

Cover Page

The Impact of Covid-19 Restrictions on TB Diagnosis in the City of Cape Town, South Africa

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List of Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
COCTDOH	City of Cape Town Department of Health
COCTMM	City of Cape Town Metropolitan Municipality
Covid-19	SARS-CoV-2 Coronavirus Disease
DATCOV	Daily Hospital Surveillance System
ETR.net	Electronic TB Register
HIV	Human Immunodeficiency Virus
HREC	University of Cape Town Human Research Ethics
MPI	Global Multidimensional Poverty Index
NCCC	National Coronavirus Command Council
NDOH	National Department of Health
NHLS	National Health Laboratory Services
PHC	Primary health care
PHCIS	Primary Health Care Information System
PHDC	Provincial Health Data Centre
PMI	Patient Master Index
PREHMIS	Patient Record and Health Management Information System
SQL	Structured Query Language
TB	Tuberculosis
TIER.net	Three Interlinked Electronic Registries
WCDOH	Western Cape Department of Health
WHO	World Health Organisation

Part A: Protocol

1 Synopsis

Title: The Impact of Covid-19 Restrictions on TB Diagnosis in the City of Cape Town, South Africa.

Background: A global decline in new tuberculosis (TB) diagnosis during the Covid-19 pandemic has been reported by the World Health Organisation (WHO). South Africa, however, is reported as having ‘no or limited departure’ from the pre-2020 downward trend in TB case notification due to disruptions during the Covid-19 pandemic. Studies in South Africa has found that there was indeed a drop in new TB diagnosis during the pandemic, and data from the Western Cape Department of Health (WCDOH) show large decline in new TB diagnosis in this province. While restrictions imposed to reduce the spread of Covid-19, such as social distancing and face-mask wearing, may have reduce transmission, the cause of the decline in new TB diagnosis is more likely to be the negative impact on health services and access to care caused by lockdown restrictions.

Purpose and Objectives: This study seeks to quantify, analyse and characterise factors associated with the observed drop in new TB diagnosis in the City of Cape Town Metropolitan Municipality (COCTMM).

Methods: Routine data on Covid-19 and TB diagnoses, collected by the WCDOH, will be analysed to identify risk factors influencing the outcome of number of daily new TB diagnoses. Relevant variables will be investigated using unstratified multiple linear regression, as well as multiple linear regression stratified between primary health care (PHC) and hospital facilities to assess the differences across these two types of health facility.

Risks and Benefits: As the study leverages individual-level clinical data, there is a risk of breach of patient confidentiality. However, data are anonymized and perturbed with no risk of relinkage or re-identification, and are managed according to stringent data protection protocols.

The study will generate insights into the causes of the decline in new TB diagnosis during pandemic situations, and will provide beneficial insights to governments and health departments, both locally and internationally, as they plan their response to possible future pandemics.

2 Background

2.1 Global Trends in TB Case Notification and Covid-19

Tuberculosis remains one of the leading global causes of death according to the 2022 WHO global Tuberculosis Report¹, and ‘in 2019 was the leading cause of death from a single infectious agent’. Good progress in reducing TB incidence and mortality had been made, with global TB incidence rates falling by 1.6% per year in the period 2000-2018, and a reduction of 11% in the total number of global TB deaths between 2015 and 2018. However, the report states that this progress has been ‘slowed, stalled or reversed’ since 2019 as a result of the Covid-19 pandemic. Global TB case-finding dipped sharply during the pandemic due to Covid-19’s negative effect on health system capacity, diagnostic services and the ability of citizens to seek care due to lockdown restrictions and concerns over the risk of accessing health facilities during a pandemic.

South Africa accounts for 3% of global TB case load and in 2019 had the 6th highest TB incidence rate globally, and the 3rd highest global incidence of Human Immunodeficiency Virus (HIV) positive TB². Before 2020, reduction in TB incidence and mortality in South Africa exceeded global trends,

with TB incidence dropping from 1230 per 100 000 people in 2010, to 615 in 2019³. With the emergence of the Covid-19 pandemic, the situation becomes less clear. There is a large body of evidence^{1,4-6} reporting that the Covid-19 pandemic disrupted TB services globally. The WHO categorizes South Africa as a country that experienced ‘no or limited departure’ from the pre-2020 downward trend in TB case notification due to disruptions during the Covid-19 pandemic, but this fails to adequately quantify the disruption to the TB response experienced in South Africa. Mahdi et al.⁷ describe a 50% decrease in TB testing during the initial stages of the pandemic in South Africa, and a sustained decline of 33% in the weekly average of microbiologically confirmed TB cases between pre-lockdown levels and the first months of the pandemic.

2.2 The Covid-19 Response in South Africa

The South African National Coronavirus Command Council (NCCC) and National Department of Health (NDOH) rapidly imposed a national state of emergency and severe lockdown in response to

increased Covid-19 case load, after the first case of Covid-19 was diagnosed in South Africa on the 5th March 2020. This was followed by a Covid-19 Risk Adjusted Strategy⁸, defining a series of alert levels⁹, determined based on the level of infection and rate of transmission of coronavirus, and the capacity of the health system to manage the burden of disease. Severe lockdown, subsequently termed alert level 5, was implemented on the 27th March 2020 and was in effect for 35 days. Citizens were restricted to their houses except for essential movement to purchase medicines, food and other essential supplies. Curfew was implemented between 8pm and 5am, and inter-provincial and national travel were prohibited. This was reduced to alert level 4 on the 1st May 2020, lasting 31 days, where curfew remained in place,



Figure 1: Alert Levels

sale of alcohol was prohibited but limited movement and exercise in public places was permitted, subject to certain conditions. Subsequent to alert level 4, the country rotated through alert levels between 4 and 1, with varying levels of restriction according to the criteria defined by the NCCC.

In addition to the Adjusted Risk Strategy, the NDOH implemented a Covid-19 surveillance system named DATCOV¹⁰. This system was initially rolled out to public sector hospitals and the National Health Laboratory Services¹¹ (NHLS), and was soon adopted by private sector hospitals, laboratories and some PHC facilities. DATCOV captured all Covid-19 test results across South Africa, as well as Covid-19 hospital admission and deaths. The effectiveness of the Risk Adjusted Strategy on Covid-19 infection waves in South Africa is hard to measure, even with the rich data available from DATCOV, but studies show that it did slow the spread of the disease and enabled the health system to prepare for the pandemic^{12,13}, and also reduced the burden on hospital services from other causes¹⁴⁻¹⁶. The NDOH defined a wave as starting when Covid-19 case load reaches 30% of the previous waves' peak, and ends when case load reaches 15% of the peak in the current wave. The

first, second and third waves, respectively driven by the Alpha, Beta and Delta variants, were severe, with increasing caseloads and high case fatality ratio (CFR). While caseload for the Omicron variant-driven fourth wave was higher, CFR dropped due to the reduced virulence of the variant, and the rollout of the immunisation campaign. Caseload and CFR of the fifth wave were markedly reduced.

2.3 The Western Cape Province

The Western Cape is one of 9 provinces in South Africa, home to almost 7 million inhabitants¹⁷ (12% of the population of South Africa). While the province has ostensibly the most advanced electronic health system, TB and HIV prevalence and outcomes lag behind other provinces due to the high levels of poverty, unemployment, crime and alcohol and drug abuse¹⁸. TB incidence in the Western Cape was last officially reported as 739.1 cases per 100 000 population in 2016¹⁹.

Calculations using new case numbers from the Western Cape TB Dashboard²⁰ and population estimates from Statistics South Africa¹⁷ show TB incidence as 782.1 in 2019 and 688.4 in 2021.

The Western Cape Department of Health (WCDOH) has implemented a Provincial Health Data Centre²¹ (PHDC), a clinical data warehouse containing data for all individuals who have accessed public health services in the past 2 decades. The PHDC leverages a unique patient identifier assigned to every public health client, known as the Clinicom number after the ClinicomTM patient registration system that was implemented in the Western Cape by InterSystems in 1998, to link individuals' clinical records across disparate health information systems. The platform ingests clinical records from multiple sources including the National Health Laboratory Services (NHLS), the two primary health care platforms, the provincial hospital system (ClinicomTM), disease-specific electronic registers such as TIER.net²² (for HIV and TB case management) and ETR.net²³ (for TB surveillance), medicine dispensing systems, emergency services, community health platforms, and others. Data are uploaded daily, allowing the province to link new records and to generate reports and statistics at an individual level to inform public health decision making and delivery of services, as well as provide better patient care. Aggregate reports, such as the TB dashboard²⁰ (figure 2) and the Covid-19 summary report (figure 3) are generated from the data.

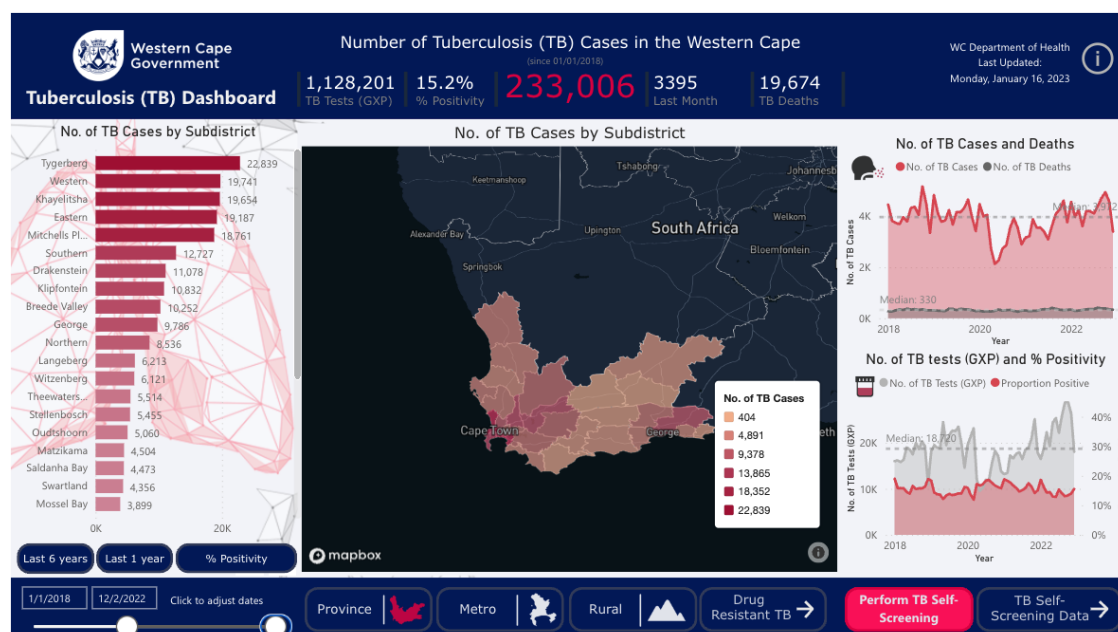


Figure 2: Western Cape TB Dashboard

2.4 The City of Cape Town Metropolitan Municipality

The Western Cape province is made up of 6 health districts, including the City of Cape Town Metropolitan Municipality (COCTMM). The COCTMM health district is high-density urban area (1 530 people per square meter), occupying just 2% of the provinces land area and servicing approximately 4 million people, over half of the population of the Western Cape. The Global Multidimensional Poverty Index (MPI) for Cape Town is one of the highest in South Africa^{24–26}, and there are high-levels of unemployment, crime, and drug and alcohol abuse. This environment, along with high prevalence of HIV, has contributed to the high incidence of TB in the city.



Provincial Health Data Centre

COVID-19 summary

Tuesday, February 8, 2022 3:00:10 PM



Integrated province-wide summaries

Evolution of the COVID-19 epidemic in the Western Cape Province

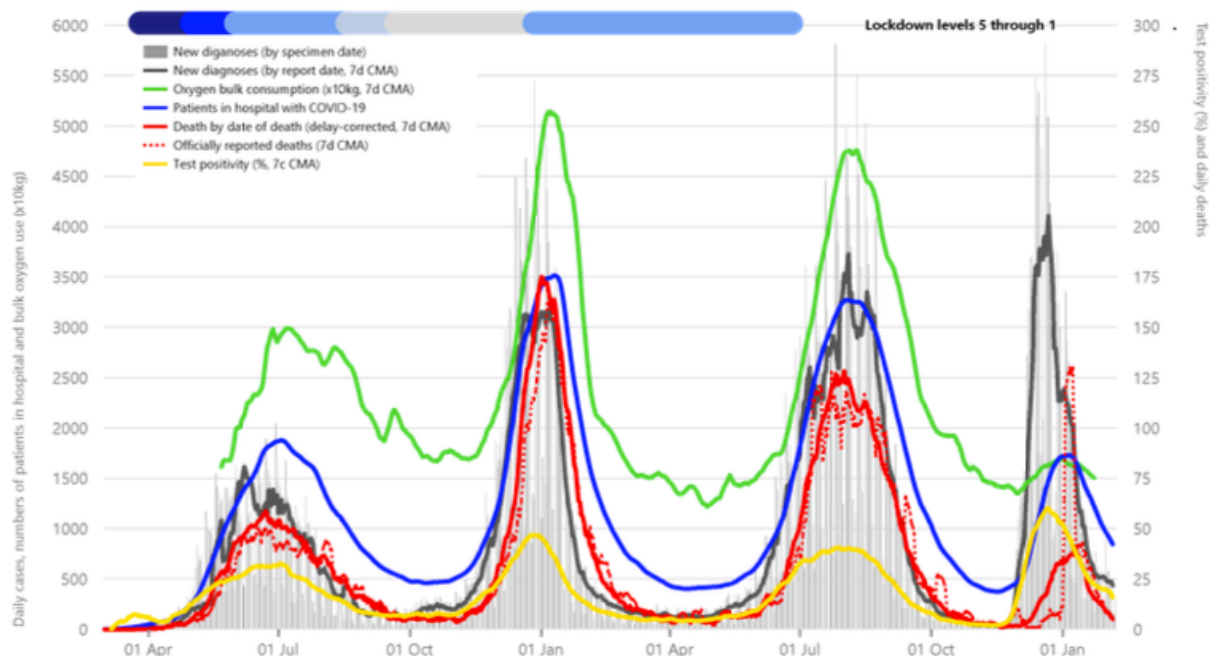


Figure 3: Western Cape Department of Health Covid-19 Summary Report, 8 February 2022

Public health services are provided by two departments of health, the WCDOH, servicing areas within the district but outside of the City of Cape Town, and the City of Cape Town Department of Health (COCTDOH) servicing the inner city. Across both departments, there are 86 primary health care facilities (clinics and community health centres) and 47 hospitals²⁷. Every facility implements an electronic data capture system; Clinicom at hospitals, the Primary Health Care Information System (PHCIS) at WCDOH facilities, and the Patient Record and Health Management Information System (PREHMIS) at COCTDOH facilities²⁸. Each is connected to the internet, and the provincial master patient index. Every patient accessing services is issued a unique Clinicom number, which is used across all services, and all data are submitted to the PHDC on a daily basis. This infrastructure

provides unique opportunities to analyse the interaction between TB and Covid-19 aetiology and other health factors.

2.5 Factors Potentially Affecting TB Incidence and Diagnosis

The availability of electronic clinical records within the PHDC has enabled the WCDOH and academic researchers to gain unprecedented insight into public health epidemiology in the Western Cape, with a number of papers published using these data^{29–32}.

