AFRICA UNIVERSITY

(A United Methodist Related Institution)

CHARACTERIZING COVID 19 BREAKTHROUGH INFECTIONS IN MANICALAND PROVINCE, ZIMBABWE

BY

KUDZAI MUREMBWE

A DISSERTATION PROPOSAL SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF PUBLIC HEALTH IN THE FACULTY OF HEALTH SCIENCES

2022

Abstract

COVID-19 has caused significant morbidity and mortality as-well as marked deterioration in economies, social relationships and educational systems. All these reasons have fueled the urgent need to develop safe and effective vaccines. Over 7 billion doses of COVID -19 vaccines have been administered globally, however, COVID-19 infections have been reported in fully vaccinated individuals. 16% of cases reported in Manicaland between 6 April and 31 December 2021 were in vaccinated individuals as such this study's aim was to determine the factors associated with Covid-19 breakthrough infections in Manicaland. A mixed methods approach utilizing both qualitative and quantitative methods was used. Secondary data analysis was done through an unmatched 1:1 case control study. A total of 4 838 study participants (2 420 cases and 2 418 controls) were included in the study. Controls were randomly selected from the Covid-19 vaccine registry while cases where sampled from the Covid-19 line list using the census method. Case were defined as a symptomatic or asymptomatic individual residing in Manicaland aged 18 years and older who received 2 doses of either Sinopharm or Sinovac and tested positive for Covid-19.The results showed that Covid-19 breakthrough infection in Manicaland were more common in males (53.1%) and affected individuals had a median age of 39 years. There was no significant association between breakthrough infections and gender ($p = 0.326$) as-well as having a comorbidity ($p=0.473$). There were five common symptoms amongst cases, however cough was the most common and present in 33.7%. Vaccine type was significantly associated with having a breakthrough infection (OR= 0.7, 95%CI: 0.6 – 0.8, $p <0.001$). Sinovac recipients were 30% less likely to get a breakthrough infection. History of contact was also significantly associated with breakthrough infections (OR= 7.6, 95%CI: 4.8 – 12.0, $p< 0.001$). Reviews of the line list revealed over 60 variables on the list with age and gender being some of the variable with a high degree of completeness. However, 76.8% of cases had missing data on comorbidities and 64.1% had no disease outcomes. There is need to encourage people to continue observing Covid-19 prevention strategies even if they are fully vaccinated. There is an urgent need to review the current Covid line list, standardise formats and terms as-well as training the users.

Key words: Breakthrough infection, Covid line list, Covid vaccine registry

Declaration Page

I declare that this dissertation proposal is my original work except where sources have been cited and acknowledged. The work has never been submitted, nor will it ever be submitted to another university for the award of a degree

Kudzai Murembwe

Student's Full Name Student's Signature (Date)

Dr Eltony Mugomeri _____ _____

Main Supervisor's Full Name Main supervisor's Signature

(Date

Copyright

Acknowledgements

I would like to acknowledge the unwavering support and technical guidance I received from my lecturer and my field supervisor, in writing this proposal. I also want to acknowledge the continued support from Edlane, Cashington, my husband, mother, siblings, friends and colleagues.

Dedication

I dedicate this dissertation to my mother, Miriam Mlambo, for being a great inspiration in my life and praying for me always

List of Acronyms and Abbreviations

Ag-RDT	Antigen-detecting rapid diagnostic testing
AIDS	Acquired Immunodeficiency Syndrome
AUREC	Africa University Research Ethics Committee
COVID 19	Corona virus disease of 2019
EPI	Expanded Programme on Immunization
HCW	Health Care worker
HIV	Human Immunodeficiency Virus
MoHCC	Ministry of Health and Child Care
RT-PCR	Reverse-Transcriptase-Polymerase-Chain-Reaction
SARI	Severe Acute Respiratory Infections
SARS- CoV-2	Severe acute respiratory syndrome coronavirus 2
WHO	World Health Organisation

Definition of terms

- Breakthrough infection is infection in a fully vaccinated individual (CDC, 2021)
- Case fatality rate describes the proportion of people who die from a specified disease among all individuals diagnosed with that same disease over a certain period of time (Harrington, 2020)
- Morbidity refers to the consequences and complications (other than death) that result from a disease(Morgan & Summer, 2008).
- Vaccine is a preparation that is used to stimulate the body's immune response against diseases (CDC, 2019)
- Vaccine efficacy is the proportional reduction of infection in a vaccinated group compared with an unvaccinated group under optimal conditions such as a randomized controlled trial(Crowcroft & Klein, 2018)
- Vaccine effectiveness (VE) is the proportional reduction of infection in a real-world immunization program delivered with normal storage and administration processes to an unselected population(Crowcroft & Klein, 2018)
- Vaccine failure is the occurrence of infection or disease in an individual who is fully vaccinated (Crowcroft & Klein, 2018)
- Reverse-transcriptase-polymerase-chain-reaction (RT-PCR) is a sensitive technique for the quantification of steady-state mRNA levels which is used for analysis of low level transcripts(Doak & Zair, 2012).

Table of Contents

List of tables

List of figures

List of Appendices

CHAPTER 1 INTRODUCTION

1.1 Introduction

In March 2020, WHO declared Covid 19 as a pandemic following the alarming spread and severity of the disease outbreak and since that time nations have been in and out of lockdowns in a bid to try and control the pandemic. Lockdowns unfortunately can only buy time and they are associated with economic, social and educational disruptions which have far reaching consequences. The morbidity and mortality associated with Covid 19 has drove the global community to urgently develop safe and effective vaccines in a bid to control the pandemic.

Vaccines on many occasions have helped in the control of infectious diseases around the world and the same is true for Covid 19. The slight difference is the speed with which the Covid 19 vaccines have been developed and approved for use which is faster than usual. More than seven vaccines have been approved for emergency use by WHO with over seven billion doses having been administered globally. Many other vaccines not yet approved by WHO are already in use in some nations that have approved their emergency use. This fast implementation is a race to achieve herd immunity within the population, before the next wave of the pandemic hits the world.

All the vaccines go through the normal process of clinical trials, however the phase three trials that have been conducted will not give all the answers pertaining to vaccine performance since they are done under ideal conditions with healthy individuals. For this reason studies on vaccine performance and effectiveness should continue while the vaccines are in use. The duration of protection of Covid

19 vaccines is still a grey areas and the same goes for risk factors for breakthrough infections and effectiveness against the new variants that keep coming up.

Zimbabwe like many other countries around the globe, rolled out its Covid 19 vaccination programme, but Covid 19 infections have continued to pop-up in the vaccinated population time and again. Unfortunately, Zimbabwe was hit by the third wave of the Covid 19 pandemic, a few months after its roll out of the Covid 19 vaccination program when vaccine coverage was still very low. While breakthrough infections are expected with any vaccine, it is important to quantify these infections so as to determine if they are within the acceptable margins, and also to identify modifiable risk factors for breakthrough infections. The correct quantification of breakthrough infections is closely related to the ability to separate true breakthrough infections and normal infections.

The study primarily set out to determine factors associated with breakthrough infections in Manicaland province for the period 6 April 2021 to 31 December 2021. The study also sought to review the existing reporting tools for vaccine breakthrough infections that make it impossible or difficult to pick true breakthrough infections. This study focused on Manicaland Province which was the 4th highest contributor to both national Covid-19 cases and deaths. The study was a secondary data analysis following case-control study methodology. This study sets the preliminary ground for Covid 19 vaccine effectiveness studies in Zimbabwe and it can be used to modify the Covid 19 vaccination program in Zimbabwe. Moreover, gap analysis will help improve the current reporting tools so that we collect useful data that can be used in Covid 19 programming

1.2 Background to the Study

Covid 19 is an infectious respiratory disease that is caused by SARS–CoV-2 virus. In 80% of people the disease is mild to moderate((WHO), 2021). As of end of October 2021, over 239 million cases had been recorded globally and of these, 2% succumbed to the disease(Medicine, 2021). While the global case fatality ratio for the disease is low compared to other pandemics in the past, Covid 19 is associated with significant morbidity and it comes with long periods of isolation and quarantine. Moreover, the disease is associated with massive economic, social and educational disruptions that has affected even the most economically strong nations.

Currently there is no definitive treatment for Covid 19, but several countries have been working on producing Covid 19 vaccines to try and reduce the morbidity and mortality that accompanies the disease. Vaccines are medical preparations that are designed to stimulate an individual's body to mount an immune response in the same way that the body would respond if infected by an infectious organism(CDC, 2019). Vaccines come in different formulations and with different mechanisms of action, but the ultimate goal is to provoke an immune response in the body. As of October 2021, seven Covid 19 vaccines had received WHO approval though many other vaccines are already is use in various countries with over 7 billion doses having been administered globally.

Zimbabwe has not been spared in the devastating effects of the Covid 19 pandemic, with the country having recorded 132 977 confirmed cases and 4 678 deaths by end of October 2021(MoHCC, 2021b). The total number of cases make up 0.8% of the Zimbabwean population with the bulk of them having occurred in the third wave of the pandemic which hit the country in June 2021 and flattened in August 2021. The highest number of new cases were recorded on the 8th of July and they were 4 213

and on July 16th the country recorded 86 Covid deaths and to date this is the highest number of documented deaths in a single day(WHO, 2021f). At the end of October, the case fatality rate (CFR) for Zimbabwe stood at 3.5%, which is significantly higher than the global CFR at 2%. The country has seen several lockdowns since 2020 when the pandemic started and this has affected a lot of businesses and the common man's livelihoods.

In February of 2021, Zimbabwe through Medicines Control Authority of Zimbabwe approved the use of five vaccines namely: Sinopharm (BIBP-CorV-(Verocells), Sinovac (CoronaVac), Bharat Biotech BBV152 Covaxin, Janssen (Johnson and Johnson – Ad26.COV2.S) and Gamaleya (SputnikV). The inactivated whole virus vaccine BIBP from Sinopharm when given in two doses 21 days apart was reported to have an efficacy of 79% (95% CI:66-87%) against symptomatic SARS-CoV-2 infection as-well as hospitalisation(WHO, 2021d). A similar vaccine but from a different company, CoronaVac from Sinovac has an effectiveness ranging between 51% to 83.5% against symptomatic SARS-CoV-2 infection and 100% efficacy against severe disease and hospitalisation(WHO, 2021e)

BBV152 (Covaxin) from Bharat Biotech is another type of inactivated vaccine that is given in 2 doses, 4 weeks apart. The phase III trial was conducted in an environment where the delta variant was the most prevalent and an efficacy of 78% (95% CI: 65-86) was reported against Covid-19 of any severity. The Janssen Ad26.COV2.S is a recombinant, replication-incompetent adenovirus type of vaccine given as a single dose that is reported to have an efficacy of 66.9% (95%CI: 59.0 – 73.4) against symptomatic SARS-CoV-2 infection at 14 days(WHO, 2021c). The efficacy against severe disease and hospitalisations increases between day 14 and day 28 from date of vaccination.

