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Factors Associated with In-Facility and Out-of-Facility COVID-19-associated Deaths in the Free State Province, South Africa from March 2020 to March 2022

By

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Masters of Science in Field Epidemiology

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Declaration

I Brian Brümmer, declare that this Research Report is my own, unaided work. It is being submitted for the Degree of Masters of Science in Field Epidemiology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

_____

(Signature of the candidate)

_____ day of August _____ 2024 _____

Dedication

This work is dedicated to those who lost their lives during the pandemic whether due to COVID-19 infection or indirectly during the pandemic. We also dedicate this to those who succeed the ones we lost, and hope that this paper is the lost voice of the vulnerable and the dead.

Presentations and Publications

The findings of this study were presented at Free State Department of Health Research Day. The descriptive statistics of this study were presented at the 8th AFENET Scientific Conference on 6 November 2023 - it won the Best Scientific Innovation award. The title was: SARS-CoV-2 post-mortem testing of out-of-hospital natural deaths - Mangaung metropolitan area, Free State Province, South Africa - August 2020 to August 2022.

Abstract

Background

The COVID-19 pandemic caused a global health crisis and has been extensively researched. The gap between reported COVID-19 deaths and excess deaths is less well characterized. The majority of research uses hospital death as an endpoint - a limitation in light of the gap in COVID-19 death reporting. Understanding the true extent and "who", "what" and "where" of COVID-19-related deaths is crucial. Our study investigates factors associated with in-facility (hospital) and out-of-facility (community) deaths using COVID-19 outbreak data from the Free State province which benefitted from improved community death surveillance. Information generated from this analysis is used to recommend potential surveillance system improvements.

Methods

This study analyzed electronic medical records from the go.data surveillance system in the Free State, South Africa, during the COVID-19 response. It assessed factors associated with community death and determined factors associated with death using subsets of community cases and hospital cases drawn from a single surveillance system.

Results

There were 201 078 COVID-19 cases in Free State, of which 179 916 were community cases and 21 162 were hospitalised cases. The 30-39 year age group made up 21% of COVID-19 cases and was the most common age group. There were 8 589 COVID-19-associated deaths of which 3 159 were in the community and 5 430 were in the hospital. The fourth wave was associated with higher odds of being a community death compared to the third wave - this was demonstrated in both univariate and multivariable analysis (4th wave OR 1.88, 95% CI 1.57-2.26; aOR 1.67, 95% CI 1.37-2.03). Among

hospitalised cases, the odds of death were lower for all waves compared to the third wave. Having an immune condition demonstrated a lower aOR of death in the hospitalised model (aOR 0.69, 95% CI 0.57-0.83) but was associated with a higher aOR of death in the community model (aOR 1.82, 95% CI 1.49-2.2).

Conclusions

The results demonstrate a difference in factors associated with death in the community versus hospitalised COVID-19 cases, under similar conditions such as variant exposure. This is suggestive of a heterogeneous population and provides insight into the "who", "what", and "where" of otherwise unreported COVID-19 deaths, suggested by excess death reports. These results preclude national cause of death reports and highlight the heterogeneity of in-facility and out-of-facility deaths. It is recommended that surveillance systems, such as the civil registration and vital statistics system, be reinforced to distinguish community and hospital deaths in near real-time to assist with evidence for action in future pandemics.

Acknowledgements

This project started well before I knew I was going to be an Epidemiologist. I first swabbed a corpse in 2020 when I was a community service Physiotherapist at the Botshabelo District Hospital in the Free State. Since then, I have met many inspiring and helpful people. I would like to thank the Botshabelo District Hospital CEO and Clinical Manager, Dr. Torres, and Dr. Moeng, for entrusting me with the responsibility and allowing me to pave a career change. I would also like to thank Akhona Tshangela and Dr. Joy Ebonwu, who noticed my work and involved me in scaling it up during 2021 and ultimately recommended me to the South African Field Epidemiology Training Programme, where I have interacted with and learned from many people, with specific mention to Mme Motshabi Modise, the provincial Epidemiologist in the Free State, Mme Dikeledi Baleni, the CDC director, and Dr. Ramasedi 'Sammy' Mokoena, the Free State Public Health Medicine Specialist. I would also like to acknowledge Prof. David Moore, who taught me the fundamentals of RStudio and programming of health-related data, encouraging me to push my skills further.

I would also like to thank all those with whom I have been in contact, including Morticians, Pathologists, Nurses, Community Health Workers, Data Clerks, and Contact Tracers who collected and collated the data we will present. This would not have been possible without the consent of the community in which we carried out our work. We hope that the evidence created here will be of eventual benefit to you.

I thank you.

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Acronyms

Africa CDC	Africa Centres for Disease Control and Prevention
CoD	Cause of Death
CRVS	Civil Registration and Vital Statistics
DATCOV	National Hospital Surveillance System to Monitor COVID-19 Admissions
HIV	Human Immunodeficiency Virus
NICD	National Institute for Communicable Diseases
NP	Nasopharyngeal
PMT	Post Mortem Test
PLWHIV	People Living with Human Immunodeficiency Virus
SA	South Africa
SAMRC	South African Medical Research Council
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
StatsSA	Statistics South Africa
TB	Tuberculosis
WHO	World Health Organization
…	…

Nomenclature

In-facility deaths	Deaths that occur in patients admitted to a health facility
Out-of-facility deaths	Deaths that occur in patients outside of a health facility
COVID-19-associated deaths	Deaths that occur in patients with a laboratory-confirmed COVID-19 infection
DATCOV	National Hospital Surveillance System to Monitor COVID-19 Admissions
Excess deaths	The difference between the expected and actual number deaths
…	…

1 Introduction

The COVID-19 pandemic, caused by the SARS-CoV-2 virus that emerged in Wuhan, China, inflicted an unprecedented global health crisis. Between 1 January 2020 and 31 December 2021, 5.9 million deaths were recorded (Wang et al. 2022) worldwide. In South Africa during the same time period, ~3.5 million cases, ~450 000 hospitalisations, and ~ 96 000 deaths were reported("NICD COVID-19 Daily Sentinel Hospital Surveillacne Report December 2022" 2022). COVID-19 deaths in South Africa (SA) were recorded from deaths in patients hospitalized for COVID-19 recorded in a hospital surveillance system called DATCOV. Developed countries use more representative strategies, leveraging Civil Registration and Vital Statistics systems to enumerate the number of COVID-19 deaths. Leveraging the National population register in SA, the estimated Excess deaths in SA in the same time period were ~300 000 (Debbie Bradshaw et al. 2022; Wang et al. 2022).

The pandemic, and virus, have been extensively researched, yet a critical gap in our understanding of the discrepancy between reported COVID-19-associated deaths and excess deaths remains. This discrepancy leads us to believe there is a knowledge gap in understanding the true "who", "what", "where", and extent of COVID-19-associated deaths.

"Information for action", often the abbreviated definition of public health surveillance,(Alexander Langmuir 1963) is as useful as it is representative of the problem - and in SA, excess death reports by the South African Medical Research Council (SAMRC) suggest COVID-19-associated deaths are underreported(S. Madhi and Nel 2021; R. E. Dorrington et al. 2021) and therefore imperfectly represented. Furthermore, most published findings on factors associated with COVID-19 death in SA predominantly use information generated from a nationally representative hospital surveillance system (DATCOV). While this system (DATCOV) may be representative of COVID-19 in-patients admitted in SA hospitals, it may not be representative of all COVID-19-associated deaths in SA as many may occur outside of hospitals (in the community)(S. Madhi and Nel 2021). Developed countries leverage their CRVS system to report deaths which benefit from established medical records

systems being available by the doctor certifying the death to record and ascribe a COVID-19 diagnosis at death, an example is the OpenSafely platform in the United Kingdom (Andrews et al. 2022)

The COVID-19 pandemic exposed the limitations of using Civil Registration and Vital Statistics (CRVS) systems for mortality reporting in SA, highlighting the need for representative real-time cause of death (CoD) information when responding to outbreaks(T. A. Moultrie et al. 2021). SA used laboratory-confirmed cases that are reported to have died to report the number of COVID-19-associated deaths in the country. Persons who die of unnatural causes, but are coincidentally diagnosed with COVID-19, are not counted as COVID-19 deaths(Nationdal Department of Health (RSA) 2020). Surveillance of COVID-19 was conducted by the National Institute for Communicable Diseases (NICD), supported by provincial departments of health and other partners.

South Africa reported approximately 102 000 COVID-19-associated deaths, yet the South African Medical Research Council (SAMRC), through an excess death calculation, estimates the true death toll is closer to approximately 330 000. An excess death calculation is the difference between the number of deaths that occurred during the pandemic above what was expected to have occurred over the same time period. The SAMRC estimates that at least 85% of the excess deaths are directly associated with COVID-19 with the remainder being collateral effects of the COVID-19 pandemic (T. Moultrie et al. 2021; R. Dorrington et al. 2021). Thus, deaths are underreported by a factor of approximately three. While excess deaths are useful to identify temporal trends and comparing between countries, it has limited information on the epidemiological triad - "where, what, and who"- and therefore excess death counts are unable to identify risk factors for COVID-19.

Identification of risk factors enables appropriate resource allocation, imperative in a resource-limited setting(Waasila Jassat, Cohen, et al. 2021). Statistics South Africa, a government entity, are legally mandated to report CoD, but do not analyse any factors associated with death. In South Africa only one system exists in the Western Cape Province of SA(Western Cape Department of Health in collaboration with the National Institute for Communicable Diseases, South Africa et al. 2021) (one of nine provinces in the country) which was able to determine risk factors for mortality in the general

population early in the pandemic; This system was critical in providing early insight into the protection associated with Tenofovir-based Antiretroviral therapy, and the increased risk of current or past tuberculosis infection on hospitalised COVID-19-associated deaths (Western Cape Department of Health in collaboration with the National Institute for Communicable Diseases, South Africa et al. 2021) however the system could not be expanded nationally.

To address the nationwide surveillance gap, the NICD launched a hospital surveillance system called DATCOV. This initiative filled key knowledge gaps relating to COVID-19 mortality and disease severity in South Africa. However, the endpoints in published findings of COVID-19 deaths have largely been limited to an in-patient population(Waasila Jassat, Cohen, et al. 2021; W. Jassat et al. 2022; Waasila Jassat, Ozougwu, et al. 2022; Waasila Jassat, Karim, Mudara, et al., n.d.; Waasila Jassat, Mudara, et al., n.d.) and may not be generalisable to all COVID-19-associated deaths in the country. Since there was triaging of patients for appropriate resource allocation, those hospitalised may be different from those who are not(T. Moultrie et al. 2021). This gap is in part, what limits our understanding of COVID-19-associated deaths.

Implementing systematic SARS-CoV-2 Post-Mortem Testing (PMT) is narrowly reported in the literature however, SARS-CoV-2 PMT is a strategy that may elucidate the gap between the reported COVID-19-associated deaths and excess deaths. That is, PMT may indicate that COVID-19-associated deaths occur outside of health facilities and contribute to the underreporting of COVID-19-associated deaths, suggested by the excess deaths report. A systematic SARS-CoV-2 PMT descriptive study conducted on 362 natural deaths registered at an academic morgue in Lusaka, Zambia, found that 51/70 (72.8%) of the positive COVID-19 deaths occurred in the community, indicating that COVID-19 infection at death was common in Africa and may be largely undocumented as many deaths occur outside of hospitals and these would have otherwise been unreported. The authors concluded with the adage that “absence of evidence is not evidence of absence”(Mwananyanda et al. 2020).

The South African National Department of Health mandated the systematic SARS-CoV-2 PMT of natural out-of-facility deaths, under the disaster management act (DMA), to improve the report-

ing of COVID-19-associated deaths(Nationdal Department of Health (RSA) 2020). However, SARS-CoV-2 PMT was more difficult to implement than envisioned. The National Institute of Communicable Disease (NICD), together with the Africa Centre for Disease Control and Prevention (CDC), and Free State Department of Health, implemented sentinel community death surveillance, with a strong focus on PMT, in two Districts of the Free State Province (Mangaung and Thabo Mofutsanyana). An intention of focussing on two large districts was to facilitate knowledge spillover to smaller, surrounding districts by sharing lessons learned during the implementation of enhanced surveillance. The sentinel death surveillance aimed providing idenitfying out-of-facility COVID-19-associated deaths.