The WCDOH was able to rapidly assess risk factors for Covid-19 in a population cohort study²⁹, finding that current and previously diagnosed TB were associated with Covid-19 death (aHR, 2.70 95% CI:1.81–4.04 and 1.51 95% CI:1.18–1.93, respectively). However, the authors found that when looking at total counts of mortality by cause, that overall TB mortality declined as the pandemic progressed, leading to a hypothesis that the Covid-19 pandemic may be associated with decreased TB mortality, possibly due to decreased exposure to infection as result of restricted social contact and the use of face-masks.

First and foremost, reduction in care-seeking behaviour, increased demand on health facilities and reduced access to these facilities due to Covid-19 restrictions resulted in a large reduction in routine testing for new TB infections³³. Deaths of these undiagnosed (and thus untreated) TB patients could have been incorrectly ascertained as Covid-19 excess deaths³⁴, and the true number of TB deaths could be underreported.

Conversely, measures and restrictions implemented by the government of South Africa³⁵ to reduce Covid-19 transmission, and changes in behaviour of citizens, may have impacted the transmission of TB. Social distancing and the use of face masks have been shown to reduce transmission of TB³⁶ and other airborne respiratory diseases, such as influenza^{37,38}. The use of public transport has been shown to increase the risk of TB transmission³⁹, and thus reduced use of public transport during Covid-19 restriction periods may have had a protective effect. However, studies also show that TB transmission is associated with household crowding^{40,41}, especially in high-density, low social-economic, high burdened TB and HIV communities such as the COCTMM⁴². Household crowding increased as citizens were confined to their homes during alert levels 3, 4 and 5 of the South African Covid-19 response, and this may have resulted in increased but unrecorded TB incidence, rather than a reduction in new infections.

Additionally, the relatively long incubation period of TB, with a median range of a few months to two years⁴³, could mean that any protective effects of Covid-19 restrictions on TB infections, or indeed any clinical increase in TB mortality due to the pandemic, may not be evident in the timeframe of this study. Even though the median time between TB diagnosis and death for patients who did not link to treatment within 30 days of diagnosis can be less than 30 days⁴⁴, and in some settings almost two thirds of those infected with TB and HIV die within three months of simultaneous TB and HIV diagnosis⁴⁵, the effect of Covid-19 restrictions is unlikely to have affected true mortality levels within the first 18 months of the pandemic.

2.6 Availability of Electronic Data

As described briefly in section 2.3, the WCDOH has implemented the PHDC, a data warehouse which ingests data from multiple sources including the National Health Laboratory Services (NHLS), a laboratory service which performs all laboratory tests for the public health system.

A probabilistic inference engine collates evidences (laboratory tests, observations, visits, dispensing) and generates disease episodes, each with a confidence score based on the strength of evidence (a positive GeneXpert test would indicate strong evidence of TB, dispensing of TB medication such as rifampicin would indicate less strong evidence of TB, and a visit to a specialized TB Hospital with no other clinical information would indicate weak evidence). Evidences are gathered and an algorithm used to generate episodes with an assigned confidence score. Episodes contain no identifiable information for a patient, these being kept in a separate database, allowing researchers to analyse data with no personally identifiable information included.

Disease cascades are then generated by linking specific disease episodes with relevant demographic data, and records are enriched with other information such as outcomes, comorbidities and other clinical events. The cascades provide a comprehensive view of each disease episode which can be used for analysis in the absence of ubiquitous disease registers.

We used the TB cascade to determine the set of events to be examined, and linked records to the Covid-19 cascade to examine the overlap of TB and Covid-19 diagnoses. Only episodes with a confidence score of 0.7 (70%) and above were included.

Linkage of individuals within the PHDC was achieved through the internal linkage engine⁴⁶, a structured query language (SQL) decision tree that routinely links each unique patient master index (PMI) record to a dominant PMI ID where the engine finds that duplicate records may exist. Linkage is based on demographic variables including first and last name, sex, age, South African National Identity number and geographic information. This study relied on the dominant PMI ID assigned to every record by the engine.

3 Justification of The Study

A clear perspective on the true impact of Covid-19 pandemic response on the number of new TB diagnoses is needed, especially in the context of the WHO Global TB report which appears to under-represent the negative impact that the pandemic had on TB diagnosis in South Africa. The causes of the apparent drop in TB diagnosis attributed to the Covid-19 pandemic need to be determined to inform public health response in the City of Cape Town, Western Cape Province, South Africa and globally, and to be adequately prepared for future public health crises.

The PHDC of the Western Cape Province holds an unprecedented amount of securely stored clinical patient information. The availability of these data provides a unique opportunity to study the effects of the Covid-19 epidemic on routine TB diagnostic services in an urban setting, and to inform public health policy and decision makers, and those delivering health services, so that they may perform effective scenario planning in the event of another pandemic.

4 Aim and Objectives

The aim of this study is to explore the effects of the Covid-19 pandemic, and the pandemic response, on the diagnosis of new TB cases in the City of Cape Town, with a focus on the impact on diagnostic services at different types of health facility.

Objectives:

- Describe the population newly diagnosed with TB in the COCTMM between 1st January 2018 and 31st December 2021

- Determine changes to daily counts of new TB diagnosis during Covid-19 lockdown.
- Assess the factors significantly associated with changes in daily counts of new TB diagnosis.

5 Study Design

A time-series analysis of *daily counts of new TB diagnosis* will be conducted using clinical and demographic data routinely collected by the WCDOH and housed in the PHDC. The number of new TB diagnoses per day will be counted and the factors associated with changes to the number of daily new TB diagnoses analysed. *Daily count of new TB diagnosis* will be labelled with temporal variables associated with the Covid-19 pandemic (*alert level*, *Covid-19 admission pressure* and *month of year*), and stratified by the *type of facility* where the diagnosis took place, either PHC (n = 161) or hospital (n = 20).

5.1 Setting, Characteristics of the Study Population, and Sampling

The study will include data from the population of the COCTMM, 20 years of age or older who have a valid date-of-birth recorded, newly diagnosed with TB within the study period of 1st January 2018 to 31st December 2021. Demographic and clinical baseline characteristics of the study population will be explored to assess association with the reduction in *daily counts of new TB diagnosis*. A sampling framework was not employed as the study population includes all eligible individuals.

5.2 Key Variables

Variables of interest are described in table 1.

5.3 Data Resources

The authors will request these data from the WCDOH PHDC. Routine health data collected by the services will be anonymized and perturbed prior to release, so that no individual in the data set can be reidentified. Where possible, aggregate data will be utilized. Due to the use of only anonymized and perturbed data, the authors are requesting a waiver of informed consent for this data set.

5.4 Data Management Plan

4.5.1 Data Analysis Environment

Data will be initially extracted into a database within the WCDOH infrastructure. Within this database, the data will be further aggregated and linked, and will be extracted in aggregated format (e.g., number of diagnoses per day) into text files. These files will remain on Department of Health servers and will be analysed using R software. Results of regression analysis and summaries of baseline characteristics will be saved to file and added to thesis materials. No raw identifiable data will be moved out of the Western Cape secure Virtual Private Network (VPN)

4.5.2 Data Anonymization

Data extracted from the clinical databases will be anonymized. No personally identifiable information is included in the extracts. The internal PMI ID is present in order to link between TB and Covid-19 cases but will not be included in the text files imported into R for regression analysis. Age of patient will be assigned to 10-year buckets, further de-identifying the data set. Address of patient is not included, and the only geographic component is the subdistrict where the case was diagnosed.

Table 1: Variables of Interest

Variable	Description	Detail	Candidate Regression Analysis
Demographic			
Age at TB Diagnosis	Categorical	- 20-29 years - 30-39 years - 40-49 years - 50-59 years - 60-69 years - >70 years	
Sex	Categorical	- Male - Female - Unknown	
Subdistrict (of new TB Diagnosis)	Categorical	- Northern - Southern - Western - Khayelitsha - Tygerberg - Eastern - Klipfontein - Mitchells Plain	
Clinical			
Previous TB Diagnosis	Categorical	Yes/No	
Number of new TB diagnosis in study period	Continuous		
HIV before new TB Diagnosis	Categorical	Yes/No	
Diabetes before TB diagnosis	Categorical	Yes/No	
Concurrent Covid-19 diagnosis and new TB diagnosis	Categorical	Yes/No	
Temporal			
Alert Level	Categorical	0 to 5	Yes
Covid-19 admission pressure	Categorical	- Absent - Low - High	Yes
Month of year	Categorical	January to December	Yes
Outcome			
Daily count of new TB diagnosis	Continuous	Unstratified	Yes
Daily count of new TB diagnosis (PHC)	Continuous	Stratified	Yes
Daily count of new TB diagnosis (Hospital)	Continuous	Stratified	Yes

4.5.3 Data Retention

Data sets will be maintained on the server for 6 months post thesis submission, and subsequently purged from the server. Data extraction SQL queries will be saved in case data need to be re-extracted at a later date.

6 Statistical Analysis

Data analysis will be conducted using SQL Server and R.

Baseline characteristics of the study variables will be described with descriptive statistics.

Relevant independent variables will be selected for linear regression (initial variables of interest are *alert level*, *Covid-19 admission pressure* and *month of year*).

Multiple linear regression will be used to assess association of independent variables with the outcome variable, the absolute *daily count of new TB diagnoses*, unstratified, and stratified by *type of facility* where diagnosis took place.

Residuals will be analysed with Shapiro-Wilks tests to confirm validity of the regression analysis.

7 Ethical Considerations

These data are routine health data from real healthcare clients, presenting the potential for risk to privacy. In order to protect against this risk, the data are maintained in the secure environment of the WCDOH, the Responsible Party, according to the POPI act of South Africa. The WCDOH will subsequently release an anonymized dataset that cannot be relinked to identify individuals for this study.

8 Stakeholders

Stakeholders include:

The Provincial and National Departments of Health, who will be able to use information about pandemic restrictions and their impact on routine care and TB diagnosis to assist with pandemic preparedness.

People living with TB in the Western Cape and accessing government health care, as well as those infected with Covid-19

The Western Cape and National general populations, who stand to benefit from better management of health services and increased access to care during public health crises

9 Conflict of Interest Statement

None

10 Budget

None

11 Potential Limitations of Study

Potential limitations include:

Lack of private sector data for risk factors and outcomes of interest (except for Covid-19) and mobility of healthcare clients between public and private sectors.

Available mortality data is reliant of WCDOH sources, and under-represents out-of-hospital deaths. Official cause of death data from the National Population Register have not been released by Statistics South Africa (StatsSA) for periods after 2018⁴⁷.

There is possible bias in the dataset due to different healthcare seeking behaviours of demographic groups in the Western Cape. Healthy (and unhealthy) men are less likely to access care and healthy young women are over-represented due to antenatal and contraceptive care access.

12 References

1. World Health Organization. Global Tuberculosis Report 2022 [Internet]. [cited 2023 Jan 29]. Available from: <https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022>
2. World Health Organization. Global tuberculosis report 2019 [Internet]. Geneva: World Health Organization; 2019 [cited 2023 Apr 16]. Available from: <https://apps.who.int/iris/handle/10665/329368>
3. Durbin RP. WHO Global tuberculosis report 2020. *Am J Physiol*. 1975 Dec;229(6):1726.
4. Migliori GB, Thong PM, Akkerman O, Alffenaar JW, Álvarez-Navascués F, Assao-Neino MM, et al. Worldwide Effects of Coronavirus Disease Pandemic on Tuberculosis Services, January–April 2020 - Volume 26, Number 11—November 2020 - *Emerging Infectious Diseases journal* - CDC. [cited 2023 Jan 30]; Available from: https://wwwnc.cdc.gov/eid/article/26/11/20-3163_article
5. Alene KA, Wangdi K, Clements ACA. Impact of the COVID-19 Pandemic on Tuberculosis Control: An Overview. *Trop Med Infect Dis*. 2020 Jul 24;5(3):123.
6. Cilloni L, Fu H, Vesga JF, Dowdy D, Pretorius C, Ahmedov S, et al. The potential impact of the COVID-19 pandemic on the tuberculosis epidemic a modelling analysis. *EClinicalMedicine*. 2020 Nov;28:100603.
7. Madhi SA, Gray GE, Ismail N, Izu A, Mendelson M, Cassim N, et al. COVID-19 lockdowns in low- and middle-income countries: Success against COVID-19 at the price of greater costs. *S Afr Med J*. 2020 Jun 19;110(8):724.
8. National Coronavirus Command Council. COVID-19 Risk Adjusted Strategy - SA Corona Virus Online Portal [Internet]. SA Corona Virus Online Portal. 2020 [cited 2023 Jan 29]. Available from: <https://sacoronavirus.co.za/covid-19-risk-adjusted-strategy/>
9. National Coronavirus Command Council. Summary of Alert Levels [Internet]. Presidency of South Africa; [cited 2023 Feb 2]. Available from: <https://www.investcapetown.com/wp-content/uploads/2020/04/summary-of-alert-levels.pdf>
10. Jassat, Waasila. DATCOV: A Sentinel Surveillance Programme for Hospitalised Individuals with Covid-10 in South Africa, 2020. *Covid-19 Special Public Health Surveillance Bulletin*. 2020 Jun 10;18(1):1–15.

11. Radebe L, Haeri Mazanderani A, Sherman GG. Evaluating patient data quality in South Africa's National Health Laboratory Service Data Warehouse, 2017-2020: implications for monitoring child health programmes. *BMC Public Health*. 2022 Jun 29;22(1):1266.
12. Made F, Utembe W, Wilson K, Naicker N, Tlotleng N, Mdleleni S, et al. Impact of level five lockdown on the incidence of COVID-19: lessons learned from South Africa. *Pan Afr Med J*. 2021 Jun 23;39:144.
13. Moonasar D, Pillay A, Leonard E, Naidoo R, Mngemane S, Ramkrishna W, et al. COVID-19: lessons and experiences from South Africa's first surge. *BMJ Glob Health*. 2021 Feb;6(2):e004393.
14. Moultrie TA, Dorrington RE, Laubscher R, Groenewald P, Parry CDH, Matzopoulos R, et al. Unnatural deaths, alcohol bans and curfews: Evidence from a quasi-natural experiment during COVID-19. *S Afr Med J* [Internet]. 2021 Jul 2 [cited 2021 Jul 30];0(0). Available from: <http://www.samj.org.za/index.php/samj/article/view/13345>
15. Chu KM, Marco J, Owolabi EO, Duvenage R, Londani M, Lombard C, et al. Trauma trends during COVID-19 alcohol prohibition at a South African regional hospital. *Drug Alcohol Rev*. 2022 Jan;41(1):13–9.
16. van Hoving DJ, van Koningsbruggen C, de Man M, Hendrikse C. Temporal changes in trauma according to alcohol sale restrictions during the South African national COVID-19 lockdown. *Afr J Emerg Med*. 2021 Dec;11(4):477–82.
17. Statistics South Africa. 2020. Mid- year population estimates. [Internet]. [cited 2023 Jan 31]. Available from: <http://www.statssa.gov.za/publications/P0302/P03022020.pdf>
18. Western Cape Government. Burden of Disease [Internet]. [cited 2023 Feb 2]. Available from: https://www.westerncape.gov.za/assets/departments/health/bod_a5_booklet_0.pdf
19. Western Cape Department of Health. World TB Day 2016 [Internet]. Western Cape Government. [cited 2023 Apr 16]. Available from: <https://www.westerncape.gov.za/news/world-tb-day-2016-0>
20. Western Cape Department of Health. Provincial TB Dashboard [Internet]. Western Cape Government. [cited 2023 Jan 29]. Available from: <https://www.westerncape.gov.za/site-page/provincial-tb-dashboard>
21. Boulle A, Heekes A, Tiffin N, Smith M, Mutemaringa T, Zinyakatira N, et al. Data Centre Profile: The Provincial Health Data Centre of the Western Cape Province, South Africa. *IJPDS* [Internet]. 2019 Nov 20 [cited 2021 May 25];4(2). Available from: <https://ijpds.org/article/view/1143>
22. Osler M, Hilderbrand K, Hennessey C, Arendse J, Goemaere E, Ford N, et al. A three-tier framework for monitoring antiretroviral therapy in high HIV burden settings. *J Int AIDS Soc* [Internet]. 2014 Apr 28 [cited 2021 May 20];17(1). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4005043/>
23. Dreyer AW, Mbambo D, Machaba M, Oliphant CEM, Claassens MM. Tuberculosis cure rates and the ETR.Net: investigating the quality of reporting treatment outcomes from primary

healthcare facilities in Mpumalanga province, South Africa. BMC Health Services Research. 2017 Mar 10;17(1):190.