There are many other vaccines in use other than the five approved for use by Zimbabwe, but one of the reasons that contributed in choosing these for use are the temperatures required for storage of the vaccines. Sinopharm, Sinovac, Covaxin are stored between 2 - 8℃(&Medical, 2021) and these can be stored in the existing EPI refrigerators that are available throughout the country. Moderna requires temperatures as low as -10℃ to -25℃ while Pfizer requires even lower temperatures of -40℃ to -86℃(&Medical, 2021). Zimbabwe at time of rollout had no capacity to store Pfizer and Moderna hence the choice of the three vaccines that could be stored in existing infrastructure.

On the 22nd of February, the country rolled out its vaccination program in a three phased approach. The first phase was in two stages with stage 1 being for high risk population particularly frontline workers like health workers, security services, immigration, and hospitality(MoHCC, 2021a). Stage II targeted the elderly population, chronic illness patients and people living in confined settlements. Phase II focused on lectures, teachers, eligible students and any other medium risk personnel while phase III targeted the low risk population(MoHCC, 2021a). Towards the end of October 2021, Zimbabwe approved the use of Sinovac in the 16-17 years age group.

The ultimate target of the Covid 19 vaccination program is to vaccinate 60% of the Zimbabwean population amounting to a total of 9 763 988. At the end of December 2021, 10 months after the roll out of the vaccine, Zimbabwe had administered 44.2% of the targeted first doses while 34.1% of target population had been fully vaccinated. As at 31 December 2021, Manicaland target population was 1 147 647 with dose 1 and dose 2 coverage being 51.9% and 40.8% respectively.

During the 10 months that the vaccination program has been running the country experienced a massive surge in the number of Covid 19 cases and some occurred in fully vaccinated individuals and these are known as breakthrough infections. A breakthrough infection is detection of SARS-CoV-2 infection in an individual who is fully vaccinated more than 14 days after completion of the recommended doses of a vaccine(CDCMMWR, 2021).

1.3 Statement of the Problem

Since the roll out of the vaccination programme in February 2021, Manicaland has recorded cases of confirmed Covid 19 in vaccinated individuals. Between 6 April and 31 December of 2021 Manicaland recorded 21 846 cases of which 16 % (3 497) occurred in fully vaccinated individuals. No vaccine is 100% effective, such that most vaccines are associated with a failure rate between 2-10%, with Hepatitis B vaccines having the highest rate of breakthrough infections. While breakthrough infections are expected with any vaccine, the expected failure rate for Covid 19 vaccines in Manicaland is not known. Moreover, the host factors, vaccine related factors and exposure factors associated with SARS-CoV-2 breakthrough infections are unknown yet some maybe modifiable.

1.4 Research Objectives

1.4.1 Broad Objective

- To determine the factors associated with Covid-19 breakthrough infections in fully vaccinated individuals in Manicaland for the period 6 April to 31 December 2021

1.4.2 Specific objectives

- To determine the host, vaccine-related factors and exposure factors associated with Covid 19 breakthrough infections in Manicaland
- To clinically characterize Covid-19 breakthrough infections among fully vaccinated individuals in Manicaland
- To review the usefulness and data quality issues in the Covid line list tool from which breakthrough infections were extracted.

1.5 Research Questions

- What are the host, vaccine- related and exposure- related factors associated with Covid 19 breakthrough infections in Manicaland?
- What are the clinical characteristics of Covid-19 breakthrough infections among fully vaccinated individuals in Manicaland?
- What are the gaps and data quality challenges in the Covid-19 line list?

1.5 Justification of the Study

No vaccine is 100% effective, but the many success stories of vaccines have been achieved through continuous improvement of the various aspects of vaccine use. The Covid 19 vaccines are very new and unlike many others they have been produced over a short period to address a crisis that has captured the world over. While there have been many effectiveness studies on these new vaccines, very few have been done in the African context, more so in the Zimbabwean context. In-order to continue improving the effectiveness of the vaccines, there is need to know factors associated with Covid 19 breakthrough infections in the affected population and this study is designed to identify some of these factors particularly in the Zimbabwean context.

1.6 Delimitation of the Study

The study was limited to individuals that were vaccinated with the two most commonly used vaccines namely, Sinopharm and Sinovac as the other three recommended for use have not been administered at a large scale.

1.7 Limitation of the Study

There were certain limitations to this study, the first one being that Covid 19 breakthrough infections that were captured were only those that presented for testing within Manicaland hence, there is a possibility of underestimation of breakthrough infections. Vaccinated individuals that never got tested but were infected by Covid-19 were not identified and those that received testing services outside Manicaland were also not captured. The study utilised existing data hence individuals who tested positive for SARS-CoV-2 but whose vaccination status was not captured were regarded as unvaccinated, yet they may have been breakthrough cases.

Thirdly, there was no SARS-CoV-2 antibody testing for participants due to lack of resources hence breakthrough infections due to waning could not be ruled out, since it is not known how long the immunity conferred by any of the two vaccines included in the study lasts. Lastly, the time between doses and the time between second dose and SARS-CoV-2 infection was not considered since the information was not available in the Covid line list. For this reason there is a chance that breakthrough infections were overestimated because infections that occurred less than 14 days from second dose were also counted as breakthrough infections.

1.8 Summary

This chapter introduces the study on breakthrough infections following vaccination and gives the background of the study. The problem statement is clearly outlined

together with the research objectives and questions. The reasons why this study is important are outlined as-well as the scope of the study and the areas of possible weakness.

CHAPTER 2 REVIEW OF RELATED LITERATURE

2.1 Introduction

This chapter reviews literature on Covid 19 breakthrough infections and related subjects to identify study designs that have been utilised in previous studies and also pick up the gaps in knowledge concerning risk factors and associations.

2.2 Theoretical Framework

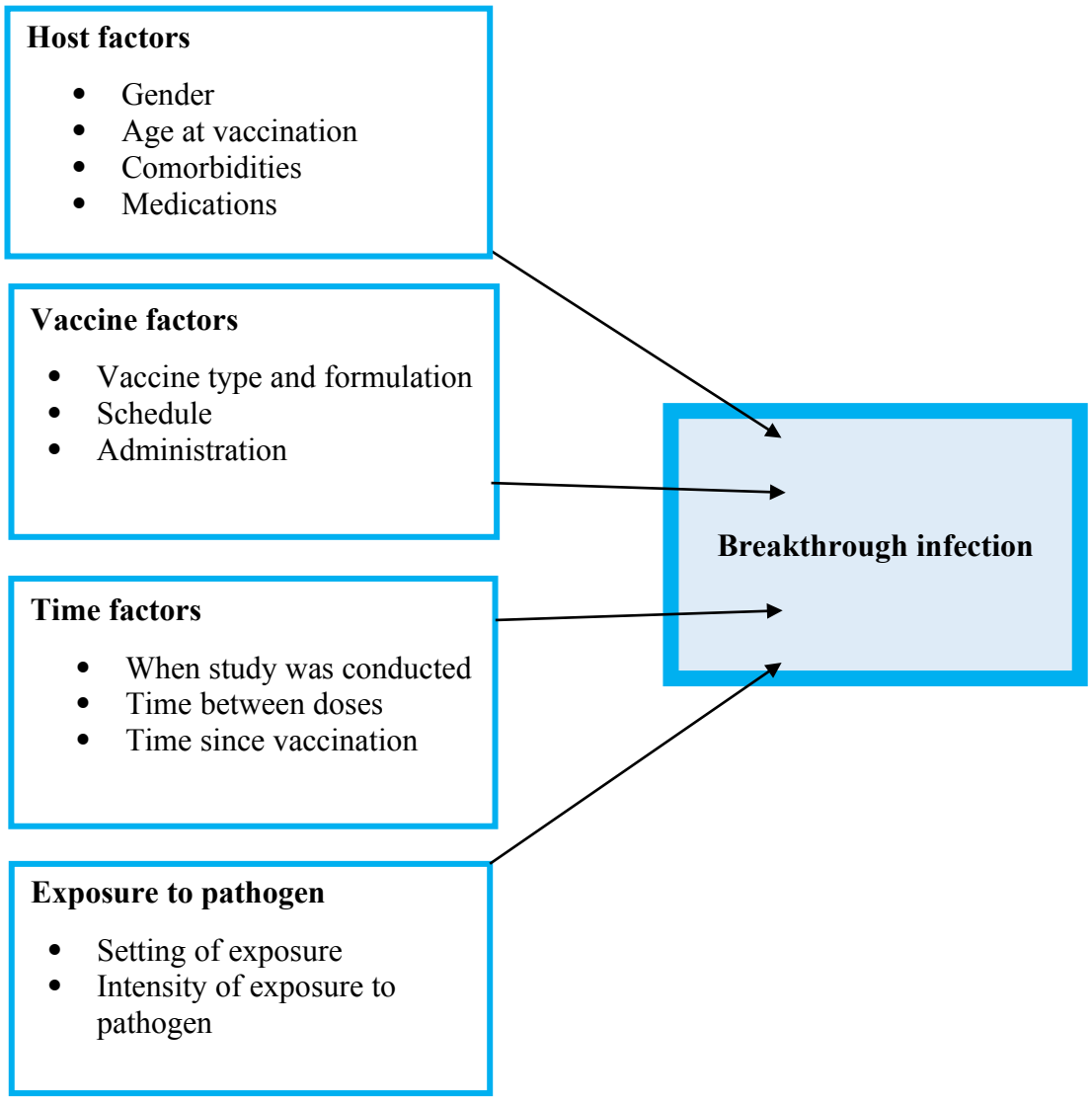

Figure 1: Theoretical framework

2.3 Relevance of the Theoretical Frame to the Study

Breakthrough infections indicate that the administered vaccine has failed to work for one reson or another. Crowcroft & Klein (2018) describe five models of vaccine failure namely, primary failure, secondary failure, exposure threshold, leaky vaccine and multimodal. The theoretical framework above focuses on primary failure and exposure threshold. The depiction in the frame is that there are host-related factors that could be associated with vaccine failure, like gender, age, comorbidities and medications taken by the host. The type of vaccine, route and schedule of administration are also potential vaccine factors that are associated with vaccine failure. The level of exposure to an infectious disease and the proximity and duration of that exposure are also potential factors associated with vaccine failure. Secondary failure is not included since Covid 19 vaccines are new hence the cases of secondary failure are difficult to identify in a setting where there is no routine checking of antibody levels in vaccinated individuals.

2.4 Vaccine failure

Crowcroft & Klein, (2018) define vaccine failure as the occurrence of infection or disease in an individual who is fully vaccinated and it can either be primary or secondary. Breakthrough infection in a fully vaccinated person who failed to mount an immune response to the vaccine is known as primary vaccine failure while in secondary vaccine failure disease occurrence is in a fully vaccinated individual who mounted a normal immune response to the vaccine but whose immunity has subsequently decreased(Crowcroft & Klein, 2018). A high vaccine effectiveness implies a low vaccine failure rate hence less breakthrough infections are expected. With the introduction of the new Covid 19 vaccines, many nations and organisations

are interested in carrying out research on vaccine effectiveness and WHO has issued several reports to guide these studies.

Vaccine failure is observed in approximately 2-10% of vaccinated persons for any vaccine, with hepatitis B vaccine being the most investigated as it has the highest number of non-responders in all known vaccines(Wiedermann et al., 2016). While this failure is expected even for Covid 19 vaccines, the risk factors, mechanisms, immunological background and clinical consequences are understudied. A few studies have been done to explore the immunological background in Covid 19 breakthrough infections such as the study by Berwerk, et al., (2021) in which testing of neutralising antibodies and ant-SIgG antibodies was perfomed for every vaccinated healthworker on the day they tested positive for Covid. This however is possible in resourceful settings with capacuty to conduct serelogic tests and determine immune response to a vaccine. In these setting distinction between primary and secondary failure is also possible as it can be proved that an individual had mounted a reaction in the first place which has since waned.