If most COVID-19-associated deaths are reported from COVID-19 hospitalised deaths and we assume those who have been hospitalised for COVID-19 are different from those who have never been hospitalised for COVID-19 and that COVID-19-associated deaths are underreported, then describing and analysing out-of-facility deaths and comparing it to in-facility deaths may aid in understanding the "who", "what" and "where" of the otherwise unreported COVID-19 deaths in SA. This may serve as an early characterisation of factors associated with death in a non-hospitalised setting in South Africa until StatsSA publishes the national CoD report. This research intends to fill the current knowledge gap between reported COVID-19-associated deaths and otherwise unreported deaths in South Africa using data from a province with active community death surveillance, distinguishin in-facility (hospital) and out-of-facility (community) deaths.

2 Literature Review

2.1 Excess deaths, who are they?

Excess deaths are, in simple terms, the difference between the expected number of deaths and the actual number of deaths recorded over a certain time period. A recent paper found that, while 5.94 million COVID-19 deaths have been reported by 191 countries between 1 January 2020 and 31 December

2021, the estimated deaths attributable to COVID-19 is 18.2 million. It concluded that improving civil registration and vital statistics systems were crucial in monitoring COVID-19 and other pandemics; and that distinguishing deaths specifically due to SARS-CoV-2 infection versus change in cause of death reporting [or indirect effects of COVID-19] be investigated(Wang et al. 2022).

Health Professionals asserted that Africa was largely spared in the early months of the COVID-19 pandemic since reported COVID-19 deaths were low. Some explanations for the low death rate were; the low importation risk of COVID-19 to Africa (Dzinamarira et al. 2020); the proposed broad-range protective effect of the BCG vaccine (Escobar, Molina-Cruz, and Barillas-Mury, n.d.); and, most biologically plausible, a low median age of the African population(Lawal 2021).

A potential explanation of low COVID-19 deaths in Africa may have been known prior to the pandemic - poor death registration coverage in Africa ("SCORE for Health Data Technical Package: Global Report on Health Data Systems and Capacity, 2020" 2021). Poor death registration coverage and poor quality of cause of death (CoD) data in Africa results from poor incentives for registration by the population and by trained personnel, fragmented systems, and other structural, social, and economic factors (Ma Fat 2018; Yokobori et al. 2021); yet, high quality CoD information is crucial to monitoring sustainable development goals(Ma Fat 2018) and accurately estimating the disease burden for policy and programme monitoring and evalutation(Phillips et al. 2015).

Weaker Civil Registration and Vital Statistics (CRVS) systems in many African countries contribute to uncertainty regarding the number of deaths and the specific causes of death, making it difficult to determine the true number of COVID-19-associated deaths. COVID-19-associated deaths certainly occur in Africa, and it is likely that most are undiagnosed, undocumented and unreported. The hypothesis of undiagnosed COVID-19 deaths was demonstrated by a study of systematic post-mortem testing in Lusaka Zambia (Mwananyanda et al. 2020) which demonstrated a high proportion (~30%) of natural deaths were diagnosed with COVID-19 post-mortem through active surveillance; these deaths would have otherwise not been reported as COVID-19 deaths.

In SA, excess deaths have been used to measure the "true" HIV/AIDS death toll during the South African governments denial of the disease (Chigwedere et al. (2008)). The system was re-purposed before the first wave of COVID-19 in SA and are comparable to other methods used globally. While it could be argued that SA has a different general population to the rest of Africa, it has a 97% coverage of death registrations (Garenne et al. 2016) making it a useful data point to provide insight into the upper bound of the true number of COVID-19 deaths in SA. SA recorded one of the highest excess deaths per 100 000 population (293/ 100 000 population) in the world(Wang et al. 2022; Karlinsky and Kobak 2021). Within SA, the Western Cape and Free State provinces were identified as having the highest and second highest highest ratio of confirmed COVID-19 deaths to excess deaths 68% and 46% respectively - they may have had the best reporting of COVID-19 deaths(T. Moultrie et al. 2021).

2.2 An overview of mortality surveillance in South Africa

Statistics South Africa (StatsSA), a government agency, has the constitutionally exclusive mandate to report the Cause of Death (CoD) information. CoD is collected through death certification conducted by a medical practitioner, on a death notification form where the sealed form is forwarded to StatSA for official coding and reporting. The CoDs in SA are reported by StatsSA annually. Critical limitations of this process include delayed dissemination(D. Bradshaw et al. 2021) (CoDs during 2019 were only published in December 2023(Africa 2023)), the absence of patient linking(Groenewald et al. 2015) (the report does not link to surveillance systems) and the high number (13.2% in latest report) of ill-defined codes without adjustment (such as died of "immunocompromise" or "old-age" are disregarded)(Pillay-van Wyk et al. 2019, 2011). Absence of patient-linking and high number of ill-defined codes make the representativeness of the StatsSA annual CoD report questionable, and its delayed dissemination make it somewhat obsolete for decision-making in the face of rapidly evolving health emergencies such as the COVID-19 pandemic.

Birth and death notifications are legally stewarded by the Department of Home Affairs and up-

dated to an electronic National Population Register (NPR), conditional on holding an SA identification number. Post-Apartheid, SA focused on improving its Civil Registration and Vital Statistics System (CRVS) and has improving birth and death registration coverage. However, the quality of cause of death (CoD) information is questionable(R. E. Dorrington et al. 2021). Unlike other countries, South Africa was unable to report COVID-19-associated deaths through the CRVS system and relied on other surveillance systems.

2.3 COVID-19 Mortality surveillance in South Africa

Since the CRVS system was unable to monitor the number of COVID-19-associated deaths, and no secondary surveillance system is legally able to leverage that system, the surveillance of laboratory-confirmed COVID-19 cases was conducted by the National Institute of Communicable Disease (NICD). This included a near real-time hospital surveillance system for COVID-19 admissions which was representative of all 666 public and private health facilities in the country (DATCOV), and line-lists from contact tracing and laboratory-confirmed case-monitoring activities, undertaken by provincial and local health departments. Deaths reported from this type of surveillance are not the cause or mechanism of death recorded by the attending medical doctor, but rather, a death occurring at the same time the deceased matched the case definition of (and was clinically compatible with) COVID-19 disease.

Laboratory-confirmed cases may only show the proportion of people who access testing and therefore may not be an accurate reflection of the true infection rate. This is a known limitation and is confirmed by the high seroprevalence of COVID-19 in SA(S. A. Madhi et al. 2022; Mutevedzi et al. 2022) and low case load relative to international trends(Dzinamarira et al. 2020).

2.4 Factors associated with COVID-19 death in South Africa

One of the earliest papers to report the risk factors of COVID-19 in South Africa was conducted in the Western Cape of SA. This paper demonstrated good data quality of co-morbidities of HIV, tuberculosis

and DM by triangulating patient-level district health systems of the general population for identifying risk-factors for COVID-19 death. COVID-19 deaths were limited to the in-patient population; later changes to testing strategy for optimal resource utilisation rendered only those >55 years of age and meeting hospital admission criteria as eligible for a COVID-19 test; leaving a large proportion of the population at risk of infection undiagnosed and the study was concluded. The paper demonstrated that, in a population with 16% PLWHIV; and controlling for viral load and immune-suppression; HIV infection doubled the adjusted Hazard Ratio of Mortality (adjusted hazard ratio (95%CI), 2.14 (1.70–2.70)) While these findings may be overestimation due to residual confounding; the research was a strong demonstration of the utility of representative and patient-level surveillance systems - a system that is not in place nationally(Western Cape Department of Health in collaboration with the National Institute for Communicable Diseases, South Africa et al. 2021). The systems used to generate data are somewhat reminiscent of the OpenSafely platform, a pseudo-anonymised patient-level data system in the United Kingdom, which provided one of the earliest publications on Risk Factors for COVID-19 in a nationally representative sample(Andrews et al. 2022; The OpenSAFELY Collaborative et al. 2020).

Data from DATCOV has since been used for multiple publications on risk factors of COVID-19 mortality, such as: increased severity of infection from wild-type to beta variant; (Waasila Jassat, Mudara, et al. 2021) the decrease in admission risk of health care workers from the wild-type to beta variants, supporting the hypothesis of some protection from acquired immunity through prior infection; (Tlotleng et al. 2022) the decoupling of cases to hospitalisation and deaths associated with the Omicron variant (S. A. Madhi et al. 2022; Waasila Jassat, Abdool Karim, et al. 2022); the decreasing Case-Fatality-Ratio from the Delta to two Omicron sub-lineages (Waasila Jassat, Karim, Ozougwu, et al., n.d.), and the importance of collecting socio-economic variables to identify vulnerable groups within the general population (Waasila Jassat, Ozougwu, et al. 2022)

An analysis of the Long Term Care Faciities (LTCF) registered on DATCOV investigated the difference in Mortality risk between LTCFs in different South African Provinces, demonstrating that

Free State and Northern Cape had the highest risk of death. (Arendse et al. 2022)

DATCOV data was also used as part of modelling and simulation models in the South African context (Modelling and Simulation Hub, Africa (MASHA), Department of Statistical Sciences, University of Cape Town, South Africa et al. 2022).

At the time of its publication (September 2021), the largest study using DATCOV data analysed 219 265 patients who had been admitted with a COVID-19 infection and reported through DATCOV. The study added crucial information on the effect of COVID-19 on mortality in a high HIV-burden population. The authors reported an in-patient HIV infection rate of 9.1% and that HIV infection increased the odds ratio (95%CI) of death by 1·34 (1·27-1·43) (Waasila Jassat, Cohen, et al. 2021). There was missing data for which the authors conducted multiple imputation chain equation to generate a complete dataset.

The largest study usign DATCOV was conducted later in the pandemic - analysing 484 699 patients. The authors conducted a spatial model which increased the resolution of the geographical hotspots and identified areas with sustained high odds of death; this suggested systemic shortcomings in districts within the Limpopo and Eastern Cape Provinces and concluded that these areas, especially those with poorer socio-economic indicators, need enhanced high-care and intensive-care resources during a public health response(Maposa et al. 2022).

2.5 Current limitations on risk-factors associated COVID-19 death in SA

A limitation of DATCOV was under-reporting of co-morbidities - likely due to patient-factors, health-system structure, and social determinants of health. It is known that large proportion of people have undiagnosed co-morbidities or, if they are diagnosed, are poorly controlled (National Department of Health (NDoH) 2019). Following the large analysis of DATCOV, the authors selected sentinel sites to conduct active surveillance on HIV, TB and Non-Communicable diseases. The prevalence of hypertension, Diabetes Mellitus (DM), HIV, and Active tuberculosis increased by 2.4%, 7.3%, 3.1%, and

1.9% respectively. The severity of newly diagnosed disease was also investigated and revealed that the proportion newly diagnosed HIV, and DM cases who were had poorly controlled disease was high - 88.4% of newly diagnosed DM cases had a glycosylated haemoglobin score of >6.5% indicating poor blood sugar control. Whether the improved data quality changed risk-factors of COVID-19 deaths, or performed better than imputation methods was not investigated(W. Jassat et al. 2022).

There are two broad limitations of papers who use DATCOV data to identify risk factors for death: Firstly, DATCOV is limited to the in-patient population; since people in low-middle income countries do not have good access to Hospitals, many die outside of facilities, even in Urban settings (Mwananyanda et al. 2020) which may bias results, since those who die in-facility may be different to those who die out-of-facility. The second has to do with health system interoperability. SA has a bounty of health information yet they exist in silos with different gatekeepers who are apprehensive of collaboration. DATCOV most notably does not link to laboratory data, vaccination data, or cause of death data collected by the CRVS system. Without improved interoperability, surveillance will rely on expensive sentinel surveillance or large datasets with poor data quality.

While COVID-19 surveillance in SA may underreport COVID-19-associated deaths, the excess deaths calculation by SAMRC provide an upper bound of the true number of COVID-19-associated deaths. To what extent the proportion of excess deaths are COVID-19-associated deaths, and "who" the excess deaths are remains uncertain.