24. Statistics South Africa, editor. The South African MPI: creating a multidimensional poverty index using census data. Pretoria: Statistics South Africa; 2014. 52 p. (Report).
25. Dooling W. POVERTY AND RESPECTABILITY IN EARLY TWENTIETH-CENTURY CAPE TOWN. The Journal of African History. 2018 Nov;59(3):411–35.
26. Smit W, de Lannoy A, Dover RVH, Lambert EV, Levitt N, Watson V. Making unhealthy places: The built environment and non-communicable diseases in Khayelitsha, Cape Town. Health & Place. 2016 May 1;39:196–203.
27. Health Systems Trust. Number of facilities by level, 2016/17. District Health Barometer [Internet]. Available from: [https://www.hst.org.za/publications/District%20Health%20Barometers/24%20\(Section%20B\)%20Western%20Cape%20Province.pdf](https://www.hst.org.za/publications/District%20Health%20Barometers/24%20(Section%20B)%20Western%20Cape%20Province.pdf)
28. Boulle A, Heekes A, Tiffin N, Smith M, Mutemaringa T, Zinyakatira N, et al. Data Centre Profile: The Provincial Health Data Centre of the Western Cape Province, South Africa. IJPDS [Internet]. 2019 Nov 20 [cited 2021 May 25];4(2). Available from: <https://ijpds.org/article/view/1143>
29. Western Cape Department of Health in collaboration with the National Institute for Communicable Diseases, South Africa, Boulle A, Davies MA, Hussey H, Ismail M, Morden E, et al. Risk Factors for Coronavirus Disease 2019 (COVID-19) Death in a Population Cohort Study from the Western Cape Province, South Africa. Clinical Infectious Diseases. 2020 Aug 29;ciaa1198.
30. van der Hoven J, Allen E, Cois A, de Waal R, Maartens G, Myer L, et al. Determining antenatal medicine exposures in South African women: a comparison of three methods of ascertainment. BMC Pregnancy and Childbirth. 2022 Jun 3;22(1):466.
31. Tamuhla T, Dave JA, Raubenheimer P, Tiffin N. Diabetes in a TB and HIV-endemic South African population: Analysis of a virtual cohort using routine health data. PLOS ONE. 2021 May 7;16(5):e0251303.
32. Dave JA, Tamuhla T, Tiffin N, Levitt NS, Ross IL, Toet W, et al. Risk factors for COVID-19 hospitalisation and death in people living with diabetes: A virtual cohort study from the Western Cape Province, South Africa. Diabetes Res Clin Pract. 2021 Jun 21;177:108925.
33. McIntosh A, Bachmann M, Siedner MJ, Gareta D, Seeley J, Herbst K. Effect of COVID-19 lockdown on hospital admissions and mortality in rural KwaZulu-Natal, South Africa: interrupted time series analysis. BMJ Open. 2021 Mar;11(3):e047961.
34. Dorrington RE, Moultrie TA, Laubscher R, Groenewald PJ, Bradshaw D. Rapid mortality surveillance using a national population register to monitor excess deaths during SARS-CoV-2 pandemic in South Africa. Genus. 2021 Dec;77(1):19.
35. Government of South Africa. About the alert system [Internet]. [cited 2023 Jan 25]. Available from: <https://www.gov.za/covid-19/about/about-alert-system>

36. Driessche KV, Mahlobo PZ, Venter R, Caldwell J, Jennings K, Diacon AH, et al. Face masks in the post-COVID-19 era: a silver lining for the damaged tuberculosis public health response? *Lancet Respir Med*. 2021 Apr;9(4):340–2.
37. Cowling BJ, Ali ST, Tiffany W. Y. Ng, Tsang TK, Li JCM, Fong MW, et al. Impact assessment of non-pharmaceutical interventions against coronavirus disease 2019 and influenza in Hong Kong: an observational study. *The Lancet Public Health*. 2020 May 1;5(5):e279–88.
38. Soo RJJ, Chiew CJ, Ma S, Pung R, Lee V. Decreased Influenza Incidence under COVID-19 Control Measures, Singapore - Volume 26, Number 8—August 2020 - *Emerging Infectious Diseases journal - CDC*. [cited 2021 Jul 27]; Available from: https://wwwnc.cdc.gov/eid/article/26/8/20-1229_article
39. Andrews J, Morrow C, Wood R. Modeling the Role of Public Transportation in Sustaining Tuberculosis Transmission in South Africa. *American journal of epidemiology*. 2013 Feb 18;177.
40. Baker M, Das D, Venugopal K, Howden-Chapman P. Tuberculosis associated with household crowding in a developed country. *Journal of Epidemiology & Community Health*. 2008 Aug 1;62(8):715–21.
41. Harling G, Ehrlich R, Myer L. The social epidemiology of tuberculosis in South Africa: A multilevel analysis. *Social Science & Medicine*. 2008 Jan 1;66(2):492–505.
42. Tadokera R, Bekker LG, Kreiswirth BN, Mathema B, Middelkoop K. TB transmission is associated with prolonged stay in a low socio-economic, high burdened TB and HIV community in Cape Town, South Africa. *BMC Infectious Diseases*. 2020 Feb 10;20(1):120.
43. Behr MA, Edelstein PH, Ramakrishnan L. Revisiting the timetable of tuberculosis. *BMJ*. 2018 Aug 23;362:k2738.
44. Osman M, Meehan SA, Delft A von, Preez KD, Dunbar R, Marx FM, et al. Early mortality in tuberculosis patients initially lost to follow up following diagnosis in provincial hospitals and primary health care facilities in Western Cape, South Africa. *PLOS ONE*. 2021 Jun 14;16(6):e0252084.
45. Zenner D, Abubakar I, Conti S, Gupta RK, Yin Z, Kall M, et al. Impact of TB on the survival of people living with HIV infection in England, Wales and Northern Ireland. *Thorax*. 2015 Jun 1;70(6):566–73.
46. Mutemaringa T, Heekes A, Boule A, Tiffin N. Record linkage for Routinely Collected Health Data in an African Health Information Exchange. *IJPDS [Internet]*. 2022 Aug 25 [cited 2023 Feb 1];7(3). Available from: <https://ijpds.org/article/view/2022>
47. Statistics South Africa. Mortality and causes of death in South Africa: Findings from death notification 2018 [Internet]. [cited 2023 Feb 3]. Report No.: P0309.3. Available from: <https://www.statssa.gov.za/publications/P03093/P030932018.pdf>

Part B: Manuscript

1 Title Page

The Impact of Covid-19 Restrictions on TB Diagnosis in the City of Cape Town, South Africa

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2 Abstract

Background: The first case of Covid-19 in South Africa was diagnosed on the 5^h March 2020 and a national alert system based on perceived Covid-19 spread and the level of health system readiness and capacity was implemented. Varying levels of lockdown restriction were mandated, from ‘full shelter in place’ (alert level 5) to minimal restrictions on social gatherings and mask-wearing (alert level 1). South Africa subsequently experienced 5 Covid-19 waves with 14 changes to alert levels. Significant reductions in recorded new tuberculosis diagnoses and tuberculosis mortality were observed during the Covid-19 pandemic. We describe and quantify effects of the Covid-19 pandemic on new tuberculosis diagnosis in Cape Town.

Methods: A time-series analysis was undertaken using routine data collected between 2018 and 2021 by the Western Cape Department of Health in the City of Cape Town. There were 87 621 tuberculosis episodes identified in 82 197 adult individuals. A multiple linear regression model was used to assess the relationship between the outcome *daily counts of new tuberculosis diagnoses* and independent variables *alert level*, the *month of year* to model seasonality of tuberculosis incidence, and the level of *Covid-19 admission pressure* as a proxy for pressure on the health services. Data were stratified according to their origin in primary health care and hospital settings, and further exploratory analysis assessed the effects of additional baseline population characteristics on the measured outcome.

Results: Across all facilities, increasing severity of lockdown restrictions had a significant, increasing impact on reduction in number of new tuberculosis diagnoses. During alert level 4, the number of daily new diagnoses reduced from pre-pandemic levels by approximately 50% ($\beta=-20$, 95% CI:-22, -17). In the stratified analysis, alert level 4 reduced daily new tuberculosis diagnosis at primary health care facilities by 80% ($\beta=-20$, 95% CI:-22,-17) and at hospital facilities by only 11% ($\beta=-1.6$, 95% CI:-2.8,-1.4). Further analysis ruled out effects from independent baseline population characteristics including age, sex and comorbidities.

Conclusions: Severity of Covid-19 restrictions had greater effect on reduction of new tuberculosis diagnosis than increased intensity of Covid-19 waves. The reduction was more pronounced at primary health care facilities, indicating that access to, and services at these facilities most likely impacted number of tuberculosis diagnoses more profoundly than at hospitals, and the resulting decreased tuberculosis testing at these facilities was the most likely contributing factor to the reduction in recorded tuberculosis diagnosis rather than a reduction in actual incidence of tuberculosis.

3 Introduction

The SARS-CoV-2 Coronavirus Disease (Covid-19) epidemic has increased the strain on health services globally, and negatively impacted general health outcomes. Global diagnosis of tuberculosis (TB) dropped significantly during the pandemic¹⁻³, an health impact mirrored in South Africa. TB remains the leading cause of death in South Africa⁴, which is one of the four countries accounting for 44% of the global TB case load¹. The South African public health system, already under a quadruple burden of disease⁵ (communicable diseases such as Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) and TB, non-communicable chronic diseases, maternal and child death, and injuries) has struggled to cope with the additional burden of Covid-19⁶.

The first case of Covid-19 in South Africa was diagnosed on the 5th March 2020. The National Department of Health (NDOH) rapidly implemented a national alert system^{7,8}, imposing varying levels of lockdown restrictions, from ‘full shelter in place’ (alert level 5) to minimal restrictions on social gatherings and a mask-wearing mandate (alert level 1). Alert levels were based on perceived Covid-19 spread and the expected level of health system readiness and capacity. South Africa subsequently experienced five Covid-19 waves, defined by the NDOH as starting when case load reaches 30% of the previous waves’ peak, with 14 changes to alert levels being implemented over this time. The first, second and third waves, respectively driven by the Alpha, Beta and Delta variants, were severe, with increasing caseloads and high case fatality ratio (CFR). While caseload for the Omicron variant-driven fourth wave was higher, CFR dropped due to the reduced virulence of the variant, and the rollout of the immunisation campaign. Caseload and CFR of the fifth wave was markedly reduced.

The Western Cape province of South Africa has a particularly high burden of TB, even within the South African context⁹. Significant reductions in new TB diagnoses^{6,10,11} and a lower-than-expected number of TB deaths were measured by the Western Cape Department of Health (WCDOH) since the beginning of the Covid-19 pandemic, with a reduction in recorded TB-attributed mortality of approximately 10%, from 3 948 deaths in 2019 to 3559 in 2020 as reported in the provincial TB dashboard¹². While the reduction in TB diagnoses in the City of Cape Town Metropolitan Municipality (COCTMM) district has been clearly identified, the reasons for the drop are unknown. The WCDOH found that current TB infection was associated with increased Covid-19 mortality¹³. However, decreasing numbers of TB-related deaths over the course of the pandemic led to a hypothesis that Covid-19 pandemic response may be associated with decreased TB mortality. Protective effects of the Covid-19 restrictions such as social distancing, mask wearing and reduction in mass transit¹⁴ may have reduced TB transmission¹⁵, while other factors such as over-crowding in high density neighbourhoods during lockdown and reduced access to health services may have had the opposite effect¹⁶. We hypothesise that changes in health care access by health care clients, and consequently the type of government health facility where TB diagnosis took place, either primary health care (PHC) or hospital, played a significant role in the decrease in recorded TB diagnosis during the pandemic, with a decrease in recorded new TB diagnosis contributing to the observed decrease in TB mortality as the pandemic progressed.

This study assesses the effects of the Covid-19 pandemic on the number of new diagnoses of TB in the COCTMM, which constitutes one of South Africa’s 58 health districts, serving approximately half of the estimated 7 million inhabitants of the Western Cape Province of South Africa in an urban environment. The study leverages routine health data collated daily from a wide variety of sources across the district’s health care services and housed in the Provincial Health Data Centre¹⁷ (PHDC) of the WCDOH.

4 Methods

4.1 Ethics

The University of Cape Town Human Research Ethics Committee (HREC) approved this study (HREC 524/2021), and permission to access data was provided by the WCDOH. No recruitment was necessary as data were routinely collected by the WCDOH, and a requirement for informed consent was waived by the University of Cape Town HREC as analysis was performed on an anonymized dataset provided by WCDOH.

4.2 Data Sources

The WCDOH has implemented a unique patient health identifier across all primary and tertiary public health services enabling the department to link patient data across multiple disparate clinical systems. The PHDC includes data for every citizen accessing the public health system in the province, ingesting data from multiple sources including the National Health Laboratory Services (NHLS), primary health care platforms, the provincial hospital system, disease-specific electronic registers, medicine dispensing systems, emergency services, community health platforms, and others.

Linkage of individuals within the PHDC was achieved through the internal linkage engine¹⁸, a structured query language (SQL) decision tree that routinely links each unique patient master index (PMI) record to a dominant PMI ID where the engine finds that duplicate records may exist. This study relied on the dominant PMI ID assigned to every record by the engine.

A probabilistic inference engine collates *evidences* (TB tests, observations, visits, dispensing) and generates de-identified disease *episodes* labelled with the PMI ID, each with a confidence score¹⁷ based on the strength of evidence (for example, a positive GeneXpert test would indicate strong evidence of TB, dispensing of TB medication such as rifampicin would indicate less strong evidence, and a visit to a specialized TB Hospital with no other clinical information would indicate weak evidence).

Disease *cascades* are then generated by linking specific disease episodes with relevant demographic data, and records are enriched with other information such as outcomes, comorbidities and other clinical events. The cascades provide a comprehensive view of each disease episode for each individual, which can be used for analysis in the absence of ubiquitous disease registers.

For this analysis, we used the TB cascade to determine the set of events to be examined, and linked records to the Covid-19 cascade to examine the overlap of individuals with TB and Covid-19 diagnoses.

4.3 Study Design

A time-series analysis of TB diagnosis events per day was conducted using these data routinely collected by the WCDOH and housed in the PHDC. We collated the number of new TB diagnoses per day and analysed the factors associated with changes to the number of TB diagnoses daily.

