THE IMPACT OF THE SARS-COV-2 PANDEMIC ON MATERNAL MORTALITY IN A SOUTH AFRICAN METROPOLE (2020-21)

Minor Dissertation

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Declaration

I, Mehreen Bhorat Hunter, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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I confirm that this report has been seen by my supervisors and any concerns raised have been dutifully addressed and resolved collaboratively.

Signature: Signed by candidate

Date: 28 August 2024

Acknowledgments

This epochal undertaking would not have been possible were it not for the unwavering support, gentle guidance and patient determination of several key individuals. My deepest appreciation goes to:

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Format

The format of this thesis follows the MMed Part III (minor dissertation) guidelines set out by the University of Cape Town, Faculty of Health Sciences with relation to Public Health medicine and Occupational Medicine, as set for approval in June 2022.

This publication-ready manuscript was sculpted in accordance with the requirements of the BMC Public Health journal (Appendix 4), which is the intended recipient of this manuscript for consideration of publication. The 'Declarations' section of the publication-ready manuscript was not duplicated as those sections are already included in other parts of this document.

The wordcount, excluding the abstract, for the publication-manuscript is 3296 words. The abstract comprises 319 words.

Throughout this thesis, the referencing style follows the Vancouver convention.

Anonymized data used in the analysis of this thesis may be made available upon reasonable request by reviewers.

Contributions

Mehreen Hunter conceptualized the study, developed the data collection tool, collected the data, cleaned and analyzed the data, interpreted the data and drafted the manuscript. **Luke Hannan** assisted with cleaning and analysis of the data as well as review of the manuscript. **Mushi Matjila** assisted with refining the focus of the study and editing and review of the manuscript. **Mary-Ann Davies** provided academic support and editing and review of the manuscript. **Emma Kalk** provided academic supervision, refined the focus of the study, assisted with data collection and participated in editing and review of the manuscript.

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List of Abbreviations

Publication-ready manuscript

1. SDG: Sustainable Development Goal
2. NCCEMD: National Committee on the Confidential Enquiries into maternal deaths
3. iMMR: Institutional Maternal Mortality Ratio
4. DHIS: District Health Information System
5. PHDC: Provincial Health Data Centre
6. ITS: Interrupted Time Series
7. UCT: University of Cape Town
8. HREC: Human Research Ethics Committee
9. NPI: Non-Pregnancy related Infection
10. FHS: Faculty of Health Sciences
11. PET: Pre-eclampsia
12. APH: Ante-partum Haemorrhage
13. PPH: Post-partum Haemorrhage

Appendix 1: Protocol

1. ICD-10: International Classification of Diseases Tenth Revision
2. Clinicom: Clinicom Hospital Information System
3. PHCIS: Primary Health Care Information System
4. PREHMIS: Patient Registration and Health Management Information System
5. NHLS: National Health Laboratory Service
6. JAC: JAC pharmacy Unit
7. CDU: Chronic Dispensing Unit
8. TIER.NET: Three Interlinked Electronic Registers
9. SINJANI: Standard Information Jointly Assembled by Network Infrastructure
10. EMS: Emergency Medical Services
11. ECCR: Electronic Continuity of Care Record
12. BOD: Burden of Disease Surveillance System
13. PACS: Picture Archiving and Communication System

Abstract

Background: During the COVID-19 pandemic there was a notable increase in maternal deaths across South Africa. Pre-pandemic, the Western Cape Province had made significant strides towards reducing maternal mortality. However, this progress was reversed in the pandemic period despite a relative protection of maternal care services. The biological impact of SARS-CoV-2 may not be the sole reason for the increase in mortality. Therefore, we aimed to evaluate the relative change in the maternal death rate for non-SARS-CoV-2-related deaths intra-pandemic versus pre-pandemic in 2019.
Methods: We conducted a retrospective cohort study involving all pregnant women with a pregnancy outcome enumerated in the Provincial Health Data Centre, in the Metro-West region of Cape Town from 1 January 2019 – 31 January 2022. Cause of in-facility maternal death and relationship to SARS-CoV-2 infection was determined by folder review. We used Interrupted Time Series (ITS) analysis to assess the impact of the pandemic period on non-SARS-CoV-2 causes of maternal mortality. Maternal characteristics reviewed included HIV status and the proportion of maternal deaths occurring in persons living with HIV were also explored. **Results:** Over 98 000 women were included with 68 deaths reviewed. The ITS model ($p = 0.01$) revealed that the pandemic was associated with a step increase of 3.12 (-1.66; 7.9) in maternal mortality rate for non-SARS-CoV-2 related deaths following the start of the pandemic. This impact was sustained with an attenuation in the maternal mortality rate reduction over time from -0.56 pre-pandemic to -0.12 intra-pandemic. Folder review of deaths revealed an increase in opportunistic infections as a cause of death relative to pre-pandemic.
Conclusion: Whilst maternal healthcare services were largely protected from service disruptions during the COVID-19 pandemic, there was a reversal of some of the progress made in reducing non-SARS-CoV-2 maternal deaths in prior years. An increase in opportunistic infections and an attenuation of the decline in maternal death rate suggest that optimising maternal health requires the well-functioning of the entire healthcare ecosystem. The indirect impact of health threats, and our responses thereto, need to be strongly considered in future management strategies.

Publication-ready Manuscript (for submission to BMC Public Health)

The Impact of the COVID-19 pandemic on maternal mortality in a South African metropole (2020-2021): A retrospective cohort study

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Abstract

Background: During the COVID-19 pandemic there was a notable increase in maternal deaths across South Africa. Pre-pandemic, the Western Cape Province had made significant strides towards reducing maternal mortality. However, this progress was reversed in the pandemic period despite a relative protection of maternal care services. The biological impact of SARS-CoV-2 may not be the sole reason for the increase in mortality. Therefore, we aimed to evaluate the relative change in the maternal death rate for non-SARS-CoV-2-related deaths intra-pandemic versus pre-pandemic in 2019.

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Conclusion: Whilst maternal healthcare services were largely protected from service disruptions during the COVID-19 pandemic, there was a reversal of some of the progress made in reducing non-SARS-CoV-2 maternal deaths in prior years. An increase in opportunistic infections and an attenuation of the decline in maternal death rate suggest that optimising maternal health requires the well-functioning of the entire healthcare ecosystem. The indirect impact of health threats, and our responses thereto, need to be strongly considered in future management strategies.

Introduction

Maternal and Child Health is a global and national priority (1). In 1998 South Africa inaugurated the National Committee on the Confidential Enquiries into Maternal Deaths (NCCEMD), a ministerial committee of key individuals involved in maintaining women's health (2), as a means of reducing maternal mortality. . The committee's mandate involves reviewing all maternal deaths within the country with the aim of providing recommendations towards improving maternal outcomes (2). In 2015 South Africa committed to the Agenda for Sustainable Development (3), including Sustainable Development Goal (SDG) 3.1 which aims to decrease the global maternal mortality ratio to below 70/100 000 live births (4). However, despite the progress in lowering maternal mortality over the last 20 years, largely due to the NCCEMD, South African healthcare systems, and maternal care, remain vulnerable to health threats (5).

Maternal deaths in South Africa increased notably during the first two years of the COVID-19 pandemic (2020-2021)(6). Data published by the NCCEMD showed that the Western Cape province (WC) had achieved the SDG 3.1 target in 2019 with an institutional Maternal Mortality Ratio (iMMR) of 50.8/100 000 live births (6). However, this achievement was undermined intra-pandemic with an iMMR of 93.3/100 000 and 102.3/100 000 in 2020 and 2021, respectively (6). While pregnant women are not more likely to acquire SARS-CoV-2 infection than the general population, it is thought that they are at risk of severe COVID-19 illness due to the immunosuppressive and cardiorespiratory changes of pregnancy (7, 8).

During the pandemic, South Africa underwent several 'lockdown' periods of varying severity to curb SARS-CoV-2 spread. Lockdown measures included closure of schools and businesses and stay-at home directives. There was also intentional de-escalation of some healthcare services to divert health responses to the growing burden of COVID-19. A study conducted amongst nurses working in primary health care facilities in a South African province highlighted that lockdown and service de-escalations impacted on the performance of other priority programs such as HIV, AIDS and TB (9). Patients were reportedly disengaged from their care, demonstrating non-compliance and neglect of their treatment plans and review dates (9). Although maternal and child services were largely excluded from intentional de-escalation (10), maternal mortality rose intra-pandemic (6). The direct impact of the SARS-Cov-2 on maternal health was evident with an increase in respiratory and other systemic manifestations in pregnancy, however, the contribution of the indirect effects of the pandemic (lockdown, service disruption, fear) on maternal health was less clear.

Most current studies investigating the effects of COVID-19 on South African healthcare stem from evaluations of aggregate data from the District Health Information System (DHIS) (6, 11, 12). The Western Cape Provincial Health Data Centre (PHDC) uses a unique identifier to link multiple sources of public sector electronic data providing a virtual cohort of individual-level data, including institutional maternal deaths. Using the PHDC, we investigated the impact of COVID-19 pandemic on in-facility non-SARS-CoV-2-related maternal mortality using a quasi-experimental interrupted time series methodology.

Methods

Study design

This was a retrospective cohort study using the PHDC data to enumerate all pregnant women in the Metro-West region of Cape Town, South Africa, from 1 January 2019 to 31 January 2022. A folder review of all in-facility maternal deaths during this period was performed to elucidate the causes of maternal mortality. The protocol for this study can be found in Appendix 1.

Setting and study population

The WC is one of nine provinces in South Africa. In the 2017-2019 triennium, the most common causes for maternal death in the WC were: Non-pregnancy Related Infections (16.55%), Medical and Surgical Disorders (11.82%) and Hypertensive Disorders of Pregnancy (8.44%) (13).

The WC is divided into five districts and one metropolitan municipality (14). The Cape Town Metropolitan Municipality is comprised of eight health subdistricts: Western, Southern, Klipfontein, Mitchell's Plain, Northern, Eastern, Khayelitsha and Tygerberg. For the purposes of referral pathways and health service delivery, the first four subdistricts comprise the Metro-West region whilst the latter four comprise the Metro-East region. Although some overlap exists, for this study, only pregnancies that had both their first antenatal visit and pregnancy outcome within the Metro-West region were included. Based on population estimates published in 2020, the population of the Metro-West drainage area in that year was 2.25 million people (15).

Data sources and collection

The PHDC was used to identify all high confidence pregnancies with a pregnancy outcome during the study period which included the periods of the first four waves of COVID-19 in the WC. Pregnancy confidence scores are used to reflect the degree of certainty with which the evidence used to infer pregnancy episodes by the PHDC reflect a true pregnancy (16). A high-confidence pregnancy is that which has either one evidence indicative of pregnancy on its own or multiple moderate-confidence-evidences indicative of pregnancy (e.g. antenatal care visits).