2.6 Post-Mortem Testing for COVID-19

The Rapid Mortality surveillance conducted by the SAMRC allowed the early identification of the disjuncture between Excess deaths and reported COVID-19 deaths in SA. In response, the Department of Health issued directives to all Hospitals and medical practitioners to conduct a SARS-CoV-2 PCR test on all persons dying of natural causes in the country(Nationdal Department of Health (RSA) 2020). This process was also regulated under the Disaster Management Act during the countries state of disaster and

hypothesized to improve the reporting of COVID-19 deaths in the country("Amendment of Directions Issued in Terms of Regulation 4(1)(a) of the Regulations Made Under Section 27(2) of the Disaster Management Act, 2002 (Act No. 57 of 2002): Measures to Address, Prevent and Combat the Spread of COVID-19 (Page 4)" 2020).

PMT was more difficult to implement than envisioned and therefore, the NICD in collaboration with Africa CDC concentrated on active mortality surveillance (focussing on PMT) select district sin SOuth Africa.

Few settings have implemented and optimised PMT for COVID-19, fewer still have published their findings. Early in the pandemic, systematic testing for COVID-19 of natural deaths post-mortem was added to the protocol of the ZPRIME study (Gill et al. 2022). Decedents whose death was being registered at the University Teaching Hospital Morgue in Lusaka, which registers approximately 80% of the area's deaths (both in-facility and out-of-facility deaths), were enrolled. The study linked tests to 364/372 of enrolled participants for COVID-19 post-mortem testing. 74.2% (268/364) of all deaths registered at the Morgue were out-of facility [community] deaths. Of the 70 deaths identified as having COVID-19 infection, 72.8% (49/70) were from the community and none had a history of an ante-mortem test. The most common co-morbidities were Tuberculosis, Hypertension, HIV/AIDS, alcohol use and DM The authors wrote in their discussion that "If our data are generalizable to other settings in Africa, the answer to the question, *'Why did COVID-19 skip Africa?'*, is that it didn't." suggesting an explanation with the adage - "an absence of evidence is not evidence of absence."

A further study was conducted in the same setting using Minimally Invasive Tissue sampling and found that of those who had a positive COVID-19 test Post-Mortem, COVID-19 cases common revealed alveolar damage and diffuse interstitial pneumonitis strongly suggestive of COVID-19 pneumonia; (Mudenda et al. 2021) with no vascular thrombi detected - this is of particular interest when we know that COVID-19 patients typically had raised D-Dimer levels and in a study at an acadmeic hosptial in the Free State demonstrated that 33.8% of patients with previous COVID-19 infection who had not been hospitalised and were now refferred for imaging with a cardiopulmonary complaint had

evidence of Pulmonary Emboli (Evbuomwan et al. 2021). Acknowledging these two studies is important when we think about the accuracy of a PMT at identifying a COVID-19 death and the mechanism of death. The common presence of interstitial pneumonitis discovered through post-mortem examination is strongly suggestive that a positive COVID-19 NP swab post-mortem is not incidental and that COVID-19 in the community was associated with pneumonia and not associated with cardiovascular and/or haematological complications.

In SA, attributing the cause of death aligned to the ICD-10 coding and was communicated by the department of health("Medical Certification of Deaths Due to COVID-19" 2020) - it mainly pertained to medical certification which, as mentioend, is mandated by the Department of Home Affairs and StatsSA and we, at the time of writing, we still do not know what the number of reported deaths through medical certification is. For Surveillance purposes, a COVID-19 death was defined as a death clinically compatible with COVID-19; Where there was a clear alternate cause or of there was a period of resolution of disease between death and primary infection, the death was not reported.

The author knows of only one other published study in which there was Systematic PMT of natural deaths in SA. This study enrolled a small sample, initially to estimate the burden of undiagnosed TB however, during COVID-19 and amendment to the protocol allowed a nasopharyngeal (NP) swab and lung biopsy to be subjected to SARS-CoV-2 testing. This revealed 3 interesting findings; rates of undiagnosed TB had decreased from prior estimates but remained high at 16.3% of the study population; COVID-19 infection was very high - 34.1% of those who received a COVID-19 test in the study sample were positive; and no TB and COVID-19 co-infection(Sabet et al., n.d.).

2.7 COVID-19 Vaccination in Souh Africa

The vaccination programme in SA has only been assessed through Phase 3 clinical trials such as the Sisonke trials - highly valuable trials which gave early access and protection to the, predominantly female and HIV co-infected, Health Care Worker population in SA. (Preiser and Fish 2022) The Sisonke

trial consisted of a single-dose Johnson and Johnson vaccine (Ad26.COV2.S) in “Sisonke 1”(Bekker et al. 2022) and then a booster of the same vaccine in “Sisonke 2”(Gray et al. 2021). The double-dose AstraZeneca Vaccine (ChAdOx1 nCoV-19) delivered with a 6-week interval (S. A. Madhi et al. 2021) demonstrated superior protection against the Delta variant in the South African Population over the Johnson and Johnson vaccine. A trial using the Moderna vaccine (mRNA-1273) as a booster after the Johnson and Johnson vaccine is currently underway as part of the “Sisonke” set of trials - known as SHERPA(“SAMRC Launches a Study to Evaluate the Effectiveness of the Moderna Booster” n.d.).

The effectiveness of SA’s vaccination programme has not been assessed in the general population as DATCOV, nor any other surveillance system been linked to the Electronic Vaccination Data System (EVDS). Information on the vaccination status, history, and dosage of patients is self-reported making the data quality around the timing and dose, poor - a population level COVID-19 effectiveness study has not been conducted. The data collected on the go.data system (used in this research) included variables for self reported vaccination status but was not usable as it was poorly populated.

2.8 Problem Statement

The difference in the reported COVID-19 deaths and the excess deaths in South Africa, together with the knowledge that COVID-19 deaths are reported primarily from an in-patient population in SA, suggest that factors associated with COVID-19 death in SA may be misrepresented.

Adjunct community-based death surveillance efforts in FS, such as SARS-CoV-2 PMT, provide more complete out-of-facility COVID-19-associated deaths data and allow us to compare them to in-facility deaths. In other words, it allows us to compare characteristics of reported COVID-19 deaths to otherwise unreported COVID-19 deaths.

By comparing the characteristics of reported deaths to otherwise unreported deaths in a province with enhanced surveillance, we may demonstrate that the surveillance of COVID-19 deaths in SA during the COVID-19 pandemic may not have been representative. Demonstrating this difference

may provide evidence that surveillance systems should be reinforced to better represent community deaths.

2.9 Research Question

Do the sociodemographic and clinical characteristics differ between in-facility and out-of-facility COVID-19-associated deaths in the Free State Province of South Africa?

2.10 Aim of the Study

To describe and compare the sociodemographic and clinical characteristics of in-facility vs out-of-facility COVID-19-associated deaths in Free-State, Africa.

1. To: Describe the epidemiology of in-facility vs out-of-facility COVID-19 cases in the Free State Province, from March 2020 to March 2022.
    a) Describe temporal trends of reported COVID-19 cases with an Epicurve
    b) Describe geographical distribution of COVID-19 cases with a map.
    c) Describe and compare COVID-19 cases by hospitalisation status;
2. To: Determine differences between in-facility and out-of-facility deaths among COVID-19-associated deaths in Free State Province, from March 2020 to March 2022.
    a) Describe and compare COVID-19 deaths by Hospitalisation status.
    b) Determine the adjusted Odds Ratio of being an out-of-hospital death compared to in-facility death.
3. To: Determine and compare factors associated with in-facility and out-of-facility COVID-19 deaths in Free State Province, from March 2020 to March 2022.

a) Report and compare the Case Fatality Ratio for Community and hospitalised cases.

b) Describe and compare COVID-19-associated deaths by Hospitalisation status.

c) Determine and compare factors associated with hospitalised and community COVID-19-associated deaths in Free State Province, from March 2020 to March 2022.;

3 Methodology

3.1 Study Design

This cross-sectional study was conducted using secondary data analysis of outbreak response records stored on the go.data case management system used. This system was used in the Free State Province of South Africa while responding to the COVID-19 pandemic.

This secondary data source was used to describe the epidemiology of COVID-19-associated deaths in the Free State Province and to compare the socio-demographic and clinical characteristics of in-facility vs out-of-facility COVID-19-associated deaths.

3.2 Study population

The study population consisted of all COVID-19 cases reported in the Free State Province between March 2020 and March 2022. The Free State Province, located in the interior of South Africa, is characterized by a low population density of 22.83 people per square kilometer. The province is divided into 5 districts.

3.3 Data sources

The dataset provided by the Free State Department of Health Data Management Team was the go.data dataset from the Free State Province. It was collected as part of routine contact tracing and outbreak response to the COVID-19 pandemic in Free-State, South Africa. COVID-19 laboratory test data was loaded onto the go.data outbreak management system daily. Laboratory test data included post-mortem tests. Call centres would contact patients or patients family members to augment laboratory data with additonal clinical and demographic data. If the patient was unable to be contacted, the team would dispatch contact tracers who would record the data. More detailed clinical infromation recorded on

DATCOV was harmonised with the go.data system by the Free State Department of Health Information Management Team. Outcomes were verified by the Provincial epidemiology and information management team. Once verified, cases and their outcomes were reported to the National level.

3.4 Data management

The Provincial datasets, maintained by the Free State Department of Health information management team were anonymised and transferred in password-protected csv to the author. Data was analysed using the latest version of R and Rstudio.

3.4.1 Imputation

Missingess was assessed for explanatory variables only. There was missing data for age, gender, developing symptoms, and the characteristics of the residence (the number of people in a residence, running water in a residence, and the type of residence). Missingness was assessed using a Chi-Square test for an associated between missingness of the explanatory variable and the outcome variable (death). There was strong evidence of an association between the characteristics of the residence and developing symptoms. Random forest Multiple Imputation chain equation with three datasets and three iterations was conducted for the age category and gender. Imputation was not conducted on the outcome variables of interest.

3.5 Outcome Variables

3.5.1 Hospitalisation and Community categorisation

Cases (including deaths) were classified as “Hospital” if they had any history of an admission to a health facility otherwise were classified as “Community”.

3.5.2 Death

Death was recorded by reporting from the post-mortem surveillance team, DATCOV, or by the family member of the deceased when contacted by contact tracing teams. Deaths were recorded in the go.data dataset as “Death: Community”, “Death: PMT” and “Death: In-Facility”. These were cross tabulated with the hospitalisation category as a sensitivity check.

3.6 Exaplanatory variables

3.6.1 Demographics

Explanatory variables were: Age Category, Gender, District.

3.6.2 Clinical characteristics

Disease-specific conditions or syndromes are limited as they are only collected in general terms by systems the condition affected. Comorbidities were collected under general categories as follows: liver condition, cardiac condition, immunological condition, respiratory condition inc. TB, neurological condition, having diabetes (DM), renal condition, is pregnant, and has malignancy.

3.6.3 Waves

Epiweeks start on a Sunday and end on a Sunday. Waves were identified when the weekly cases per 100 000 population exceed 30 per epiweek as per proposed definition use in South Africa (“Proposed Definition of COVID-19 Wave in South Africa” 2021). Mid-year population estimates (MYPE) were sourced from StatsSA(Statistics South Africa 2022) and used for incidence calculations per epiweek of the year the case occurred in.

Incidence was calculated using the formula:

$$\text{Incidence} = \left(\frac{\text{Number of Cases in Epiweek of Year i}}{\text{Population of Year i}}\right) \times 100000$$

3.7 Ethical Consideration

Ethical clearance to conduct this study was obtained through the University of the Witwatersrand Human Research Ethics (Medical) (HREC), (clearance number: M230322) (Appendix 1). Institutional Permission was granted from the Free State Department of Health. (Appendix 2)

3.8 Analysis

3.8.1 Objective 1

Describe the epidemiology of COVID-19 cases in the Free State Province, from March 2020 to March 2022.