2. 5 Vaccine and host related factors

Covid 19 vaccines are new and unlike, vaccines made in the past, the time period between development and use in real life settings was very short such that many questions still exist on their performance. Phase III trials usually involve healthy participants, as such, use in real life settings that are far from ideal and can yield different outcomes. Most vaccine related factors to vaccine failure are modifiable as these usually centre on scheduling, timing, dosing and cold chain maintenance(Wiedermann et al., 2016), but the type of vaccine and its formulation can also be factors that contribute to breakthrough infections The potential host related factors of breakthrough infections are vast and include age, sex, gender,

genetic factors, comorbidities, obesity, health status, co-administered medicines and level of exposure.

The two vaccines mostly used in Zimbabwe have been approved for use by WHO and they have undergone phase III trials Sinopharm (BIBP) phase III trial was not designed to demonstrate efficacy against severe disease hence this is not known. Moreover, the trial did not include pregnant women, persons with comorbidities and persons aged above 60 years(WHO, 2021d). (Wiedermann et al., 2016)In the Sinovac trials, the 60 years and above age group was poorly represented as such effectiveness in this group is also not known for Sinovac. The ideal age for Covid 19 vaccination for the best outcome is not known as it has been administered to all ages above 18 in the case of Zimbabwe.

There are comorbidities that are associated with severe disease or death in Covid 19 patients. While trials can try and include some of the more common co-morbidities there are some that will be left out for one reason or another. In the Covaxin phase III trial, the comorbidities included were cardiovascular diseases, respiratory diseases, diabetes, liver disease and obesity(WHO, 2020) while the Sinovac trial only focused on hypertension and obesity(WHO, 2021e). In a study on breakthrough infections in patients with systemic autoimmune rheumatic diseases, Cook, et al., (2021), propose that the medications taken by patients have potential to blunt the immune response thereby compromising vaccine efficacy which may lead to breakthrough infections.

Zimbabwe being a low income economy is heavily burdened with communicable diseases, but the burden of non-communicable disease is also high in the communities, hence it is important to know the performance of the vaccine in the affected populations. On communicable diseases, both vaccines namely Sinopharm

and Sinovac had their trials done in settings with low HIV prevalence as such there are gaps in knowledge on the performance of the vaccines in settings with high HIV burden. Zimbabwe has an HIV prevalence of 12.9%(ZIMPHIA, 2020) and people living with HIV and AIDS benefited in the second phase of the Zimbabwe Covid 19 rollout program and it is important to assess vaccine performance in this population.

2.6 Time related factors

Vaccines have recommended schedules in which they should be administered and these are based on studies that will have been done prior to use of the vaccines in the real world(Crowcroft & Klein, 2018). Clinical trials are conducted under ideal conditions with healthy individuals such that the recommended schedules may vary when the vaccines are used in the real world where there are many confounders. Vaccine effectiveness is also known to wane over time, such that the time between last dose of vaccine and infection is of importance when studying breakthrough infections (Belongia et al., 2015). During outbreaks or surges in infections, the exposure to the virus is markedly high, thus risk of infection is very high even for vaccinated individuals compared to when there are very few cases occurring in the community (Crowcroft & Klein, 2018). Manicaland experienced two Covid 19 waves between February and December 2021

The study period for this particular study includes, the third and fourth wave of the pandemic, where there were a significant number of new infections and Covid-related deaths. It is unfortunate that for this study, the available data does not indicate time of vaccination, time between doses and time between last dose and SARS-CoV-2 infection, hence the relationship between these time frames and breakthrough infections cannot be analysed.

2.7 Exposure to SARS-CoV-2 infection.

The whole point of providing Covid 19 vaccines is to try and cut the chain of transmission and also reduce disease severity in those who get breakthrough infections. The impact of these vaccines will be noted in the change in epidemiology of the disease but the world is continuously being exposed to new Covid 19 variants time and again, which masks this epidemiological shift. In an outbreak investigation of breakthrough infections in fully vaccinated gold miners in French Guiana, the gamma variant of SARS-CoV-2 was found to be the causative strain in these vaccinated miners (Vignier et al., 2021). Zimbabwe experienced a massive rise in Covid 19 cases worse than the first two waves and this also included some vaccinated individuals. However, to attribute this to new variants would be difficult as resources are not available to determine the variant affecting each individual.

Crowcroft & Klein, (2018), also describe a mechanism of failure known as exposure threshold in which if pathogen exposure is high enough, the vaccine will fail despite antibodies being above the protective level like is seen with tetanus vaccines. Brown, et al., (2021) investigated an outbreak in Barnstable County, Massachussets were the vaccination coverage was 69% and the bulk of cases were vaccinated individuals. Key features of this outbreak were large public gatherings were the exposure was high and there was high transmission. The introduction of Covid 19 vaccines in Zimbabwe, was immediately followed by a massive rise in SARS-CoV-2 transmission within the community and this could have been a potential mechanism leading to breakthrough infections.

2.8 Vaccine effectiveness evaluation

WHO through its report on Estimating Covid 19 vaccine effectiveness recommends 5 types of observational study designs namely cohort studies, case-control, test

negative design case-control studies, screening method and regression discontinuity. (WHO, 2021a). Torvaldsen & Mclntyre (2002), point out that there are many potential bises in these observational studies and these should be put into consideration in the study design and analysis stage.

Case-control studies are also a popular design in studies that evaluate vaccine effectiveness, however the recommendation is that cases and controls be enrolled at the same time , with cases being the vaccinated persons who still get infected by SARS-CoV-2 while controls are vaccinated but are not infected. The design is efficient in terms of cost and time but choosing an unbiased control group maybe challenging. Berwerk, et al., (2021), in the study in Israel among health care workers also conducted a matched case-control analaysis to identify possible correlates of breakthrough infection. In this study identification of controls will be done using the Covid 19 vaccine registry.

Cohort studies allow for estimation of risk reduction of disease among vaccinated persons and vaccine effectiveness, however they require a large sample size and maybe costly in follow-ups(Torvaldsen & Mclntyre, 2002). This study design if done retrospectively can only work in a setting with good vaccination records, such as detailed vaccination databases. Most studies that utilise this design have been done in populations were active follow up can be done, for example in healthcare workers like in the study by Berwerk, et al., (2021) done in Israel. Another cohort study was done in a prison where staff members and prisoners routinely got tested following their vaccination(Brinkley-Rubinstein et al., 2021).

Breakthrough infection occur in 2-10% of the population thus can be classified as an uncommon event that will result in a small study population relative to the number of

people that will be vaccinated. Berwerk, et al., (2021) in their study on breakthrogh infections all the 39 positive cases that occurred in the vaccinated population were included in the study. In an almost similar study by Cook, et al., (2021), the 16 systemic autoimmune rheumatic disease patients that had breakthrough infection were included in the study. These two studies utilised the census method of sampling were the researcher utilises an entire population with a characteristic of interest in the study.

In vaccine effectiveness studies there is standard information that should be collected from participants which will aid in identifying factors that are associated with breakthrough infections. Antonelli, et al. (2021), in their study for risk factors and disease profile post Covid 19 vaccination utilised a COVID Symptom study mobile phone application. Application users self reported data which included: demographics, geographical location, cymptoms, Covid 19 test reults, health risk factors and vaccination details.

WHO (2021) in its guiding document on Estimating Covid-19 vaccine effectiveness against (SARI), the following elements are critical: patient's age, gender, area of residents, signs and symptoms, date of symptom onset, vaccination status, dates of each of the doses, type of vaccine, comorbidities, chronic medications, smoking history, occupation, exposure level, type of Covid test conducted and outcome of disease episode. It follows that any data collecting tool that is going to be used in the study of breakthrough infections should have these parameters at the minimum. The Covid line list is currently the only source document for individuals that have contracted Covid and it has seen many modifications since the pandemic started, but weather it collects adequate information to analyse breakthrough infections is not known.

2.8 Symptom profiles in breakthrough infection cases

Studies suggest that covid 19 vaccines are associated with a decrease in the severity of symptoms and in most cases individuals are asymptomatic(Antonelli et al., 2021). However, most of these studies have been on mRNA vaccines with very few conducted in the inactivated vaccines like Sinopharm and Sinovac. In the study by Godwell et al., (2022) in unvaccinated individuals the most common symptoms were headache, anosmia, dry cough, sore throat and fever. However, though it is a Zimbabwean study, the group of particpants may not be representative as it was largely made up of teenagers.

2.9 Covid 19 line list data quality and usefulness

Between 2020 and 2021 major public health decions with far reaching impacts were made based on Covid-19 surveillance data. Decisions to impose and lift lockdowns were informed by the number of Covid-19 cases at that particular time and these were collated from the different line lists submitted by districts and provinces, in the case of Zimbabwe. Trends analysis and clinical characterisation was done based on information from these line lists.

A line list is an epidemiological database used in outbreaks to organise and analyse information about time, place and person (CDC, 2020). In the face of the pandemic line lists have been used globally but the Covid-19 pandemic exposed data quality frailties that exist globally (Costa-Santos et al., 2021). In Portugal, Costa-Santos et al. (2021), carried out a study in which some of the main outcomes were frequency of cases with missing information and frequency of cases with impossible values for each of the variable on the Portuguese surveillance database. In this study they went further to compare data sets for two months and pick inconsistences on certain indivudals (Costa-Santos et al., 2021)

2.8 Summary

This chapter outlines the theoretical framework for vaccine failure, identifies gaps in the existing literature and details literature findings on factors that may be associated with Covid 19 breakthrough infections as-well as the study designs that have been utilised in carrying out studies on breakthrough infections.

CHAPTER 3 METHODOLOGY

3.1 Introduction

This chapter describes the study setting, study population, study period together with the sample size and the sampling techniques that was used. The data collection tools that were utilised and the methods of data analysis that were employed are also detailed in this chapter. Ethical considerations will also be stated.

3.2 The Research Design

The study employed a mixed method approach where secondary data analysis was done using quantitative methods and the Covid line list review used qualitative methods. The secondary data analysis was an unmatched 1:1 case control study that utilised the Manicaland Covid line list. Case control is one of the designs recommended by WHO because it is inexpensive, efficient and requires a small sample size(WHO, 2021a).

Munnangi & Boktor (2022) described that, case-control studies are used to determine the degree of associations between multiple risk factors and outcomes as such it was the ideal design for the study. The qualitative enquiry was based on key informant interviews and expert opinion of the researcher.

3.3. Study site

The primary data was collected from Manicaland one of the ten provinces of Zimbabwe, located on the eastern part of the country. The province is the second-most populous in Zimbabwe, with an estimated population of 1 912 745 based on the 2017 Inter-censual demographic survey (Zimstat, 2017) of which 1 147 647 people were eligible for vaccination as at 31 December 2021. Manicaland is the third-most densely populated province as it covers 36 479km² and it has seven

administrative districts illustrated in Figure 2 below. Popular economic activities are agriculture (tea, coffee, fruits, and timber), mining (diamond and gold), manufacturing and tourism. In most of its districts it boarders Mozambique as such there is a lot of traffic in some of its districts like Mutare.

