Evaluating the implementation and uptake of the Universal Tuberculosis sputum testing by GeneXpert Ultra in HIV infected pregnant women in City Health PHC facilities, Cape Town.

Kay Joseph

Student number: 4004353

A mini thesis submitted in partial fulfilment of the requirements for the degree of Master in Public Health at the School of Public health, University of Western Cape

Supervisor: Dr Martina Lembani

March 2023

Ten Key Words

Tuberculosis

TB case detection

South Africa

Systematic TB Screening

HIV infected pregnant women

Four-symptom screening

Sputum TB testing

Maternal and neonate TB outcome

Active case finding and

Universal TB sputum testing

List of Abbreviations

AFB	Acid fast bacilli
ARV	Anti-retroviral
BANC	Basic Antenatal Care
CD4 count	Cluster of differentiation 4
HCT	HIV counselling and testing
HIV	Human immunodeficiency Virus
IGRA	Interferon-gamma release assay
MHS	Metro Health System
MGIT	Mycobacteria Growth Indicator Tube
MTB	Mycobacterium Tuberculosis
NPRI	Non-pregnancy related infections
PHC	Primary Health care
PMTCT	Prevention of Mother to Child Transmission of Communicable Infections
PTB	Pulmonary Tuberculosis
PREHMIS	Patient record and Health Information System
SC	Symptom screening clinic
TST	Tuberculin Skin Testing
TPT	Tuberculosis Preventive Therapy
TUTT	Targeted Universal Tuberculosis Testing
UC	Universal testing clinic
Urine TB LAM antigen	Urine Tuberculosis Lipoarabinomannan Antigen test

Definitions of key terms

- **Active case finding:** The systematic screening of specific risk groups for the identification of people with suspected active TB.
- **Extra pulmonary TB**: Disease involving organs other than the lungs: e.g., pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones and meninges.
- **Four TB symptom Screen:** Current cough, night sweats, weight loss or fever of any duration in an HIV infected person.
- **GeneXpert MTB/RIF Ultra**: TB sputum test used to confirm diagnosis. The GeneXpert MTB/RIF assay is used, which is a molecular test identifying Mycobacterium Tuberculosis (MTB). It also detects Rifampicin (RIF) resistance.
- **Initial Loss to follow-up:** A person diagnosed with microbiologically confirmed TB and not started on anti-TB treatment.
- **Loss to follow-up**: Patient who has disengaged from treatment for two consecutive months or more during the treatment period.
- **Presumptive TB case:** Refers to a patient who presents with symptoms or signs suggestive of TB.
- **Pulmonary TB**: Disease involving the lung parenchyma.
- **Sputum culture:** The examination of a sputum sample using culture is the inoculation of a clinical sputum specimen onto culture media and incubating for up to six (6) weeks to detect of growth or no growth during this incubation period; the presence or absence of acid-fast bacilli as an indicator of Mycobacterium tuberculosis infection.

- **Sputum smear microscopy**: The examination of sputum under a microscope, after appropriate preparation, for determining the presence of Acid-fast bacilli, in supporting the diagnosis of Mycobacterium Tuberculosis infection.
- **Systematic screening:** The systematic identification of people at risk of TB, in a focussed target group, through symptoms screening. Once patients screen positive, they test for TB.
- **TB case detection:** The ratio of notified TB cases to incident TB cases per year.
- **TB Cured Outcome:** Patient who commenced anti-TB treatment with a confirmed positive smear or culture, converted and has a negative sputum test at the end of treatment or at least 30 days prior to the last month.
- **TB Treatment Completed Outcome:** Patient that commenced anti-TB treatment with a positive smear of culture and has completed treatment but does not have a negative smear/ culture in the last month of treatment and on at least one previous occasion more than 30 days prior. The smear examination or the results might not have been done or available be available, at the end of treatment.

Abstract

Background

Tuberculosis contributed 33.2% of all non-pregnancy related infections (NPRI) causes of South African maternal mortality, in 2017. The disease contributed 22 of the 46 maternal deaths due to NPRI, in the Western Cape. The early diagnosis of Tuberculosis is therefore imperative in pregnancy to prevent harmful maternal and infant effects. The South African National Department of Health included Universal Tuberculosis sputum testing by GeneXpert Ultra in HIV infected pregnant women in their October 2019 HIV and ART guidelines. It was subsequently adopted the Western Cape Consolidated Guidelines for HIV treatment, in January 2020.

Aim

The aim of this study was to evaluate the operational uptake of the current Universal testing of TB in HIV infected pregnant women in PHC facilities in Cape Town.