A histogram (as an epicurve) with number of cases per epiweek was plotted. The number of cases was plotted on the y-axis and epiweek on the x-axis. A choropleth map was used to represent the number of COVID-19 cases per District. The total number of cases per district was represented by a colour gradient and plotted on a map of the Free State Province using a shape (.shp) file. The explanatory variables of all COVID-19 *cases* were described using frequency and proportions of categorical variables. The overall and by hospitalisation status was described. Differences in the proportions of explanatory variables by hospitalisation status were tested using the pearson Chi-squared test.

3.8.2 Objective 2

Describe and compare factors associated with being a COVID-19 community death in the Free State Province, from March 2020 to March 2022. Explanatory variables included the demographic and clin-

ical characteristics outlined above and the outcome variable was community or hospital death. Explanatory variables of COVID-19-associated *deaths* were described using frequency and proportions. The overall and by hospitalisation status was described. Differences in the proportions of explanatory variables by hospitalisation status was tested using the pearson Chi-squared test or Fischers test when the expected value of cells was less than 5. The odds ratio (OR) associated with being a community death was calculated using a dataset that was subsetted to only include deceased individuals. The null hypothesis is that the odds of community death is equal across all explanatory variables. We conducted univariate logistic regression on each factor associated with community death. We then conducted multivarmultivariate logistic regression, employing forward and backward stepwise variable selection. The model with the lowest Akaike Information Criterion (AIC) was utilized to guide the variable selection and direction of selection. Interactions between all comorbidities were assessed, but none were found to be significant and therefore were not included in the final model. Collinearity was assessed using a variance inflation factor of >3 to indicate collinearity - no collinearity was detected. Influential observations were identified using HAT-values to identify potentially influential observations.Potentially influential observations were omitted from the model to see if it influenced results. No explanatory variables change significance or change the interpretation of the model.

3.8.3 Objective 3

Describe and compare factors associated with being a COVID-19 community death in the Free State Province, from March 2020 to March 2022. Point estimate and Confidence intervals for community and hospital CFR were calculated and presented. The case fatality ratio (CFR) per age group was plotted for community cases and hospitalised cases separately. The plots were critically appraised.

The formula for the Case Fatality Ratio (CFR) is:

$$\text{CFR} = \left(\frac{\text{Number of Deaths}}{\text{Number of Confirmed Cases}} \right) \times 100$$

Explanatory variables of COVID-19 cases and deaths were described using frequency and proportions of categorical variables. Explanatory variables included the demographic and clinical characteristics outlined above and the outcome variable was death. Two models were critically appraised, the "hospitalised model" comprised of only in-facility cases, while the "community model" comprised of non hospitalised cases.

The overall characteristics of cases and deaths, stratified by hospitalisation status were described. Differences in the proportions of explanatory variables between cases and deaths within each strata were tested using the pearson Chi-squared test, or Fischers test when the expected value of cells was less than 5.

Factors associated with community-death and hospitalised-death, were determined using the odds ratio (OR) associated with death among a subset of community COVID-19 cases only (known as the "community model") and then another set of odds ratios (OR) for factors associated with deaths among hospitalised cases only (known as the "hospitalised model"). The null hypothesis for each model was that the odds of death did not differ between explanatory variables. We first determined OR for factors associated with each death using univariate logistic regression. Multivariable logistic regression was then employed using forward and backward stepwise variable selection. The model with the lowest Akaike Information Criterion (AIC) was utilized to guide the variable selection and direction of selection. Interactions between all comorbidities was assessed, but none were found to be significant. Reference categories for age, wave, and district were based on the highest proportion of deaths. Results from both regression analyses were presented in tabular format for critical appraisal. Collinearity was assessed using a variance inflation factor of >3 to indicate collinearity - no collinearity was detected. Influential observations were identified using HAT-values to identify potentiallyinfluential observations.Potentially influential observations were omitted from the model to see if it influenced results. No explanatory variables change significance or change the interpretation of the model.

The multivariable logistic regression model is of the form:

$$\log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + ... + \beta_n x_n$$

Where:

p is the probability of the event occurring,

$x_1, x_2, ..., x_n$ are the predictor variables,

$\beta_0, \beta_1, ..., \beta_n$ are the coefficients of the model.

We present the Odds Ratio (OR) of each coefficient by exponentiating each coefficient:

$$\text{OR} = e^{\beta_i}$$

4 Results

4.1 Objective 1 Epidemiology of COVID-19 cases: Where, what and who.

The epidemiology of COVID-19 cases in the Free State Province, from March 2020 to March 2022, is described in this section using a table of descriptive statistics which also compared the community and hospitalised cases. An epicurve with different waves are also plotted. A choropleth map of cases per district in Free State is also visualised.

4.1.1 Descriptive statistics of all COVID-19 Cases

Table 3: Demographics and other characteristics of all, hospitalised, and community COVID-19 cases in Free State, South Africa (March 2020-2023)

Characteristic	**Overall**, n(%)= 201 078 (100)	**Community**, n(%)= 179 916 (89)	**Hospitalised**, n(%)= 21 162 (11)	**p-value**[1]
Age Category, N (%)				<0.001
0-9	9,663 (4.8)	8,805 (4.9)	858 (4.1)	
10-19	24,116 (12)	22,953 (13)	1,163 (5.5)	
20-29	30,463 (15)	28,772 (16)	1,691 (8.0)	
30-39	42,202 (21)	39,291 (22)	2,911 (14)	
40-49	35,484 (18)	32,259 (18)	3,225 (15)	
50-59	30,350 (15)	26,092 (15)	4,258 (20)	
60-69	16,996 (8.5)	13,344 (7.4)	3,652 (17)	
70-79	8,003 (4.0)	5,793 (3.2)	2,210 (10)	
80+	3,801 (1.9)	2,607 (1.4)	1,194 (5.6)	
Gender, N (%)				0.093
Female	116,206 (58)	103,862 (58)	12,344 (58)	
Male	84,872 (42)	76,054 (42)	8,818 (42)	
District, N (%)				<0.001
Fezile Dabi	29,538 (15)	26,596 (15)	2,942 (14)	
Lejweleputswa	37,031 (18)	31,922 (18)	5,109 (24)	
Mangaung	83,900 (42)	76,653 (43)	7,247 (34)	
Thabo Mofutsanyane	40,492 (20)	36,933 (21)	3,559 (17)	
Xhariep	10,117 (5.0)	7,812 (4.3)	2,305 (11)	
Wave Id, N (%)				<0.001
Pre-1st Wave	1,982 (1.0)	1,584 (0.9)	398 (1.9)	
1st Wave	55,526 (28)	47,591 (26)	7,935 (37)	
Pre-2nd Wave	3,347 (1.7)	2,603 (1.4)	744 (3.5)	
2nd Wave	18,147 (9.0)	14,789 (8.2)	3,358 (16)	
Pre-3rd Wave	5,054 (2.5)	4,099 (2.3)	955 (4.5)	
3rd Wave	79,234 (39)	72,942 (41)	6,292 (30)	
Pre-4th Wave	2,349 (1.2)	2,025 (1.1)	324 (1.5)	
4th Wave	33,585 (17)	32,511 (18)	1,074 (5.1)	
Post-4th Wave	1,854 (0.9)	1,772 (1.0)	82 (0.4)	
Cardiac condition, N (%)	15,048 (7.5)	11,626 (6.5)	3,422 (16)	<0.001

Characteristic	**Overall**, n(%)= 201 078 (100)	**Community**, n(%)= 179 916 (89)	**Hospitalised**, n(%)= 21 162 (11)	**p-value**[1]
Immunological condition, N (%)	5,363 (2.7)	4,364 (2.4)	999 (4.7)	<0.001
Respiratory condition inc TB, N (%)	1,727 (0.9)	1,393 (0.8)	334 (1.6)	<0.001
Neurological Condition, N (%)	362 (0.2)	266 (0.1)	96 (0.5)	<0.001
Has Diabetes (DM), N (%)	6,197 (3.1)	4,301 (2.4)	1,896 (9.0)	<0.001
Renal condition, N (%)	187 (<0.1)	98 (<0.1)	89 (0.4)	<0.001
Is Pregnant, N (%)	775 (0.4)	576 (0.3)	199 (0.9)	<0.001
Has Malignancy, N (%)	1,419 (0.7)	1,138 (0.6)	281 (1.3)	<0.001
Liver condition, N (%)	113 (<0.1)	81 (<0.1)	32 (0.2)	<0.001
Death, N (%)				<0.001
Alive	192,489 (96)	176,757 (98)	15,732 (74)	
Died	8,589 (4.3)	3,159 (1.8)	5,430 (26)	

[1] Pearson's Chi-squared test

There were 201 078 COVID-19 cases, of which 179 916 were in the community and 21 162 were hospitalised. Most of the cases occured in Mangaung who also had the highest proportion of hospitalised cases. Manguang had the highest proportion of cases in the province and can be visualised in Figure 2.

Table 3 shows the demographic characteristics of the overall, hospitalised and community COVID-19 cases in the Free State. The overall population showed Female predominance (58% female) and this proportion did not differ between the community and hospitalised cases. The 30-39 year age group made up 21% of COVID-19 cases and was the most common age group. The community cases generally had a higher proportion of younger age groups compared ot the hospitalised cases. The highest proportion of both hospitalised and community cases was in the third wave.

The Free State province experienced four waves (Figure 1) (where the weekly incidence exceeded 30 cases per 100 000 population). The first and third wave showed peaks and sustained transmission whereas the second and fourth showed distinct peaks which were not sustained.

4.1.2 Epicurve of waves COVID-19 cases and COVID-19 deaths

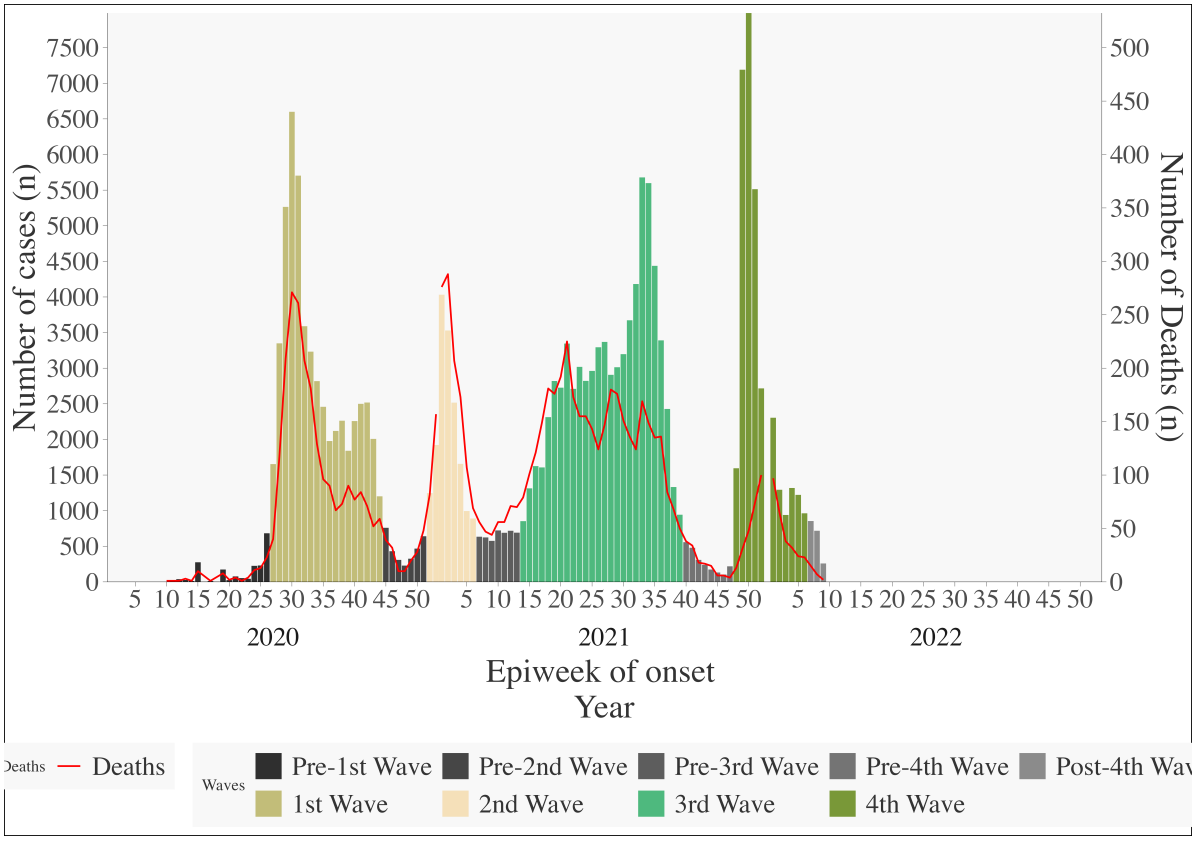

Figure 1: Epicurve of COVID-19 cases and deaths in Free State South Africa from March 2020 to March 2023 *Red line indicates the number of deaths and is plotted on a secondary axis