Manicaland rolled out its vaccination program on the 22nd of February and this was just after the second wave of the Covid-19 pandemic. At the time of the roll out, Manicaland had 3 678 confirmed Covid 19 cases, a recovery rate of 79.8% and a case fatality rate of 5.1% (MoHCC, 2021).

Figure 2: Map of Manicaland

3.4 Study population

The study targeted individuals residing in Manicaland who were aged 18 years and older and had received 2 doses of either Sinopharm or Sinovac. The study also utilised key informants that use the Manicaland line list namely Mutare city health information officer, District Environmental health Officer, Provincial health information officer, Provincial epidemiology and disease control officer and

3.4.1 Case definition

In this study a case was defined as a symptomatic or asymptomatic individual residing in Manicaland aged 18 years and older who received 2 doses of either Sinopharm or Sinovac and tested positive for Covid-19 on RT-PCR or Ag-RDT.

3.4.2 Control definition

A control was defined as an individual residing in Manicaland aged 18 year and older who received 2 doses of either Sinopharm or Sinovac and had never tested positive for Covid-19.

3.4.3 Inclusion criteria

- Individual residing in Manicaland during the year 2021
- Individual aged 18 years and older
- Individual vaccinated with 2 doses of either Sinopharm or Sinovac

3.4.4 Exclusion criteria

- Individuals that received 2 doses of any other vaccine that is not Sinopharm or Sinovac
- Fully vaccinated individuals that tested positive before the 6th of April 2021

3.5 Study period

This secondary data analysis focused on the period 6 April 2021 to 31 December 2021. The 6th of April coincides with the 15th day from the day of the 2nd dose for an individual who was vaccinated on the first day of the roll out. This helps eliminate obvious non-breakthrough infections.

3.6 Sample size and sampling techniques

All Covid-19 infections in vaccinated individuals in Manicaland were identified from the Covid line list, thus the Census method of sampling was utilised. The minimum required sample size was determined using the formula recommended by (WHO, 2021b)

$N = (z/d)^2 [1/A (1–A) + 1/CP_2 (1–P_2)]$, where N is the minimum number of participants required for the study, C is the control to case ratio (e.g. C = 1 denoting 1 controls for every case); P2 denotes vaccine coverage in the population being studied and in this study the coverage used will be 30%; $A = P_2 (1- VE)/[1-P_2 (VE)]$ where VE denotes the anticipated vaccine effectiveness which will be 50% in this study; z denotes the (1-α) percentage point of the standardized normal distribution at $\alpha = 0.05$ and thus $z = 1.96$ and d is determined by solving the equation $W(\hat{\beta},\hat{d}) = \exp(\hat{\beta})(\exp(\hat{d})-(\exp(-\hat{d}))$ where $\hat{d}=z\hat{\sigma}$ where $W(\hat{\beta},d)$ denotes the CI width, The number of controls needed are then calculate as C*N1.

For this study the minimum number of cases required was 1 133 and using the formula C*N1 for a 1: 1 case control study the minimum number of controls required was 1133. Controls were selected from the Covid 19 vaccine registry and systemic random sampling was done on a list of individuals aged 18 years and older who that

had received two doses of either sinopharm or Sinovac and had never tested positive for Covid prior to the 31st of December.

3.7 Data Collection Instruments

The secondary data analysis utilised pre-existing data in the form of the Manicaland Covid line list and the Covid 19 vaccine registry. The Covid line list records all reported confirmed Covid-19 cases and variables include the patient's demographics, occupation, comorbidities, symptoms, vaccination information, Covid 19 exposure, Covid-19 testing details, isolation details and the final disease outcome. The Covid line list exists in a Microsoft Excel format. The Covid-19 vaccine registry is available on DHIS2 and it captures client demographics, occupation, comorbidities, medications, vaccination information, history of Covid 19 infection and exposure. The extracted variables used for the secondary analysis were informed by a questionnaire from WHO, Estimating COVID-19 vaccine effectiveness against severe acute respiratory infections (SARI) hospitalisations associated with laboratory-confirmed SARS-CoV-2: An evaluation using the test-negative design: guidance document, (2021).

A semi structured interviewer administered questionnaire was used to collect information on the usefulness and quality of data that was collected on the Covid-19 line list. The Manicaland Covid-line list was also analysed for completeness and consistency by the researcher.

3.8 Data extraction procedure

Authority was sought from MoHCC to utilise the Zimbabwe national Covid line list and the Covid-19 vaccine registry for the purposes of research. The variables extracted from the line list for the purposes of the study were: unique patient

identifier, age, gender, district, province, symptoms, comorbidities, and profession, history of Covid 19 exposure or contact, vaccination status, number of doses, type of vaccine, disease severity and disease outcome. To reduce errors and loss of data, filters were used to identify all patients listed as vaccinated who appeared on the line list. From this selection, all patients aged 18 years and older and had received 2 doses of either Sinopharm or Sinovac were filtered and these became potential study participants under the cases group.

In the review of the line lists, variables of interest in the study were analysed with the main outcomes of interest being the number of cases with missing information and the number of cases with invalid entries in the following variables: reporting date, age, gender, province, comorbidities, date of results, history of exposure to a case, occupation sector, vaccination status, number of doses, vaccine type and outcome. This analysis was done at four levels that is among all the Covid positive cases in Manicaland, secondly among those that had reported that they had received a vaccine regardless of the number of doses, thirdly among those that were fully vaccinated with any type of vaccine and lastly among the study participants who met the case definition.

3.9 Pretesting tools

Pretesting of data extraction tool and data extraction procedures and data collection procedure was done using the Mutare City Covid Line list which is an extract of the Manicaland Covid line list and the Sakubva clinic vaccine registry.

3.10 Data management and analysis

In Microsoft excel, data was cleaned for errors, duplications, missing data fields, inconsistent data and out of range data. In terms of missing data, complete case

analysis by variable was employed. STATA version 15 was used to generate medians, frequencies, and proportions. Bivariate analysis was performed, in which variables were measured against the outcome of interest, breakthrough infection and odds ratios were calculated and their 95% confidence intervals were recorded. A multivariate analysis using a stepwise backwards logistic regression model was performed to control for confounding and identify independent factors. Variables included in the logistic regression model were those with a p-value ≤ 0.250 (Sperandei, 2014).Variable with a p-value < 0.05 were considered to be statistically significant.

For the qualitative aspect of the study, data collected through the semi-structured interviewer administered questionnaire was processed and analysed using manual thematic coding.

3.11 Ethical Consideration

Permission to conduct the study and to utilise the Covid line list and Covid-19 vaccine registry was obtained from Ministry of Health and Child Care. The data upon being received from the ministry was de-identified and kept confidential in a password protected folder and password protected laptop. Ethical approval to conduct the study was sought from AUREC and this was granted. Written and informed consent was obtained for the four key informants that participated in the study and this participation was voluntary and participants were free to opt out at any stage in the study.

3.12 Summary

This chapter detailed the study methodology that was utilised by describing the study design, study setting, population under study, sampling technique to be used, data

collection tools and procedure and data analysis together with ethical considerations that guided the study.

CHAPTER 4 DATA PRESENTATION, ANALYSIS AND INTERPRETATION

4.0 Introduction

This chapter presents the findings of the secondary data analysis and the interpretations as-well as the information gathered from the semi-structured questionnaires. Univariate, bivariate, and multi-variate analysis were conducted to characterise breakthrough infections and to identify associated factors.

4.1 Sociodemographic characteristics of participants

The extracted data was for 4 838 participants with 2 420 being cases and 2 418 being controls. 46.2% of participants were females and the median age was 39 years with an interquartile range of 30 to 50 years for both groups. 49% of the study participants were unemployed while 14.1% of cases and 32.8% of controls were frontline workers (Table 1). There was a statistically significant difference in occupation between the two groups ($p < 0.001$) but no significant difference in age and gender.

Table 1: Sociodemographic characteristics

	Case n (%)	Control n (%)	P value
Age median (IQR)	39 (30 – 50)	39 (30 – 50)	0.645
Gender			
Female	1 135 (46.9)	1 100 (45.4)	0.326
Male	1 285 (53.1)	1 318 (54.6)	
Age group			
18 – 20	117 (4.8)	116 (4.8)	
21 – 35	806 (33.3)	836 (34.5)	0.550
36 – 50	887 (36.6)	831 (34.3)	
51 – 65	409 (16.9)	422 (17.4)	
66 and above	203 (8.4)	217 (9.0)	
Occupation			
Frontline	273 (14.1)	751 (32.8)	<0.001*
Unemployed	1 515 (78.2)	558 (24.4)	
Finance-admin	56 (2.9)	549 (24.0)	
Other	3 (0.2)	267 (11.7)	
Production	90 (4.7)	165 (7.2)	

*shows significant differences between cases and controls ($p< 0.05$)

4.2 Clinical characteristics

The common symptoms amongst individuals with breakthrough infection were fever, sore throat, cough, shortness of breath and runny nose. Cough was the most common symptom occurring in 51.3% while shortness of breath was the least common occurring in only 6.9% (Table 2). 67.4% of breakthrough infections occurred in the 4th quarter of 2021 and this coincides with the 4th wave of the pandemic which hit the country in November (Figure 3).

Table 2 Clinical characteristics

Characteristic variable	Frequency	Percentage
Fever		
Yes	475	19.7
No	1 935	80.3
Sore throat		
Yes	569	27.2
No	1 522	72.8
Cough		
Yes	780	33.7
No	1 536	66.3
Shortness of breath		
Yes	106	4.5
No	2 240	95.5
Runny nose		
Yes	730	30.5
No	1 622	69.5

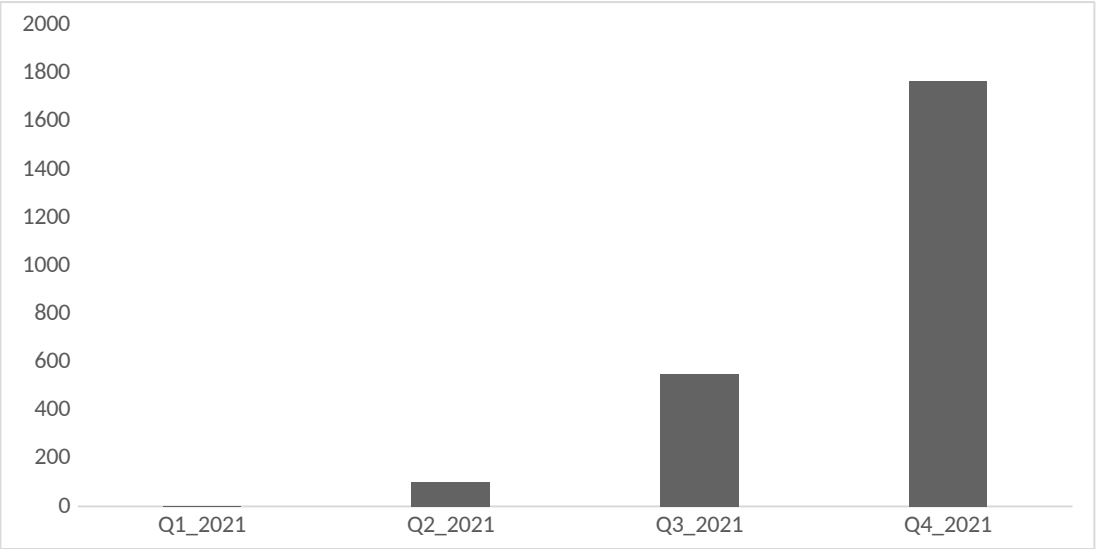

Figure 3 Distribution of breakthrough infections across the year

4.3 Association between host factors and breakthrough infection

53.1% of cases and 54.5% of controls were male, while 2.7% of cases and 3.1% of controls had comorbidities. In determining the host factors that could predict the odds of getting a breakthrough infection in vaccinated individuals, gender and having a comorbidity were insignificant with (p =0.326) and (p = 0.473) respectively (Table 3). Therefore, gender and having a comorbidity are not predictors of breakthrough infections.

