduct the ***IMPAC19TB study*** for the period starting **01 January 2017** and ending **31 December 2022**.

4.2. The User will receive the Dataset(s) **periodically** per ***two time periods (specified above),*** from the designated Department official.

**4.3.** In addition to the User, the individuals, or classes of individuals, who are permitted to use or receive the Dataset(s) for purposes of the Identified Project include: **Dr Karen Jennings, Dr Sue-Ann Meehan, Dr Rory Dunbar.**

5. User Responsibilities:

5.1. The User will not use or disclose the Dataset(s) for any purpose other than permitted by this Agreement pertaining to **IMPAC19TB** for which written approval was granted.

5.2. The User agrees that the Dataset(s) provided will not be released to any third party that is not included by the provisions of the agreement between the primary parties, without the written permission of the Department. A third party will be required to complete an agreement as well.

5.3. The User agrees that the Department will be provided with an opportunity to comment and give feedback prior to the finalisation of any report/publication derived from the Dataset(s) according to the following conditions:

**5.3.1.** The data will be used to compile ***(progress reports and a final report)*** for *(South African Medical Research Council**) and will be used for a mini-thesis for Dr Jennings's MPH, submitted to the University of the Western Cape*.

5.3.2. The report will be sent to the Department for perusal prior to finalisation. The latter should respond or react within 31 working days on the report being issued. If this period lapses it will be interpreted as a confirmation that the Department acknowledges the presentation and interpretation of data as correct and factual in the report.

5.4. The User will ensure that the Department is acknowledged in any output resulting from the use of the data including.

5.5. The User will communicate any data quality issues identified to the Department, to improve the dataset.

5.6. The User agrees that any use of the Dataset(s) or reliance by the User on any of the Dataset(s) is at the User's own risk and that Department shall not be held liable for any loss or damage howsoever arising as a result of such use.

5.7. The User agrees that he/she will make no statement nor permit others to make statements indicating or suggesting that interpretations/views drawn from the findings are those of the Department.

5.8. The User agrees that he/she will maintain confidentiality in accordance with item 6. Below.

6. Data Security and Confidentiality:

All Dataset(s) from the Western Cape Department of Health are to be treated as confidential and used in accordance with the following security standards:

6.1. Database storage: At a minimum the database must have user-level security, may not be housed on laptops or external media unless these are encrypted. Ideally the data should be stored on a central server with restricted access and not be stored on portable computer equipment like memory sticks, external hard drives and laptops.

6.2. The Data Sets(s) must be password protected and such passwords are not to be shared with anyone other than the principle user.

6.3. Data may not be linked to personally identifiable records from any other source unless prior approval has been explicitly granted.

6.4. File storage: At a minimum files will be stored with AES encryption e.g. 7-zip, and 15 character passwords which include numbers, special characters and letters.

6.5. Passwords and files may not be provided together but using two different methods of communication e.g. data zipped and e-mailed while password is SMS'ed to User.

6.6. When the timeframe for the agreed utilisation of the data expires (see item 4.1. above) the data must be destroyed in all its forms.

7. In making information available, the Department of Health reserves the right to set conditions in which its staff (including academic staff in joint provincial posts) should be invited to participate in any research undertaken that uses the data they have generated with a view to co-authorship of the final report/s.

8. The User accepts that this data is routinely collected as part of service delivery and therefore the data quality may not be of the highest quality.

9. Failure to adhere to the written agreement can and may be sanctioned

**Signatories:**

| **Muhammad Osman** |  | **12 Nov 2021** |
|---|---|---|
| User's Name (Print) | Signature | Date |
| Dr M Moodley |  | 8 July 2022 |
| Department of Health (Designated authority) | Signature | Date |