Maternal death was defined as an in-facility death during pregnancy up to 42 days post-partum (17). For the folder-review, two independent medical practitioners extracted data from the folders and/or electronic medical records using a standardized data abstraction form. Deaths were classified according to the categories of COVID-19-relatedness (18) developed by members of the Western Cape Department of Health and Wellness to understand changes in

the COVID-19 death profile over time (supplementary appendix 1). Additionally, deaths were classified by the NCCEMD categories of maternal death (supplementary appendix 2). Any disputes were resolved through consensus.

Outcomes

The primary outcome was the in-facility maternal death rate per month for non-SARS-CoV-2-related deaths. The secondary outcome was cause of maternal death.

Statistical analysis

Frequency, proportion, median and interquartile range measurements were used for descriptive statistical analyses and continuous variables. A chi-square test was used to test for an association between categorical variables and the pre-post pandemic years in the study. These variables included: prevalence of comorbidities, the proportion of no antenatal visits, pregnancy outcomes and causes of death. Chi-square tests were also used to compare the number of Opportunistic Infections (OI) in the post-pandemic years to pre-pandemic 2019 where the expected frequency was greater than 1 (19). Where the expected frequency was less than one, the Fisher's Exact test was used.

An interrupted time series analysis (ITS) was performed to analyse the rate of maternal deaths per 10 000 pregnancy outcomes during the period 1 January 2019 to 31 January 2022, with an interruption in March 2020 when the COVID-19 pandemic and lockdown responses started in South Africa. Whilst only one interruption was included in this analysis (the start of the pandemic), the COVID-19 pandemic period included four distinct waves: wave 1: 03 May 2020 – 16 August 2020; wave 2: 08 November 2020 – 07 February 2021; wave 3: 23 May 2021 – 19 September 2021; wave 4: 28 November 2021 – 30 January 2022 (20). To ascertain the impact of the pandemic on non-SARS-CoV-2-related deaths, all deaths attributed to SARS-CoV-2 were removed from the dataset for this part of the analysis. Segmented linear regression models were fitted to the data and ordinary least squares was used to estimate the model parameters (21). A Durbin-Watson test was performed to test for autocorrelation in the residuals. The ITS model was also used to predict the counterfactual maternal mortality (what the mortality rate would have been had the interruption not taken place) based on the trend of maternal deaths pre-COVID-19. We used these models to determine the impact of the pandemic on maternal mortality through an immediate and a sustained effect. Immediate effects were evaluated as a step change in observed rate from the pre-pandemic period to the rate immediately following

the interruption. The sustained impact of the interruption on the outcome was assessed by comparing the gradient of the observed mortality rate over time against the counterfactual gradient.

Ethical approval

Approval was obtained from the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee (UCT FHS-HREC - HREC 215/2022) and from the relevant facilities within the Metro-West region of Cape Town. A waiver of informed consent was granted as the study posed a minimal risk to participants, their welfare interests were unlikely to be adversely affected, and the scope of this study rendered the research impractical to conduct without it (22).

Results

Descriptive characteristics of included patients

This cohort included 98 212 pregnant women including 68 maternal deaths (Table 1). There was a slight decrease in recorded pregnancies with outcomes during the pandemic vs. before, with some notable differences in pregnancy characteristics across the years. The proportion of live births across the years studied was also noted to be different with a decrease in 2021 relative to pre-pandemic 2019. The proportion of pregnant women who had no antenatal visits during their pregnancy differed markedly from 2019 to 2021 ($p < 0.001$) with an increase from pre-pandemic 15% to 17% in 2020 followed by a drop to 12% by 2021. The prevalence of HIV in this population differed across the years, decreasing from 20% in 2019 to 18% by 2021 ($p < 0.001$).

Table 1: Descriptive characteristics of pregnant women utilizing public health care in the Metro-West region of the Cape Town from 2019 to 2021.

		2019	2020	p-value[$]	2021	p-value[$]
Number recorded pregnancies with outcomes (n)		33306	32805	-	32101	-
Maternal deaths (n)		27	17	-	24	-
COVID-19-related deaths (n%)		N/A	5 (29%)	-	12 (50%)	-
Age (years) at pregnancy first evidence (median, IQR)		27 (23;32)	28 (23;33)	-	28 (23;33)	-
Number and proportion of pregnancies with comorbidities (n; %)						
HIV	Positive	6 651 (20%)	6 170 (19%)	<0.01[#]	5 784 (18%)	<0.01[#]
Hypertension	Pre-existing	1 407 (4%)	1 421 (4%)	0.51	1 486 (5%)	0.01[#]
	Gestational	392 (1%)	405 (1%)	0.52	328 (1%)	0.06
Diabetes	Pre-existing	399 (1%)	425 (1%)	0.27	420 (1%)	0.23
	Gestational	330 (1%)	339 (1%)	0.55	306 (1%)	0.72
TB	During pregnancy	175 (0.5%)	159 (0.5%)	0.49	149 (0.5%)	0.29
Number and proportion of recorded antenatal visits per pregnancy (n; %)						
No contact		4 981 (15%)	5 619 (17%)	<0.01[#]	3 969 (12%)	<0.01[#]
1-4 visits		20 505 (62%)	20 571 (63%)	0.74	21 347 (66%)	<0.01[#]
5-8 visits		5 151 (15%)	4 468 (14%)	<0.01[#]	4 616 (14%)	<0.01[#]
≥9 visits		2 669 (8%)	2 147 (7%)	<0.01[#]	2 169 (7%)	<0.01[#]
Number and proportion of pregnancies by outcomes* (n; %)						
		n = 33556	n = 33019		n = 32310	
Live birth		29 496 (88%)	29 375 (89%)	<0.01[#]	27 837 (86%)	<0.01[#]
Miscarriage		776 (2%)	669 (2%)	0.01[#]	1 081 (3%)	<0.01[#]
Stillbirth		506 (2%)	509 (2%)	0.75	513 (2%)	0.42
Termination		2 371 (7%)	2 137 (6%)	<0.01[#]	2 551 (8%)	<0.01[#]
Unknown		407 (1%)	329 (1%)	<0.01[#]	328 (1%)	0.02[#]
Gestational age (in weeks) at first antenatal visit*						
		n = 33 093	n = 32 583		n = 31 856	
Median (IQR[%])		20 (14;28)	20 (14;31)	-	19 (13;25)	-

**Includes outcomes from and multiple pregnancies with each multiple counted separately*
***Excludes encounters <4 weeks after estimated date of conception as these visits are unlikely to be pregnancy related*
[$] p-value based on Chi-square tests (comparison to pre-pandemic 2019)
[#] p-value <0.05

Causes of maternal death

The proportion of all maternal deaths (SARS-CoV-2 and non-SARS-CoV-2-related; Figure 1) due to Non-pregnancy Related Infections (NPI) increased from 11% pre-pandemic in 2019 to 35% (p = 0.07) and 75% (p = <0.01) of all-cause mortality in 2020 and 2021 respectively, which was the

most common cause of maternal mortality intra-pandemic. In contrast, the most common cause of maternal mortality in 2019 was Medical and Surgical Disorders (26%).

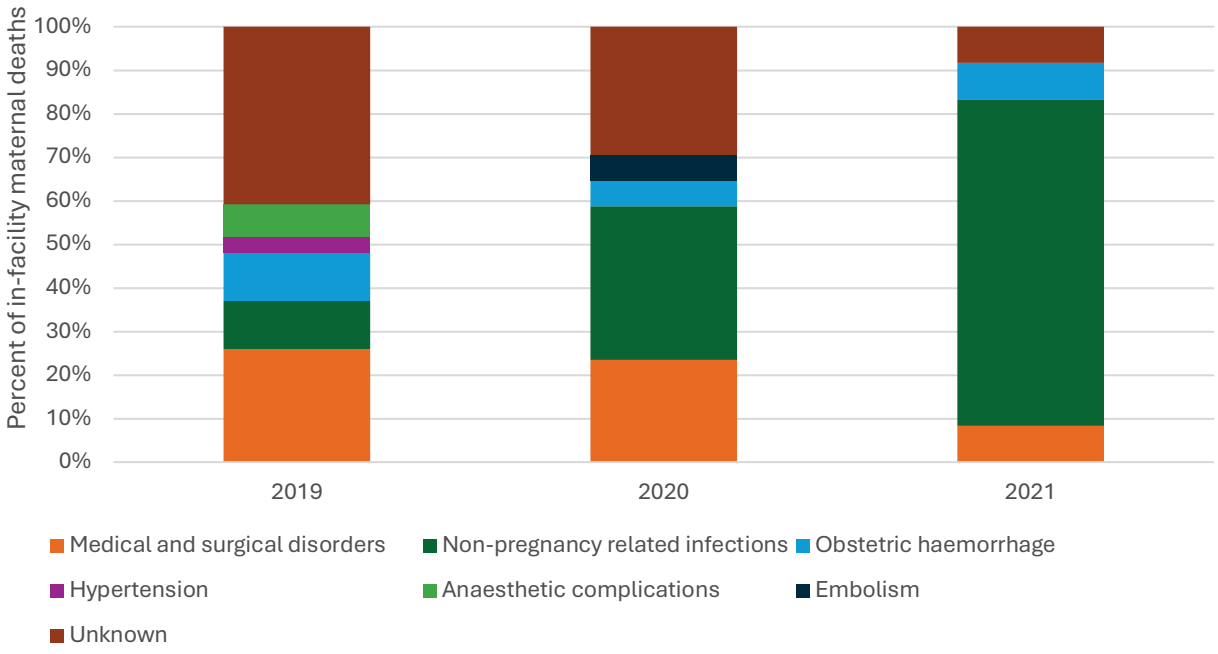

Fig 1: Percent of maternal deaths due to different causes in the Western Cape in 2019 (n = 27), 2020 (n = 17) and 2021 (n = 24)

There were 17 SARS-CoV-2-related deaths in 2020 and 2021, all classified as 'severe COVID-19' (18) with deaths attributable to COVID-19 pneumonia. Although infection with SARS-CoV-2 accounted for most NPI deaths during the pandemic (83% in 2020 and 67% in 2021), Figure 2 highlights an increase in OI as causes for maternal mortality in 2020 (17%) and 2021 (17%), in contrast to 2019 (0%). The absolute numbers of OIs across the years were small (≤3 per year) and so this increase was not statistically significant ($p = 0.39$ and $p = 0.098$ for 2020 and 2021 vs 2019 respectively). The OIs were Cryptococcal Meningitis, Pneumocystis Jiroveci Pneumonia and Tuberculosis. Of those with death due to OIs in 2020 and 2021, 100% and 67% of individuals were known to be living with HIV antenatally, respectively. All OI deaths in those not known to be living with HIV (33% of OI deaths in 2021) were attributable to tuberculosis.