4.4 Setting and Participants

The base dataset included all new TB episodes diagnosed at public health facilities within the COCTMM between the study period of 1st January 2018 to 31st December 2021, drawn from the TB cascade data. The study period includes 2 years prior to the pandemic to give sufficient sense of monthly trends. Episodes with a confidence score of less than 0.7 were removed from this set. The participants of the study were the distinct list of individuals

contained in the remaining data. Inclusion criteria were individuals 20 years of age or older at first TB diagnosis. Those with an invalid age at first TB diagnosis, recorded as either not present or over the age of 110 years old, were excluded.

4.5 Characteristics of Study Population

Summary statistics were generated based on characteristics of the participants at time of first TB diagnosis during the study period. *Age at TB diagnosis*, *sex*, *previous TB*, *previous HIV* and *previous diabetes* diagnoses were determined from the PHDC TB cascade. *Number of TB episodes* during the study was a count of TB episodes with a first evidence date within the study period. *Age at TB diagnosis* was categorized into ten-year ranges. The *Concurrent TB and Covid-19 diagnosis* variable was determined by linking the TB and Covid-19 data sets through the PMI ID, and counting the number of TB diagnoses with a positive Covid-19 test within 14 days of the TB first evidence date.

4.6 New TB Diagnoses during study period

The dataset of all new TB diagnoses made during the study period, across every public health facility in the COCTMM, was used to assess factors most likely associated with changes to the number of diagnosis per day. A timeseries dataset was produced, consisting of one record per day, with the *daily count of TB diagnoses*, based on the TB first evidence date. *Daily count of TB diagnoses* were additionally stratified by *facility type*, either PHC or hospital depending on where the diagnosis took place. Each record was labelled with the *alert level* implemented by the NDOH on that day, with alert level 0 indicating the absence of Covid-19 restrictions and increasing alert level numbers reflecting more stringent restrictions. *Percent hospital TB diagnosis* was calculated as count of hospital-diagnosed new TB cases as a percentage of total number of new TB diagnoses across all facilities per day.

4.7 Factors influencing numbers of new TB diagnoses

Each record in the timeseries dataset was labelled with additional categorical variables: *Month of year* to model the normal seasonal fluctuation in TB incidence detailed in existing studies¹⁹, *Covid-19 admission pressure*, as a proxy for pressure on the health services, categorized into 3 levels according to number of Covid-19 admissions to the districts public health facilities per day. Records were labelled as Absent where there were 0 admissions per day, Low for less than 136 admissions per day, and High for 136 or more admissions per day, based on the median number of admissions per day of 136 (IQR: 114-188) since the first Covid-19 hospital admission on 1st March 2020.

Multiple linear regression was performed to assess whether independent categorical variables *alert level*, *month of year* and *Covid-19 admission pressure* were significantly associated with the outcome variable, the *daily count of new TB diagnoses* across all facilities. Subsequent multiple linear regressions were then run on subsets of the data stratified by *facility type*.

Shapiro-Wilks statistical tests were used to confirm the distribution of regression residuals for each model.

4.8 Additional factors potentially affecting number of TB diagnoses

Further exploratory analysis assessed the potential effect of additional independent variables on *daily count of new TB diagnoses*, to investigate whether these additional factors could have affected health seeking behaviour or access to TB diagnostic services during the Covid-19 pandemic, and whether they should be included in the regression analysis. The demographic variables of *sex*, *age at TB diagnosis* and *subdistrict* where TB was diagnosed were considered, as well as clinical variables indicating whether the individual had previously been diagnosed with TB, diabetes or HIV. *Concurrent TB and Covid-19*

diagnosis, defined as a Covid-19 positive test within 14 days before or after the TB diagnosis, was included. These characteristics were defined at time of event for each TB diagnosis in the dataset, and the data were stratified by alert level for further analysis.

4.9 Statistical Methods and Analysis

Microsoft SQL Server (2022 RTM – build 16.0.1000.6) was used to filter and link cascades and ancillary data and to prepare the timeseries dataset of event counts by day. Multiple linear regression was performed in R statistical software (version 4.2.0 - 2022-04-22. Data requested from the WCDOH was gathered by provincial analysts and made available within the secure PHDC SQL Server environment. Data linkage, cleaning and aggregation was performed within this environment, and anonymized extracts were prepared for analysis in R.

4.10 Study Size

Routinely collected and linked data in Western Cape allows for a large study size. All new TB diagnoses in the COCTMM were analysed and no sampling framework was required. With a total study population of almost 100 thousand individuals, containing all eligible healthcare clients, the study is assumed to be exhaustive in terms of participants, and sufficiently statistically powered to draw valid conclusions.

5 Results

5.1 Participants

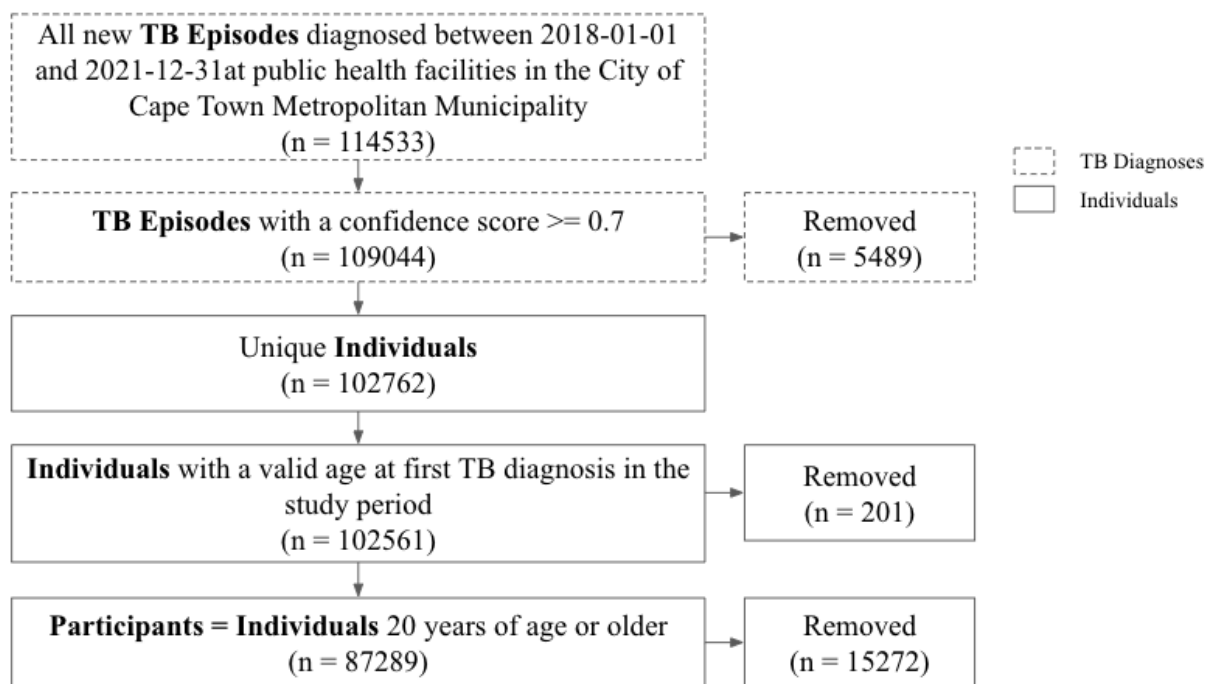


Figure 1: Flow diagram summarising set of TB diagnosis events used to determine the study population, with inclusion criteria. Dotted lines indicate distinct TB episodes (where there may be more than one per individual), solid lines indicate unique individuals in the dataset.

There were 114 533 episodes of TB with a TB first evidence date - the date of diagnosis - between 1st January 2018 and 31st December 2021, in the COCTMM. Of these, 109 044 were of high confidence. The initial set of participants were the 102 762 unique individuals that had been diagnosed with TB. Individuals below the age of 20 years (15 272) and with an

invalid age (unknown or over 110 years old) were excluded, leaving a population of 87 289 individuals (Figure 1).

5.2 Characteristics of Study Population

The median age of the population was 35 years (IQR: 25 – 45), with 57.6% of participants being male. The majority of the population (93.7%) were diagnosed with TB once during the study period, a small number of individuals were diagnosed twice (5.8%), with the remainder (0.54%) having more than two TB diagnoses during the period. Approximately 25% been previously diagnosed with TB, 35% were HIV positive before their first TB diagnosis during the study period, and 7% had previously received a diagnosis of diabetes. A small number (1.32%) had received a Covid-19 diagnosis concurrent with the their diagnosis of TB (Table 1).

Table 1: Characteristics of the study population ($n = 87\,289$)

Characteristic	n (%)
Age	
20-29	21 538 (24.67)
30-39	27 921 (31.99)
40-49	19 248 (22.05)
50-59	11 375 (13.03)
60-69	5 020 (5.75)
70+	2 187 (2.51)
Sex	
Female	36 824 (42.19)
Male	50 294 (57.62)
Unknown	171 (0.20)
TB	
Previous TB Diagnosis	22 011 (25.22)
TB episodes during study	
1 Episode	81 784 (93.69)
2 Episodes	5 034 (5.77)
More than 2 episodes	471 (0.54)
Comorbidities	
HIV Before TB Diagnosis	30 195 (34.59)
Diabetes Before TB Diagnosis	6 891 (7.89)
Concurrent Covid-19 (within 14 days)	1 152 (1.32)

5.3 New TB Diagnoses during study period

Alert levels were rolled out sequentially depending on Covid-19 transmission and health system readiness (Figure 2). Alert level 5, full lockdown restriction, was implemented only once at the beginning of the pandemic. Alert level 4, drastic restrictions on personal movement, was implemented twice, once immediately after alert level 5 and a second time as the 3rd Covid-19 wave peaked (Delta variant²⁰). Alert levels 3, 2, and 1 were successively less

severe, with alert level 1 mandate reduced to solely mask-wearing and social distancing. These were rotated according to peaks and troughs in the Covid-19 waves. The daily number of Covid-19 admissions, used as a proxy for pressure on the health system, can be seen spiking as a characteristic of each successive Covid-19 wave in the province.

Total new TB diagnoses show seasonal fluctuation before the beginning of the pandemic, with *percent hospital TB diagnosis* spiking during these periods. Significant drops in total diagnoses can be seen during the pandemic, with corresponding spikes in *percent hospital TB diagnosis*. Decline in PHC diagnoses track with decline in total diagnoses, with less of a decline in hospital diagnosis.

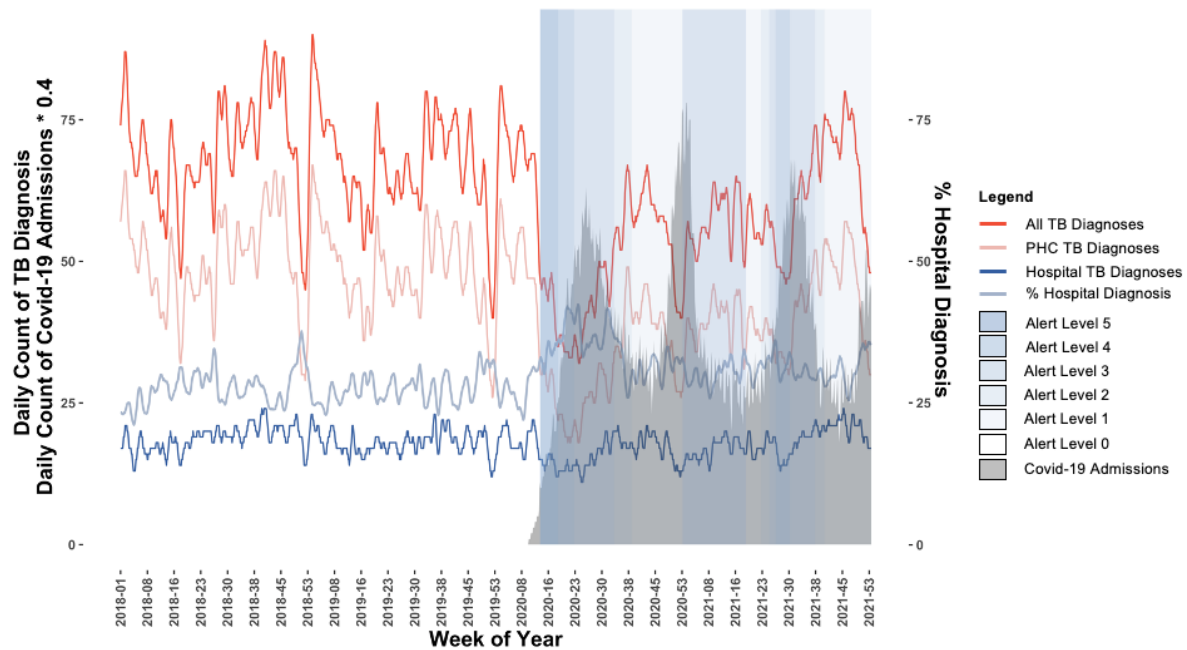


Figure 2: Absolute measures of total TB diagnosis (red), PHC-diagnosed TB (pink), hospital-diagnosed TB (dark blue) and percentage hospital diagnosis (light blue). X Axis: Week of the year, and year, shown in 4 week intervals. Alert levels are indicated with shaded light blue bands and admission pressure in grey. Spikes in percentage hospital diagnosis (light blue) align with seasonal changes and changing alert levels during successive waves of the Covid-19 pandemic

Table 2 summarizes all facility, PHC facility and hospital TB diagnosis counts stratified by alert level. There were 96 777 episodes of TB diagnosed during the study period of 1 461 days, from the cohort of 87 289 individuals, with an average of 1.07 (SD=0.28) TB diagnoses per individual.

Baseline *percent hospital TB diagnosis* before Covid-19 (alert level 0) was 27.27%. This increased with increased severity of lockdown. The highest *percent hospital TB diagnosis* was observed during alert level 4, with 36.54% of cases diagnosed in hospitals. Alert level 5, with more severe restrictions, showed a slightly smaller *percent hospital TB diagnosis* of 34.21%, and an average total daily TB diagnosis count of 44, on average 4 less than alert level 4.

Table 2: Number of new TB diagnosis stratified by government-stipulated pandemic alert level and facility type

Alert Level	Days per Alert Level	Total TB Diagnosis Count			% Hospital Diagnosis	Average TB Diagnosis Count per Day		
		All Facilities	Hospitals	PHC		All Facilities	Hospitals	PHC
0	816	60113	16392	43721	27.27%	73	20	53
1	221	14169	4421	9748	31.20%	64	20	44
2	68	4365	1362	3003	31.20%	64	20	44
3	262	14185	4614	9571	32.53%	54	17	36
4	59	2381	870	1511	36.54%	40	14	25
5	35	1564	535	1029	34.21%	44	15	29
Total	1461	96777	28194	68583	29.13%	66	19	47

5.4 Factors influencing numbers of new TB diagnoses

Table 3 shows results of linear regression on 1 461 days of data, with the outcome (dependent) variable being *daily count of new TB diagnosis*, and *alert level*, *Covid-19 admission pressure* and *month of year* as independent variables, or risk factors. Regression was run on three strata, the first where *daily count of new TB diagnosis* was for all facilities, the second for solely PHC facilities, and the third for solely hospital facilities. Independent variables remained the same for all three models, these being associated with each respective day in the time series data.