4.1.3 Map of case distributions across districts

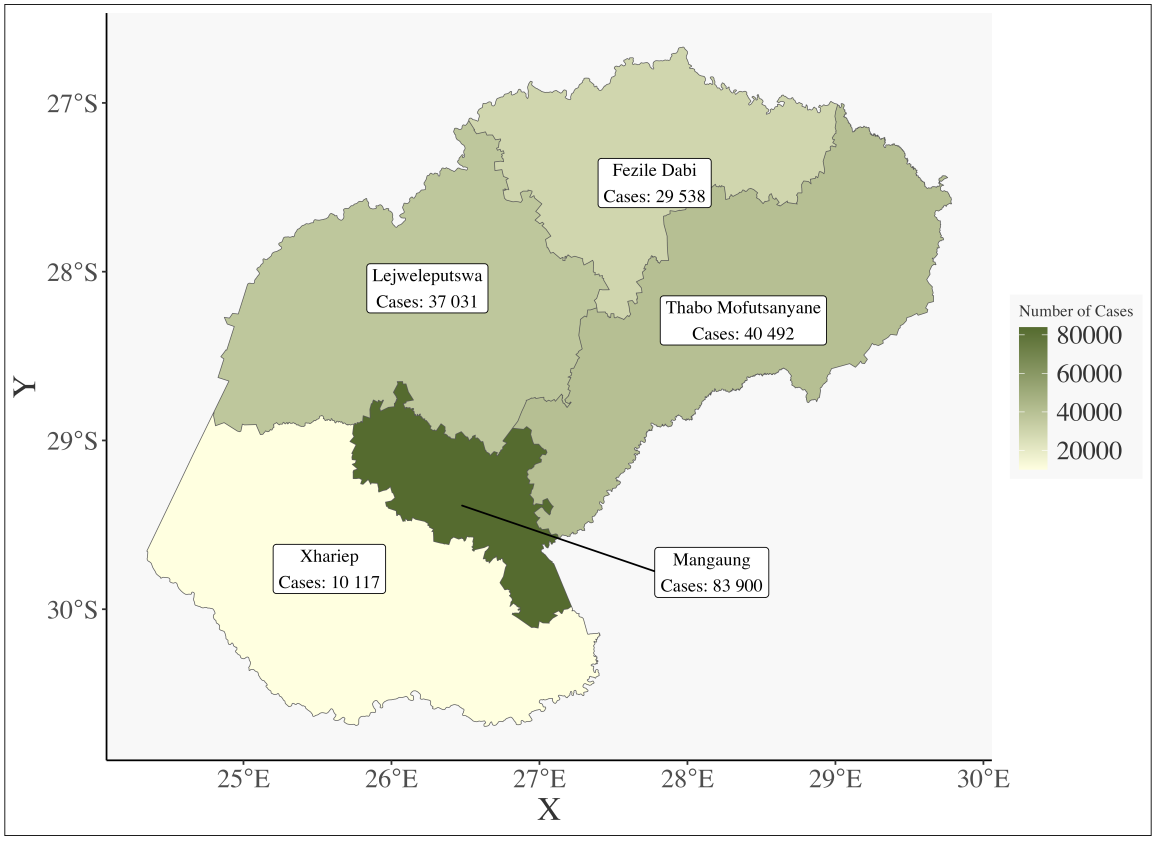

Figure 2: Map of Reported COVID-19 Cases by district in Free State, South Africa (March 2020-2023)

4.2 Objective 2 Factors associated with being a community death

The factors associated with being a community death in the Free State Province, from March 2020 to March 2022, are described in this section. The descriptive statistics of COVID-19 deaths are presented in Table 4. The odds ratio of being a community death among all COVID-19 deaths in Free State is presented in a Table 5. The odds ratio of being a community death is presented to demonstrate the differences between community and hospitalised deaths.

4.2.1 Descriptive statistics and comparisons between community and hosptial COVID-19-associated deaths.

Table 4: Comparison of hospitalised and community COVID-19-associated deaths in Free State, South Africa (March 2020-2023)

Characteristic	Overall, N=8 589	Community, N=3 159	Hospitalised, N=5 430	p-value[1]
Age Category, N (%)				<0.001
0-9	503 (5.9)	270 (8.5)	233 (4.3)	
10-19	66 (0.8)	38 (1.2)	28 (0.5)	
20-29	184 (2.1)	83 (2.6)	101 (1.9)	
30-39	464 (5.4)	175 (5.5)	289 (5.3)	
40-49	775 (9.0)	257 (8.1)	518 (9.5)	
50-59	1,594 (19)	490 (16)	1,104 (20)	
60-69	2,260 (26)	797 (25)	1,463 (27)	
70-79	1,674 (19)	592 (19)	1,082 (20)	
80+	1,069 (12)	457 (14)	612 (11)	
Gender, N (%)				<0.001
Female	4,998 (58)	1,923 (61)	3,075 (57)	
Male	3,591 (42)	1,236 (39)	2,355 (43)	
District, N (%)				<0.001
Fezile Dabi	1,237 (14)	486 (15)	751 (14)	
Lejweleputswa	1,781 (21)	278 (8.8)	1,503 (28)	
Mangaung	2,950 (34)	928 (29)	2,022 (37)	
Thabo Mofutsanyane	2,305 (27)	1,360 (43)	945 (17)	
Xhariep	316 (3.7)	107 (3.4)	209 (3.8)	
Wave Id, N (%)				<0.001
Pre-1st Wave	83 (1.0)	16 (0.5)	67 (1.2)	
1st Wave	2,174 (25)	491 (16)	1,683 (31)	
Pre-2nd Wave	187 (2.2)	62 (2.0)	125 (2.3)	
2nd Wave	1,359 (16)	470 (15)	889 (16)	
Pre-3rd Wave	400 (4.7)	171 (5.4)	229 (4.2)	
3rd Wave	3,679 (43)	1,543 (49)	2,136 (39)	
Pre-4th Wave	138 (1.6)	74 (2.3)	64 (1.2)	
4th Wave	545 (6.3)	314 (9.9)	231 (4.3)	
Post-4th Wave	24 (0.3)	18 (0.6)	6 (0.1)	
Cardiac condition, N (%)	1,389 (16)	548 (17)	841 (15)	0.024
Immunological condition, N (%)	268 (3.1)	123 (3.9)	145 (2.7)	0.002
Respiratory condition inc TB, N (%)	101 (1.2)	35 (1.1)	66 (1.2)	0.66
Neurological Condition, N (%)	23 (0.3)	8 (0.3)	15 (0.3)	0.84
Has Diabetes (DM), N (%)	767 (8.9)	251 (7.9)	516 (9.5)	0.015
Renal condition, N (%)	45 (0.5)	13 (0.4)	32 (0.6)	0.27
Is Pregnant, N (%)	11 (0.1)	2 (<0.1)	9 (0.2)	0.35
Has Malignancy, N (%)	103 (1.2)	37 (1.2)	66 (1.2)	0.86

Characteristic	Overall, N=8 589	Community, N=3 159	Hospitalised, N=5 430	p-value[1]
Liver condition, N (%)	20 (0.2)	10 (0.3)	10 (0.2)	0.22

[1]Pearson's Chi-squared test; Fisher's exact test

There were 8 589 COVID-19-associated deaths of which 3 159 were in the community and 5 430 were in the hospital. The proportion of lower age categories (0-9, 10-19) and 80+ were higher among community deaths than hospitalised deaths (8.5% vs 4.3%; 1.2% vs 0.5%; 14% vs 11% respectively). A higher proportion of females died in the community compared to hospital (61% vs 57%). Mangaung had the highest proportion of hospitalised deaths (37%) and Thabo Mofutsanyane had the highest proportion of community deaths (43%) with Mangaung having the second highest (29%). The third wave of COVID-19 had the highest proportion of both community and hospitalised deaths (49% and 39%). The 1st wave had a lower proportion of community to hospital deaths (16% vs 31%) whereas the fourth wave had a higher proportion of community to hospital deaths (9.9% vs 4.3%). The proportion of community deaths with an immune condition was higher than the proportion of hospital deaths with an immune condition (3.9% vs 2.7%) and cardiac condition (17% vs 15%), and the proportion of DM was lower in the community deaths than hospitalised deaths (7.9% vs 9.5%). Other comorbidities showed no evidence that their proportions differed between community and hospitalised deaths.

4.2.2 Odds of being a community death among all COVID-19 deaths in Free State

Table 5: Univariate and multivariable Odds Ratio of community death among all COVID-19 deaths in Free State, South Africa (March 2020-2023)

	Univariate		Multivariate	
Characteristic	**OR (95% CI)[1]**	**p-value**	**aOR (95% CI)[1]**	**p-value**
Age Category				
60-69	—		—	
0-9	2.13 (1.75 to 2.59)	<0.001	1.56 (1.26 to 1.92)	<0.001
10-19	2.49 (1.52 to 4.12)	<0.001	2.67 (1.57 to 4.60)	<0.001
20-29	1.51 (1.11 to 2.04)	0.008	1.44 (1.03 to 2.01)	0.030
30-39	1.11 (0.90 to 1.37)	0.32	1.03 (0.82 to 1.29)	0.80
40-49	0.91 (0.77 to 1.08)	0.29	0.90 (0.74 to 1.08)	0.25
50-59	0.81 (0.71 to 0.93)	0.003	0.82 (0.71 to 0.95)	0.008
70-79	1.00 (0.88 to 1.15)	0.95	1.01 (0.87 to 1.16)	0.94
80+	1.37 (1.18 to 1.59)	<0.001	1.25 (1.06 to 1.47)	0.007

	Univariate		Multivariate	
Characteristic	**OR (95% CI)[1]**	**p-value**	**aOR (95% CI)[1]**	**p-value**
Gender				
Female	—		—	
Male	0.84 (0.77 to 0.92)	<0.001	0.90 (0.82 to 1.00)	0.044
District				
Mangaung	—		—	
Thabo Mofutsanyane	3.14 (2.80 to 3.51)	<0.001	3.18 (2.82 to 3.58)	<0.001
Lejweleputswa	0.40 (0.35 to 0.47)	<0.001	0.43 (0.37 to 0.50)	<0.001
Fezile Dabi	1.41 (1.23 to 1.62)	<0.001	1.50 (1.30 to 1.73)	<0.001
Xhariep	1.12 (0.87 to 1.42)	0.38	1.18 (0.91 to 1.52)	0.20
Wave Id				
3rd Wave	—		—	
Pre-1st Wave	0.33 (0.18 to 0.56)	<0.001	0.48 (0.27 to 0.83)	0.012
1st Wave	0.40 (0.36 to 0.46)	<0.001	0.44 (0.39 to 0.50)	<0.001
Pre-2nd Wave	0.69 (0.50 to 0.93)	0.018	0.69 (0.49 to 0.95)	0.025
2nd Wave	0.73 (0.64 to 0.83)	<0.001	0.64 (0.56 to 0.74)	<0.001
Pre-3rd Wave	1.03 (0.84 to 1.27)	0.76	0.83 (0.66 to 1.04)	0.11
Pre-4th Wave	1.60 (1.14 to 2.26)	0.007	1.37 (0.95 to 1.97)	0.094
4th Wave	1.88 (1.57 to 2.26)	<0.001	1.67 (1.37 to 2.03)	<0.001
Post-4th Wave	4.15 (1.74 to 11.5)	0.003	5.52 (2.19 to 15.9)	<0.001
Cardiac condition	1.15 (1.02 to 1.29)	0.024		
Immunological condition	1.48 (1.16 to 1.88)	0.002		
Respiratory condition inc TB	0.91 (0.60 to 1.37)	0.66		
Neurological Condition	0.92 (0.37 to 2.11)	0.84		
Has Diabetes (DM)	0.82 (0.70 to 0.96)	0.015	0.71 (0.60 to 0.85)	<0.001
Renal condition	0.70 (0.35 to 1.30)	0.27		
Is Pregnant	0.38 (0.06 to 1.48)	0.22	0.29 (0.04 to 1.23)	0.13
Has Malignancy	0.96 (0.64 to 1.44)	0.86		
Liver condition	1.72 (0.71 to 4.20)	0.23	2.43 (0.91 to 6.42)	0.071