Methodology

This study was an observational before-and-after study design. A secondary data analysis was done comparing screening, testing and case detection of TB in HIV infected pregnant women in 2018/2019 (prior to Universal Testing policy implementation) and in 2020/2021 (after the introduction of this new TB testing policy). Extracted records of HIV infected pregnant women at their first antenatal visits linked to TB sputum test results and the Electronic TB register.

The study population records included women aged between 15 and 50 years old, attending their first antenatal visit at 67 (2018/2019) and 69 (2020/20201) City health PHC facilities respectively. The main treatment outcome was to determine the adherence to the policy and whether it led to increased testing and detection of more microbiologically confirmed cases. Multivariate logistic regression applied to determine an association between patients that were TB sputum tested and other patient factors. Ethics approval obtained from the UWC Biomedical Research Ethics Committee. The City Health department granted approval to the access of patient data.

Results

Initially 7235 records from Prehmis were analysed. Eighty-one percent (81%) of patients for both cohorts were between the ages of 25 to 40 years. Sixty-nine percent (69%) and 67% of women booked before 20 weeks. TB screening at first antenatal visit for both cohorts were relatively the same at 16.8% and 15.9%. Sputum testing significantly increased by 13-fold from 1.26% (n=42) in 2018/2019 to 14.28% (n=557) in 2020/2021. There was also an increase in women that tested at their first antenatal visits from 17% (n=7) to 78 %(n=432) with p-value <0.01. Sputum samples sent for GeneXpert increased from 2.4% to 15%. There was no association between being sputum tested and other patient factors such as cohort, age, ART initiated and gestational age at first antenatal visit.

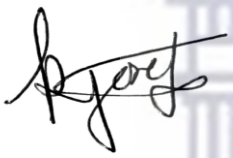
Conclusion

The key finding of this study is that the policy uptake at primary health care level resulted in more women tested by rapid molecular tests, as prescribed by WHO. However, the scale of testing will have to be elevated to meet the TB strategic goals of eradicating Tuberculosis globally.

Declaration

I declare that **'**Evaluating the implementation and uptake of the Universal Tuberculosis sputum testing by GeneXpert Ultra in HIV infected pregnant women in City Health PHC facilities, Cape Town', is my own work. I have not submitted this work to any other university. All the sources referenced appropriately.

Kay Joseph 20th March 2023



Acknowledgements

- This Master`s degree is dedicated to my parents, who have taught me that there are many races in life. The ones that speak to your internal values will propel you to build the courage to participate. These unknown journeys will contribute to the richness of your life.

- Gratitude to my supervisor, Dr Martina Lembani, for your gentle direction throughout the entire process.

- Appreciation of family and friends that have motivated and encouraged me at every obstacle and success on this race.

- Lastly, thank you to Judy Taylor, Vanessa Diedericks, Lizo Bango and Muhammad Osman for your endless support, especially at the last phase of this journey.

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Chapter 1: Introduction

1.1 Background

Tuberculosis (TB) remains one of the top 10 causes of mortality in lower and lower-middle income countries according to the Global Health Observatory data (WHO, 2020b). In 2020, an estimated 9.9 million people globally contracted Tuberculosis, with 5.8 million people diagnosed and reported with Tuberculosis. The treatment success rate for people treated for TB was 88% in 2020 (WHO, 2021a). African regions represent 25% of global cases, with South Africa contributing 3.3% of TB cases in 2020 (WHO, 2021a). The country had an estimated total TB incidence of 328000 cases, of which 71% estimated cases were people living with HIV in 2020 (WHO, 2021a). Women (older than 15 years) accounted for 37% of notified cases (new and relapse), with the majority between the ages of 15 and 45 years old (WHO, 2021a). This significantly affects the health of pregnant women. Furthermore, in 2017 Tuberculosis also contributed 33, 2% of all non-pregnancy related infections (NPRI) causes of maternal mortality, in South Africa (NDOH, 2017). Twenty-two (22) of the 46 maternal deaths due to non-pregnancy related infections (NPRI) were due to TB in the Western Cape (Petro, 2017).

As one of the most common causes of maternal mortality in high HIV burden areas, early accurate Tuberculosis diagnostics in pregnancy remain important, in view of multiple negative effects on both maternal and infant health (Hoffmann *et al.*, 2013). Health care workers screened all basic antenatal care (BANC) patients systematically for TB, prior to the 2019 policy amendment. This entailed symptom screening and identifying high-risk groups. If screened positive for TB symptoms, then the patient was sent for diagnostic TB testing (WHO, 2021b).