The unstratified regression model was shown to be statistically significant (F-statistic = 109.1, p-value < 0.001, adjusted $R^2 = 0.5713$), suggesting that approximately 57% of the output variable, *daily count of new TB diagnosis*, may be explained by the independent variables in the model. The *alert level* variable had a large effect on reduction in daily TB diagnosis, with effect increasing with the increasing severity of restrictions associated with each alert level. Of particular interest is alert level 4 which had the highest significant effect ($\beta = -20$, 95% CI: -22, -17), reducing average daily diagnosis by 50%. Alert level 5 reduced diagnosis by 40.9% ($\beta = -18$, 95% CI: -21, -15). Alert levels 1, 2 and 3 reduced diagnosis by 10.6%, 14.2% and 22.2% respectively. Increased *Covid-19 admission pressure* similarly increased the effect, with low and high pressure reducing TB diagnosis by 5.7% and 8.5% respectively. *Month of year*, baselined in April, showed increasing TB diagnosis in the spring and summer months, with the exception of December ($\beta = -3.2$, 95% CI: -5.1, -1.1).

Regression on each stratified dataset (hospital-diagnosed and PHC-diagnosed TB) showed similar trends with respect to the association of *admission pressure* and *month of the year* with the *daily count of new TB diagnosis*, with admission pressure showing increasing effect on reduction in new TB diagnoses, and summer months showing increased new TB diagnoses, except for December. There was, however, a marked difference in the association of the *alert level* variable with the outcome between the two strata. For hospital-diagnosed TB, the association was only significant at alert levels 4 ($\beta = -1.6$, 95% CI: -2.3, -1.0) and 5 ($\beta = -1.5$, 95% CI: -2.2, -0.82), compared to a much larger association for PHC-diagnosed TB at alert level 4 ($\beta = -20$, 95% CI: -22, -17) and alert level 5 ($\beta = -15$, 95% CI: -18, -12). A far larger association was seen for PHC-diagnosed TB at all alert levels, with most of the effect seen in the unstratified dataset appearing to be attributed to this stratum. At alert level 4, *daily count*

of new TB diagnosis was reduced by an average of 11.4% for hospital-diagnosed and 80% for PHC-diagnosed TB respectively.

Table 3: Results of multiple linear regression on unstratified and stratified datasets

Characteristic	All			Hospital			PHC		
	Beta	95% CI ¹	p-value	Beta	95% CI ¹	p-value	Beta	95% CI ¹	p-value
Alert level									
0	—	—		—	—		—	—	
1	-6.8	-8.1, -5.4	<0.001	0.28	-0.04, 0.61	0.089	-7.7	-8.9, -6.4	<0.001
2	-9.1	-11, -7.0	<0.001	0.19	-0.30, 0.68	0.5	-9.8	-12, -8.0	<0.001
3	-12	-13, -10	<0.001	-0.16	-0.48, 0.15	0.3	-12	-14, -11	<0.001
4	-20	-22, -17	<0.001	-1.6	-2.3, -1.0	<0.001	-20	-22, -17	<0.001
5	-18	-21, -15	<0.001	-1.5	-2.2, -0.82	<0.001	-15	-18, -12	<0.001
Admission Pressure									
Absent	—	—		—	—		—	—	
High	-5.6	-8.0, -3.3	<0.001	-1.9	-2.5, -1.4	<0.001	-2.2	-4.4, 0.03	0.053
Low	-3.8	-5.4, -2.2	<0.001	-1.2	-1.6, -0.80	<0.001	-1.7	-3.2, -0.23	0.023
Month of Year									
April	—	—		—	—		—	—	
May	1.6	-0.25, 3.5	0.09	0.33	-0.13, 0.79	0.2	2.5	0.73, 4.2	0.006
June	1.2	-0.64, 3.1	0.2	1.2	0.72, 1.6	<0.001	0.47	-1.3, 2.2	0.6
July	6	4.1, 7.8	<0.001	1.8	1.3, 2.2	<0.001	6.1	4.4, 7.9	<0.001
August	8.1	6.3, 10	<0.001	2.5	2.0, 2.9	<0.001	6.6	4.9, 8.3	<0.001
September	12	9.8, 14	<0.001	2.5	2.1, 3.0	<0.001	10	8.5, 12	<0.001
October	13	11, 15	<0.001	2.7	2.2, 3.1	<0.001	11	9.7, 13	<0.001
November	11	9.3, 13	<0.001	2.5	2.0, 2.9	<0.001	9.3	7.6, 11	<0.001
December	-3.2	-5.1, -1.2	0.001	1.1	0.60, 1.5	<0.001	-2.9	-4.7, -1.1	0.001
January	11	8.7, 12	<0.001	1.2	0.79, 1.7	<0.001	9.9	8.3, 12	<0.001
February	6.9	5.0, 8.7	<0.001	0.06	-0.38, 0.51	0.8	7.6	5.9, 9.3	<0.001
March	2.7	0.90, 4.5	0.003	0.56	0.13, 0.99	0.01	3.6	2.0, 5.3	<0.001
¹ CI = Confidence Interval									

5.5 Additional factors potentially affecting number of TB diagnoses

An exploratory analysis of additional factors that might impact the number of new TB diagnoses in this population group was undertaken. Population pyramids describing age distribution between males and females show generally similar age and gender distributions for new TB diagnoses taking place across alert levels 0, 1, 2 and 3, with more men being diagnosed with TB (Figure 3). Age at TB diagnosis was higher for men than for women. An

increase in the proportion of new TB diagnoses in females is observed during alert levels 4 and 5.

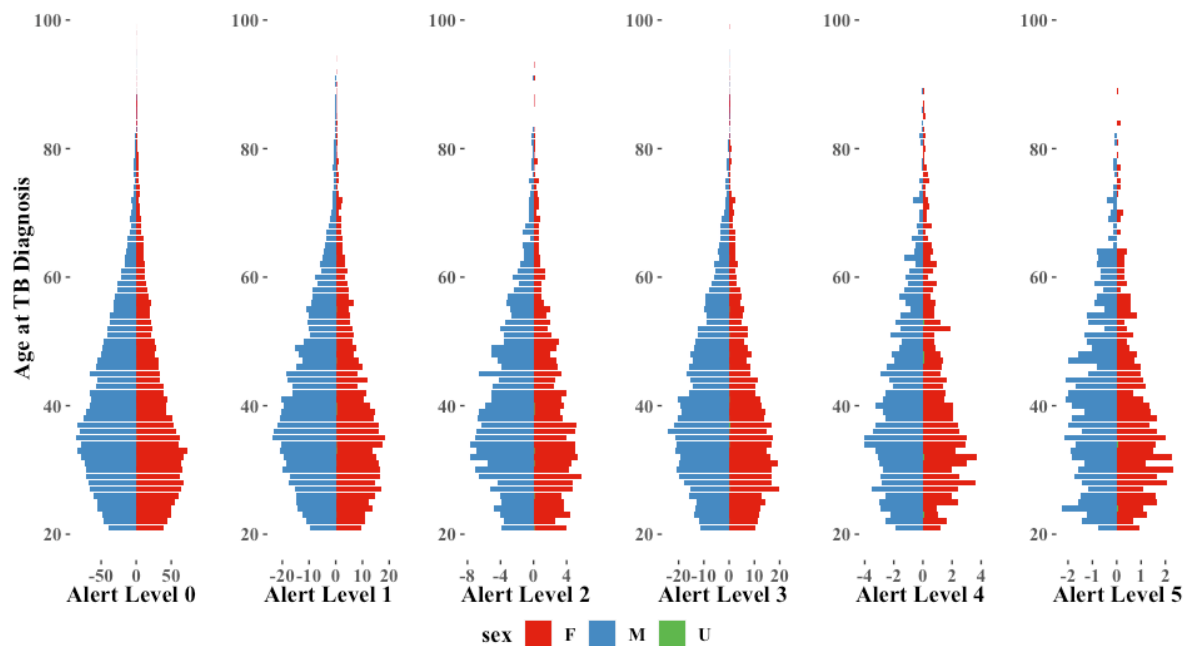


Figure 3: Population pyramids summarizing the distribution of age and sex (females in red, males in blue) per alert level, indicating an increase in proportion of women diagnosed with TB as opposed to men during alerts levels 4 and 5.

That geographic distribution of TB diagnoses appears consistent across the 8 subdistricts of the City of Cape Town Metropolitan Municipality during the different alert levels (Figure 4). Distribution of cases with previous HIV, previous diabetes, and previous TB diagnoses, (Figure 5), indicates a slight increase in proportion of new TB diagnoses where TB and HIV were previously diagnosed for the individual, most marked at alert level 5.

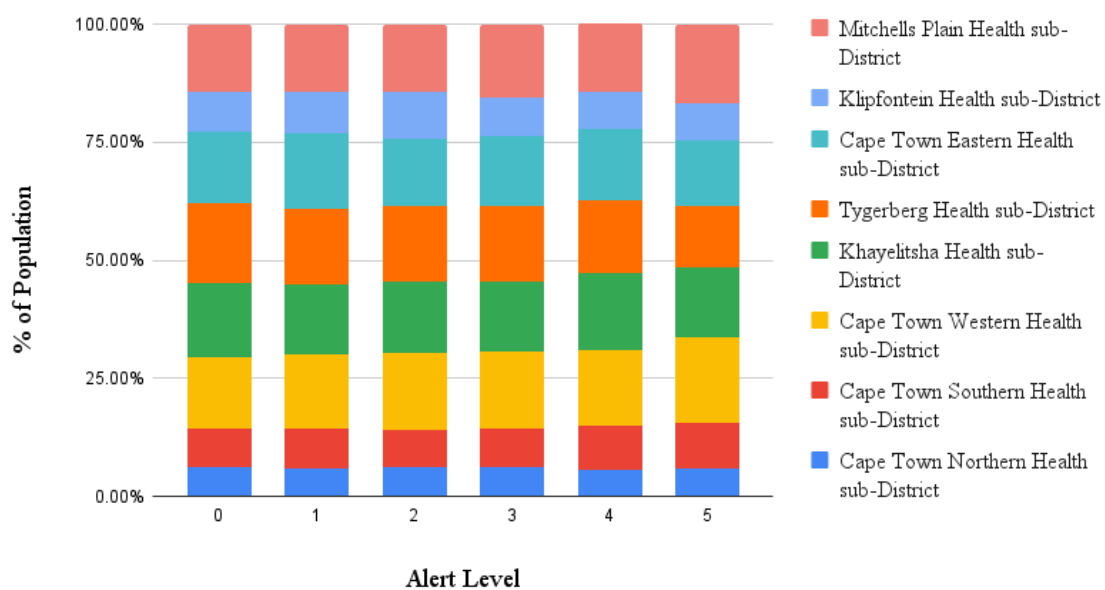


Figure 4: Proportion of TB Diagnoses for each subdistrict by alert level, showing marginal differences in proportions of TB diagnosed at each subdistrict across alert levels.

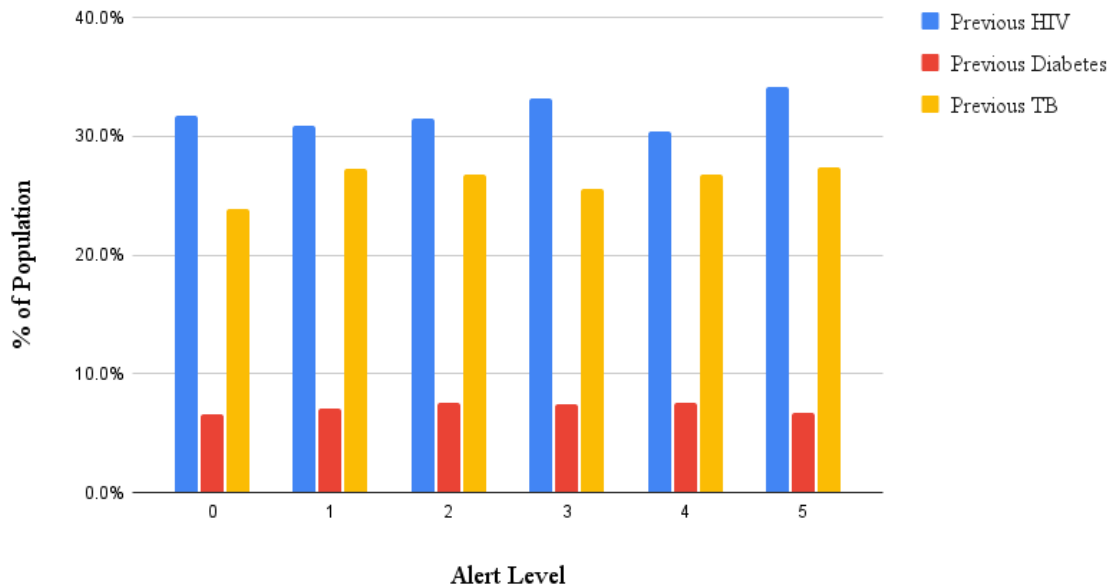


Figure 5: Proportion of TB diagnoses with previous HIV (blue), TB (yellow) and diabetes (red), indicating a slight increase in proportion of TB diagnosis with previous TB and HIV across alert levels.

6 Discussion

6.1 Participants

It is generally recognised that there are high rates of TB in Western Cape²¹, and that while numbers did fall during Covid-19, the number of new TB cases across the province continues to reflect the significant health burden of this infectious disease. The Western Cape and COCTMM have high rates of recurrent TB^{22,23}, and we observe that in this study 6.3% of individuals with a new TB diagnosis during the study period had a subsequent new TB diagnosis within the same period of only 4 years.

6.2 Characteristics of the Study Population

Age at TB diagnosis distribution within the population is consistent with previous studies²⁴, with the greatest proportion of diagnoses occurring in the 30-39 year age group. A greater number of males than females were diagnosed with TB during the study period, and generally at a slightly older age, also consistent with known patterns of TB burden of disease in South Africa²⁵.

Covid-19 diagnosis within 14 days of TB diagnosis was examined to determine if Covid-19 testing had an effect on the likelihood of concurrent TB testing, or vice-versa. An example of this kind of co-diagnosis is the common diagnosis of HIV at the same time as a new TB diagnosis²⁶. However, the small number of co-diagnoses for Covid-19 and TB indicates that it is unlikely that there was any such relationship between TB and Covid-19 testing. Routine Covid-19 testing for individuals accessing health facilities during the pandemic was common, but in PHC settings Covid-19 antigen test results were not routinely captured electronically and thus less likely to be included in the PHDC Covid-19 cascade. While protocols were in place to test individuals for TB at the same time they were tested for Covid-19 at public health facilities, anecdotal reporting suggests this practice was not implemented effectively (personal communication, Dr Arne Von Delft, TB Epidemiology, WCDOH).

6.3 New TB Diagnoses during study period

The average number of TB diagnosis per day dropped according to increased severity of alert level, with the exception of alert level 5, when the most severe restrictions were implemented at the beginning of the pandemic (Table 2). Alert level 5 showed a slightly reduced average number of TB diagnoses per day as compared to alert level 4. This is likely due to the low pressure on health services at the start of the pandemic as alert level 5 was implemented in mid-March 2020, well before Covid-19 admissions began to peak. Covid-19 admissions per day increased towards the end of alert level 5 and continued to rise through the subsequent period of alert level 4, peaking during alert level 3.