[1]OR = Odds Ratio, CI = Confidence Interval

The regression in Table 5 presents the odds of being a community death among all COVID-19 deaths in Free State. Accounting for other afctors, age groups between 30-39, 40-49, and 70-79 showed no difference in the odds of being a community death compared to 60-69 age group (p>0.05). Being in the age groups 0-9 (aOR 1.56, 95% CI 1.26-1.92), 10-19 (aOR 2.67 95% CI 1.57-4.6), 20-29 (aOR 1.44 95% CI 1.03-2.01), 50-59 (aOR 0.82 95% CI 0.71-0.95) and 80+ (aOR 1.25, 95% CI 1.06-1.47) was associated with increased odds of being a community death compared to the 60-69 age group (reference group). The univariate regression demonstrated that being male was associated with a lower odds of being a community death compared to females, however this effect was weaker when controlling for other factors (OR 0.84, 95% CI 0.77-0.92; aOR 0.91, 95% CI 0.82–1.00). Being in Thabo Mofutsanyane was associated with the highest odds of being a community death when compared to Mangaung (aOR 3.18, 95% CI 2.82-3.58). The first and second waves were associated with a lower

odds of being a community death whereas the fourth wave was associated with a higher odds of being a community death compared to the third wave - this was demonstrated in both univariate and multi-variable regression (4th wave OR 1.88, 95% CI 1.57-2.26; aOR 1.67, 95% CI 1.37-2.03). Only three comorbidites were included in the multivariable model and only one was significant at the 5% level which was having DM - it was associated a lower odds of being a community death (aOR 0.75, 95% CI 0.63-0.89).

4.3 Objective 3 Factors associated with death in the community vs and factors associated with death in the hospital.

4.3.1 Case Fatality Ratio in the communtiy and hosptial COVID-19 cases.

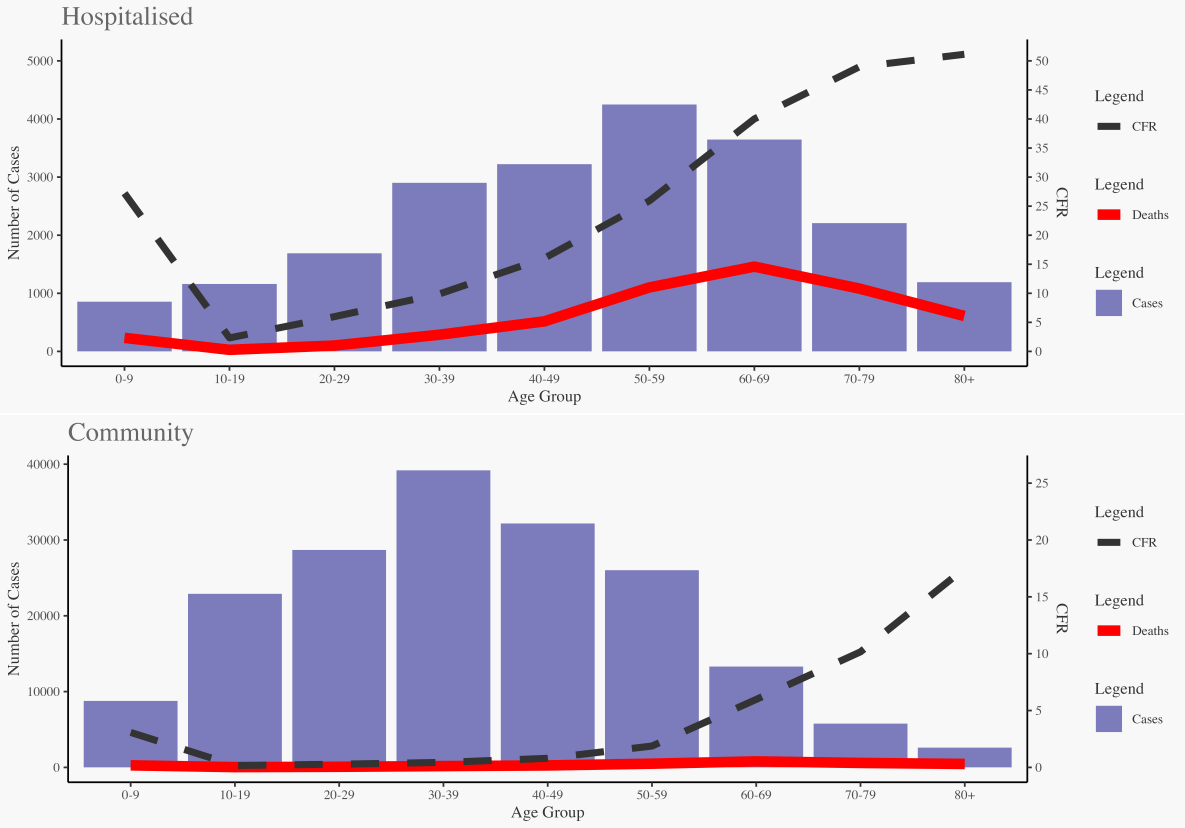

Figure 3: COVID-19 Cases, deaths and CFR by hosptialisation status Free State, South Africa (March 2020-2023)

Figure 3 shows the different age structure and CFR in the hospitalised and community COVID-19 case populations. The overall CFR for the community cases is 1.8% Interestingly, the pre-4th wave pe (95% CI 1.7-1.8) and has a more distinct peak at the 80+ age group, however is very low for all other age groups with a small rise in the 0-9 year age groups. The CFR in the hospitalised population is 25.7% (95% CI 25.1-26.2) and has a steep decline from the 0-9 to the 10-19 age category and then a steady rise to the older age categories.

4.3.2 Stratifed table of cases and deaths by Community and Hosptialisation status

Table 6: Demographics and other characteristics of cases and deaths among community and hospitalised COVID-19 cases in Free State, South Africa (March 2020-2023)

	Community			Hospitalised		
Characteristic	**Alive**, N=176757	**Died**, N=3159	**p-value**[1]	**Alive**, N=15732	**Died**, N=5430	**p-value**[2]
Age Category, N (%)			<0.001			<0.001
0-9	8,535 (4.8)	270 (8.5)		625 (4.0)	233 (4.3)	
10-19	22,915 (13)	38 (1.2)		1,135 (7.2)	28 (0.5)	
20-29	28,689 (16)	83 (2.6)		1,590 (10)	101 (1.9)	
30-39	39,116 (22)	175 (5.5)		2,622 (17)	289 (5.3)	
40-49	32,002 (18)	257 (8.1)		2,707 (17)	518 (9.5)	
50-59	25,602 (14)	490 (16)		3,154 (20)	1,104 (20)	
60-69	12,547 (7.1)	797 (25)		2,189 (14)	1,463 (27)	
70-79	5,201 (2.9)	592 (19)		1,128 (7.2)	1,082 (20)	
80+	2,150 (1.2)	457 (14)		582 (3.7)	612 (11)	
Gender, N (%)			<0.001			0.003
Female	101,939 (58)	1,923 (61)		9,269 (59)	3,075 (57)	
Male	74,818 (42)	1,236 (39)		6,463 (41)	2,355 (43)	
District, N (%)			<0.001			<0.001
Fezile Dabi	26,110 (15)	486 (15)		2,191 (14)	751 (14)	
Lejweleputswa	31,644 (18)	278 (8.8)		3,606 (23)	1,503 (28)	
Mangaung	75,725 (43)	928 (29)		5,225 (33)	2,022 (37)	
Thabo Mofutsanyane	35,573 (20)	1,360 (43)		2,614 (17)	945 (17)	
Xhariep	7,705 (4.4)	107 (3.4)		2,096 (13)	209 (3.8)	
Wave Id, N (%)			<0.001			<0.001
Pre-1st Wave	1,568 (0.9)	16 (0.5)		331 (2.1)	67 (1.2)	
1st Wave	47,100 (27)	491 (16)		6,252 (40)	1,683 (31)	
Pre-2nd Wave	2,541 (1.4)	62 (2.0)		619 (3.9)	125 (2.3)	
2nd Wave	14,319 (8.1)	470 (15)		2,469 (16)	889 (16)	
Pre-3rd Wave	3,928 (2.2)	171 (5.4)		726 (4.6)	229 (4.2)	
3rd Wave	71,399 (40)	1,543 (49)		4,156 (26)	2,136 (39)	
Pre-4th Wave	1,951 (1.1)	74 (2.3)		260 (1.7)	64 (1.2)	
4th Wave	32,197 (18)	314 (9.9)		843 (5.4)	231 (4.3)	
Post-4th Wave	1,754 (1.0)	18 (0.6)		76 (0.5)	6 (0.1)	
Cardiac condition, N (%)	11,078 (6.3)	548 (17)	<0.001	2,581 (16)	841 (15)	0.11
Immunological condition, N (%)	4,241 (2.4)	123 (3.9)	<0.001	854 (5.4)	145 (2.7)	<0.001
Respiratory condition inc TB, N (%)	1,358 (0.8)	35 (1.1)	0.031	268 (1.7)	66 (1.2)	0.013
Neurological Condition, N (%)	258 (0.1)	8 (0.3)	0.15	81 (0.5)	15 (0.3)	0.024
Has Diabetes (DM), N (%)	4,050 (2.3)	251 (7.9)	<0.001	1,380 (8.8)	516 (9.5)	0.10
Renal condition, N (%)	85 (<0.1)	13 (0.4)	<0.001	57 (0.4)	32 (0.6)	0.026
Is Pregnant, N (%)	574 (0.3)	2 (<0.1)	0.010	190 (1.2)	9 (0.2)	<0.001
Has Malignancy, N (%)	1,101 (0.6)	37 (1.2)	<0.001	215 (1.4)	66 (1.2)	0.40
Liver condition, N (%)	71 (<0.1)	10 (0.3)	<0.001	22 (0.1)	10 (0.2)	0.47

[1]Pearson's Chi-squared test; Fisher's exact test
[2]Pearson's Chi-squared test

Table 6 demonstrated contrasting gender differences between the two study populations and death. The proportion of females who died in the community is higher than the proportion of female

cases in the community (61% vs 58%, p-value <0.001) however, the proportion of females dying in the hospital is lower than the proportion of female community cases (59% and 57%, p-value <0.001). Thabo Mofutsanyane had the largest proportion of community deaths (43%) and Manguang had the largest proportion of Hospital deaths (37%) and these showed statistically different proportions to the cases from each of these districts (p-value 0.001). Immune conditions (including HIV) had a higher proportion among those who died in the community compared to cases (3.9% among community deaths vs 2.4% among community cases, p-value <0.001) yet, immunological conditions were less common in those who died at hospital that cases in the hospital (2.7% among hospital deaths vs 5.4% among hospital deaths, p-value <0.001).