Table 3 Bivariate analysis: Association between host factors and breakthrough infections

Characteristic variable	Case n (%)	Control n (%)	OR (95%CI)	P value
Gender				
Female	1 135 (46.9)	1 100 (45.5)	0.9 (0.8– 1.1)	0.326
Male	1 285 (53.1)	1 318 (54.5)		
Comorbidity				
Yes	33 (2.7)	75 (3.1)	0.9 (0.5 – 1.3)	0.473
No	1 202(97.3)	2 347(96.9)		

4.4 Association between vaccine type and breakthrough infection

As illustrated in Table 4 below 52.1% of study participants had received Sinopharm, while 47.9% had received Sinovac. In determining the vaccine factors associated with breakthrough infection, on bivariate analysis vaccine type was statistically significant (OR=0.8, 95%CI: 0.7 – 0.9, (p =0.001). The results show that individuals who received Sinovac where 20% less likely to have a breakthrough infection.

Table 4 Bivariate analysis: Association between vaccine type and breakthrough infection

Characteristic variable	Case n (%)	Control n (%)	OR (95%CI)	P value
Type of vaccine				
Sinovac	1 161 (47.9)	1 280(52.8)	0.8 (0.7 – 0.9)	0.001
Sinopharm	1 261 (52.1)	1 142 (47.2)		

4.5 Association between Covid-19 contact and breakthrough infection

3.3% of study participants had reported contact with a Covid-19 positive case. Amongst cases, 5.6 % had a history of contact with a positive case as illustrated in Table 5 below. There was a statistically significant association between history of contact with a positive case and having a breakthrough infection (OR=5.9, 95%CI: 3.8 -9.2), p < 0.001). Vaccinated individuals with a history of contact with a confirmed Covid-19 case were 5.9 times more likely to get a breakthrough infection compared to those with no history of contact with a confirmed case.

Table 5 Bivariate analysis: Association between Covid-19 exposure and breakthrough infection

Characteristic variable	Case n (%)	Control n (%)	OR (95%CI)	P value
Contact with a positive case				
Yes	136 (5.6)	24 (1.0)	5.9 (3.8 – 9.2)	<0.001*
No	2 284 (94.4)	2 398 (99.0)		

4.7 Main factors associated with breakthrough infections

A hierarchical logistic regression was conducted to determine and rank factors according to their contribution to break through infections. All significant associations noted on bivariate analysis were included in the regression model. Having a comorbidity was insignificant on bivariate analysis but it was included in this model because literature has shown that individuals with comorbidities are at a higher risk of contracting Covid-19. On multivariate analysis vaccine type was significantly associated with a breakthrough infection (OR=0.7, 95%CI: 0.6 – 0.8), p< 0.001) as -well as history of contact with a positive case (OR= 7.6, 95%CI: 4.8 – 12, p < 0.001).)

Table 6 Multivariate analysis (adjusted): Main factors associated with breakthrough infections

Characteristic Variable		OR (95%CI)	P value
Vaccine type			
	Sinovac	0.7 (0.6 – 0.8)	<0.001*
	Sinopharm	1	
Comorbidity			
	Yes	0.9 (0.6 – 1.4)	0.64
	No	1	
Contact with a positive case			
	Yes	7.6 (4.8– 12.0)	<0.001*
	No	1	

4.8 Usefulness and data quality of the Covid line list

Four key informants who are users of the line list at different levels were interviewed as key informants and among them where individuals who record cases on the line list and share with the provincial team, look up cases to follow up at district level,

merges line lists from all districts into one list that is shared with the national health information team and lastly another individual who analyses the data and monitors disease trends in the province.

Table 7: Key informant feedback

Attribute	Summary findings
Usefulness	100% of participants indicated that the system was useful in describing the basic demographics of patients, mapping of cases and identifying possible breakthrough infections. Identification of true breakthrough infections from the list was impossible because the list has no vaccination dates. Analysis of patient outcomes however, was reported by 100% of participants to be difficult because of huge variations in the outcome variable. "*The outcomes are difficult to analyse because districts make different entries in that column ranging from recovered, died, home isolated, absconded, active, admitted and in most of the sections it is blank, at the end of the day you are not sure if the patient died or recovered which are the only two outcomes we are interested in."*, said one of the key informants.
User experience and data quality	All four participants indicated that the line list was easy to use in sections were data is complete and comprehensible, however they all highlighted several challenges. *"I use information from the clinics to make these entries so I can only input information that is shared with me. In some cases they use abbreviations that I am unable to define so I end uploading the*

data at it is" said one of the users responsible for recording cases in the line list. The same informant also expressed concern on the number of variables on the line list. *"There are too many variables on that list and one is bound to make mistakes if they have to record over 50 variables for one individual. Moreover, the source documents I work with have blanks on the bulk of those variables which is proof enough that no one is asking for this information from the clients".*

Participants also indicated that there are too many date variables that are recorded, however on making entries the same date is presented in different formats making it difficult in some cases to identify when the case actually happened because date of testing will be different from date of diagnosis by many months "*In some cases 7 March 2021 maybe written as 03/07/2021 on the testing date and 07/03/2021 on the date of receiving test results, you are then stuck as to when the case happened because the date format keeps being changed for the same client".*

Participants indicated that data was incomplete in 80% of cases and incomprehensible in 25% of cases.

The reviewed Covid line list had 60 data fields that were supposed to be completed for each Covid-19 case reported. 9 of the 60 variables were date variables collecting information on; case reporting date, date of first consultation, date of testing, date of onset of symptoms, date of detection at point of entry, date of receiving results, date of admission, date of outcome, date of discharge. For 90% of cases on the list, only the reporting date and date of testing were recorded suggesting that some of the date

variables were no longer relevant. Most clients on the list had received a rapid antigen test, which would suggest that they had received results on the same day of testing, but in some instances there were different dates for such clients. Date of outcome was missing in 95% of cases.

The line list had a variable for case identity of positive contacts allowing for entry of up to 5 positive contacts. In 98% of cases there were no case identifiers for positive contacts in the form of unique numbers or names. The Covid line list ideally should record positive cases only, however the reviewed list had a variable for laboratory test result which was blank in 73% of cases on the list. In as much as there were 60 variables, some vital information such as vaccination dates for the two doses, chronic medicines were not available. Moreover, there are no standard words, phrases or formats such that when merging line lists from different districts, some of the information is not comparable. The many data fields increased the number of errors and lowered the degree of completeness of the line list. Table 8 below depicts the proportion of individuals with missing information, particularly on variables that were vital to this study.

Table 8 Proportion of missing data on the Covid line list

Variable n=% missing	**All Cases N=25 542**	**Vaccinated N = 4 302**	**Fully vaccinated N=3 444**	**Study participants N = 2 420**
Age	2.68	0.9	0.81	0
Gender	0.6	0.07	0.06	0
Comorbidities	76.8	49	46	34.1
Vaccination status	45.4	0	0	0
Number of doses	*	10.4	0	0
Type of vaccine	*	35.1	29.1	0
Outcome	64.1	70	73	79.2

*The list has individuals that were infected prior to commencement of vaccination, hence their vaccination status and number of doses was blank on the line list.

Age and gender had a high degree of completeness when compared with the other variables. Entries in these two sections were valid and ages within range. In the comorbidities variables, 76.8% of individuals on the Manicaland line list had blanks reflecting a low degree of completeness. In some fields with entries, abbreviations used were unfamiliar such that the disease condition could not be identified for grouping purposes. 64.1% of cases had no listed disease outcomes. Amongst the 19.8% study participants who had a listed outcome, only 8.5% had a comprehensible outcome in the category died or recovered.

Vaccination information particularly on number of doses and vaccine type were missing in some cases. Number of doses was missing in 10.4% of vaccinated individuals, while 6.3% of them had invalid entries like 4 or more doses. 35.1% of vaccinated individuals had no listed vaccine type and this was a reason for exclusion from the study.

CHAPTER 5 DISCUSSION

5.0 Introduction

This chapter discusses the study findings and makes comparison with existing literature on Covid-19 breakthrough infections. The chapter also provides critical recommendations to the Manicaland province MoHCC directorate and its DHEs.

5.1 Discussion

This study analysed data for 4 838 participants from Manicaland aged 18 years and older who had received two doses of either Sinopharm or Sinovac.

5.1.1 Host, vaccine and exposure factors associated with breakthrough infections

In this study the median age of people with breakthrough infection was 39 years with 54.5% being males. This distribution is almost similar to the one noted in the study by Tian et al. (2022), where median age of breakthrough infection cases was 33 years and 69% were males. This study revealed that age was not significantly associated with breakthrough infections similar to findings by Alishaq et al. (2021) in the study of vaccinated healthcare workers in Qatar, however contrary to the United states veterans study in which older age was a risk factor. Basso et al. (2022), found that male gender was associated with a higher risk of breakthrough infections which is different from the current study. Despite more males being affected, there was no statistically significant association between being male and having a breakthrough infection.

Presence of comorbidities was not associated with getting breakthrough infections and this finding is similar to that of Alishaq et al. (2021) in a study of healthcare workers in Qatar in which presence of comorbidities was not associated with higher

risk of getting a breakthrough. In other studies where individual disease conditions have been analysed Basso et al. (2022), found that diabetes and obesity were associated with a higher risk of breakthrough infections. Sun et al. (2022), from their cohort study found that immune dysfunction was a risk factor for breakthrough infections. In our study, comorbidities were self-reported by both cases and controls and at times these are not volunteered if the client is not asked about them, so there may be gaps in information.

On multivariate analysis, vaccine type was significantly associated with breakthrough infections (OR=0.7, 95%CI: 0.6 – 0.8, p < 0.001), with Sinovac recipients being 30% less likely to contract a breakthrough infection. Tian et al. (2022) compared occurrence of breakthrough infections in patients who had received the two inactivated vaccines from China and they found a significant difference between the two groups ($p = 0.020$ and $p = 0.009$). Sinopharm had more symptomatic patients and more patients with moderate disease compared to Sinovac. In the current study there was no comparison of disease severity between the two vaccines. However, in that same study by , Sinopharm recipients had a much longer time from full vaccination to first positive nucleic acid test (176.79 ± 95.53 days) than those who received Sinovac (23.50 (15.50, 75.25) days) ($p < 0.001$). In the current study, period between full vaccination and infection could not be established due to absence of vaccination dates for the cases.