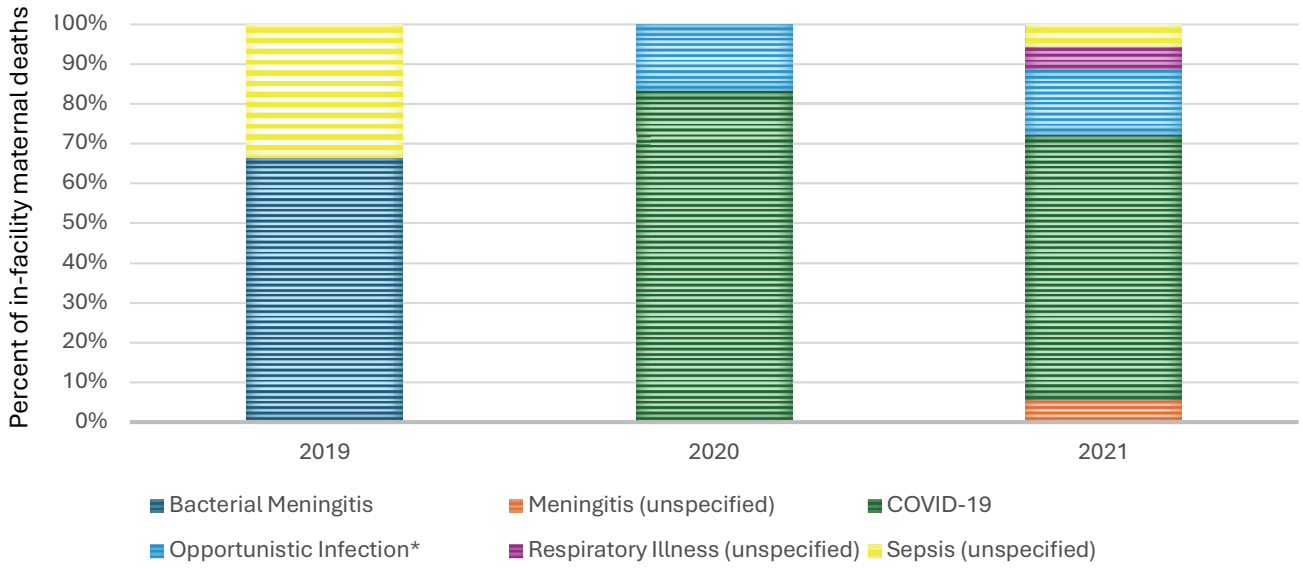

Fig 2: 100% stacked bar graph of proportion of maternal deaths due to different non-pregnancy related infections in the Western Cape in 2019 (n = 3), 2020 (n = 6) and 2021 (n = 18).

When considering causes of death by HIV status, 43% of deaths not associated the SARS-CoV-2 infection over the period of the study occurred in persons living with HIV (PLHIV).

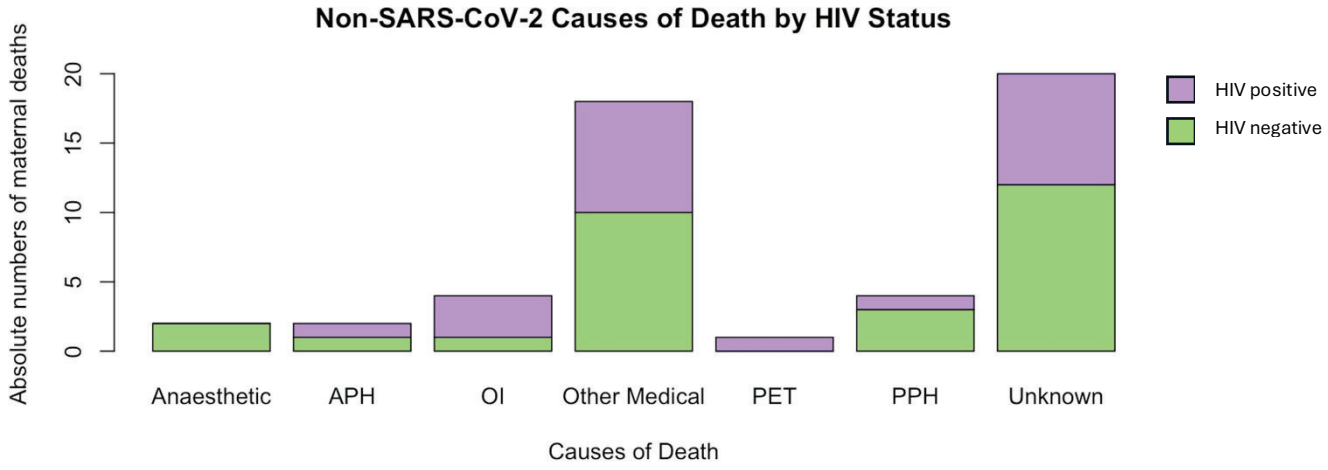

Fig 3: Bar chart denoting the causes of maternal death by HIV status.

Maternal Mortality Rate

There was an increase in number of maternal deaths in Metro-West during the 2nd and 3rd COVID-19 waves (Figure 4).

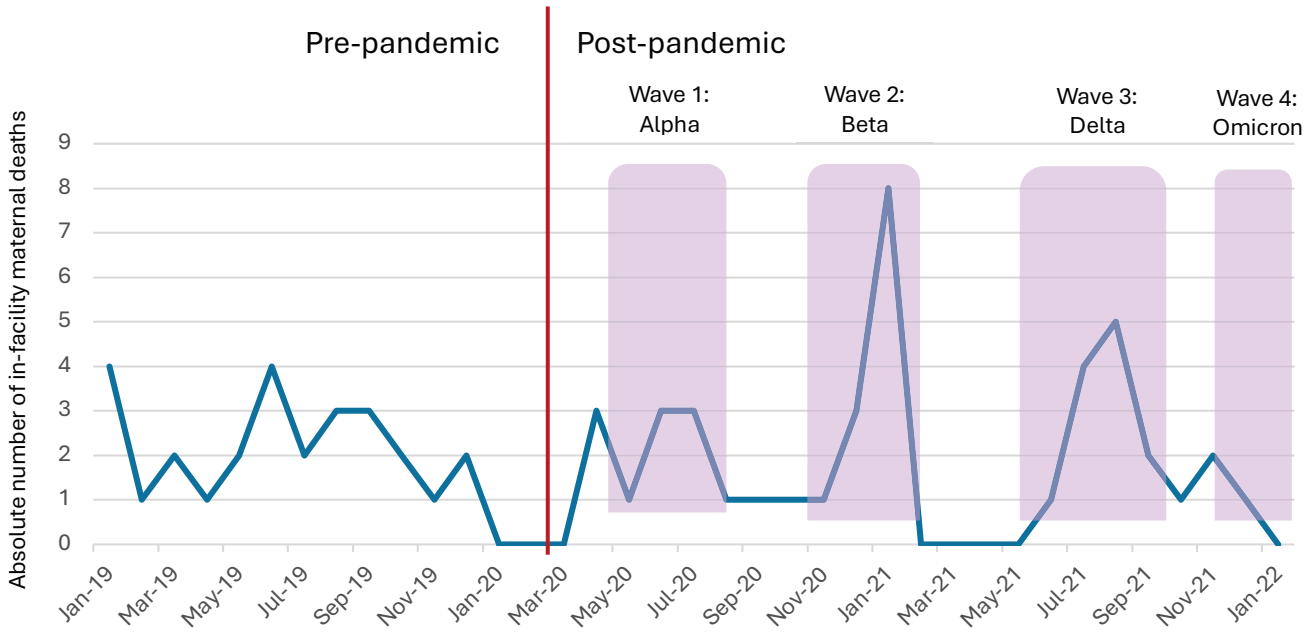

Fig 4: Absolute number of maternal deaths in the Metro-West region of Cape Town from January 2019 to January 2022. The purple shaded areas show the dates of the four COVID-19 waves in this period and the associated predominant variant.

Table 2: Interrupted time series (ITS) regression model showing the impact of the COVID-19 pandemic period on non-COVID-19-related in-facility maternal mortality rate in the Western Cape public sector from 2019-2021.

Model Fit	Variable	co-efficient	95% Confidence Interval	p-value
F-statistic: 4.279 (p 0.01)	Intercept	11.17	(7.24; 15.1)	<0.001
	Time (months)	-0.59	(-1.02;-0.16)	0.009
	COVID-19 pandemic period	3.12	(-1.66; 7.9)	0.193
	Time_covid (months)	0.47	(-0.02; 0.96)	0.061

To determine the impact of the pandemic period on non-SARS-CoV-2-related causes of death, all deaths attributed to SARS-CoV-2 were removed from the subsequent analysis (n = 51/68 deaths remained). The start of the COVID-19 pandemic was associated with a step increase of 3.12 (-1.66;7.9) /10,000 pregnancy outcomes (p = 0.19) in maternal mortality rate for non- SARS-CoV-2-related deaths. This was an obvious deviation from the downward trend during the pre-pandemic period (Figure 4). The impact was sustained over time with a gradient change from a -0.59 (p = 0.001) mortality rate reduction per month pre-pandemic to a gradient of -0.12 (p = 0.061) per month post-pandemic (Table 2). This indicates that even though the maternal mortality rate per month for non-SARS-CoV-2 related deaths continued to decline post-

pandemic, the gradient of reduction was attenuated. The Durbin-Watson test, a statistical test for autocorrelation in different time series, revealed a value of 1.755 (p = 0.099) which supports the assumption that the values in this data are independent, and each subsequent value is not influenced by nor dependent on the previous value.