4.3.3 Table of odds of death among community cases and odds of death among hospitalised cases in Free State

Table 7: Univariate and multivariable Odds of death between ever hospitalised and Never hospitalised Cases of COVID-19

	Community Univariate		Hosptial Univariate		Community Multivariate		Hospital Multivariate	
Characteristic	**OR (95% CI)[1]**	**p-value**	**OR (95% CI)[1]**	**p-value**	**aOR (95% CI)[1]**	**p-value**	**aOR (95% CI)[1]**	**p-value**
Age Category								
60-69	—		—		—		—	
0-9	0.50 (0.43 to 0.57)	<0.001	0.56 (0.47 to 0.66)	<0.001	0.46 (0.40 to 0.53)	<0.001	0.50 (0.42 to 0.59)	<0.001
10-19	0.03 (0.02 to 0.04)	<0.001	0.04 (0.02 to 0.05)	<0.001	0.03 (0.02 to 0.03)	<0.001	0.04 (0.03 to 0.05)	<0.001
20-29	0.05 (0.04 to 0.06)	<0.001	0.10 (0.08 to 0.12)	<0.001	0.05 (0.04 to 0.06)	<0.001	0.09 (0.08 to 0.12)	<0.001
30-39	0.07 (0.06 to 0.08)	<0.001	0.16 (0.14 to 0.19)	<0.001	0.08 (0.07 to 0.09)	<0.001	0.16 (0.14 to 0.18)	<0.001
40-49	0.13 (0.11 to 0.15)	<0.001	0.29 (0.26 to 0.32)	<0.001	0.13 (0.12 to 0.15)	<0.001	0.28 (0.25 to 0.31)	<0.001
50-59	0.30 (0.27 to 0.34)	<0.001	0.52 (0.48 to 0.58)	<0.001	0.32 (0.28 to 0.35)	<0.001	0.51 (0.46 to 0.56)	<0.001
70-79	1.79 (1.60 to 2.00)	<0.001	1.44 (1.29 to 1.60)	<0.001	1.88 (1.68 to 2.11)	<0.001	1.50 (1.34 to 1.67)	<0.001
80+	3.35 (2.96 to 3.79)	<0.001	1.57 (1.38 to 1.79)	<0.001	3.61 (3.17 to 4.10)	<0.001	1.64 (1.43 to 1.87)	<0.001
Gender								
Female	—		—		—		—	
Male	0.88 (0.81 to 0.94)	<0.001	1.10 (1.03 to 1.17)	0.003	0.97 (0.90 to 1.04)	0.37	1.05 (0.98 to 1.13)	0.15
District								
Mangaung	—		—		—		—	
Thabo Mofutsanyane	3.12 (2.87 to 3.40)	<0.001	0.93 (0.85 to 1.02)	0.14	2.46 (2.25 to 2.69)	<0.001	0.95 (0.86 to 1.05)	0.29
Lejweleputswa	0.72 (0.63 to 0.82)	<0.001	1.08 (1.00 to 1.17)	0.066	0.59 (0.51 to 0.68)	<0.001	1.17 (1.07 to 1.28)	<0.001
Fezile Dabi	1.52 (1.36 to 1.70)	<0.001	0.89 (0.80 to 0.98)	0.015	1.14 (1.02 to 1.28)	0.025	0.87 (0.79 to 0.97)	0.014
Xhariep	1.13 (0.92 to 1.38)	0.22	0.26 (0.22 to 0.30)	<0.001	0.98 (0.80 to 1.20)	0.87	0.42 (0.35 to 0.49)	<0.001
Wave Id								
3rd Wave	—		—		—		—	
Pre-1st Wave	0.47 (0.28 to 0.75)	0.003	0.39 (0.30 to 0.51)	<0.001	0.59 (0.34 to 0.94)	0.038	0.47 (0.35 to 0.62)	<0.001
1st Wave	0.48 (0.44 to 0.53)	<0.001	0.52 (0.49 to 0.56)	<0.001	0.54 (0.49 to 0.60)	<0.001	0.47 (0.43 to 0.51)	<0.001
Pre-2nd Wave	1.13 (0.86 to 1.45)	0.35	0.39 (0.32 to 0.48)	<0.001	1.03 (0.78 to 1.34)	0.81	0.38 (0.31 to 0.47)	<0.001
2nd Wave	1.52 (1.37 to 1.69)	<0.001	0.70 (0.64 to 0.77)	<0.001	1.14 (1.02 to 1.27)	0.024	0.64 (0.58 to 0.71)	<0.001
Pre-3rd Wave	2.01 (1.71 to 2.36)	<0.001	0.61 (0.52 to 0.72)	<0.001	1.85 (1.55 to 2.19)	<0.001	0.64 (0.54 to 0.75)	<0.001
Pre-4th Wave	1.76 (1.37 to 2.21)	<0.001	0.48 (0.36 to 0.63)	<0.001	1.46 (1.13 to 1.87)	0.003	0.51 (0.38 to 0.69)	<0.001
4th Wave	0.45 (0.40 to 0.51)	<0.001	0.53 (0.46 to 0.62)	<0.001	0.43 (0.38 to 0.48)	<0.001	0.52 (0.44 to 0.62)	<0.001
Post-4th Wave	0.47 (0.29 to 0.73)	0.002	0.15 (0.06 to 0.32)	<0.001	0.45 (0.27 to 0.70)	0.001	0.13 (0.05 to 0.29)	<0.001
Cardiac condition	3.14 (2.85 to 3.45)	<0.001	0.93 (0.86 to 1.02)	0.11			0.52 (0.47 to 0.57)	<0.001
Immunological condition	1.65 (1.37 to 1.97)	<0.001	0.48 (0.40 to 0.57)	<0.001	1.82 (1.49 to 2.20)	<0.001	0.69 (0.57 to 0.83)	<0.001
Respiratory condition inc TB	1.45 (1.01 to 1.99)	0.032	0.71 (0.54 to 0.92)	0.013			0.61 (0.45 to 0.81)	<0.001
Neurological Condition	1.74 (0.79 to 3.28)	0.12	0.54 (0.30 to 0.90)	0.026			0.48 (0.25 to 0.84)	0.014
Has Diabetes (DM)	3.68 (3.22 to 4.19)	<0.001	1.09 (0.98 to 1.21)	0.10	1.36 (1.18 to 1.56)	<0.001	0.87 (0.78 to 0.98)	0.028
Renal condition	8.59 (4.57 to 14.9)	<0.001	1.63 (1.05 to 2.50)	0.027	3.52 (1.78 to 6.51)	<0.001	1.53 (0.95 to 2.43)	0.078

	Community Univariate		Hosptial Univariate		Community Multivariate		Hospital Multivariate	
Characteristic	**OR (95% CI)**[1]	**p-value**	**OR (95% CI)**[1]	**p-value**	**aOR (95% CI)**[1]	**p-value**	**aOR (95% CI)**[1]	**p-value**
Is Pregnant	0.19 (0.03 to 0.60)	0.020	0.14 (0.06 to 0.25)	<0.001	0.32 (0.05 to 1.01)	0.11	0.35 (0.16 to 0.66)	0.003
Has Malignancy	1.89 (1.34 to 2.59)	<0.001	0.89 (0.67 to 1.16)	0.40	0.76 (0.53 to 1.06)	0.13	0.73 (0.54 to 0.98)	0.040
Liver condition	7.90 (3.82 to 14.6)	<0.001	1.32 (0.60 to 2.71)	0.47	6.16 (2.79 to 12.4)	<0.001		

[1]OR = Odds Ratio, CI = Confidence Interval

Table 7 shows OR and aORs for factors associated with death from the hospitalised population and community populations. To note that the hospital and community regressions are separate with odds of death determined from cases and deaths from community *or* hospitalised COVID-19 cases.

Under univariate analysis male gender showed a higher odds of death in the hospitalised model (OR 1.10, 95% CI 1.03-1.17) and a lower odds of death among the community model (OR 0.87, 95% CI 0.81-0.94). However, once accounting for other factors, there was insufficient evidence to reject the null hypothesis of a difference in the odds associated with death in males in the community and hospital models.

COVID-19 waves were compared to the third wave of COVID-19 which had the highest number of deaths. The first and fourth wave were associated a lower adjusted odds of death in the community model (First - aOR 0.54, 95% CI 0.49-0.60; Fourth - aOR 0.43, 95% CI 0.38-0.48). The second and pre-third and pre-fourth waves were associated with a higher aOR of death in the community (Second - aOR 1.14, pre-third - aOR 1.85 95% CI 1.55-2.19; pre-fourth aOR 1.46, 95% CI 1.13-1.87). All waves were associated with a lower OR of death in the hospital model compared to the 3rd wave.

Having a cardiac condition was not included in the multivariable community model but was associated with a lower aOR of death in the hospitalised model (aOR 0.52, 95% CI 0.47-0.57). Having an immune condition demonstrated a lower aOR of death in the hospitalised model (aOR 0.69, 95% CI 0.57-0.83) but was associated with a higher aOR of death in the community model (aOR 1.82, 95% CI 1.49-2.2); similarly having DM showed a slightly lower aOR of death in the hospital model (aOR 0.87, 95% CI 0.78-0.98) but a higher aOR in the community model (aOR 1.36, 95% CI 1.18-1.56).

5 Discussion

5.1 Demographic differences and surveillance

The age and gender structures differed notably between community and hospital deaths suggesting significant heterogeneity. This may introduce bias when using only hospital deaths as an endpoint in

analyses which affect community-level practices and outcomes such as the case with COVID-19. We find that younger ages have a higher odds of dying in the community and a relationship may also exist between genders. Public health messaging during the pandemic focussed on those age 65 and older, males and those with comorbidities of being most at risk of having severe COVID-19 and death. This is evident as it is those groups who showed a higher odds of being a community death among those who died. This suggests that messaging may have been effective in reaching its intended audience, but the representation of deaths in outside of risk groups in the community may have been under appreciated in surveillance during the pandemic in SA.

Understanding health-seeking behaviours and their effect on death in different age and gender groups remains intriguing, albeit challenging as those who die cannot be interviewed. Emphasizing the importance of characterizing deaths by hospital and community settings is crucial for generalisability to the overall population. Characterisation of community and hospital death proportions in Africa, perhaps by consolidating HDSS sites is an initial step in explaining this heterogeneity and healthcare-seeking behaviour. In terms of pandemic preparedness, aswell as sentinel hospital surveillance, sentinel community surveillance the triangulates health related data of those in the community may also be highly valuable for decision-making

5.2 Comorbidities

The evidence of relationship between of having an immune condition on community deaths but not in hospital is intriguing. Early evidence showed protective effect of Tenofivir chemotherapy however (Western Cape Department of Health in collaboration with the National Institute for Communicable Diseases, South Africa et al. 2021), since data on whether these patients were receiving care is not available, it is assumed that those who died in the community had poor access to HIV medication since well controlled HIV should not increase the risk of deat since, according to a study in KZN, ART initiations and testing went down during the COVID-19 pandemic, but not ART collection rates (Dorward et al. 2021). Nonetheless, the importance of representative surveillance and the importance

of continuing care to vulnerable groups even during a pandemic should not be discounted.

DM was associated with an increased odds of death in the community cases, which is in line with current local (Western Cape Department of Health in collaboration with the National Institute for Communicable Diseases, South Africa et al. 2021; W. Jassat et al. 2022) and global evidence (Dessie and Zewotir 2021; Mwananyanda et al. 2020; The OpenSAFELY Collaborative et al. 2020) and highlights the need for Non-Communicable disease surveillance and management strategies in SA. DM demonstrated a small but statistically significant association with a lower odds of death in the hospitalised cases, successful management of newly and previously diagnosed DM patients with COVID-19 was demonstrated in the Western Cape - which also used telemedicine referral mechanisms - they suggested that adequate triage of patietns was crucial in improving outcomes and having a lower mortality rate than expected (Van Der Westhuizen et al. 2021). Free State, who used go.data to conduct contact tracing and identify patients for referral may explain some how poor outcomes were avoided.

5.3 Waves

The Omicron variant, which was generally associated with the fourth wave in SA, was associated (Davies et al. 2022; Gray et al. 2021; Hussey et al. 2022; Waasila Jassat, Karim, Mudara, et al., n.d.) with the lowest risk of hospitalisation and mortality. The fourth wave experienced the lowest absolute numbers of death in Free State and demonstrated a lower odds of death compared the the third wave in both the community and hospital model. Interestingly the pre-fourth wave was associated with an increased odds of being a community death. While this may be an artefact of behavior change with a lower perceived risk of COVID-19 resulting from the vaccination campaign in the country and the "fatigue" of the pandemic, it does suggest that COVID-19 deaths were different between the hospital and community under similar conditions (such as the variant exposure).