A greater drop was observed in PHC-diagnosed TB than in hospital-diagnosed TB, increasing *percent hospital TB diagnosis*. This suggests that primary healthcare services were more negatively impacted by the lockdown restrictions. Similar increases in *percent hospital TB diagnosis* can be seen before alert levels were implemented (Figure 2) specifically over public holidays in South Africa (Easter and December holidays), when PHC facilities are closed but hospitals remain open, supporting the interpretation that this effect is the result of reduced access to PHC facilities.

6.4 Factors influencing numbers of new TB diagnoses

We observe a similar general pattern of peak TB infection in the spring and summer months (September to February in the Southern Hemisphere) as reported in existing studies^{19,27}. The effect was baselined against the month of April, with TB diagnoses increasing in the spring and summer months. In December we see a subsequent decrease in TB diagnoses, hypothesised to be due to disruptions to the health services over the end-of-year holidays. This effect was attributed to the PHC stratum, as hospitals continue to function during public holidays while PHC facilities may be closed. Conversely, hospital-diagnosed new TB is seen to increase in December.

Alert level had the greatest and most significant association with reduction in daily numbers of TB diagnoses. However, most of the effect was observed in the primary health care stratum and hospitals appear to have been marginally impacted as they continued to function during successive alert levels, while access to and operation of PHC services were disrupted. Reports from frontline health workers²⁸ suggest that individuals were presenting with more severe illness at hospitals during the pandemic than previously, an indication that those individuals were failing to be diagnosed at early stages of disease at PHC facilities.

The effect of admission pressure was more equally distributed across the hospital and PHC strata. The larger disparity across the strata in the associations of TB diagnoses with the alert level and month variables was not observed here, likely due to hospitals dealing with the increased number of Covid-19 admissions which would have negatively affected diagnostic services at hospitals at these times.

6.5 Additional factors potentially affecting number of TB diagnoses

Additional variables of *sex*, *age at TB diagnosis*, *subdistrict* of TB diagnosis, *previous TB*, *previous HIV* and *previous diabetes* diagnosis for each TB diagnosis in the dataset were used in a preliminary analysis to determine if they may also have had an association with the number of TB diagnoses counts per day. While these variables were unlikely to have affected overall TB diagnosis per day, proportions of the population labelled with these variable changed slightly according to alert level. The increase in the proportion of new TB diagnoses attributed to females during alert levels 4 and 5 could be attributed to continued peri-natal visits to health facilities by women of child-bearing age, while men were less likely to present at facilities during these more restrictive alert levels. It thus seems likely that decreased

access to PHC TB testing during higher alert levels disproportionately impacted men, and may have exacerbated existing gender-based differences in healthcare-seeking behaviour²⁹. Increased proportion of TB diagnoses with previously diagnosed TB and HIV during alert levels 4 and 5 supports the evidence that an increased proportion of individuals were presenting at hospitals with more severe symptoms²⁸.

7 Conclusion

While we are unable to determine the burden of undiagnosed TB, diagnosis of new TB was significantly reduced during the Covid-19 pandemic. *Alert level* was the most significant factor associated with a reduction in TB diagnoses, indicating that access and operation of health services for TB testing was most likely disrupted by restrictions, far more so at PHC facilities, with apparently limited impact on hospital services. Reduction in numbers of TB diagnoses was most likely a factor of less TB testing at PHC facilities due to individuals having less access, and facilities being closed. *Covid-19 admission pressure* contributed to a lesser extent to the reduction in TB diagnoses, more so at hospitals than PHC facilities. Other demographic and clinical variables assessed in this study had negligible effect.

As the intensity and severity of the Covid-19 infection waves decreased, TB diagnosis rapidly surpassed pre-pandemic levels, with a median number of daily TB diagnosis of 4 246 in the first quarter of 2022 vs 4 050 in the first quarter of 2020¹². These dynamics support the conclusion that pandemic-related limited access to care impacted access to diagnostic testing, but pandemic alert level restrictions did not reduce the actual prevalence and incidence of TB in the province.

Understanding these dynamics will allow public health institutions to perform effective scenario planning in the event of another pandemic, to ensure that PHC services in particular are maintained for the population. Findings will help to inform pandemic preparedness for the health service, specifically in terms of maintaining access to key diagnostic and general health services, in other African and global South contexts

8 Potential limitations of the study

The availability of routinely collected high quality and ubiquitous individual level data on TB diagnosis collected by the WCDOH is a strength of this study.

Attribution of hospital admissions and in-hospital mortality to Covid-19 disease is robust due to the DATCOV³⁰ Covid-19 surveillance system. However, challenges in determining other reasons for hospital admission and mortality (including TB), and low confidence in recorded TB treatment outcomes and time between TB diagnosis and treatment, hampered analysis of TB outcomes and the study relied solely on TB diagnosis data.

The PHDC lacks data for healthy public health clients who are less likely to attend public health facilities if they are not ill. Women access healthcare more frequently for contraceptives and maternal care. We recognise that this may bias our gender-based interpretation of health care service use, especially during times of disrupted health service. Also, the data are restricted to public sector health services and exclude private health services which are accessed by the higher socio-economic sector of the population, accounting for approximately 20% of the population while consuming approximately 80% of the national health spend in South Africa³¹. This makes it difficult to interpret socio-economic factors that impact our finding.

We know that the number of new Covid-19 diagnosis underestimates the true incidence of Covid-19 in the population^{31–33} and skews the data towards strongly symptomatic cases for

which health care clients would have accessed care and been tested. For this study, we have assumed that the representative data have a consistent level of under-reporting and that general trends may be interpreted within this context.

9 Future directions

We aim to further explore the dynamics of new TB diagnoses *within* each alert level timeframe as we observe in these data the largest reduction in new TB diagnoses at the beginning of each peak of Covid-19 admissions. Further investigation should be undertaken to examine the health-seeking behaviours of women of child-bearing age with respect to perinatal health visits and access to contraception during the pandemic. We further recognise that mortality statistics available to the NDOH and WCDOH under-represent out of hospital deaths and further analysis should be conducted using official mortality statistics once they are released⁴.

10 Other Information

10.1 Conflict of Interest

None

10.2 Author Contributions

Professor Nicki Tiffin, South African National Bioinformatics Institute, University of the Western Cape

Professor Andrew Boulle, Centre for Infectious Disease & Epidemiology Research, School of Public Health & Family Medicine, University of Cape Town

10.3 Funding sources

None

10.4 Accessibility raw data, and programming code

Data and programming code are available from the WCDOH on request.

11 References

1. Durbin RP. WHO Global tuberculosis report 2020. *Am J Physiol*. 1975 Dec;229(6):1726.
2. Pai M, Kasaeva T, Swaminathan S. Covid-19's Devastating Effect on Tuberculosis Care — A Path to Recovery. *N Engl J Med*. 2022 Apr 21;386(16):1490–3.
3. The Global Fund. TB Testing in 2020 Dropped Drastically due to COVID-19 [Internet]. Available from: <https://www.theglobalfund.org/en/news/2021/2021-03-24-tb-testing-in-2020-dropped-drastically-due-to-covid-19/>
4. Statistics South Africa. Mortality and causes of death in South Africa: 2018 [Internet]. [cited 2023 Jan 26]. Available from: <https://www.statssa.gov.za/publications/P03093/P030932018.pdf>
5. Achoki T, Sartorius B, Watkins D, Glenn SD, Kengne AP, Oni T, et al. Health trends, inequalities and opportunities in South Africa's provinces, 1990–2019: findings from the Global Burden of Disease 2019 Study. *J Epidemiol Community Health*. 2022 May;76(5):471–81.

6. Abdool Karim Q, Baxter C. COVID-19: Impact on the HIV and Tuberculosis Response, Service Delivery, and Research in South Africa. *Curr HIV/AIDS Rep.* 2022 Feb;19(1):46–53.
7. National Coronavirus Command Council. COVID-19 Risk Adjusted Strategy - SA Corona Virus Online Portal [Internet]. 2020 Apr [cited 2023 Feb 2]. Available from: <https://sacoronavirus.co.za/covid-19-risk-adjusted-strategy/>
8. Government of South Africa. About the alert system [Internet]. [cited 2023 Jan 25]. Available from: <https://www.gov.za/covid-19/about/about-alert-system>
9. du Toit T, Esterhuizen TM, Tiffin N, Abulfathi AA, Reuter H, Decloedt EH. Incident tuberculosis disease in patients receiving biologic therapies in the Western Cape, South Africa from 2007 to 2018. *BMC Infectious Diseases.* 2020 Nov 30;20(1):900.
10. Moultrie, Harry, Kachingwe, Elizabeth, Ismail, Farzana. Impact of Lockdown on TB testing in South Africa [Internet]. 2020 Sep. Available from: https://www.researchgate.net/profile/Elizabeth-Kachingwe/publication/346396453_Impact_of_Lockdown_on_TB_testing_in_South_Africa/links/5fbf9e65458515b797703b1b/Impact-of-Lockdown-on-TB-testing-in-South-Africa.pdf
11. Moultrie, Harry, Ismail, Nazir. Impact of COVID-19 intervention on TB testing in South Africa [Internet]. National Institute for Infectious Diseases; 2020 Oct [cited 2023 Feb 3]. Available from: <https://www.nicd.ac.za/wp-content/uploads/2020/05/Impact-of-Covid-19-interventions-on-TB-testing-in-South-Africa-10-May-2020.pdf>
12. Western Cape Department of Health. Provincial TB Dashboard [Internet]. Western Cape Government. [cited 2023 Jan 29]. Available from: <https://www.westerncape.gov.za/site-page/provincial-tb-dashboard>
13. Western Cape Department of Health in collaboration with the National Institute for Communicable Diseases, South Africa, Boulle A, Davies MA, Hussey H, Ismail M, Morden E, et al. Risk Factors for Coronavirus Disease 2019 (COVID-19) Death in a Population Cohort Study from the Western Cape Province, South Africa. *Clinical Infectious Diseases.* 2020 Aug 29;ciaa1198.
14. Andrews J, Morrow C, Wood R. Modeling the Role of Public Transportation in Sustaining Tuberculosis Transmission in South Africa. *American journal of epidemiology.* 2013 Feb 18;177.
15. Alene KA, Wangdi K, Clements ACA. Impact of the COVID-19 Pandemic on Tuberculosis Control: An Overview. *Trop Med Infect Dis.* 2020 Jul 24;5(3):123.
16. Baker M, Das D, Venugopal K, Howden-Chapman P. Tuberculosis associated with household crowding in a developed country. *Journal of Epidemiology & Community Health.* 2008 Aug 1;62(8):715–21.
17. Boulle A, Heekes A, Tiffin N, Smith M, Mutemaringa T, Zinyakatira N, et al. Data Centre Profile: The Provincial Health Data Centre of the Western Cape Province, South Africa. *IJPDS* [Internet]. 2019 Nov 20 [cited 2021 May 25];4(2). Available from: <https://ijpds.org/article/view/1143>

18. Mutemaringa T, Heekes A, Boulle A, Tiffin N. Record linkage for Routinely Collected Health Data in an African Health Information Exchange. IJPDS [Internet]. 2022 Aug 25 [cited 2023 Feb 1];7(3). Available from: <https://ijpds.org/article/view/2022>
19. Fares A. Seasonality of Tuberculosis. *J Glob Infect Dis*. 2011;3(1):46–55.
20. Yang W, Shaman JL. COVID-19 pandemic dynamics in South Africa and epidemiological characteristics of three variants of concern (Beta, Delta, and Omicron). Dimitrov D, Kana BD, Moore M, editors. *eLife*. 2022 Aug 9;11:e78933.
21. Prevalence of bacteriologically confirmed pulmonary tuberculosis in South Africa, 2017–2019: a multistage, cluster-based, cross-sectional survey | Elsevier Enhanced Reader [Internet]. [cited 2023 Jan 29]. Available from: <https://reader.elsevier.com/reader/sd/pii/S1473309922001499?token=BE7D00B4C7051CDC860066989450CAFF7385C794A937637098316CAED2EFDF3F89E32D3EF29DD4299D397E50C7B8B7AF&originRegion=eu-west-1&originCreation=20230129075935>
22. Hermans SM, Zinyakatira N, Caldwell J, Cobelens FGJ, Boulle A, Wood R. High Rates of Recurrent Tuberculosis Disease: A Population-level Cohort Study. *Clinical Infectious Diseases*. 2021 Jun 1;72(11):1919–26.
23. Molemans M, Leth F van, McKelly DH, Wood R, Hermans S. Neighbourhood risk factors of recurrent tuberculosis in Cape Town: a cohort study using geocoded notification data. *J Epidemiol Community Health*. 2023 Jan 1;77(1):56–62.
24. Wood R, Liang H, Wu H, Middelkoop K, Oni T, Rangaka MX, et al. Changing prevalence of TB infection with increasing age in high TB burden townships in South Africa. *Int J Tuberc Lung Dis*. 2010 Apr;14(4):406–12.
25. Perumal R, Naidoo K, Padayatchi N. TB epidemiology: where are the young women? Know your tuberculosis epidemic, know your response. *BMC Public Health*. 2018 Mar 27;18:417.
26. World Health Organization. Global Tuberculosis Report 2022 [Internet]. [cited 2023 Jan 29]. Available from: <https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022>
27. Andrews JR, Cobelens F, Horsburgh CR, Hatherill M, Basu S, Hermans S, et al. Seasonal drivers of tuberculosis: evidence from over 100 years of notifications in Cape Town. *The International Journal of Tuberculosis and Lung Disease*. 2020 May 1;24(5):477–84.
28. Andrea S M, Morden E, Botha B, Boulle A, Paleker M, Davies MA, et al. COVID-19 wave 4 in Western Cape Province, South Africa: Fewer hospitalisations, but new challenges for a depleted workforce. *SAMJ: South African Medical Journal*. 2022 Feb;112(2):68–70.
29. Osei-Yeboah R, Tamuhla T, Ngwenya O, Tiffin N. Accessing HIV care may lead to earlier ascertainment of comorbidities in health care clients in Khayelitsha, Cape Town. Kadengye DT, editor. *PLOS Glob Public Health*. 2021 Dec 22;1(12):e0000031.

30. Jassat W, Mudara C, Ozougwu L, Tempia S, Blumberg L, Davies MA, et al. Increased mortality among individuals hospitalised with COVID-19 during the second wave in South Africa [Internet]. medRxiv; 2021 [cited 2023 Jan 29]. p. 2021.03.09.21253184. Available from: <https://www.medrxiv.org/content/10.1101/2021.03.09.21253184v1>
31. Motsoaledi DA. White Paper on National Health Insurance. 2015;
32. Kleynhans J, Tempia S, Wolter N, von Gottberg A, Bhiman JN, Buys A, et al. SARS-CoV-2 Seroprevalence in a Rural and Urban Household Cohort during First and Second Waves of Infections, South Africa, July 2020–March 2021. *Emerg Infect Dis.* 2021 Dec;27(12):3020–9.
33. Coovadia H, Jewkes R, Barron P, Sanders D, McIntyre D. The health and health system of South Africa: historical roots of current public health challenges. *The Lancet.* 2009 Sep 5;374(9692):817–34.

Part C: Appendices

1 Ethics Approval - UCT HREC

 UNIVERSITY OF CAPE TOWN UNIVERSITEIT VAN KAPSTAD		 FACULTY OF HEALTH SCIENCES Human Research Ethics Committee HEALTH SCIENCES FACULTY UNIVERSITY OF CAPE TOWN	
FHS016: Annual Progress Report / Renewal			
HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☒ Approved	Annual progress report	Approved until/next renewal date	30-8-23
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee			Date Signed 24/8/22

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.