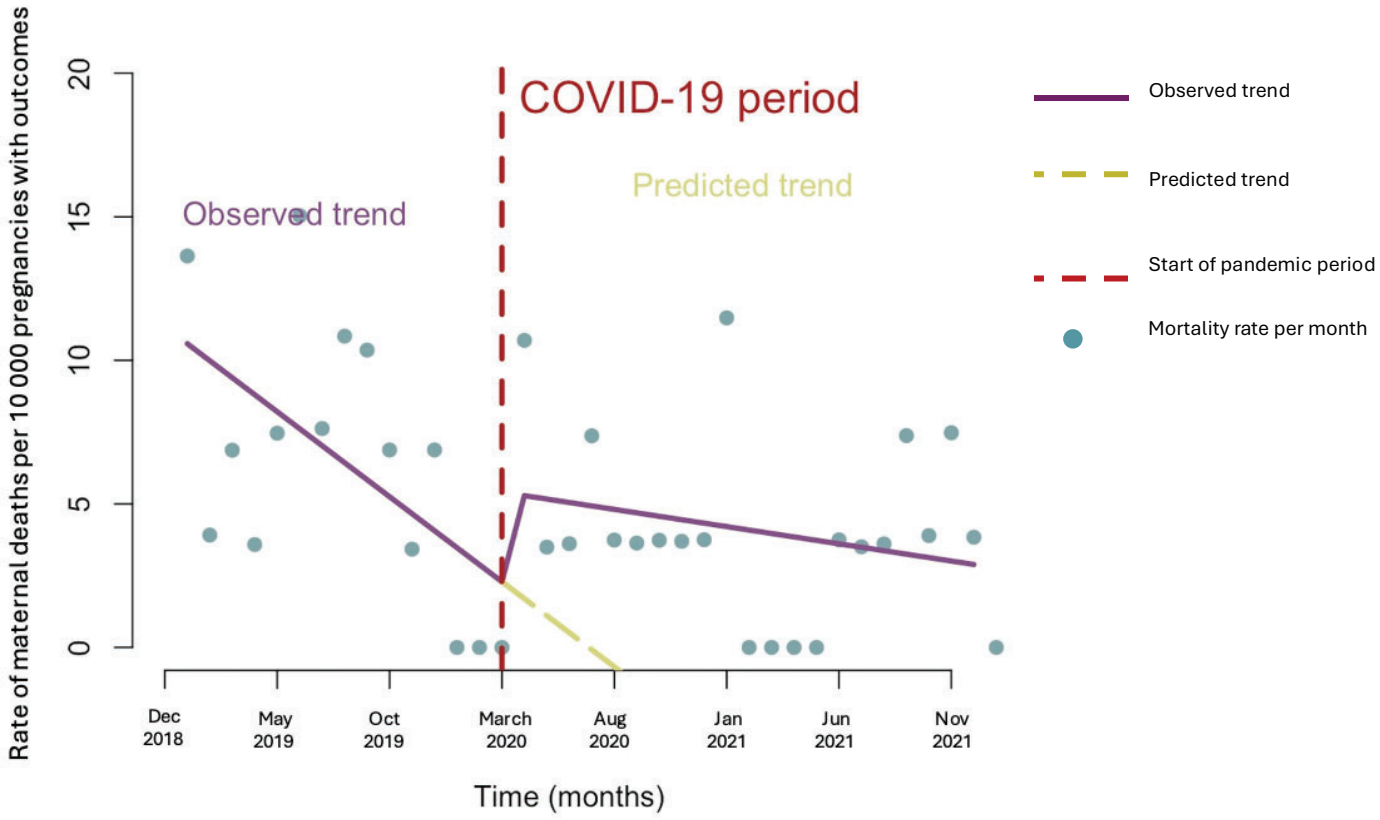

Fig 5: Scatter plot with Interrupted Time Series (ITS) regression lines showing the impact of the COVID-19 pandemic on non-COVID-18-related maternal deaths

Discussion

This study highlighted the expected increase in institutional /in-facility maternal deaths attributed to non-pregnancy related infections in 2020 and 2021 relative to pre-pandemic 2019. When examining non- SARS-CoV-2-related deaths during the pandemic period compared with pre-pandemic trends, there was a step increase in non- SARS-CoV-2-related maternal mortality rate and an attenuation of the declining trend achieved pre-pandemic. Despite low numbers, granular examination of maternal deaths revealed a worrying increase in deaths due to OIs during the pandemic period, especially in persons living with HIV (PLHIV), despite PLHIV comprising a lower proportion of pregnancies in the post-pandemic period relative to pre-pandemic 2019, in the study population.

According to the NCCEMD, the iMMR in both South Africa and the Western Cape (WC) increased in the intra-pandemic period relative to 2019 (6). By the end of 2021, the iMMR in the WC was more than double pre-pandemic 2019 figures (6). Our review of the 68 maternal deaths (17 of which were attributed to SARS-CoV-2 infection) in the Metro-West referral area demonstrated a sizable increase in the contribution of NPI to mortality accounting for 11% of deaths in 2019 vs. 35% and 75% in 2020 and 2021, respectively. Although deaths from COVID-19-pneumonia accounted for most NPI deaths, the increase of opportunistic and AIDS-related infections reversed progress documented in the 2014-2016 Saving Mothers' Report which outlined that maternal deaths due to HIV were declining, as a result of the roll out of antiretroviral treatment (23). While maternal health services were relatively protected during the pandemic period, challenges in the optimal management of chronic conditions, including HIV, and service de-escalations(24) to combat the burden of the pandemic may have resulted in these findings, particularly as the findings were more marked in 2021.

While overall provincial figures showed an increase in absolute number of in-facility maternal deaths in 2020/2021 vs. 2019, our data for the Metro-West region showed a decrease in absolute number of in-facility maternal deaths. The introduction of the lockdown in March 2020 provoked a movement of people from the urban areas back to rural areas of origin (12) and it is possible that pregnant women left Cape Town during this time. Additionally, as this study only captured pregnancies which had both their first antenatal visit and pregnancy outcome occur in the Metro-West region, those pregnancies which did not follow this referral pathway would not have been included. These factors may have played a role in the observed decrease in both pregnancies and absolute number of deaths in Metro-West despite an overall provincial increase in maternal deaths and iMMR (6).

A third observation was the correlation of increased number of deaths during each wave of COVID-19. This was particularly evident during the second and third waves in which the Beta and Delta variants dominated respectively. A combination of natural immunity, vaccine-acquired immunity (vaccination program began on 17 February 2021) and changes in virulence of subsequent SARS-CoV-2 variants could account for the tapering of deaths during the 4th COVID-19 wave of which was dominated by the Omicron variant. There may not have been increased maternal deaths in Wave 1 for various reasons including: timing; the knock-on systemic effects of reduced health care access not yet demonstrating a significant impact on deaths.

Lastly, the proportion of pregnant women using antenatal care increased in 2021 relative to both 2019 and 2020. The reasons for this are likely multifactorial and could include the relaxing of lockdown restrictions in the later months of the pandemic and growing evidence outlining the increased risk pregnant women faced in light of SARS-CoV-2 infection (8). Vaccination became available for pregnant women in late 2021(6) and this may have additionally contributed to more women attending healthcare facilities. In contrast, the decrease in antenatal care access in 2020 could be linked to lockdown restrictions, fear and linked patient migration patterns previously discussed.

A key finding in this study was the notable increase in the number and proportion of deaths due to OI, highlighting the consequences of health system strains on the management of chronic infectious diseases. The ITS analysis demonstrated an immediate increase and sustained effect of the pandemic period on the non-SARS-CoV-2 related maternal death rate, suggesting that there may have been unintended consequences to mitigation and containment strategies. Studies using similar methodologies in Chile (25) and Brazil (26) also found increases in MMR intra-pandemic versus the projected values, but did not exclude deaths related to SARS-CoV-2. Excluding these deaths in our analysis allowed for a more direct interpretation of the non-biological impact of SARS-CoV-2 on maternal deaths.

Strengths and limitations

A major strength of the study was the inclusion of nearly 100 000 enumerated pregnancies with access to electronic data on individual-level characteristics. Granular examination of maternal deaths allowed for an in-depth review of the indirect impact of the pandemic period on maternal mortality.

Our study had several limitations. Only a sub-section of the Cape Town Metropolitan was included. The numbers of evaluated maternal deaths were consequently low resulting in our study being under-powered to show statistically significant differences in non-SARS-CoV-2-related maternal mortality rate. We included pregnancies from 2019 to 2021, meaning the pre-pandemic period used to predict the trend of maternal deaths was narrow, affecting the reliability of the counterfactual gradient. This narrow time period was used as a function of practicality given the time required to perform in-depth folder reviews for the identified maternal deaths across various facilities in the Metro-West region of Cape Town. Our study included all

those pregnancies with a pregnancy outcome during the study period and not specifically only those pregnancies that had their entire course either pre or post-pandemic. It is therefore acknowledged as a potential study limitation that this could have led to a form of misclassification for those pregnancies that began in the pre-pandemic period but had their outcome in the post-pandemic period. If the pregnancy outcome was influenced by the early course of pregnancy, this could have led to a misattribution of the effect of care earlier in the pregnancy to the post-interruption period. As the burden of disease and patient profiles are not symmetrical across the metropole, the results of this study may not be generalizable outside the Metro-West. The use of the PHDC limited our population to those individuals using healthcare services in the public sector only, further impacting on generalizability. The use of routine data meant that we could not control for data quality and account for missing data which carries the risk of misclassification. Due to the limited population under review and challenges with the use of routine data, calculating the iMMR was unreliable. Routine data sources rely on adequate documentation of information and some outcomes remained unclassified, affecting the reliability of the live birth figures. Mortality rates per 10 000 pregnancy outcomes were thus utilized in this study rather than per 100 000 live births which is used when calculating iMMR. As the folder reviews were done retrospectively using clinical notes taken for operational purposes, the documentation of information may not have been exhaustive including regarding detailed information on every aspect of their entire antenatal course and chronic care management. Inconsistencies and gaps in the data were present which made the evaluation of some individual risk factors challenging and affected our ability to adequately determine the cause of death in several patients, resulting in several “unknown” causes of death. Lastly, SARS-CoV-2 infection was a competing risk for other causes of death. This means that the total number of deaths due to other causes and the full impact of service de-escalation may have been masked as some deaths that would have otherwise occurred due to other aetiologies may have occurred due to SARS-CoV-2 infection.

Conclusion

Maternal health outcomes are dependent on the adequate coordination of a functional, sustainable and contextually appropriate healthcare system. The COVID-19 pandemic period resulted in a notable increase of maternal deaths due to opportunistic infections, especially in PLHIV, and an attenuation of the decrease in the maternal death rate relative to pre-pandemic 2019. Although maternal health services were largely protected from intentional de-escalation,

all facets of a health system are interlinked and disruptions in one area have a knock-on effect on other services on the platform. Responses to future health threats should consider the indirect impact that such response may have on patients, particularly on vulnerable population groups.