Distribution of cases across the study period, support exposure threshold mechanism that is coined by Crowcroft and Klein (2018), where they point out that protection thresholds from vaccines are not static because with high enough exposure to a pathogen, infection can still occur in the face of high circulating antibodies. The 4th quarter of 2021 is the period when Zimbabwe was hard hit by the 4th wave of the

pandemic with the highly infectious Omicron variant being the predominant variant. 73% of breakthrough infections occurred in the 4th wave of the pandemic.

Contact with a positive case was significantly associated with breakthrough infections (OR=7.6, 95%CI: 4.8 – 12.0, p<0.001). This finding is similar to that of Alishaq et al. (2021) wherein, history of contact was associated with higher risk of breakthrough infection and they explain that healthcare workers involved in the study generally had routine tests done and those with a contact also got tested more than those without. In the present study, Zimbabwe had a policy to follow up and test contacts of all positive cases. While the contact that was measured was known contact, in the 4th wave more and more people became contacts without knowing.

5.1.2 Clinical characterisation

In this study symptomatic infections were featured by cough, runny nose, sore throat, fever and shortness of breath. Cough was the most common symptom with a frequency of 33.7% amongst cases and this occurrence was almost similar to the 31.4% reported by (Tian et al., 2022) . Tian et al. (2022) also reported the occurrence of sore throat to be 4% among vaccinated individuals which is similar to the occurrence of shortness of breath in 4.5% of individuals with breakthrough infections in this study. Runny nose the second most common symptom in this study was reported by 30.7% of cases. Fever one of the most recognised symptom of Covid-19 was reported by 19.7% of cases in this study almost similar to Bergwerk et al. (2021) where 21% reported a fever though the most common symptom was nasal congestion occurring in 36% of breakthrough cases.

The occurrence of these symptoms in this study, is also influenced by the line list from which the data is extracted. The line list is designed to give yes and no responses for the listed five symptoms, as such these are probed from the patient.

The other symptoms, in most cases have to be volunteered by the patient in which case they maybe missed if the patient does not volunteer the information and the clinician does not probe for those other symptoms. Moreover, some symptoms are subjective, what may be regarded as a problem in some communities, in others it is considered a minor problem and patients will not report it. Antonelli, et al., (2021), reported that sternutation was more common in vaccinated people compared to unvaccinated. This would be difficult to determine in a setting like Manicaland, where very few people would report that they are sneezing more than usual.

Language is also a barrier when describing symptoms, because there are no Shona or Ndebele words to describe some of the symptoms like, nasal congestion. Often it is translated to mean runny nose, when they are different things

5.3 Gaps and Data quality of the Covid-19 line list.

In Zimbabwe, the Covid-19 line list is the only data source that contains data on all individuals that have been reported to have tested positive for SARS-Cov-2, as such this has been used to make major public health decisions in this country. It is also the source document for any characterisation of the pandemic in the country on a large scale. For these reasons the quality and completeness of the data captured in the Covid line list is of critical importance.

The study found a high degree of completeness on age and gender. However, there was a low degree of completeness on other variables like comorbidities, vaccine type, number of doses and outcomes similar to findings by (Costa-Santos et al., 2021). Low degree of completeness limits the usefulness of collected data (Costa-Santos et al., 2021). Missing information on comorbidities creates potential underestimation of prevalence of comorbidities amongst Covid-19 cases (Hall and

Farrell, 2022). This is likely a contributing factor to the finding made in this study that comorbidities were not significantly associated with breakthrough infections.

In this study the data quality challenges begin from the source because entries are done manually and on paper, with high volume of patients errors are inevitable. In the uploading into excel sheet, sometimes staff members with no Excel experience are tasked to do that which leads to more errors, an observation by (Hill and Farrell, 2022). Moreover there were 60 variables on the reviewed line list and this compromises quality from the data entry process and beyond.

In some variables there was use of inconsistent terms a finding similar Costa-Santos et al. (2021) in their study of the Portuguese epidemiological surveillance dataset. The outcome variable had the most inconsistencies and one of the contributing factors is lack of drop downs and forcing functions as highlighted by Hill and Farrell (2022) in their study. However, a contributing factor to the missing outcomes is that reporting facilities are usually not aware of outcomes of home isolating patients. This is worse in situations when there are too many cases and the health authorities have no capacity to follow up. Moreover, there are no systems to report and update outcomes, an observation that was made by Hill and Farrell (2022), wherein even if the outcome is known, unless the patient died, the outcome is rarely updated.

The findings of this study suggest that reducing the number of times data is transferred from one media to another will minimise errors. The variables should be reduced so that the list captures critical data that is informative yet minimal. Standardisation of terms, date formats, abbreviations and use of drop downs, forcing functions Hill and Farrell, (2022), are some of the strategies that can make line lists easier to use abbreviations and date formats will reduce the number of errors in the

line list. Training of data collectors and data entry staff members is also a critical aspect in improving data quality. Improving data quality will increase the usability of the line list. As such there is need for an urgent review of the line list so that only critical and useful information is collected.

5.4 Conclusion

Secondary analysis of Covid infection and vaccination data from Manicaland for the period 6 April to 31 December 2021 revealed that history of contact with a positive case was significantly associated with breakthrough infections and recipients of Sinovac were 30% less likely to get a breakthrough infection when compared with Sinopharm recipients. Cough and runny nose were the most common symptoms in individuals with breakthrough infections. The Covid line list from where the cases were extracted had a high degree of completeness on age and gender, but very low on critical variables like vaccine type, number of doses, vaccination status and disease outcomes. Urgent review of the line list is recommended as-well as further research to conduct vaccine effectiveness within the Zimbabwean community.

5.4 Recommendations

Area	Recommendation	Responsible person
Covid 19 national line list	• Urgent review of the line list to reduce number of variables • Training for HCW who do entries into the line list • Use of standard date formats and standard words for certain variables – option is to use drop down menus so that responses to each variable are standardised. e.g Outcome should either be Recovered or Died • The tool should not be able to complete the next variable if critical variables are not filled in (forcing functions) • Inclusion of dates of vaccination for 1st, 2nd dose or 3rd dose where applicable • Biweekly quality assessment of data being collected at district level • Quarterly review of relevance of each of the collected variables • Establishment of an online version of the line list to reduce data extractions between district, province and national level	• MoHCC Health Information
Covid vaccine registry	• There was an initiative to have this registry online, however only a small fraction of individuals have been uploaded, and districts need to be retrained and encouraged to continue the entries. The information already exists in paper registers. • There is need to link this vaccination database and the Covid line list this will help to conduct vaccine effectiveness studies, Covid 19 breakthrough infections risk factor identification, determination of incidence of breakthrough infections amongst the vaccinated population.	• MoHCC Health Informatics and Health information department
Covid-19 risk factors	• Individuals should be encouraged to continue observing Covid-19 prevention strategies even if they have been vaccinated, particularly in settings of high infection rates, or in cases where an individual as many positive cases around	• Health Promotion • Epidemiology and disease control

	them	department

REFERENCES

Alishaq, M., Nafady-Hego, H., Jeremijenko, A., Al Ajmi, J. A., Elgendy, M., Vinoy, S., Fareh, S. B., Veronica Plaatjies, J., Nooh, M., Alanzi, N., Kaleeckal, A. H., Latif, A. N., Coyle, P., Elgendy, H., Abou-Samra, A.-B., & Butt, A. A. (2021). Risk factors for breakthrough SARS-CoV-2 infection in vaccinated healthcare workers. *PLOS ONE*, 16(10), e0258820. https://doi.org/10.1371/journal.pone.0258820

Antonelli, M., Penfold, R. S., Merino, J., Sudre, C. H., Molteni, E., Berry, S., . . . Steves, C. J. (2021). Risk factors and disease profile of post-vaccination SARS-Cov-3 infection in UK users of the COVID symptom stufy app: a prospective community-based, nested, case-control study. *The Lancet Infectious Diseases*. doi:https://doi.org/10.1016/S1473-3099(21)00460-6

Basso, P., Negro, C., Cegolon, L., & Larese Filon, F. (2022). Risk of Vaccine Breakthrough SARS-CoV-2 Infection and Associated Factors in Healthcare Workers of Trieste Teaching Hospitals (North-Eastern Italy). *Viruses*, 14(2), 336. https://www.mdpi.com/1999-4915/14/2/336

Belongia, E. A., Sundaram, M. E., McClure, D. L., Meece, J. K., Ferdinands, J., & Jeffrey, J. (2015). Waning vaccine protection against influenza A (H3N2) illness in children and older adults during a single season. *Vaccine, 33*(1), 246-251. doi:https://doi.org/10.1016/j.vaccine.2014.06.052

Berwerk, M., Gonen, T., Lustig, Y., Amit, S., Lipsitch, M., Cohen, C., . . . Regev-Yochay, G. (2021). Covid-19 Breakthrough Infections in vaccinated health care workers. *The New England Journal of Medicine, 385*(16), 1474 -1484. doi:https://dx.doi.org/10.1056%2FNEJMoa2109072

Brinkley-Rubinstein, L., Peterson, M., Martin, R., Chan, P., & Berk, J. (2021). Breakthrough SARS-CoV-2 infection in prison after vaccination. *New England Journal of Medicine, 385*(11), 1051-1052. doi:https://doi.org/10.1056/nejmc2108479

Brown, C. M., Vostok, J., Johnson, H., Burns, m., Gharpure, R., Sami, S., . . . Laney, A. S. (2021). Outbreak of SARS-CoV-2 Infections, Including COVID-19 Vaccine Breakthrough Infections, Associated with Large Public Gatherings - Barnstable County, Massachusetts, July 2021. *MMWR. Morbidity and Mortality Weekly Report, 70*(31), 1059 - 1062. doi:http://dx.doi.org/10.15585/mmwr.mm7031e2

CDC. (2019). *Vaccines and Immunizations: The Basics*. Retrieved from Centers for Disease Control and Prevention: https://www.cdc.gov/vaccines/vac-gen/imz-basics.htm

CDC. (2021, December 17). *The Possibility of COVID-19 after Vaccination: Breakthrough Infections*. Retrieved from Centers for Disease Control and Prevention: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/effectiveness/why-measure-effectiveness/breakthrough-cases.html

CDCMMWR. (2021). COVID-19 Vaccine Breakthrough Infections Reported to CDC — United States, January 1–April 30, 2021. *MMWR.Morbidity and Mortality Weekly Report, 70*. doi:10.15585/mmwr.mm7021e3

Cook, C., Patel, N. J., D'Silva, K. M., Hsu, T. Y., Dilorio, M., Todd, D., . . . Wallace, Z. S. (2021). Clinical characteristics and outcomes of COVID-19 breakthrough infections among vaccinated patients with systemic autoimmune rheumatic diseases. *Annals of the rheumatic diseases*. doi:http://dx.doi.org/10.1136/annrheumdis-2021-221326

Costa-Santos, C., Neves, A. L., Correia, R., Santos, P., Monteiro-Soares, M., Freitas, A., Ribeiro-Vaz, I., Henriques, T. S., Pereira Rodrigues, P., Costa-Pereira, A., Pereira, A. M., & Fonseca, J. A. (2021). COVID-19 surveillance data quality issues: a national consecutive case series. *BMJ Open*, 11(12), e047623. https://doi.org/10.1136/bmjopen-2020-047623