Please clarify your plan for research-related activities during COVID-19 lockdown.

Please use the latest form found on our website:

<http://www.health.uct.ac.za/hrs/research/humanethics/forms>

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol Information

Date (when submitting this form)	11 August 2022		
HREC REF Number	524/2021	Current Ethics Approval was granted until	30-08-2022
Protocol title	EFFECTS OF THE COVID19 PANDEMIC RESPONSE ON TUBERCULOSIS INCIDENCE AND MORTALITY IN THE CITY OF CAPE TOWN		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes	☒ No	
If yes, could you please provide the HREC Reference number for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			



Principal Investigator	Prof Nicki Tiffin
Department / Office	Integrative Biomedical Sciences
Internal Mail Address	ntiffin@sanbi.ac.za

1.1 Does this protocol receive US Federal funding?	☐ Yes	☒ No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?	☐ Yes	☒ No
Note: Any annual approvals for Full Committee review MUST be submitted on the monthly HREC submission dates. (Please send electronic copy for full committee review to hrec-submission@uct.ac.za)		

If yes in 1.2 please complete section 1.3 below for invoicing purposes

1.3 Ethics Renewal Fee

Please (tick ✓) appropriate box for billing purposes:

Submission Type	Description	New fee /Vat (incl.)	Tick ✓
Research funded solely from UCT departmental/divisional/group budget	Annual evaluation of research progress report for re-certification	R0,00	☐
Non-sponsored student research for degree purposes at UCT/Other Universities & Colleges	Annual evaluation of research progress report for re-certification	R0,00	☐
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Full Committee Approval	R7000,00	☐
Annual re-certification / Progress report (FHS016 Form)	Clinical Trial & International Grant Funded Research - Annual evaluation of research progress report for re-certification for Expedited review	R3 710,00	☐
Annual re-certification / Progress report (FHS016 Form)	National grant funded research - Annual evaluation of research progress report for re-certification for Full Committee Approval	R6000,00	☐
Annual re-certification / Progress report (FHS016 Form)	National Grant funded research for Annual evaluation of research progress report for re-certification for Expedited review	R1 500,00	☐

NB: Protocols funded by UCT (e.g. departmental funding / student research) and by certain grant funding organizations (e.g. MRC, NRF, CANSA,) are exempt from these charges.

Please provide details for invoicing, either complete section 1 or 2 :

1. Invoice billing – Directly to Sponsor

Sponsor's name	
Billing Address of Sponsor:	



Vat Number:	
Contact person	
Telephone number	
Email Address	
2. Internal Journal Billing:	
Fund Number:	
Cost Centre Number:	
Account Holder Name:	
Division of Account Holder:	

2. List of documentation for approval

N/A

3. Protocol status (tick ✓)

☐	Open Enrolment
☐	Closed to enrolment (tick ✓)
☒	Research-related activities are ongoing
☐	Research-related activities are complete, long-term follow-up only
☐	Research-related activities are complete, data analysis only
☐	Main study is complete but sub-study research-related activities are ongoing
☐	Study is closed → Please submit a Study Closure Form (FHS010)

4. Enrolment

Number of participants enrolled to date	NA
Number of participants enrolled, since last HREC Progress report (continuing review)	NA
Additional number of participants still required	NA

5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	NA
---	----

6. Cumulative summary of participants

Total number of participants who provided consent	NA
Number of participants determined to be ineligible (i.e. after screening)	NA
Number of participants currently active on the study	NA
Number of participants completed study (without events leading to withdrawal)	NA
Number of participants withdrawn at participants' request (i.e. changed their mind)	NA
Number of participants withdrawn by PI due to toxicity or adverse events	NA
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	NA
Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up.	NA
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	NA

7. Progress of study

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report as well as any relevant comments/issues you would like to report to the HREC:
The protocol has been implemented in accordance with the ethics guidelines. This is an epidemiological study of citizens who accessed public health service in the City of Cape Town between 2017 and 2021, focused on TB and Covid19 diagnosis and outcomes. Data sets have been prepared in accordance with Western Cape Department of Health policies, and analysis needs to be conducted. There are no amendments to the protocol. I am requesting a renewal of the existing ethics approval.

Several manuscripts are currently in preparation

8. Protocol violations and exceptions (tick ✓ all that apply)

☒	No prior violations or exceptions have occurred since the original approval
☐	Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved
☐	Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported, are attached for review

9. Amendments (tick ✓ all that apply)

☒	No Prior amendments have been made since the original approval
☐	Prior amendments have been reported since the last review and have already been approved
☐	New protocol changes/ amendments are requested as part of this continuing review (See note below)

Note: If new protocol changes are being requested in this review, please complete an amendment form (FHS006).

Specific changes in the amended protocol and consent/assent forms must be **bolded**, *italicised* or tracked and all changes must include a rationale.

10. Adverse events

10.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established.

NA

10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)?

☐ Yes ☐ No ☒ Not applicable

If yes, please describe:

11. Summary of Monitoring and Audit Activities (tick ✓)

11.1 Was this study monitored or audited by an external agency (e.g. SAHPRA, FDA)?

☐ Yes ☐ No ☒ Not applicable

11.2 Did a Data and Safety Monitoring Board publish a report?		
☐ Yes	☐ No	☒ Not applicable

11.3 If yes, please identify the agency and attach a summary of the findings.					
Agency Name		Report attached	☐ Yes	☐ No	☐ Not applicable
		DSMB report attached	☐ Yes	☐ No	☐ Not applicable

11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?	
☐ Yes	☒ No
If yes, please explain:	

12. Level of risk (tick ✓)

12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:	
☐	Increased
☐	Decreased
☐	Shown no change
If there has been a change, please explain:	
NA	

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk.
NA

13. Insurance

Please confirm that valid no fault insurance is still in place? (tick ✓)			
☐ Yes	☐ No	☒ Not Applicable – N/A	
If yes, please complete the following:			
Insurer's name:			
Policy no.		*Coverage Period:	
For UCT sponsored studies please liaise the Insurance office via fhs.sponsorship@uct.ac.za regarding the required documentation and information required obtain a renewed UCT No-fault Insurance Certificate.			

14. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)	
☐ Yes	☒ No
If yes, please explain and if necessary, attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form FHS013):	

15. Signature

My signature certifies that the above is complete and correct.			
Signature of PI		Date	22 June 2022

2 Data Access Approval - Western Cape Department of Health

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:	Pierre	Surname:	Dane
Designation / Rank:	Database Engineer	Date:	08/08/2022
Organisation:	Student UCT		
Email:	Pierre.dane@westerncape.gov.za	Tel/Cell:	0836808274

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	☒ Non-identified individualised data X	☐ Identified individualised data
Please provide a short description of the data requested. Please attach a list/attach a list of the variables required.			
SQL Scripts for extraction are attached to this request			
Facilities: fac_id, fac_name, fac_type, fac_category from facility.lu.fac and facility.lu.fac_attributes for facilities in City of Cape Town district TB Cascade: id, sex, pmi_dominant_id, episode_number, previous_tb_episodes, most_recent_episode, is_deceased, died_of_tb, tb_date_of_death, active_tb, tb_episode_first_inference_date, next_episode_start_date, tb_first_evidence_date, tb_treatment_start_date, hospital_treatment_only, tb_treatment_status, tb_last_evidence_date, episode_confidence_score, admission, tb_cascade_outcome, tb_first_evidence_subdistrict, diabetes, diabetes_first_evidence_date, hiv_status_before_tb, tb_first_evidence_fac_id, age_at_tb_from_reporting, cscd.tb_by_dominant for patients with first_evidence_fac_id included in the facility list (above), between 2016-01-01 and 2021-12-31 Covid Cascade: pmi_dominant_id, date_of_death, Covid_reported_death, Composite Covid date of death, Composite Covid date of death_source, date of death_source, Covid_19_Related_Death, date_of_diagnosis, reinfection, first_episode_date_of_diagnosis, second_episode_date_of_diagnosis, Hospitalised, Admission_date, first_positive_test_date, outcome, date_of_death_test for patients in the TB dataset (above), linked on pmi_dominant_id, before 2022-01-01 TB Tests: tested_date, fac_id, common_concept, common_result, subdistrict for all tests from facilities in the facility list (above) between 2016-01-01 and 2021-12-31			
Do you have a National Health Research Database ref no.?	Yes	No	Number:
Time period the data should cover:	Start date: 01/01/2016		End date: 31/12/2022
Frequency of Access: (please tick appropriate option)	Once-off ☒ X		Periodically
If periodically, please specify time frames for access:			
Is the data to be used for research purposes?	Yes ☒ X		
Please provide a brief motivation for this request, highlighting the purpose for which the data will be used Data will be used for my MPH thesis 'The impact of the Covid-19 pandemic on TB diagnosis in the City of Cape Town, South Africa'. Deidentified data from the TB and Covid-19 cascades will be used to determine differences in the daily number of TB diagnosis cross lockdown levels and Covid-19 waves. Number of TB diagnosis will be stratified between primary and tertiary (hospital) diagnosis settings.			
Study not funded			
Do you have a security protocol for handling the data (attach	Yes ☒ X		No

5th Floor, 8 Riebeeck Street, Cape Town, 8001, PO Box 2060, Cape Town, 8000

detail if necessary)?		
PHDC Manager- Technical assessment and comments: A simple, well circumscribed request asking for a single tranche of non-identified individualised data. From Pierre (23 01 23) I've reduced the scope quite a lot and I'm not looking at mortality or treatment of TB, just diagnosis.		☐ Feasible Where relevant: ☐ Protocol cover ☐ Ethics ☐ Consent docs
Assigned PHDC analyst:	PHDC Manager Signature:	Date:
Assigned Time:		

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

Name:	Melvin	Surname:	Moodley
Designation / Rank:	Director	Signed:	
Application Approved:	Yes ☒ No ☐	Date:	dd/mm/yyyy 6 February 2023

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

.....Pierre Dane....., hereafter "the User"

- 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.
- 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).
- The User agrees that the Department is the owner of the Dataset(s).
- Permitted Uses and Disclosures:
 - Except as otherwise specified herein, the User may make all uses and disclosures of the (Insert name of Data Set/s) Dataset(s) necessary to conduct the (Insert Project name/Report name for which access was granted) for the period starting (insert date User will receive Dataset(s)) and ending (insert date agreement expires).
 - The User will receive the Dataset(s) **once-off/periodically** (delete whatever is not applicable) per (insert frequency), from the designated Department official.
 - 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: (insert names of persons who may use or receive the dataset).
- User Responsibilities:
 - The User will not use or disclose the Dataset(s) for any purpose other than permitted by this Agreement pertaining to (Insert Project name/Report name) 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 *(insert document name)* for *(insert for whom/what the document is intended)*.
 - 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:

Pierre Dane

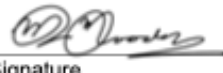
User's Name (Print)

Signature 

Date 08/08/2022

Dr M Moodley

Department of Health (Designated authority)

Signature 

Date 6 February 2023

3 Western Cape Department of Health - TB Episode and Reporting Tools



Department of Health and Wellness

Provincial Health Data Centre

Health Intelligence

phdc_pgwc@westerncape.gov.za

TB Episode and Reporting Tools

1 TB Episode

1.1 Episode Overview

Health conditions can either be chronic (once in a lifetime and ongoing) or acute (can occur multiple times in a lifetime with variable duration and have an outcome). We call these health conditions episodes. A person may only have one episode per chronic health condition but could have multiple episodes per acute health condition. We programmatically infer the health conditions a person may have by identifying if their electronic health data correspond with evidence of a condition.

For each episode, with the input of clinicians and researchers, we compile a list of evidences that can be identified in the routinely available health data that can be used to infer the episode. The types of evidence include (but are not limited to) drugs dispensed, laboratory test results, admissions, diagnosis and procedure coding, observational data captured, and activities (RMR type data). Every evidence is combined into a single record per patient per episode that includes key information such as the first and last evidence dates, treatment start dates, facilities, and evidence of the outcome.

TB is an example of an acute health condition which may become chronic in some instances.

1.2 Episode Evidences

Evidence (details provided next to the name in bold where extra clarification may be useful)	Category	Strength	Treatment	Data sources
GeneXpert Positive	Laboratory	High	No	NHLS
LPA Positive	Laboratory	High	No	NHLS
Culture Positive	Laboratory	High	No	NHLS
Microscopy Positive	Laboratory	High	No	NHLS
Microbiology Culture. Patients with evidence of TB in another microbiology culture recorded in NHLS. This would have been recorded against a culture that is not on the standard list of TB culture tests used by NHLS.	Laboratory	High	No	NHLS
TB drug regimen dispensed. Any patient who has evidence of electronic dispensing for four or more of the drugs used to treat TB that are part of standard regimens or had evidence of treatment provided in a register.	Pharmacy	High	Yes	JAC, PHCIS
TB Outcome Recorded. Certain Outcomes recorded into a TB register: TREATMENT COMPLETED, CURED, TREATMENT FAILURE, Other Country, Other Province, DIED	Observations	Outcome	No	PHCIS, PREHMIS, ETR, EDR, TIER
Diagnosis codes indicate TB	Diagnosis	Weak-Moderate	No	CLINICOM, ECCR, HECTIS, BOD
TB Register Entry. Any entry in a TB register including PHCIS, PREHMIS, ETR, EDR and TIER (*only use treatment specific entries for treatment evidence).	Observations	Weak-Moderate	Yes*	PHCIS, PREHMIS, ETR, EDR, TIER
TB Treatment Start Recorded	Observations	Weak-Moderate	Yes	PHCIS, PREHMIS
TB Regimen Recorded	Observations	Weak-Moderate	No	ETR, TIER, PREHMIS, EDR, ECCR

Two or more TB drugs dispensed	Pharmacy	Supporting	No	JAC, PHCIS
PREHMIS Treatment Visit	Activities	Supporting	Yes	PREHMIS
PHCIS Treatment Visit	Observations	Supporting	Yes	PHCIS
GeneXpert Trace Positive	Laboratory	Supporting	No	NHLS
Admission to TB hospital. <i>This evidence was recently reduced in strength to a supporting evidence as most patients who have TB and are admitted to a TB hospital have other evidence of TB, and TB hospitals are used as step-down facilities or to provide other treatment. It is difficult to ascertain from the admissions data collected whether or not the patient was admitted for TB care.</i>	Encounters	Supporting	No	CLINICOM

1.3 Episode Rollup

All evidences are combined into one line per episode using a programmatic “rollup”. For chronic conditions, all evidences are combined into one line per patient for their lifetime and episodes are closed only by a death record. For acute conditions, all evidences are combined into one line per episode based on a rolling window that is set for each condition.

For TB, the potential window extends until three years after the last evidence date.

1.4 Episode Confidence

Every evidence that is used to infer an episode contributes to our confidence in that episode.

Additional types of evidence and/or re-occurrence of the same evidence strengthens the episode.