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Supplementary Appendix 1

Classification of deaths according to their relation to COVID-19 infection

Category	Description	
Severe COVID-19	Biochemical and/or clinical confirmation of SARS-CoV-2 Evidence of COVID-19 pneumonia	
COVID-19 associated	Biochemical and/or clinical confirmation of SARS-CoV-2 No evidence of COVID-19 pneumonia The presence of another medical condition/obstetric complication is more likely the primary cause of death with COVID-19 precipitating either admission or death	
COVID-19 incidental	Biochemical and/or clinical confirmation of SARS-CoV-2 Asymptomatic COVID-19 illness The presence of another medical condition/obstetric complication is more likely the primary cause of death with COVID-19 not precipitating admission or death, or there is explicit documentation by the attending clinician that the COVID-19 diagnosis was incidental	
No evidence of COVID-19	No biochemical and/or clinical confirmation of SARS-CoV-2	
Indeterminate	Insufficient information to determine primary cause of death or other pathology cannot be excluded as the primary cause of death	

Supplementary Appendix 2

Causes of Death classification by the NCCEMD

Coincidental cause: *MVA, other accidents, assault, rape, other (specify)*	
Medical and Surgical disorders: *Cardiac/cardiomyopathy, Cardiac/rheumatic heart disease, Cardiac/other, Endocrine, GIT, CNS, Respiratory, Haematological, Genito-urinary, Psychiatric/suicide, Psychiatric/substance abuse, Psychiatric/other, Neoplasm, Auto-immune, Skeletal , Other (specify)*	

Non-pregnancy-related infections: *PCP pneumonia, other pneumonia, TB, influenza, endocarditis, UTI, appendicitis, malaria, cryptococcal meningitis, other meningitis, Kaposi's sarcoma, toxoplasmosis, cholera, hepatitis, gastroenteritis, wasting syndrome, other (specify)*	
Ectopic pregnancy: *<20 weeks, >20 weeks (extrauterine pregnancy)*	
Miscarriage: *Septic, haemorrhage (non- traumatic), uterine trauma, GTD, following legal TOP*	
Pregnancy-related sepsis: *Chorioamnionitis with ruptured membranes, chorioamnionitis without ruptured membranes, puerperal sepsis after NVD, puerperal sepsis after CD, bowel trauma at CD*	
Obstetric haemorrhage: *Abruption with/without hypertension, placenta praevia, other APH not specified* *Ruptured uterus with/without previous CD,* *After vaginal delivery: uterine atony, vaginal/cervical trauma, retained placenta with/without Morb Adherent Placenta, inverted uterus, other PPH not specified.* *Bleeding during CD with/without Morbidly adherent placenta, Bleeding after CD*	
Hypertension (HPT): *Chronic HYPT, gestational HYPT, pre-eclampsia with/without severe features, eclampsia, HELLP, liver rupture*	
Anaesthetic complications: *General, Epidural , Spinal anaesthetic, Sedation*	
Adverse drug reactions: *ARV meds, TB meds, other meds, herbal meds, blood transfusion reaction*	
Embolism: *Pulmonary embolus, amniotic fluid embolus*	
Suicide:	
Unknown: *Death at home or outside health services, no primary cause found, lack information*	

Supervisor Declaration

This section has been submitted separately on PeopleSoft.

Appendices

Appendix 1: Protocol

1. Introduction

1.1. Background and Rationale

The COVID-19 pandemic has left an irrevocable mark on health care systems and governance structures the world over. As it continues to morph and test the limits of medical innovation and care, its effects – both direct and indirect – continue to plague communities, stressing public health responses and forcing careful consideration of the damage that containment strategies (such as lockdowns) could have versus the damage of unchecked community transmission.

Maternal and Child Health remains a global and national priority, with the World Health Organization including indicators for these health outcomes in their 17 Sustainable Development Goals(6). It has been determined that women in sub-Saharan Africa have a 1 in 38 risk of pregnancy-related mortality compared to women in Western Europe whose risk is estimated at 1 in 11 700.(7). Despite large strides being made in South Africa over the last 20 years towards reducing maternal mortality, challenges in healthcare systems remain(7). Some of the measures taken to reduce maternal mortality rates since 1997 include the formation of the Confidential Enquiry into Maternal Deaths (NCCEMD), the re-engineering of Primary Health Care (PHC) which coincided with the launch of the Campaign for Accelerated Reduction of Maternal Mortality in Africa (CARMMA) by the African Union, and the implementation of skills packages.(6). Re-engineering of PHC included improvement of clinical governance through the introduction of District Clinical Specialist Teams as well as ward-based outreach since 2012.(6). In order to combat the contribution that knowledge and skills shortages by staff have on maternal mortality, skills development programs such as the ESMOE (Essential Steps in the Management of Obstetric Emergencies) were implemented(6). These strategies, as well as increased access to termination of pregnancy resources and maternal HIV testing and improved treatment access, assisted in increasing antenatal care (first visit) coverage in South Africa from 74.9% in 2015 to 83.2% in 2019 as well as reducing maternal mortality from 320 per 100 000 live births in 2012 to 120 per 100 000 live births in 2019(6). In the Western Cape, data from the NCCEMD in 2016 demonstrated a total of almost 300 000 deliveries in the triennial 2014 – 2016 with an institutional maternal mortality ratio of 68.3 per 100 000 live births (8). This translates to an absolute number

of 195 maternal deaths (excluding coincidental cases). This iMMR has been relatively stable since 2005 (8).

While there is no global consensus on which indicators best represent the quality of maternal care(9), proxy markers include early presentation for antenatal care, utilization of termination of pregnancy services, the age of women at conception, as well as stillbirth and perinatal mortality rates. For the purposes of looking at maternal health, specifically, the first three markers can provide some context behind maternal outcomes as well as, perhaps, understanding the number of antenatal visits had during the course of care.

Nevertheless, maternal and child health outcomes are dependent on the adequate co-ordination of a functional, sustainable and contextually appropriate healthcare system. The advent of COVID-19 not only devastated the health of infected individuals in communities but it placed added stress on the weak-points of the existing healthcare infrastructure and systems in the country. It proved to rescind some of the progress that was made in reducing maternal mortality. In terms of the impact in the Western Cape, the number of individuals attending primary health care facilities decreased by approximately 33% from March- December 2020 compared to the same period in 2019 and the number of women attending antenatal visits before 20 weeks' gestation also decreased by approximately 7.5% from March-December 2020 compared to 2019(10). Mortality due to infection with SARS-CoV-2, lockdown restrictions and the capacity constraints placed on the health system likely all contributed to the observed proportional increase in in-facility maternal mortality of approximately 82% in the Western Cape (11).

Quantifying the *indirect* effects of the COVID-19 pandemic on maternal mortality would prove to be useful in fully understanding the contribution of background, individual risk factors, health system issues and policy to healthcare outcomes. This has not yet been explored in the South African context during the COVID-19 pandemic and, as a result, serves as the rationale behind the study.

1.2 Literature Review

Search Strategy

A thorough search of the PubMed and MedLine databases was performed using the key words: "maternal mortality" OR "maternal death" AND "COVID-19" OR "SARS-CoV-2" OR "Coronavirus". The search yielded 29 relevant results in English. After a title and abstract evaluation, 9 studies were reviewed in-depth. In addition to this search, manual searches of key references and articles suggested by experts and colleagues in the field were also reviewed. Grey literature in the form of institutional and organizational reports and documents were also included in this literature review.

Context

Almost 2 years since being declared a pandemic by the World Health Organization (WHO), COVID-19, an infectious illness caused by the SARS-CoV-2 virus, continues to significantly contribute towards morbidity and mortality, with more than 258 million cases and over 5 million deaths worldwide.(11, 12). On the 5th of March 2020, South Africa documented its first case of COVID-19 and after 23 months of battling the pandemic through 4 waves, South Africa has born witness to more than 3.6 million cases and over 296 000 excess natural deaths(13, 14). While there have been multiple studies that observed those with comorbidities and immunosuppression being at increased risk of infection, fewer studies exist that examine the relationship between mortality, during the time of the COVID-19 pandemic, and other vulnerable population groups, such as pregnant women.(15). South African data from 2020 revealed a 30% increase in maternal deaths nationally in comparison to pre-COVID years(10, 16, 17). This is on par with international studies describing an increase in maternal mortality of 37%(18). However, it is unclear to what extent the indirect effects of COVID-19 on maternal health care contributed to this observed increase.

COVID-19 and Pregnancy

While pregnant women are not more likely to acquire COVID-19 infection than the general population and, according to data from the United Kingdom (and not accounting for differences between variants), more than 67% of COVID-19 infections experienced antenatally are asymptomatic, it is theorized that pregnant women are particularly at risk of severe COVID-19 illness, due to the immunosuppressive and cardiorespiratory changes of pregnancy (16, 19). Infection with SARS-CoV-2 during pregnancy has also been linked to an increase in the incidence of preterm delivery, hypertensive disorders of pregnancy, stillbirth, thromboembolic disease and

caesarean section delivery(16). However, while these links have been established, they do not account for the psychological and socio-political impact of COVID-19 on maternal health outcomes nor the impact of a health system under pressure. A model-based study estimating the impact of disruptions of routine services on maternal and child health outcomes due to COVID-19, predicted an increase in maternal deaths of between 9-39% per month in low- and middle-income countries, depending on the level of reduction in pertinent healthcare services (20, 21). In this modelling study, alterations in the macroenvironment of health care leading to supply-chain disruptions for essential medications, alterations in workforce and decreased access to healthcare (which, if ordinarily optimal, serve to reduce deaths due to postpartum heamorrhage, pre-eclampsia and maternal sepsis) is postulated to account for 60% of the increase in maternal deaths (21). This alludes to a postulation that the majority of excess maternal deaths are not necessarily related to COVID-19 infection itself. Therefore, it is imperative to note the exact causes for maternal mortality to better understand what changes need to be implemented to prevent any further increases and, perhaps, even observe a decrease in the number of lives lost.

Maternal Mortality in South Africa

South Africa is a middle-income country with avoidable factors identified in more than 60% of its maternal deaths (22). As of 1997, maternal deaths are a notifiable condition in South Africa (23). Currently, the most common causes of maternal mortality in South Africa, have been identified as:

Table 2: Common causes of Maternal Mortality in South Africa(6)

Non-Pregnancy related Infections (mainly due to HIV and TB)	**26.0%**
Hypertensive Disorders of Pregnancy	**17.8%**
Obstetric Hemorrhage	**16.8%**
Medical and Surgical Disorders in Pregnancy	**12.6%**
Pregnancy-related Sepsis	**9.5%**

Impact of COVID-19 on Maternal Mortality in South Africa

With the introduction of COVID-19 into South Africa in 2020, a general, increase in maternal mortality was observed.(17) However, the aetiologies behind this increase have not yet been explored. Alongside this metric, a decline in the use of sexual and reproductive healthcare services was noted, despite a relatively consistent use of maternity services. A difference in effect between provinces was also noted with both the migration of patients out of cities and into

their resource-constrained hometowns, as well as the burden of COVID-19 in the metropolitan areas resulting in an inability to adequately attend to routine emergencies (17).