GeneXpert MTB/Rif assay was introduced as first line test, for all TB presumptive cases in 2011 (Osman, 2015). The low sensitivity of TB symptom screening in HIV infected pregnant women has been reported through studies: Including Martinson`s cluster-randomized control trial (RCT), comparing universal sputum testing of HIV infected pregnant women to symptom-based testing (Martinson *et al.*, 2017). This study reported a 10-fold increase in case detection, with the universal TB sputum testing (Martinson *et al.*, 2017). Leading to the recommendation of more sensitive TB diagnostics (Martinson *et al.*, 2017).

1.2 Universal TB testing with Gene Xpert Ultra for HIV positive pregnant women policy

The Universal TB testing by GeneXpert policy was introduced in 2019, following recommendation from Martinson (2017) study. The policy was initially included in the South African National ART Clinical Guidelines for the management of HIV (2019) , followed by inclusion to the Western Cape Consolidated Guidelines for HIV Treatment in 2020 (WCGH, 2020b).

According to the policy, all pregnant women that have unknown or negative HIV status must receive testing through HIV testing services (HTS) (NDOH, 2019). The health care worker will request a GeneXpert and send two sputum specimens (regardless of symptoms), once the patient tests positive for HIV. Results will follow in 2 days. The laboratory performs a reflex TB culture and LPA on the second specimen, if HIV infection is indicated (KTU, 2021). Antiretroviral therapy (ART) is started same day, if patient is asymptomatic. The symptomatic patient waits, until the GeneXpert results are available. Patients that have positive GeneXpert (if Rifampicin susceptible) results are placed onto the Drug sensitive regimen which includes 4 drugs

(Rifampicin/Isoniazid/ Ethambutol and Pyrazinamide). Medical officer assesses symptomatic clients with negative results (KTU, 2021).

1.3 Problem Statement

Physical and hormonal changes in pregnancy attribute to the poor performance of TB symptom screening. These changes can mask TB symptoms such as weight loss and fatigue (Hoffmann *et al.*, 2013). This screening limitation is of great concern, as early TB detection in HIV infected pregnant women can avoid harmful implications to both maternal and foetal health (Hoffmann *et al.*, 2013). Devastating consequences of TB disease progression in pregnancy include two-fold risk of premature babies, six-fold increase of perinatal death (Bekker *et al.*, 2016) and development of immune reconstitution inflammatory syndrome (Hoffmann *et al.*, 2013).

In response to the implications of delayed TB diagnosis in pregnancy (Bekker *et al.*, 2016) and the significant reported increase of TB case detection when testing all HIV infected pregnant women (Martinson *et al.*, 2017), the South African health department implemented the Universal TB testing with GeneXpert Ultra policy in 2019 (NDOH, 2019).

There is limited research on TB case detection and incidence in HIV infected pregnant women post policy implementation.

1.4 Purpose of the Study

City of Cape Town reported an antenatal first visit coverage rate of 93.9% in 2019. This progress however, juxtaposed with a high in-facility maternal mortality ratio of 53.2 maternal deaths/100000 live births (Massyn *et al*., 2020). The inefficiency of the

TB cascade within health care is illustrated by only 23% of 70% symptomatic patients, receiving a sputum test and the deterioration of the TB success rate from 79.7% to 76% (below the target of 90%) (Massyn *et al.*, 2020). The data reported 83% of HIV-TB co-infected patients commenced antiretroviral therapy (Massyn *et al.*, 2018). Poor performance of communicable conditions and maternal mortality indicators together with the results of Martinson's study, necessitate early assessment of the operational uptake of this guideline.

The study reports on the policy uptake of the Targeted Universal TB testing (TUTT) of HIV positive antenatal patients. It identifies possible operational challenges of TUTT in other high-risk groups such as HIV positive population, household contacts and patients with previous TB (Lebina, 2021). Sub-objectives include linkage to care and treatment outcomes. The findings of this study will contribute to informing policy and decision makers on programmatic implementation of future TB interventions.

1.5 Significance of the study

As one of the high burden diseases in South Africa, tuberculosis carries a significant risk within the HIV population. Early tuberculosis detection in HIV positive pregnant women is imperative to avoid serious life-threatening implications and to limit infection spread in the community and households. The reported findings will assist in highlighting the operationalizing of the Universal TB testing in HIV positive pregnant women, in a real-life setting.

1. 6 Conclusion

Globally and locally, TB remains one of the most serious threats to obstetric health in lower and middle-income countries (LMICs) (WHO, 2021a). There has been limited research since the implementation of the Universal testing of TB with GeneXpert in HIV infected pregnant women.