At present this measure of confidences is quantitative, such that the higher the score the more evidence there is to support the episode. Evidences are weighted based on 4 strength categories:

- High confidence, defining: This evidence is enough on its own to infer an episode. For example, an elevated viral load test is indicative of HIV positive patients. (Score assigned = 0.7)
- Evidence of an episode-specific outcome: This evidence indicates that an episode has come to an end, and on its own it is enough to infer an episode. For example, a woman giving birth is indicative of pregnancy. (Score assigned = 0.8)
- Weak-moderate confidence: This evidence should be cautiously used on its own. For example, some ICD10 diagnosis codes, particularly ones captured prior to discharge, have been shown to be error prone, and in many cases, we prefer to assign a low confidence episode on the basis of a ICD10 code alone. However, if a patient received multiple diagnosis codes in a valid time period, the confidence in that episode will increase. (Score assigned = 0.25)
- Supporting evidence: This evidence could not infer an episode on its own, but would improve the confidence in an existing episode. For example, dispensing of nausea meds and iron and folate supplements can strengthen a pregnancy episode in that they are evidence of continued care, but is not enough to start the episode on its own. (Score assigned = 0.1)

The confidence score assigned to an episode is a decimal value that ranges from 0-1. As a rule of thumb, scores greater than or equal to 0.7 have at least one high confidence evidence, or more than 5 weak-moderate confidence evidences. Although this can be used for quick filtering, we

would suggest that users interpret their confidence in the episode based on the evidence used to infer it.

Individual evidence scores (including independent instances of the same evidence) are combined using the following formula to get a value between 0 and 1:

$$1 - (1 - [\text{weight of evidence}_1]) * (1 - [\text{weight of evidence}_2]) \dots * (1 - [\text{weight of evidence}_N])$$

We also have negating evidences that can be used to remove an episode. For example, negative HIV tests within a few days of a positive test, without further evidence of HIV most likely indicates a false positive test and the HIV episode should be removed.

In the case of TB, an episode with a combined evidence score of ≥ 0.6 is regarded as a high confidence episode.

1.5 Episode Termination

As already noted, TB is generally an acute health condition. The following factors would cause termination of an active TB episode:

1. A definitive outcome is reported in a register:

Treatment Success (= Cured + Treatment Completed), Treatment Failure, Other Country, Other Province, Died

- Note that these register entries **do not** end a TB episode: "Loss to Follow-Up, MDR TB, Moved out, Transferred Out, Rif Resistance, Still on Treatment, XDR TB, etc."
- Exception: "Transferred out of Province" is treated as a 'conditional' definitive outcome (i.e. terminates an episode). However, if there is a future encounter in the province within 3 years of being transferred out, the relevant TB episode is 'opened' again in the absence of other definitive outcome data

2. TB diagnosis reported as false positive by a clinician

3. Patient is known to have died (date of death was recorded: "is_deceased" in PHDC)

4. Certain time elapses: 3 years since last known TB evidence

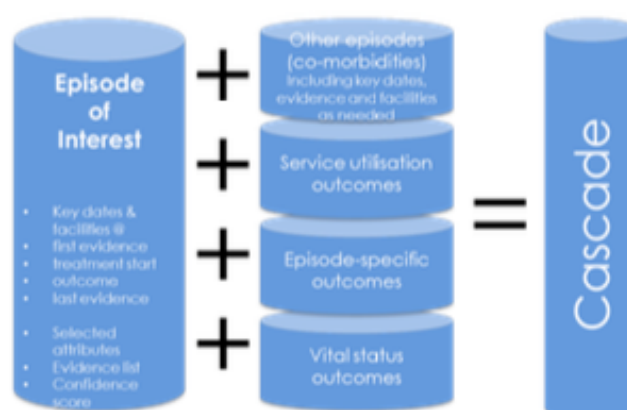
2 TB Cascade

2.1 Description

A cascade provides a comprehensive view of the patient's health episode including key dates, evidence, outcomes and co-morbidities that are relevant for patient management. The cascades are created at a patient level and provide a cohort for both individual management and aggregate level analysis. For management at the individual patient level, cascades are linked to Single Patient Viewer (SPV) so that the patient's electronic medical record can be examined. They are optimised for operational and management purposes, and are easily aggregated by region or attributes.

The core underlying dataset for cascades is the episode/episodes it describes. In addition to the primary episode for the cascade, other episodes, service utilisation outcomes, episode specific outcomes, vital status outcomes are combined to produce a line per patient in the cascade.

This is illustrated below:



The TB Cascade Line List lists all patients with one or more episodes of TB.

2.2 Definitions

2.2.1 In Register

- Any entry in a TB register including PHCIS, PREHMIS, ETR, EDR and TIER

2.2.2 TB Last Active Date

- The Outcome date in the register for an outcome of Died, Treatment Completed, Treatment success, Treatment Failure or Cured, Other Province, Other Country
- In the absence of an outcome date, the date of the last TB evidence

2.2.3 Active TB (TTAL)

- A patient with a high confidence TB episode (episode confidence score ≥ 0.6), no date of death or TB outcome date and the last TB evidence is less than 1096 days ago and there is no evidence of treatment at a primary healthcare (PHC) facility

2.2.4 TB Treatment Status

See TTAL 3.2.2

2.2.5 TB Cascade Outcome

- Died of TB
 - See below 2.2.6
- Transferred Out of WC
 - Register outcome of Other Country or Other Province
- Unsuccessful Treatment
 - Register outcome of Treatment Failure
- Successful Treatment
 - Register outcome of: Treatment completed, Treatment Success or Cured
- Potential Care Interruption
 - Patient received PHC-level TB treatment, but more than 6 weeks have passed since the last known TB evidence (i.e. a TB-specific encounter)
- Post LTFU

- Patient received PHC-level TB treatment, but more than 6 weeks have passed since the last known health encounter of any type (i.e. not TB-specific)
- PHC Treatment
 - Patient is receiving PHC-level TB treatment and no more than 6 weeks have passed since the last TB Treatment evidence
- Hospital Treatment Only
 - Where there is evidence of TB Treatment at a hospital only
- PHC Visit No Treatment
 - Where there is a PHC visit but no record of TB Treatment
- PHC Visit No Treatment
 - Where there is no record of a PHC visit or TB Treatment

2.2.6 Died of/with TB

- Where there is evidence of death during a patient's most recent TB episode
AND the treatment outcome is one of (Died, Treatment Completed, Treatment success, Treatment Failure or Cured)
AND the date of death is < 366 days after the treatment outcome date
- Where there is evidence of death during a patient's most recent TB episode
AND the treatment outcome is NOT one of (Died, Treatment Completed, Treatment success, Treatment Failure or Cured)
AND the date of death is < 1096 days after the last TB evidence date

3 TB Treatment Action List (TTAL)

3.1 Description

The TB Treatment Action List (TTAL) is intended to be a shorter version of the complete TB line list, downloaded from a bespoke report link on SPV. It lists all patients with active TB (i.e. with an active, high confidence TB episode) having a "Treatment Status" requiring action (i.e. pre- or post-treatment loss to follow-up; LTFU) at the facility where (or for which) the list is being drawn.

3.2 Definitions

3.2.1 Allocated Treatment Facility

A patient is allocated to a facility according to the following decisional hierarchy:

Order	Allocation	Reason
1	Manually (re)allocated	Facility allocation entered or changed via SPV
2	Last TB Register Record Facility	Last register record facility in PHCIS, PREHMIS, EDRWeb, Tier or ETR
3	Last TB Treatment Received Facility	Any TB treatment facility (TTF) at which the patient last received treatment
4	Last TB Lab Test Facility	Any TB testing facility at which the patient last had a TB test
5	Last TB Treatment Facility referred to	Last TTF that the patient was referred to, if known (e.g., via ECCR)
6	Last Visit at TB Treatment Facility	Last TTF visited (any type of encounter qualifies at any time, i.e. can precede TB episode)
7	Last Visit at Primary Care Facility	Any PHC encounter at any time which does not meet the above criteria (to refine further)
8	Geocoding	Geocoding functionality is being explored for cases in which facility allocation cannot be achieved via the steps above

If no automated allocation is possible (e.g., patient diagnosed at a non-treating or unknown facility, has no record of visits to a TTF, and no clear geographic allocation is possible automatically) the patient will be flagged for manual resolution by the District TB Manager or appropriate counterpart.

3.2.2 TB Treatment Status

Pre-treatment LTFU (loss to follow-up) - newly diagnosed with active TB, but not yet on any treatment:

- “No treatment started” (implies hospital diagnosis without PHC follow-up)
- “No treatment started, but visited PHC” (PHC visit occurred on or after TB diagnosis date)

• **Post-treatment LTFU** - previously received treatment, but no evidence of current treatment:

- “Treated in Hospital only” (and discharged before treatment was completed)
- “Potential Care Interruption” (PCI)
 - Patient received PHC-level TB treatment, but more than 6 weeks have passed since the last known TB evidence (i.e. a TB-specific encounter)
 - Less conservative (greater sensitivity) than “Post LTFU” below, and therefore more prone to false positives
- “Post LTFU” = LTFU after PHC treatment or care interruption
 - Patient received PHC-level TB treatment, but more than 6 weeks have passed since the last known health encounter of *any type* (i.e. not TB-specific)
 - More conservative (greater specificity) than PCI above, and therefore more prone to false negatives
 - Replaces PCI status where applicable; this is a more definitive evidence/status of LTFU, since PHC encounters are captured real-time on the electronic clinic registries (PHCIS and PREHMIS)

A reported outcome of “Treatment Success” or “Treatment Failure” replaces all the above treatment statuses and removes a patient from the TTAL.

4 Covid-19 Adjusted Risk Strategy – Summary of Alert Levels


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SUMMARY OF ALERT LEVELS

5 ALERT LEVELS	ALERT LEVEL 4	ALERT LEVEL 3	ALERT LEVEL 2	ALERT LEVEL 1
OBJECTIVE				
Drastic measures to contain the spread of the virus and save lives.	Extreme precautions to limit community transmission and outbreaks, while allowing some activity to resume.	Restrictions on many activities, including at workplaces and socially, to address a high risk of transmission.	Physical distancing and restrictions on leisure and social activities to prevent a resurgence of the virus.	Most normal activity can resume, with precautions and health guidelines followed at all times. Population prepared for an increase in alert levels if necessary.
SECTORS PERMITTED				
Only essential services as per existing regulations.	All essential services, plus a limited number of sectors with a low rate of transmission and high economic or social value.	A wider range of sectors permitted with a low to moderate risk of transmission that can be effectively mitigated.	Most sectors permitted, with limitations remaining where the risk of transmission is high.	All sectors permitted.
RETAIL PERMITTED (including stores, eCommerce and informal traders)				
Only essential goods, including food, medical products, cleaning and hygiene products, fuel, and winter goods such as blankets and heaters.	All essential goods, as well as books, stationery and office equipment. Alcohol may be sold within restricted hours, and in limited quantities, for off-site consumption. Restaurants and fast food outlets may open for delivery only.	All retail permitted at levels 5 and 4, as well as clothing stores and hardware stores.	All retail permitted. Restaurants and fast food outlets may open for delivery and take-away.	All retail permitted. Restaurants may open, with stringent social distancing measures.
MOVEMENT				
You must stay at home unless you are an essential worker. You may leave home only to purchase essential goods or seek medical care. No inter-provincial movement of people, except for transportation of goods and exceptional circumstances (e.g. funerals).	You must stay at home except to go to work, do shopping where necessary, or seek medical care. No inter-provincial movement of people, except to return to usual place of residence, for transportation of goods and exceptional circumstances (e.g. funerals). Curfew in place between 7pm and 5am. Walking, jogging and cycling permitted.	All South Africans are encouraged to stay at home as far as possible, and limit their interactions with others. No inter-provincial movement of people, except to return to usual place of residence, for transportation of goods and exceptional circumstances (e.g. funerals).	All South Africans are encouraged to stay at home as far as possible, and limit their interactions with others. Movement between provinces at levels 1 and 2. Movement from provinces at a higher level to those with a lower level may be restricted.	You may leave home, but take precautions while interacting with others. Interprovincial movement allowed, with restrictions on international travel. Curfew lifted.
GATHERINGS				
All public gatherings are prohibited.	All public gatherings are prohibited.	All public gatherings are prohibited.	All public gatherings are prohibited.	All public gatherings are prohibited.
TRANSPORT				
Bus services, taxi services, e-hailing and private motor vehicles may operate at restricted times, with limitations on vehicle capacity and stringent hygiene requirements.	Passenger rail, bus services, taxi services, e-hailing and private motor vehicles may operate subject to directions.	Limited domestic air travel, with a restriction on the number of flights per day and authorisation based on the reason for travel.	Limited domestic air travel, with a restriction on the number of flights per day and authorisation based on the reason for travel.	Domestic air travel restored.
EDUCATION Directions to be issued by the Minister of Basic Education and Minister of Higher Education, Science and Innovation				

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REPUBLIC OF SOUTH AFRICA



5 Instructions for Authors – South African Medical Journal

Author Guidelines

SAMJ Policies

Type of articles considered by the SAMJ

The *SAMJ* will no longer limit the articles accepted to those that have 'general medical content', but is intending to capture the spectrum of medical and health sciences, grouped by relevance to the country's burdens of disease. This content will include research in the social sciences and economics that is relevant to the medical issues around our burden of disease. Please see 'A new vision for the *SAMJ* – and a call for papers' for a full discussion of the new directions for the *SAMJ*.

We accept the following types of articles:

- Research
- Reviews
- Clinical trials
- Editorials
- In Practice (Previously Forum incl. Case Reports)
- Correspondence
- Obituaries
- Book reviews
- Ad hoc supplements e.g. guidelines, conference/congress abstracts, Festschrifts*

The following articles are by invitation only:

- Guest editorial
- Continuing Medical Education (CME)

*Contact claudian@hmpg.co.za for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

Authorship

Named authors must consent to publication. Authorship should be based on: (i) substantial contribution to conceptualisation, design, analysis and interpretation of data; (ii) drafting or critical revision of important scientific content; or (iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org)

If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing.

Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions.

Author contributions should be listed/described in the manuscript.

Conflicts of interest

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Manuscript preparation

Preparing an article for anonymous review

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Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.

- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, **full** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state 'none'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and °C), e.g. '40 kg' and '20 cm' but '50%' and '19°C'.
- Please be sure to insert proper symbols e.g. μ not u for micro, α not a for alpha, β not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.
- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

****NB:** Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'
- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. *J Genet Counsel* 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text .

Structured abstract

- This should be 250-400 words, with the following recommended headings:
 - o **Background:** why the study is being done and how it relates to other published work.
 - o **Objectives:** what the study intends to find out
 - o **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
 - o **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
 - o **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Here is an example of a good abstract.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc) that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the $\pm$ symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.

- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF or jpeg form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain)*. –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
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- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

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Rather:

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NB: Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must **not** be used.

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,^[2] and others.^[3,4-6]

- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
 - Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
 - Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
 - Volume and issue numbers should be given.
 - First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
 - Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
- o On the Crossref homepage, paste the article title into the 'Metadata search' box.
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 - o Provide as follows, e.g.: <https://doi.org/10.7196/07294.937.98x>

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. <http://dx.doi.org/10.1000/hgjr.182>
 - *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
 - *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
 - *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. <http://www.who.int/whr/2002> (accessed 16 January 2010).
 - Legal references
- Government Gazettes:
National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.
In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.
 - Provincial Gazettes:
Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.
 - Acts:
South Africa. National Health Act No. 61 of 2003.
 - Regulations to an Act:
South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).
 - Bills:
South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.
 - Green/white papers:
South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.
 - Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)

Rex v Jopp and Another: Name of the parties concerned

1949: Date of decision (or when the case was heard)

(4): Volume number

SA: SA Law Reports

11: Page or section number

(N): In this case Natal - where the case was heard. Similarly, (C) would indicate Cape, (G) Gauteng, and so on.

NOTE: no . after the v

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