Nationally, institutional maternal deaths in the public sector increased by 22.7% from March – December 2020 which translates to an escalation of the institutional maternal mortality ratio (iMMR) from 90.5/100 000 live births from March - December 2019 to 106.8/100 000 for the same period in 2020.(10) The Western Cape Province, in particular, noted the largest proportional increase in the in-facility Maternal Mortality in 2020 compared to 2019 at 82.1% while the province with the second highest increase, Kwa-Zulu Natal, was approximately 50%.(10) Therefore, it is of utmost importance that the impact of the multiple challenges experienced by patient-related factors and those of the existing health systems be explored to ascertain the contribution these factors may have had on this proportional increase. Some of these challenges include: health seeking behavior changes due to, amongst other reasons, fears of contracting the virus, resource shortages, disruptions in healthcare infrastructure owing to numbers of people with COVID-19 requiring care, and the disruptions in health systems due to lockdown measures.(9)

It must be noted, however, that analysis of mortality data during the COVID-19 pandemic is complex due to the heterogeneity of reporting of COVID-19 related deaths between different countries (24). The criteria applied to attribute a death to COVID-19 and the population from which these data are derived are not uniform; therefore, before commencing any analysis, clear definitions of a "COVID-19-related death" and a "non-COVID-19-related death" are required. The Western Cape Department of Health undertook to create a classification of deaths relating to whether COVID-19 illness was causative, contributory, incidental or indeterminate (Table 3).

Table 3: Classification of deaths according to their relation to COVID-19 infection(3)

Categories		**Description**
Severe COVID-19		Evidence of COVID-19 pneumonia
No COVID-19 pneumonia	COVID-associated	No evidence of COVID-19 pneumonia Presence of another medical condition as the primary cause of mortality
	Incidental	Asymptomatic COVID-19 infection COVID-19 illness did not precipitate admission or death

Indeterminant		Insufficient information to exclude other pathologies being the primary cause of mortality

"Gaps" in currently available literature

Most of the current studies investigating the effects of COVID-19 on South African healthcare comes from evaluations of the District Health Information System (DHIS)(10, 17). While this system is useful for aggregate data, it does not allow for the analysis of patient-level data or for investigating associations between individual characteristics, service use and outcomes. The establishment of the Western Cape Provincial Health Data Centre (PHDC) in 2015, however, closes this gap by allowing for both the servicing of clinical needs based on individual patient data, as well as allowing for research and analysis based on linked anonymized data.(25) While this system does have its limitations in that it only services the public sector in South Africa and not the private sector, the fact that approximately 85% of the total South African population uses public sector healthcare means that use of the PHDC for analysis can provide reasonable insight into the state of public health and healthcare in the Western Cape (10).

A detailed descriptive review of in-facility maternal deaths in the Metro-West region of Cape Town during the SARS-Cov-2 pandemic (2020 – 2022) compared with maternal deaths in 2019 i.e., in the year preceding SARS-CoV-2 will be performed in this study.

By comparing mortality data from before the pandemic to that seen during it, and comparing the trend of observed deaths not related to SARS-CoV-2 infection intra-pandemic to the counterfactual trend determined by pre-pandemic numbers, estimations as to the indirect effects of the pandemic on maternal mortality can be determined. The results of this study would go a long way towards informing future policy and informing stakeholders of the unintended consequences of various public health decisions. Therefore, the urgency to form a sustainable and more comprehensive approach to this and future pandemics can be highlighted.

1.3 Aim

To determine the impact of the SARS-CoV-2 pandemic on in-facility maternal mortality in the Metro-West region of Cape Town, South Africa, in comparison to pre-pandemic 2019.

1.4 Objectives and Statistical Hypotheses

Objective 1

To determine and compare the all-cause in-facility maternal mortality ratios (iMMR) in each of 2019, 2020 and 2021 in the Metro-West region of Cape Town, South Africa.

Hypothesis Objective 1: There is an observable increase in in-facility maternal mortality ratios during the COVID-19 pandemic compared to pre-pandemic 2019.

Table 4: Risk factors of interest for Maternal Mortality

Individual-level Risk Factors
Age at first evidence of pregnancy
Gestational Age at booking
Number of recorded antenatal visits
Maternal Comorbidities: • HIV • TB • Hypertension • Diabetes

Objective 2

To determine the contribution of defined causes (Tables 1 and 5) of maternal death to iMMR over each of 2019, 2020 and 2021 in the Metro-West region of Cape Town, South Africa.

Hypothesis Objective 2: There is an observable increase in all common causes of maternal mortality intra-pandemic compared to the pre-pandemic 2019.

Table 5: Common causes of interest for Maternal Mortality in South Africa

Non-Pregnancy related Infections (mainly due to HIV and TB)
Hypertensive Disorders of Pregnancy
Obstetric Hemorrhage
Medical and Surgical Disorders in Pregnancy
Pregnancy related Sepsis

Objective 3

To determine if there is an increased risk from death from non-COVID causes intra-pandemic compared to pre-pandemic 2019.

Hypothesis Objective 3: The trend of the rate of maternal deaths from non-COVID causes relative to pregnancy outcomes intra-pandemic is higher than the trend of the rate of maternal deaths relative to pregnancy outcomes month-on-month pre-pandemic.

2. Methods

2.1 Study population, Source and Type of Data

Secondary data obtained from the Provincial Health Data Centre (PHDC) in the Western Cape will be used for the analyses outlined in this protocol. A cohort of pregnant women fitting the inclusion criteria (Table 6) will be identified through the PHDC. The PHDC will also be used to identify maternal deaths in this region and during this time period so that the contributions of known causes of maternal death (Table 5) and risk factors (Table 4) for each cause of death during this period can be assessed.

The PHDC was established in 2015 with the aim to link the information across a number of electronic record systems, through a unique patient identifier, for the purposes of collecting patient-level data with the intent of positively impacting health service delivery both directly through clinical tools and indirectly through actionable health system intelligence. The PHDC allows for the review of both aggregate and granular data allowing for more comprehensive analyses of the health system and its patients in the Western Cape.(25)

Some of the data sources incorporated into the PHDC, useful to this analysis include, but are not limited to,: Clinicom, PHCIS, PREHMIS, NHLS, JAC, CDU, Tier.Net, SINJANI, EMS, ECCR, MomConnect, DOB and PACS.

Aggregate data to review the associations between risk factors and maternal mortality pre- and intra-pandemic will be used while granular data will be used for an in-depth folder review of identified maternal mortality cases.

Table 6: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Women with high confidence pregnancy scores from the PHDC	Women with low confidence pregnancy scores from the PHDC
Women a pregnancy outcome from 1st January 2019 to 31st January 2022 with both their first evidence of pregnancy and outcome having occurred in the Metro-West region of Cape Town.	Women without an identified pregnancy outcome after 31st January 2022.

	Pregnant women with either a first evidence of pregnancy or outcome having occurred outside of the Metro-West region of Cape Town.

2.2 Study Design

A retrospective cohort study will be conducted using a cohort of pregnant women defined within the PHDC. A folder review of all in-facility maternal deaths occurring between the aforementioned dates will be conducted and a quasi-experimental Interrupted Time Series Analysis performed to predict the counterfactual based on the trend of maternal deaths pre-COVID-19 and compare this to the observed deaths that occurred post the start of the COVID-19 pandemic.

2.3 Data Collection

The 'maternity cascade' from the PHDC will be used to identify all pregnant women meeting inclusion criteria for this study (Table 6). This data will be extracted on an aggregate level with granular data only being sought for those women who have the outcome of interest: maternal death.

In-facility maternal deaths identified through the PHDC will have their electronic records reviewed and a paper folder-review will be used to supplement the digitally available information where deficiencies or discrepancies in information are identified.

A data extraction form (Appendix 1) will be used to extract the relevant data from the electronic records (and/or paper folders) uniformly for the purposes of analysis. Deaths will be classified according to the categories in Tables 1 and 5 and the risk factors of interest according to those listed in Table 4.

Data extraction will be performed by two independent medical practitioners and any disputes will be resolved through consensus and, where necessary, a 3rd party Obstetrician's review.

2.4 Data Limitations

The limitations of the PHDC is that it can only service Public Sector cases and, as such, access to the Private Sector data is not possible for the aggregate analyses of this study. As South Africa

has two parallel healthcare streams, the data included in this analysis can only provide comprehensive information for one of those streams.

In addition, as this data is collected for a defined, retrospective cohort the researchers are reliant upon the patient notes for information. These notes were taken for operational purposes and not research, therefore, the note-taking may not have been entirely exhaustive. The folder review is subject to the documentation that took place and available records which means there may be inconsistencies or incomplete information identified. This, therefore, introduces some limitations of the quality of the data and a potential risk of misclassification. The folder review performed by two independent clinicians will try to mitigate some of this error but it remains a limitation of this study.

2.5 Management of Results

2.5.1 Return of Results

As this analysis makes use of secondary data in an aggregate format and folder review of cases with a mortality outcome, results will not be returned to the participants specifically. Instead, the results and conclusions of the study will be shared with the Western Cape Department of Health and the National Department of Health. A Peer-reviewed manuscript and/or conference presentation will also be completed and shared with the broader global community.

3 Statistical Considerations/Measurement

3.1 Sample Size

The PHDC enumerates approximately 100 000 high confidence pregnancies per year. The maternal deaths are estimated to be approximately 68/100 000 live births per year pre-COVID-19 pandemic. We want to anticipate an 82% increase based on local literature for the Western Cape of which 60% is attributable to health system factors or the indirect effects of the COVID-19 pandemic.

This study will be limited to the Metro-West region of Cape Town which enumerates approximately 30 000 pregnancies will be enumerated per year. Whilst all maternal death events occurring in the geographical area of interest over the three years will be included, this number is anticipated to be small and so the study may be underpowered.

3.2 Statistical Analyses

Collected data will be transcribed onto an excel spreadsheet and saved in both .xls and .csv formats with password protection. The .xls file will then be imported into "R-studio" v 1.4.1106 for further statistical analysis. No patient identifiers will be collected, individuals will be given a different, random, natural number (study number) which will represent a single participant.

Frequency, proportion, median and interquartile range measurements will be used for descriptive statistical analysis.

Frequency tables will be used to evaluate the results of Objective 2 to describe the data. The relative contributions of the common causes of maternal mortality to the overall metric will be determined during each of 2019, 2020 and 2021 and differences in these contributions will be assessed.

To ascertain the impact of the pandemic on non-COVID-19 related deaths, all deaths attributed to the SARS-CoV-2 pathogen will be removed from the dataset for this part of the analysis. Using an Interrupted Time Series (ITS) analysis, segmented linear regression models will be fitted to the data to estimate the model parameters. To check for autocorrelation of the data, a Durbin-Watson test will be performed.