6 Study limitations

This research used secondary data from routine outbreak investigation practices. While these routine practices were supplemented with active community surveillance, the nature of the study is vulnerable to selection bias - Those who were admitted to hospital may be systematically different to those who were not, as selection was not random. Whether the patient was hospitalised or not may be due to person-level factors, including knowledge attitudes and beliefs, or more upstream determinants such as access to appropriate level of care. While it is important to acknowledge studies with this type of bias, this bias is partly what the research seeks to demonstrate of routine surveillance- that the heterogeneity of the population may not captured by hospital surveillance alone.

While this study adds quality to what happened outside of hospitals in SA, it is still constrained by the lack of comprehensive clinical and demographic information. Imputed data may account for the lack of complete information for demographic variables collected (age and sex), but not for clinical details. While this clinical information does exist, is stored either in hard copy form or in protected surveillance systems with gatekeepers apprehensive of collaboration and data sharing. This highlights the necessity for a more integrated approach to disease surveillance in SA.

The harmonisation of DATCOV and go.data may not be perfect. Publicly availble records, using DATCOV as a data source, enumerate the the total number of COVID-19 cases that required hospitalization at approximately 31,000 in the Free State during the same period, whereas our study reported around 21,000 cases("NICD COVID-19 Daily Sentinel Hospital Surveillacne Report December 2022" 2022). The admission records from the national Hospital Surveillance System were not adequately synchronized before DATCOV was discontinued. This suggests that go.data (the data source of this reearch) may underestimate the total number of cases hospitalised however, the total number of deaths between the two systems is agreeable. Unfortunately, this issue was not anticipated during the protocol stage of our project and resolving it would necessitate additional permissions from gatekeepers, which are currently unfeasible for the timelines of this project, however a full data linkage project

should be undertaken. Ensuring this synchronisation would not change the results and interpretation of objective 2, but may change objective 3, in which direction the results may change cannot be accurately determined with the available information.

Despite the remarkable surveillance efforts undertaken during the COVID-19 pandemic, the under-representation of hospitalisations in this dataset and lack of detailed clinical information highlights the fragmented and non-interoperable nature of electronic health data systems in SA. Although there are existing sentinel surveillance systems with enhanced data collection, it would be ideal to harmonize routine electronic medical records from various sources such as NHLS, EDRWeb, TIER.net, and EVDS in the population we have studied. Implementing this approach could showcase the feasibility and utility of interoperable electronic medical records system generate evidence from routine and programmatic data which may be more representative of the population it serves than the population that sentinel sites serve.

It is important to recognise that in this study ,COVID-19-associated deaths simply represent a death in someone who, at the time of their death, met the case definition for COVID-19 (laboratory confirmation) and did not have a clear alternative cause (such as unnatural death via gun shot or motor vehicle accident).

While it may seem arbitrary to discuss the landscape of integrating Cause of Death reports, it is important to mention what the barriers to this infromation are and why this research is valueable now. Cause and mechanism/manner of death information for those who died during the COVID-19 pandemic in SA is not yet available. In the current legal landscape, the department of health provides medical practitioners to certify deaths and assign causes, but does not allow the systematic collection of this data by anyone other than StatisticSA (the Department of Health is also excluded). StatsSA is the only organization to have the legal mandate to collect and report the mechanism and cause of deaths from the CRVS system. Considering the current approximately five-year delay in this process, it is anticipated that the official statistics regarding the cause of death collected by the CRVS process for this period will be available in 2028. So while we acknowledge that the deaths recorded here may

not represent be accurate of the true cause of death of the cases, this may be the only representation of COVID-19-associated deaths in the general population (hospital and community) occurring in SA.

7 Conclusion

The study aimed to describe and compare the sociodemographic and clinical characteristics of in-facility vs out-of-facility COVID-19-associated deaths in Free-State, SA. The Free State recorded 8 589 deaths, of which 5 430 were hospitalised and 3 159 died in the community. Thabo Mofutsanyane and Mangaung experienced the highest and second highest number of community deaths and these were districts where active community deth surveillance was strongly implemented. We were able to demonstrate a difference in the age and gender structure of the hospitalised and community COVID-19 cases and deaths in SA. We demonstrated that, among those who died, those who were in the 0-9, 10-19, 20-29 and 80+ age group, and died in the 4th wave were associated with a higher odds of being a community death. Aside from the 80+ age group, these were considered generally lower risk groups for death from COVID-19 in public messaging.

Among community cases, the 70-79 and 80+ age group, the the 2nd, pre-3rd and pre-4th wave period (compared to the 3rd wave), having an immune condition, having diabetes, having a renal condition or liver condition was associated with a higher odds of death. Among hospitalised cases, all waves were associated with a lower odds of death compared to the 3rd wave. When controlling for other factors, gender did not show evidence of a different associated odds of death in the community and hospital models.

The analysis sheds light on the substantial heterogeneity of COVID-19 deaths that occured in hospitalised patients compared to non- hospitalised patietns in the community. Additionally, factors associated with death from the hospitalised cases compared to the in hospital cases appear different. The analysis deomnstrated that suvreillance that includes community cases and deaths reveal a more heterogenous population than hospitalised cases and deaths only. This is crucial for understanding the

true burden of COVID-19 in the population and for informing public health interventions.

8 Recommendations

We recommend that differentiating between community and hospital deaths in surveillance systems is implemented or, if a new surveillance system is created, that it be incorporated in the design. We do not currently have a good estimate of the proportion of hospital versus community deaths yet we know that these two types of death are different as was demonstrated by this research. We also strongly recommend that, during pandemics, while hospital surveillance is somewhat easier to gather and analyse, community data is essential to understand what is happening on the ground and should inform on-the-ground interventions specifically targeting vulnerable groups such as the young and those with immune-compromising conditions. While we demonstrated that infromation used to infrom policy should include immproved community surveillance, it will still be of limited value if the surveillance is unable to relay infromation to policy makers in near real-time. To ensure pandemic preparedness and response in terms of the international health regulations and Integrated Disease Surievallance and response (IDSR), South Africas CRVS system needs to be rapidly streamlined. This should facilitate the prompt dissemination of Cause of Death (CoD) information, including the crucial differentiation between hospital and community settings to policy makers and relevant stakeholders.

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Appendix 1 - Ethical clearance

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research and Innovation)

TO: Mr B Brumer
School of Public Health
Medical School
University

E-mail: brianb@nicd.ac.za

CC: Supervisor: Ms J Ebonwu; Messrs I Maposa and R Mokoena <joye@nicd.ac.za>
and <HREC-Medical Research Office@wits.ac.za>

FROM: Mr Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2023/08/21

REF: R14/49

PROTOCOL NO: **M230322** (This is your ethics application reference number. Please quote it in all enquiries, oral or written, relating to this study.)

PROJECT TITLE: *Factors associated with in-facility and out-of-facility COVID 19-related deaths, Free State Province, South Africa - March 2020 to March 2022*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to Government funding of the University.

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

R49 Mr B Brumer

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M230322

NAME: (Principal Investigator) Mr B Brumer

DEPARTMENT: School of Public Health
Medical School
University

PROJECT TITLE: *Factors associated with in-facility and out-of-facility COVID 19-related deaths, Free State Province, South Africa - March 2020 to March 2022*

DATE CONSIDERED: 2023/03/31

DECISION: Approved unconditionally

CONDITIONS:

NOTE: If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>

SUPERVISOR: Ms J Ebonwu; Messrs I Maposa and R Mokoena

APPROVED BY:
Professor P Ruff, Chairperson, HREC (Medical)

DATE OF APPROVAL: 2023/08/21 **EXPIRY DATE:** 2028/08/20

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **March** and therefore reports and re-certification will be due in the month of **March** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator Date

Appendix 2 - Institutional permission

health
Department of Health
FREE STATE PROVINCE

03 August 2023

Mr. B Brummer
School of Public health
Wits University
Johannesburg

Dear Mr. B Brummer

Subject: Factors Associated with In-Facility and Out-Of-Facility COVID-19 Related Deaths, Free State Province, South Africa - March 2020 to March 2022.

- Permission is hereby granted for the above-mentioned data request on the following conditions:
- The request will only be for the below mentioned Covid-19 data elements, (**please see annexure A on page 2**).
- The data requested for "***Factors Associated with In-Facility and Out-Of-Facility COVID-19 Related Deaths, Free State Province, South Africa - March 2020 to March 2022.***" is only for the purpose of this research study for Mr. B Brummer only.
- The use of these Data Sets in research communication, scholarly papers, journals and the like is encouraged, but the authors of these communications and documents are required to acknowledge/cite the Free State Department of Health as the source of the Data.
- Mr. B Brummer agrees that he will not provide/publish any reports/statements without prior discussion with and permission of Director in Health Information Management of the Free State Department of Health.
- The User agrees that Confidentiality of information will be ensured, and the data will not be shared with any other researcher.
- Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).
- The User is therefore permitted to use only the above-mentioned data elements for the purpose of the study.
- No financial liability will be placed on the Free State Department of Health by Mr. B Brummer.
- You are encouraged to present your study findings/results at the Free State Provincial Health Research Day.

Trust, you find the above in order.

Kind Regards

Mr. MNG Mahlatsi
HEAD: HEALTH

Date: 10/08/2023

Head: Health
PO Box 227, Bloemfotein, 9300
4th Floor, Executive Suite, Bophelo House, cnr Maitland and, Harvey Road, Bloemfotein
Tel: (051) 408 1527Fax: (051) 408 1556 e-mail:sebeelats@fshealth.gov.za@fshealth.gov.za/chikobvup@fshealth.gov.za
www.fs.gov.za

Annexure A

Explanatory (independent) Variables		
Covariate	**Definition**	
	Type	**Description**
Age	Continuous	Age at death
Sex	Binary	Reported sex
Race	Categorical	Reported race
Residential Subdistrict	Categorical	Sub-District where death occurred
Residential District	Categorical	District where death occurred
Testing laboratory	Categorical	Laboratory who conducted test
Occupation	Categorical	Occupation description ie. Healthcare worker, administration
Ever Hospitalised	Binary	Was the patient ever at hospital during infection
ICU admission	Binary	Was the patient ever admitted to ICU
Length of Stay	Continuous	Difference between date of admission and date of outcome.
Comorbidity	Binary	Presence of comorbidities
Hypertension	Binary	Presence of Hypertension
Diabetes	Binary	Presence of Diabetes
Chronic Cardiac Disease	Binary	Presence of Chronic Cardiac Disease
HIV/AIDs	Binary	Presence of HIV/AIDs
Previous TB infection	Binary	Presence of Previous TB infection
Current TBinfection	Binary	Presence of Current TB infection
Renal Disease	Binary	Presence of renal disease
Date of test	Continuous	Date that the test was conducted
Date of death	Continuous	Date that the case died.
Wave analysis	Categorical	Pre-1st wave, 1st Wave, pre-2nd Wave, 2nd Wave etc. Wave is defined as the week in which the weekly incidence surpassed 30 per 100 000 cases nationally. This may be adjusted based on local trends.
Treatment hospital	Categorical	Facility that the case was treated at (if treated)
Outcome (dependent variables)		
Context of death or recovery	Categorical	In facility death, out-of-facility death ante- mortem test, PMT, recovery with admission history, recovery with no admission history.

Appendix 3 - Turnitin Receipt

final_HDR.pdf

ORIGINALITY REPORT

21%	17%	17%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.medrxiv.org Internet Source	1%
2	wiredspace.wits.ac.za Internet Source	1%
3	hdl.handle.net Internet Source	1%
4	academic.oup.com Internet Source	1%
5	www.wjgnet.com Internet Source	1%
6	gh.bmj.com Internet Source	<1%
7	www.hst.org.za Internet Source	<1%
8	Thabo Mabuka, Nesisa Ncube, Michael Ross, Andrea Silaji, Willie Macharia, Tinashe Ndemera, Tlaleng Lemeke. "The impact of non-pharmaceutical interventions on the first	<1%