Crowcroft, N. S., & Klein, N. P. (2018). A framework for research on vaccine effectiveness. *Vaccine, 36*(48), 7286-7293. doi:https://doi.org/10.1016/j.vaccine.2018.04.016

Doak, S. H., & Zair, Z. M. (2012). Real-time reverse-transcription polymerase chain reaction: technical considerations for gene expression analysis. *Methods in molecular biology, 817*, 251-270. doi:https://doi.org/10.1007/978-1-61779-421-6_13

Godwell, N., Daniel, C., Emmanuel, G., Notion, G., Patience, J. T., & Mufuta, T. (2022). SARS-CoV-2 Infection among Students at a High School, Mashonaland West, Zimbabwe, December, 2020. Journal of Interventional Epidemiology and Public Health, 5(6). https://doi.org/10.11604/JIEPH.supp.2022.5.1.1205

Harrington, R. A. (2020, May 5). Case fatality rate. *Encyclopedia Britannica*. Retrieved from https://www.britannica.com/science/case-fatality-rate

Hill, T. E., & Farrell, D. J. (2022). A Typology of COVID-19 Data Gaps and Noise From Long-Term Care Facilities: Approximating the True Numbers. Gerontology and Geriatric Medicine, 8, 23337214221079176. https://doi.org/10.1177/23337214221079176

Johns Hopkins University of Medicine. (2021). *Coronavirus Resource Center*. Retrieved from Jonhs Hopkins University of Medicine: https://coronavirus.jhu.edu/map.html

MELiNG Biology &Medical. (2021). *COVID-19 Vaccine Storage Solution-Solutions-Zhongke Meiling Cryogenics*. Retrieved from https://www.melingbiomedical.com/en/solutions/vaccine-storage-solution/

Ministry of Health and Child Care (MoHCC). (2021). *Zimbabwe Covid-19 SitRep 22/02/2021.* Harare: Ministry of Health and Child Care. Retrieved from http://www.mohcc.gov.zw/index.php?option=com_phocadownload&view=category&id=15&Itemid=742

MoHCC. (2021). *Covid vaccine deployment and rollou plan.* Harare: GoZ. Retrieved from http://www.mohcc.gov.zw/index.php?option=com_phocadownload&view=category&download=245:coordination-pdf&id=25:coordination-planning-and-monitoring&Itemid=746

MoHCC. (2021). *Zimbabwe Sitrep 31/10/2021.* Harare: MoHCC.

Morgan, R. K., & Summer, R. (2008). Chronic Obstructive Pulmonary Disease. *International encyclopedia of Public Health*, 709-717. doi:https://doi.org/10.1016/B978-012373960-5.00213-6

Sperandei, S. (2014). Understanding logistic regression analysis. *Biochemia medica,* 24(1), 12-18.

Sun, J., Zheng, Q., Madhira, V., Olex, A. L., Anzalone, A. J., Vinson, A., Singh, J. A., French, E., Abraham, A. G., Mathew, J., Safdar, N., Agarwal, G., Fitzgerald, K. C., Singh, N., Topaloglu, U., Chute, C. G., Mannon, R. B., Kirk, G. D., & Patel, R. C. (2022). Association Between Immune Dysfunction and COVID-19 Breakthrough Infection After SARS-CoV-2 Vaccination in the US. *JAMA Intern Med*, 182(2), 153-162. https://doi.org/10.1001/jamainternmed.2021.7024

Tian, D., Song, Y., Zhang, M., Pan, Y., Ge, Z., Zhang, Y., Ren, X., Wen, J., Xu, Y., Guo, H., Yang, P., Chen, Z., & Xu, W. (2022). Genomic, immunological, and clinical analysis of COVID-19 vaccine breakthrough infections in Beijing, China. *Journal of Medical Virology*, 94(5), 2237-2249. https://doi.org/https://doi.org/10.1002/jmv.27636

Torvaldsen, S., & Mclntyre, P. B. (2002). Observational methods in epidemiologic assessment of vaccine effectiveness. *Communicable Diseases Intelligence quarterly report,, 26*(3). Retrieved from https://pubmed.ncbi.nlm.nih.gov/12416713/

Vignier, N., Berot, V., Bonnave, N., Peugny, S., Ballet, M., Jacoud, E., . . . Epelboin, L. (2021). Breakthrough Infections of SARS-CoV-2 Gamma Variant in Fully Vaccinated Gold Miners, French Guiana, 2021. *Emerging Infectious Diseases, 27*(10), 2673 - 2676. doi:https://doi.org/10.3201/eid2710.211427

WHO. (2020). *Interim recommendations for use of the BHarat Biotech BBV152 COVAXIN vaccine against COVID-19.* WHO. Retrieved from

https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-bbv152-covaxin

WHO. (2021). *Estimating COVID-19 vaccine effectiveness against severe acute respiratory infections (SARI) hospitalisations associated with laboratoy-confirmed SARS-CoV-2: An evaluation using the test-negative design: guidance document.* Copenhagen: WHO Regional Office for Europe. Retrieved from https://apps.who.int/iris/handle/10665/341111

WHO. (2021). *Evaluation of Covid 19 vaccine effectiveness.* Retrieved from https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccine_effectiveness-measurement-2021.1

WHO. (2021). *Interim recommendations for the use of the Janssen Ad26.COV2.S(COVID-19) vaccine.* WHO. Retrieved from https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-Ad26.COV2.S-2021.1

WHO. (2021). *Interim recommendations for use of the inactivated COVID-19 vaccine BIBP developed by China National Biotec Group(CNBG), Sinopharm.* Retrieved from https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE-recommendation-BIBP

WHO. (2021). *Interim recommendations for use of the inactivated COVID-19 vaccine, CoronaVac, developed by Sinovac.* WHO. Retrieved from https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-Sinovac-CoronaVac-2021.1

WHO. (2021). *WHO Coronavirus (COVID-19)*. Retrieved from Zimbabwe situation : https://covid19.who.int/region/afro/country/zw

Wiedermann, U., Garner-Spitzer, E., & Wagner, A. (2016). Primary vaccine failure to routine vaccines:Why and what to do? *Human Vaccines &Immunotherapeutics, 12*(1). doi:https://doi.org/10.1080/21645515.2015.1093263

World Health Organisation (WHO). (2021). *Coronavirus disease (Covid-19)*. Retrieved from World Health Organization: https://www.who.int/health-topics/coronavirus#tab=tab_1

ZIMPHIA. (2020). *ZIMBABWE.* Retrieved from https://phia.icap.columbia.edu/wp-content/uploads/2020/11/ZIMPHIA-2020-Summary-Sheet_Web.pdf

Zimstat. (2017). *Manicaland Provice, District Population Projection Report.* Harare. Retrieved from https://www.zimstat.co.zw/wp-content/uploads/publications/Population/population/District-Projections/District-Population-Projection-Report-Manicaland.pdf

Appendix 1 Questionnaire

Section A. Administrative Information

1. Form completion date (dd/mm/yyyy) ___/___/___

2. Unique patient ID …….

3. Date of SARS-CoV-2 testing ……..

Section B. Personal Information

1. Date of birth (dd/mm/yyyy) or age ___/___/___ or age: ____

2. Sex ☐ Female ☐ Male ☐ Do Not Know

3. Is the patient a healthcare worker*? ☐ Yes ☐ No ☐ Do not know

4. What is the patient's occupation? ☐_____ ☐ Do not know

5. What is the patient's height (in m)? ☐_____☐ Do not know

6. What is the patient's weight (in kg)? ☐_____ ☐ Do not know

Section C. Medical History

1. Which of the following Chronic Medical Conditions does the patient have?

a. Cancer ☐ Yes ☐ No ☐ Do not know

b. Chronic cardiac disease, except hypertension ☐ Yes ☐ No ☐ Do not know

c. Hypertension ☐ Yes ☐ No ☐ Do not know

d. Chronic kidney disease ☐ Yes ☐ No ☐ Do not know

e. Chronic liver disease ☐ Yes ☐ No ☐ Do not know

f. Chronic respiratory disease ☐ Yes ☐ No ☐ Do not know

g. Asthma ⁞ Yes ⁞ No ⁞ Do not know

h. Diabetes ⁞ Yes ⁞ No ⁞ Do not know

i. Immunocompromised, transplant and HIV ⁞ Yes ⁞ No ⁞ Do not know

j. Neurological disease ⁞ Yes ⁞ No ⁞ Do not know

k. Rheumatologic disease ⁞ Yes ⁞ No ⁞ Do not know

l. Anaemia or other blood disorder ⁞ Yes ⁞ No ⁞ Do not know

m. Tuberculosis ⁞ Yes ⁞ No ⁞ Do not know

2. Is the patient taking any medicines ⁞ Yes ⁞ No If yes, specify

_____

3. Smoking status ⁞ Never smoked ⁞ Former smoker (> 1 yr) ⁞ Current smoker

4. Is the patient pregnant? ⁞ Yes ⁞ No ⁞ If yes, trimester ⁞ 1 ⁞ 2 ⁞ 3 ⁞ Do not know

Section D. Vaccination

1. Has the patient received a COVID-19 vaccine?

a. Dose 1 ⁞ Yes ⁞ No If yes, date: ___/___/___

- Name/brand:

⁞ Sinopharm ⁞ Sinovac ⁞ Do not know ⁞ Other, specify _____

b. Dose 2 ⁞ Yes ⁞ No If yes, date: ___/___/___

- Name/brand:

⁞ Sinopharm ⁞ Sinovac ⁞ Do not know ⁞ Other, specify _____

c. Vaccination status ascertainment:

⁋ Vaccination registry ⁋ Vaccination card ⁋ Patient interview ⁋ Relative interview

⁋ Other, specify _____

Section E: Exposure to SARS-CoV-2

1. Did the patient test positive for SARS-CoV-2? ⁋ Yes ⁋ No If yes, date: ___/___/___
2. At the time of testing positive, did the patient come into contact with a known positive case? ⁋ Yes ⁋ No
3. If yes, was the contact vaccinated? ⁋ Yes ⁋ No
4. If yes was the contact a household contact? ⁋ Yes ⁋ No (household contact resides in the same household or shares a working space with patient)
5. How many other household contacts were present in the patient's life at the time of testing positive? _____

Appendix 2 Key informant questionnaire

1. How often do you use the Covid-19 line list?

   Daily ☐ Weekly ☐ Monthly ☐

2. What do you use the line list

   for? .....

   .....

   .....

3. For your purposes, is the line list useful? Yes ☐ No ☐
4. Is the line list useful for creating epidemic curves? Yes ☐ No ☐
5. State your reasons for the answer above?

   ……

   ……..

6. Is the line list useful in analysing patient outcomes Yes ☐ Not useful ☐
7. State reasons for your answer above?

   ……

   ……

8. From the line list, can one identify breakthrough infections? Yes ☐ No ☐
9. State reasons for your answer above?

   ……

10. Have you noted any data quality issues with the line list? Yes ☐ No ☐
11. If your answer is yes, what are the challenges you have come across?

    ……

    ……

    ……..