This ITS model will be used to evaluate the impact of the COVID-19 pandemic on non-COVID-19 related maternal deaths by comparing the observed rate of death from the pre-pandemic period to the rate of death immediately following the start of the pandemic as well as the subsequent rate over time.

4 Ethical and Operational Considerations

4.1 Ethical Approval

The ethical principles outlined in the Belmont Report will be adhered to as well as the National Department of Health's Ethics in Health Research guidelines. Approval for conducting this research will be sought from the Human Research Ethics Committee from the University of Cape Town and the Western Cape Provincial Research Committee.

4.2 Risk/Benefit Consideration

4.2.1 Risks

This study involves minimal risk as it only includes the use of secondary data. The only risk anticipated will be a breach of confidentiality which would result in a loss of privacy. However, every effort will be made to ensure that the data is secured at all stages of use with access permitted only to select individuals. These measures will be further explored in section 4.5 'Data Management'. As this is a minimal risk study examining secondary data and a folder review will only be performed on cases with a mortality outcome, no interaction with the study participant, for the purposes of this research, will take place.

4.2.2 Benefits

The benefits of this study lies in the advancement of knowledge and the use of the results of this study to help inform policy, practices and intervention strategies going forward both with regards to responses to future COVID-19 waves but also for any future pandemic or health system strain that may arise.

4.3 Waiver of Informed Consent

Given the scope of this study and that the study population, retrospectively, encompasses all those women who meet inclusion criteria across the entirety of the Western Cape, this research cannot practically be conducted without the waiver of informed consent being granted. Therefore, this request for a waiver meets all three conditions highlighted in the South African Ethics in Health Research Principles, Processes and Structures (2015). To address the minimal risk of a loss of confidentiality, identifiable information that will be required for the folder review, of mortality cases, in order to collect granular data on the circumstances surrounding the patient's antenatal course, risk factors and circumstances surrounding their demise, will not be translated onto the data extraction form. An anonymised study participant number will be used as an identifier linking the information to the individual but the identifiable particulars of the

patient will be kept separate from the data form. In doing so, the rights and wellbeing of the study participants will not be affected. Details surrounding the securing of patient information and valuing the privacy and confidentiality of participants is further discussed in sections 4.4 and 4.5. For the cases that do not have a mortality outcome, only routinely collected data and records will be used in this study. These study participants will be de-identified upon reception of the dataset from the Provincial Health Data Centre.

4.4 Privacy and Confidentiality

Any potential risk of a breach of confidentiality will be mitigated through careful and secure management of the data, further described in section 4.5. In addition, all collected data will be de-identified before analysis and any necessary identifiers will be kept separate from the analysis. A random study number will be assigned to each mortality case that will be reviewed in-depth, thereby respecting the confidentiality of the individuals included in the study. Both researchers who will be conducting the folder review are medical professionals and bound by the respect for doctor-patient confidentiality. Both have completed Human Subjects Protection training.

4.5 Data Management

4.5.1 Access

Privacy and confidentiality of study participants will be respected through ensuring that all collected data will be de-identified at the time of analysis. All identifiers will be kept separate from the analysis and in a password-protected excel spreadsheet. Data for analysis will be securely stored in password-protected .csv and .xls files. Only the Master's student, MMed supervisors and the academic supervisor will have access to this data. Once a journal article is drafted for the purpose of publication, reviewers will also have access to the de-identified data upon request. Once data linkage is complete, all analysis will be conducted on anonymized datasets.

4.5.2 Storage

The de-identified data in .csv and .xls files will be stored for 5years after completion of this study. The data will remain in password-protected documents and inaccessible by any other party other than those individuals stipulated in section 4.4.1. Data with patient identifiers will be stored in

excel documents with a password as well for a period of 5years. Both sets of data will be kept on the hard drive of the Master's student's work-based computer.

4.5.3 Disposition and Retention of Study Records

After the conclusion of the 5year period, all documents related to the data collection of this study (both the identified and de-identified records) will be permanently deleted off the hard drive of the Master's student's work-based computer.

4.6 Publication and Data Sharing Policies

The findings from this study will be shared with the Western Cape Department of Health and the National Department of Health. A Peer-reviewed manuscript and/or conference presentation will also be completed and shared with the broader global community. In this way, the learnings from this research will serve to benefit the local, national and global community by increasing the knowledge base and serving as a tool that will help guide future policy and how it is associated with maternal mortality.

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Appendix 2: Data Collection Form

The impact of the SARS-CoV-2 pandemic on maternal mortality in a South African metropole (2020 – 2021)

Date of Data Extraction: dd/mm/yyyy

Allocated Study Number: _____

ID of Data Extractor: _____

Was the case sent for panel/senior review?

Y	N

1. Demographics and details of the deceased

Age at first evidence of pregnancy: _____

Gravidity (before index delivery): _____

Parity (before index delivery): _____

Gestation (in weeks at time of death/at delivery): _____

Days since delivery/miscarriage: _____

2. Admission Details

Date of admission: dd/mm/yyyy

Date of death: dd/mm/yyyy

Reason for admission: _____

3. Antenatal Care

Did patient book her pregnancy:

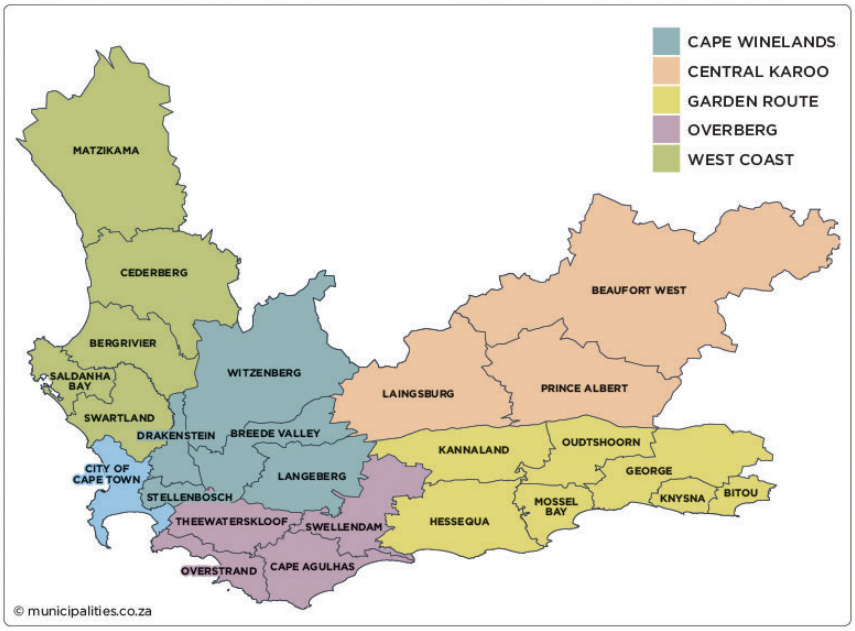
Y	N

If "Y" at what Gestational Age did she book (in weeks):

<14	14-	20-	>26

Number of total antenatal visits: ☐

Sub-District of first antenatal visit *(circle relevant)*:



4. **Risk Factors**

Pre-existing Hypertension	**Pre-existing Diabetes Mellitus**	**HIV**
TB: Current	Gestational Hypertension	Gestational Diabetes
TB: Past	SARS-CoV-2 (Biochemical confirmation) test date: dd/mm/yyyy	
Pre-eclampsia	SARS-CoV-2 (Clinical confirmation only)	
Other:		

5. **Index Pregnancy Outcome**

Delivery status

Undelivered	**Vaginal (unassisted)**	**Vaginal (assisted)**	**Caesarean Section**

Outcome

Miscarriage	**Stillborn**	**Live Birth**

6. **Primary Cause of Death**

Classification of deaths according to their relation to COVID-19 infection *(tick applicable)*

Category	**Description**	
Severe COVID-19	Biochemical and/or clinical confirmation of SARS-CoV-2 Evidence of COVID-19 pneumonia	
COVID-19 associated	Biochemical and/or clinical confirmation of SARS-CoV-2 No evidence of COVID-19 pneumonia	

	The presence of another medical condition/obstetric complication is more likely the primary cause of death with COVID-19 precipitating either admission or death	
COVID-19 incidental	Biochemical and/or clinical confirmation of SARS-CoV-2 Asymptomatic COVID-19 illness The presence of another medical condition/obstetric complication is more likely the primary cause of death with COVID-19 not precipitating admission or death, or there is explicit documentation by the attending clinician that the COVID-19 diagnosis was incidental	
No evidence of COVID-19	No biochemical and/or clinical confirmation of SARS-CoV-2	
Indeterminate	Insufficient information to determine primary cause of death or other pathology cannot be excluded as the primary cause of death	

Cause of Death *(tick ONE applicable category and circle the appropriate subcategory)*

Coincidental cause: *MVA, other accidents, assault, rape, other (specify)*	
Medical and Surgical disorders: *Cardiac/cardiomyopathy, Cardiac/rheumatic heart disease, Cardiac/other, Endocrine, GIT, CNS, Respiratory, Haematological, Genito-urinary, Psychiatric/suicide, Psychiatric/substance abuse, Psychiatric/other, Neoplasm, Auto-immune, Skeletal , Other (specify)*	
Non-pregnancy-related infections: *PCP pneumonia, other pneumonia, TB, influenza, endocarditis, UTI, appendicitis, malaria, cryptococcal meningitis, other meningitis, Kaposi's sarcoma, toxoplasmosis, cholera, hepatitis, gastroenteritis, wasting syndrome, other (specify)*	
Ectopic pregnancy: *<20 weeks, >20 weeks (extrauterine pregnancy)*	
Miscarriage: *Septic, haemorrhage (non- traumatic), uterine trauma, GTD, following legal TOP*	
Pregnancy-related sepsis: *Chorioamnionitis with ruptured membranes, chorioamnionitis without ruptured membranes, puerperal sepsis after NVD, puerperal sepsis after CD, bowel trauma at CD*	

Obstetric haemorrhage: *Abruption with/without hypertension, placenta praevia, other APH not specified* *Ruptured uterus with/without previous CD,* *After vaginal delivery: uterine atony, vaginal/cervical trauma, retained placenta with/without* *Morb Adherent Placenta, inverted uterus, other PPH not specified.* *Bleeding during CD with/without Morbidly adherent placenta, Bleeding after CD*	
Hypertension (HPT): *Chronic HYPT, gestational HYPT, pre-eclampsia with/without severe features, eclampsia, HELLP, liver rupture*	
Anaesthetic complications: *General, Epidural , Spinal anaesthetic, Sedation*	
Adverse drug reactions: *ARV meds, TB meds, other meds, herbal meds, blood transfusion reaction*	
Embolism: *Pulmonary embolus, amniotic fluid embolus*	
Suicide:	
Unknown: *Death at home or outside health services, no primary cause found, lack information*	

Notes:

Appendix 3a: Ethical Approval from UCT-FHS-HREC

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

12 April 2022

HREC REF: 215/2022

Dr E Kalk
School of Public Health & Family Medicine
Falmouth Building-FHS
Email: Emma.kalk@uct.ac.za
Student: imehreen.hunter@westerncape.gov.za

Dear Dr Kalk

PROJECT TITLE : THE IMPACT OF THE SARS-COV-2 PANDEMIC ON MATERNAL MORTALITY IN THE WESTERN CAPE, SOUTH AFRICA (2020-2021)-
(MASTERS CANDIDATE-DR MEHREEN HUNTER)

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

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

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, our letter dated 02 February 2022 provides guidance found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Approval is granted for one year until the 30 April 2023.

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

The HREC acknowledge that the student: Dr Mehreen Hunter will also be involved in this study.

Please quote the HREC REF 215/2022 in all your correspondence.

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

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

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Appendix 3b: Institutional Ethical Approvals

Western Cape Government

GROOTE SCHUUR HOSPITAL
Enquiries: Dr Bernadette Eick
e-mail: GSHResearch.Request@westerncape.gov.za

Dr Emma Kalk
School of Public Health

E-mail: emma.kalk@uct.ac.za

Dear Dr Kalk

RESEARCH PROJECT: WC_202204_022 The Impact of the SARS-CoV2 Pandemic on Maternal Mortality in the Western Cape South Africa (2020 – 2021)

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 April 2024**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) **Confidentiality must always be maintained.**
d) No additional costs to the hospital should be incurred as indicated in your Annexure 2 i.e. Lab, consumables or stationery. **If access to TRACK Care/NHLS is required, kindly attach our letter of approval to the application form and approach Information Management to assist with data.**
e) **No patient folders may be removed from the premises or be inaccessible.**
f) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
g) **Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).**
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) If the researcher is not GSH staff member, a supernumerary contract is required before commencement of the research.
m) Please contact Michelle Riley (Patient Fees) at ext. 2276 to ascertain if there will be charges for conducting the Research and to obtain a quote or to discuss charges
n) **Kindly submit a copy of the publication or report to this office on completion of the research.**
o) **At no time should any posters encouraging patients to partake in research, be displayed within a clinical area.**
p) **Please adhere to ALL COVID-19 regulations and Groote Schuur Hospital policies.**
q) **All Clinical Trials to be registered on Clinicom with Michelle Riley or Rowan James. michelle.riley@westerncape.gov.za / rowan.james@westerncape.gov.za**

I would like to wish you every success with the project.

Yours sincerely

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 27 April 2023
C.C. Mr. L. Naidoo, Mr. A. Mohamed, Professor M. Matjila, Dr S. Murray

G46 Management Suite, Old Main Building,
Observatory 7925
Tel: +27 21 404 6288 fax: +27 21 404 6125

Private Bag X,
Observatory, 7935
www.westerncape.gov.za/health

Dr Mehreen Hunter

University of Cape Town

e-mail: mehreen.hunter@westerncape.gov.za; Ashleigh.levendall@westerncape.gov.za

RESEARCH PROJECT: The impact of the SARS-CoV-2 pandemic on maternal mortality in the Western Cape, South Africa (2020 – 2021)

Dear Dr Hunter

You are granted permission to proceed with your research at Mowbray Maternity Hospital until 4 July 2023.

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with your research.
c) No additional costs to the hospital should be incurred.
d) **As there is only one records clerk, folder requests should be given two weeks in advance, and no pressure should be applied for a quick service. Only 50 folders per week may be requested at one time**.
e) No patient folders may be removed from the premises or be inaccessible.
f) Please provide the researcher with a copy of this letter as verification of approval.
g) Confidentiality must be maintained at all times.
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) On completion of your research, please forward any recommendations/findings that can be beneficial in terms of further action, development or policy review.
j) Please forward a copy of the publication or report on completion of the research.

Good luck with your project.

Yours sincerely

Dr Chantal Stewart

Chair

MMH Research Committee

4/7/2022

Western Cape Government
Health

STRATEGY & HEALTH SUPPORT
Health.Research@westerncape.gov.za
tel: +27 21 483 0866: fax: +27 21 483 6058
5th Floor, Norton Rose House,, 8 Riebeek Street, Cape Town, 8001
www.capegateway.gov.za)

REFERENCE: WC_202204_022
ENQUIRIES: Dr Sabela Petros

University of Cape Town
Anzio Road
Observatory
7935

For attention: Dr Emma Kalk, Dr Mehreen Hunter, Prof Mushi Matjila

Re: The impact of the SARS-CoV-2 pandemic on maternal mortality in the Western Cape, South Africa (2020 – 2021)

Thank you for submitting your proposal to undertake the above-mentioned study. We are pleased to inform you that the department has granted you approval for your research.
Please contact the following people to assist you with any further enquiries in accessing the following sites:

Mitchells Plain Hospital	**Jonathan Naude**	**021 377 4760**
Victoria Hospital	**Dr Graeme Dunbar**	**021 799 1211**

Kindly ensure that the following are adhered to:

1. Arrangements can be made with managers, providing that normal activities at requested facilities are not interrupted and the constraints caused by the Covid-19 epidemic above are respected and adhered to.
2. Researchers, in accessing provincial health facilities, are expressing consent to provide the department with an electronic copy of the final feedback (**Annexure 9**) within six months of completion of research. This can be submitted to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).
3. In the event where the research project goes beyond the *estimated completion* date which was submitted, researchers are expected to complete and submit a progress report (**Annexure 8**) and an updated ethics clearance letter to the provincial Research Co-ordinator (Health.Research@westerncape.gov.za).
4. The reference number above should be quoted in all future correspondence.

Yours sincerely

PROF. V ZWEIGENTHAL
DIRECTORATE: HEALTH INTELLIGENCE
DATE: 9 June 2022
CC

Western Cape Government

DEPARTMENT OF HEALTH
NEW SOMERSET HOSPITAL

Dr. Donna Stokes
Chief Executive Officer
Donna.Stokes@westerncape.gov.za | Tel: 021 402 6408

Date: 20th September 2023

Dear Dr Hunter

PERMISSION TO CONDUCT A RESEARCH AT NEW SOMERSET HOSPITAL

I am pleased to inform you that your request to conduct research at New Somerset Hospital has been approved.

- Research aimed at investigating the indirect effects of COVID-19 on maternal mortality.

Please feel free to contact Ms Rene Abrahams who is our Medical Records Manager to make the necessary arrangements to gain access to the required patient folders.

Her contact details below:

- Email address: rene.abrahams2@westerncape.gov.za
- Telephone no. 021 402 6340.

Please note that no files may be removed from the premises and that the data collection should not negatively impact the daily activities of the staff at our Medical Records Department.

You will be required to produce this approval letter when requesting patient folders from the Medical Records Department.

Wishing you all the best with the research study.

Yours sincerely,

Dr. Donna Stokes
Chief Executive Officer
New Somerset Hospital

Appendix 4: BMC Public Health publication guidelines (for authors)

Criteria

Research articles should report on original primary research or new experimental or computational methods, tests or procedures. Manuscripts reporting results of a clinical trial must conform to CONSORT 2010 guidelines. Authors of randomized controlled trials should submit a complete CONSORT checklist alongside their manuscript, available at www.consort-statement.org. Research articles may also report on systematic reviews of published research provided they adhere to the appropriate reporting guidelines which are detailed in our editorial policies. Please note that non-commissioned pooled analyses of selected published research and bibliometric analyses will not be considered. Studies reporting descriptive results from a single institution or region will only be considered if analogous data have not been previously published in a peer reviewed journal and the conclusions provide distinct insights that are of relevance to a regional or international audience.

Data sharing

BMC Public Health strongly supports open research, including transparency and openness in reporting. Further details of our Data availability policy can be found on the journal's About page.

Professionally produced Visual Abstracts

BMC Public Health will consider visual abstracts. As an author submitting to the journal, you may wish to make use of services provided at Springer Nature for high quality and affordable visual abstracts where you are entitled to a 20% discount. Click here to find out more about the service, and your discount will be automatically be applied when using this link.

Preparing your manuscript

The information below details the section headings that you should include in your

manuscript and what information should be within each section.

Please note that your manuscript must include a 'Declarations' section including all of the subheadings (please see below for more information).

Title page

The title page should:

- present a title that includes, if appropriate, the study design e.g.:
  - "A versus B in the treatment of C: a randomized controlled trial", "X is a risk factor for Y: a case control study", "What is the impact of factor X on subject Y: A systematic review"
  - or for non-clinical or non-research studies a description of what the article reports
- list the full names and institutional addresses for all authors
  - if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the “Acknowledgements” section in accordance with the instructions below
  - Large Language Models (LLMs), such as ChatGPT, do not currently satisfy our authorship criteria. Notably an attribution of authorship carries with it accountability for the work, which cannot be effectively applied to LLMs. Use of an LLM should be properly documented in the Methods section (and if a Methods section is not available, in a suitable alternative part) of the manuscript.
- indicate the corresponding author

Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. Reports of randomized controlled trials should follow the CONSORT extension for abstracts. The abstract must include the following separate sections:

- **Background:** the context and purpose of the study
- **Methods:** how the study was performed and statistical tests used
- **Results:** the main findings
- **Conclusions:** brief summary and potential implications
- **Trial registration:** If your article reports the results of a health care intervention on human participants, it must be registered in an appropriate registry and the registration number and date of registration should be stated in this section. If it was not registered prospectively (before enrollment of the first participant), you should include the words 'retrospectively registered'. See our editorial policies for more information on trial registration

Keywords

Three to ten keywords representing the main content of the article.

Background

The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

Methods

The methods section should include:

- the aim, design and setting of the study
- the characteristics of participants or description of materials
- a clear description of all processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses
- the type of statistical analysis used, including a power calculation if appropriate

Results

This should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

Discussion

This section should discuss the implications of the findings in context of existing research and highlight limitations of the study.

Conclusions

This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

List of abbreviations

If abbreviations are used in the text they should be defined in the text at first use, and a list of abbreviations should be provided.

Declarations

All manuscripts must contain the following sections under the heading 'Declarations':

- Ethics approval and consent to participate
- Consent for publication
- Availability of data and materials
- Competing interests
- Funding
- Authors' contributions
- Acknowledgements
- Authors' information (optional)

Please see below for details on the information to be included in these sections.

If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.