.....***END***……

Appendix 3 Data collection tool

Age	Gender	Occupation	Province	Symptoms	Date of diagnosis	Comorbidities	Vaccination status	No of doses	Vaccine type	No of known contacts	Level of contact	Disease severity	Outcome

Appendix 4 Consent form for key informants

My name is Kudzai Murembwe, a final year Master of Public Health student from Africa University. I am carrying out a study to Characterise Covid 19 breakthrough infection in Manicaland for the period April to December 2021. I am kindly asking you to participate in this study as a key informant by responding to my questionnaire through a face to face interview.

Purpose of the study:

The purpose of the study is to determine the host, vaccine and exposure factors associated with Covid 19 breakthrough infections and to review the Covid line list. The study is for academic purposes, but information from this study will assist Ministry of Health and Child Care to note gaps if any and design effective programs that respond to the community's needs.

Procedures and duration

The eligible participants for this study are health workers that use the Covid-19 line list on a daily basis in carrying out their duties or making decisions. You have been purposively selected as a possible participant because you meet the stated selection criteria. About 4 participants will be enrolled in this study. If you decide to participate, you will be asked to undergo a face to face interview while completing this questionnaire. The interview will take about 45 minutes.

Risks and discomforts

The risks of participating in this study are minimal. It is possible that you may feel uncomfortable with some of the questions I will ask you. You can choose to skip or to discontinue the interview if you feel uncomfortable.

Benefits

There are no direct benefits to you for participating in this study. I am hoping that findings from this study will be used to improve Covid 19 vaccination programme.

Confidentiality

If you participate in the study you will be assigned a participant identity to be used on the questionnaire as no personal details will appear on the questionnaire. Any information that is obtained in connection with this study that can be identified with you will remain confidential and will be disclosed only with your permission. All study records will be kept in secure, locked filing cabinets, separate from any information that identifies you personally like this consent form. Your name will not be used in any reports or publications that may arise from this study. Under some circumstances, the University or Medical Research Council of Zimbabwe may need to review records for compliance audits only.

Voluntary participation

Participation in this study is voluntary. If you decide not to participate in this study, your decision will not affect your future relationship with Mutare City Council. If you chose to participate, you are free to withdraw your consent and to discontinue participation without penalty at any time.

Questions

Before you sign this form, please ask any questions on any aspect of this study that is unclear to you.

Authorisation

If you have decided to participate in this study please sign this form in the space provide below as an indication that you have read and understood the information provided above and have agreed to participate.

---------- ----------

Name of Research Participant (please print) Date

Signature of Research Participant or legally authorised representative

If you have any questions concerning this study or consent form beyond those answered by the researcher including questions about the research, your rights as a research participant, or if you feel that you have been treated unfairly and would like to talk to someone other than the researcher, please feel free to contact the Africa University Research Ethics Committee on telephone (020) 60075 or 60026 extension 1156 email aurec@africau.edu

Name of Researcher: KUDZAI MUREMBWE

Appendix 5 Description of variables in the Covid-19 line list

Variable	Variable description
Unique case ID	Unique case identifier is assigned to each individual who test positive for Covid. It is assigned at district level (NUMERICAL)
Reporting Date (dd/mm/yyyy)	Date the case is reported to district health information office in the format day/ month /year (DATE)
First Name	Individual's name (TEXT)
Last Name	Family name / surname (TEXT)
Age (yrs)	Age of patient in years at the time of disease onset as per the individual's official birth certificate (NUMERICAL)
Age (months)	Age of patient in months at the time of disease onset as per the individual's official birth certificate (for patients aged < 2 years) (NUMERICAL)
Sex (M/F)	Gender of the reported cases (M/F)
Place of residence admin level 1 (province)	Province in which the individual resides (TEXT)
Place of residence admin level 2 (district)	District in which the individual resides (TEXT)
Place of residence admin level 3(Health Zone/Town):	City or town in which individual resides (TEXT)
Place of residence admin level 4(village):	Exact address and suburb in which individual resides (TEXT)
Reporting health facility/institution	Hospital or clinic where the case was diagnosed (TEXT)
Where the case was diagnosed, admin level 1 (province)	Province in which the case was diagnosed which may be different from the usual province of residence (TEXT)
Where the case was diagnosed, admin Level 2 (district):	District in which the case was diagnosed which may be different from the district of residence (TEXT)
Detected at point of entry	Was the case detected at a border or an airport (Y/N)
Date detected at point of entry (dd/mm/yyyy)	The date at which the case was detected at the border or the airport in the format day/ month /year (DATE)
Case epi-classification	Epidemiological classification of the case. Is the case suspected, probable or confirmed (TEXT)
Case Classification (Local/Imported)	Is the case secondary to local transmission or it was imported from outside the country. (Y/N)
Date of first consultation at this HF (dd/mm/yyyy)	Date on which the individual was consulted at the health facility pertaining to Cocid-19 in the format day/

	month /year (DATE)
Date of onset of first symptoms (dd/mm/yyyy)	Date when the individual started experiencing Covid-19 symptoms in the format day/ month /year (DATE)
Admission to hospital?	Was the individual admitted to hospital for Covid-19 (Y/N)
For this episode, date first admitted in hospital (dd/mm/yyyy)	Date on which the case was admitted to hospital for Covid-19 in the format day/ month /year (DATE)
Other clinical complications (specify)	State the clinical signs and symptoms that the individual has (TEXT)
Fever	Does the individual have a hot body (Y/N)
Sore throat	Does the individual have a sore throat (Y/N)
Cough	Is the individual coughing (Y/N)
Runny nose	Does the individual have a runny nose (Y/N)
Shortness of breath	Is the individual breathless (Y/N)
Other sign/symptoms, specify	List any other symptoms /signs mentioned by patient that may not be on the list (TEXT)
Patient has pre-existing conditions (Y/N)	Does the individual have other disease that existed prior to this episode of Covid-19 (Y/N)
Patient pre-existing conditions (specify)	List the diseases that the individual already had prior to the current episode of Covid-19 (TEXT)
Sector of Occupation (Health, Mining, Retailing, Education, Manufacturing, Tourism and hospitality, Banking, Agriculture, Security, Transport, Other Specify)	In which sector of the economy is the individual employed – Choose from the categories listed which are (Health, Mining, Retailing, Education, Manufacturing, Tourism and hospitality, Banking, Agriculture, Security, Transport, Other) use other if the sector is not on the given list and Unemployed or retired if individual falls in that group. Self-employed individuals have a sector.
Categorize the profession of the patient	Give the exact profession of the individual (example: teacher, nurse, doctor)
Has the patient travelled in the last 14 days	Did the individual travel outside their usual place of residence or outside the country (TEXT)
Specify country/Province/District	Depending on where the individual travelled to, specify the country if they travelled across the border, or the province if they travelled within the country, or the district if they travelled within the province. (TEXT)
Specify date of departure from the country/province/district (dd/mm/yyyy)	Indicate the date on which the individual departed from the place they had travelled in the format day/ month /year (DATE)
Has the patient visited any health care	Did the individual visit any clinic or hospital in the past

facilities in the last 14 days	14 days? (Y/N)
Has the patient had close contact with a person with acute respiratory infection in the last 14	Has the individual been in contact with anyone with a flu, cold, cough or Covid-19.(Y/N)
Specify where the patient had close contact with a person with acute respiratory infection	Did the individual have close contact (defined as spending more than 15 minutes within a distance of less than a metre without face masks) with anyone with a flu, cough, cold or Covid-19 (Y/N)
Other exposures (specify)	Has the individual been exposed to Covid-19 or someone with acute respiratory infection by other means not listed above (TEXT)
Has the patient had contact with a probable or confirmed cases?	Has the patient had contact with someone who is likely to have Covid-19 or someone who has been confirmed to have Covid-19 (Y/N)
Case ID number of confirmed or probable case 1	Individual gives name of the confirmed case they had contact with and this is used to identify the case ID number of the confirmed case on the line list. That case ID number is the entry that is made in this section (NUMERICAL)
Case ID number of confirmed or probable case 2	If the individual has had contact with more than one case, specify case ID number of second confirmed case (NUMERICAL)
Case ID number of confirmed or probable case 3	If the individual has had contact with more than two cases, specify case ID number of third confirmed case (NUMERICAL)
Case ID number of confirmed or probable case 4	If the individual has had contact with more than three cases, indicate case ID number of the fourth confirmed case (NUMERICAL)
Specify close contact setting	Specify the nature of the close contact setting by describing if contact occurred at home, work, school, etc (TEXT)
Sample collected	Was a sample collected (Y/N)
Sample type	Was the sample nasopharyngeal, oropharyngeal or both? (Choose from the three options)
Date of Sample Taken (dd/mm/yyyy)	Specify the date on which the sample was collected from the individual in the format day/ month /year (DATE)
Lab Performed	What is the type of laboratory test done on the individual's sample? RT-PCR or Rapid Antigen Test , choose between the two (TEXT)

Lab Result for COVID19	Was the result positive or negative? Choose between the two (TEXT)
Lab Results Date (dd/mm/yyyy)	Specify dates on which the results were received in the format day/ month /year (DATE)
Re-infection Yes/No	Is this the individual's first episode of Covid-19 (Y/N)
If yes? Indicate last period of infection	Indicate the date they had the last episode of Covid-19 in the format day/ month /year (DATE)
Vaccinated (Yes/No)	Did the individual receive any Covid-19 vaccine dose (Y/N)
Number of Doses	How many doses did the individual receive, responses range between 0 – 3 (NUMERICAL)
Type of Vaccine	What is the name of the vaccine that the individual received (TEXT)
Outcome	What was the individual's disease outcome? Did the patient recover/ die.
Date of outcome (dd/mm/yyyy)	Date on which the individual died or was declared recovered in the format day/ month /year (DATE)
Date of discharge (If alive and hospitalized) (dd/mm/yyyy)	If the individual was admitted to hospital for Covid-19, indicate the date they were discharged if they are alive, in the format day/ month /year (DATE)

Appendix 6 Approval letter from Ministry of Health and Child Care

Telephone Nos.: 77107
Fax Nos.

Telegraphic Address: "PROVMED"
Bulawayo

ZIMBABWE

Reference:
PROVINCIAL MEDICAL DIRECTOR
(BULAWAYO PROVINCE)
Mhlahlandlela Building
10th Avenue/Basch Street
P.O. Box 441
Bulawayo, Zimbabwe

20 January 2022

Att: Kudzai Murembwe

Dear Madam

RE: REQUEST FOR PERMISSION TO CONDUCT A STUDY ON COVID -19 BREAKTHROUGH INFECTIONS AND TO UTILISE A DE-IDENTIFIED COVID-19 LINE LIST AND VACCINE REGISTRY

Reference is made to your request above. I have no objection to your carrying out the above mentioned study or accessing the de-identified COVID-19 line list and Covid-19 vaccine registry for the purposes of research, on condition that you obtain the necessary ethical clearance from the relevant board prior to commencing your research.

Note that you will be required to present your findings when the research is concluded

PROVINCIAL MEDICAL DIRECTOR
MATABELELAND NORTH
2022 -01- 24
P.O. Box 441, Bulawayo
Zimbabwe Tel: +263977919

DR M SIAMUCHEMBU
MBChB, MPH, FCS-ECSA
PROVINCIAL MEDICAL DIRECTOR – BULAWAYO METRO

sm/ms