The rest of the thesis is organised as follows: The literature review chapter describes research studies focussed on burden of TB, case finding and systematic screening in HIV infected pregnant patients. Secondly, chapter 3 explains the methodology used in this study including the analysis of secondary routine data. This is followed by chapter 4, which presents study results. Chapter 5 discusses the results and their relevance to previous studies and current context of TB testing among HIV infected pregnant women. Lastly, chapter 6 provides a summary and recommendations of the study in terms optimizing TB case detection in this vulnerable group of patients.

Chapter 2: Literature review

2.1 Introduction

TB in HIV infected pregnant women increases the risk of mortality by 400%, and accounts for 15-34% of indirect causes of maternal mortality globally (WHO, 2019). TB attributed 33.2% of non-pregnancy related infections in 2017, which contributed 25% of all maternal mortality in South Africa (Petro, 2017). Most high burdened countries have limited data available on the prevalence of TB, despite the detrimental impact on maternal health (Zumla *et al*., 2014). This literature review focusses on evidence from various studies on the burden of TB disease, TB diagnostics and TB case detection used in HIV infected pregnant women.

2.2 Burden of TB disease in HIV-infected pregnant women

The importance of integrating TB in child and maternal health care packages, has been supported by Sugarman`s (2014) estimation of global burden of TB disease in pregnant women. Using existing antenatal, TB demographics and indicators across 217 countries to calculate the TB burden. The study reported an estimated 216599 pregnant women with active TB in 2011 globally. The greatest burden reported in the African region with an estimated 89400 cases. The study succeeded in highlighting the burden of TB in pregnant women and identified a large proportion of missed active cases in high burden areas (Getahun, 2012).

South African local studies also started investigating case detection, diagnostics and the outcomes of TB in HIV pregnant women, as TB was one of the leading causes of death in HIV high burden settings. Gounder`s (2011) cross sectional study reported on

the integration of TB case detection in BANC and Prevention mother-to-child transmission programs (PMTCT) in Soweto, South Africa. This research demonstrated high numbers of active TB in HIV positive pregnant women with an incidence of 688 cases per 100000 vs 201 cases per 100000 in the HIV negative group (Gounder *et al.*, 2011). Despite limitations such as using four question symptom screening and exclusion of Chest X Ray diagnoses (due to pregnancy) that led to underestimation of TB detection, the study highlighted the need for integrating TB screening, as well as TB preventative treatment in both ART and PMTCT services in the local setting (Gounder *et al.*, 2011). Subsequent studies in the African and local context have reported on the burden of TB disease in the pregnant population, with focussed lenses on HIV infected women. One of the few South African studies conducted in the last 5 years comparing Universal sputum testing versus symptom-based screening in HIV infected pregnant women, also reported on a TB prevalence of 3.7% (screened with universal sputum testing) and 0.37% (Symptom screened) (Martinson *et al.*, 2017). Hamda`s (2020) cross sectional study in Botswana reported TB prevalence amongst HIV infected pregnant women of 1.45%. An investigation of case detection amongst pregnant and postpartum women in Eswatini, also reported a TB prevalence of 5% in HIV pregnant women (Pasipamire, 2020).

2.3 TB case finding in HIV infected pregnant women

The lack in sensitivity of the four-symptom TB screening tool was highlighted by the cross-sectional study, involving 1415 HIV positive women accessing care at South African antenatal facilities (Hoffmann *et al*., 2013). The study was a comparison between HIV positive pregnant women that were symptom screened versus the result of their sputum tests results (included direct /culture). The study reported a 28% sensitivity on symptom screening, as 73% of women with a confirmed positive culture

were asymptomatic (Hoffmann *et al.*, 2013). The suboptimal performance of the WHO screening tool was also evident in a Kenyan study, reporting on the low sensitivity (43%) and specificity (81%) (LaCourse, 2016). Other diagnostic tools assessed: Sensitivity and specificity of the GeneXpert (43% and 99%), TB smear (0% and 99%) and LAM (0% and 95%) (LaCourse, 2016). These research findings identified the concerning high amount of false negative results, which potentially could compromise the TPT program (LaCourse, 2016).

Subsequently a South African randomized control study was conducted, comparing HIV positive pregnant patients that had been symptom screened (SC) versus patients that were universally TB sputum tested (Martinson *et al.*, 2017). In the SC group (n=937) only women were that had positive symptoms were TB tested, whereas all women in the UC group (n=1095) were tested by GeneXpert and later culture. Case finding reported a10-fold increase in the Universal sputum-testing group compared to the SC group. The UC group also reported lower numbers of infant deaths. The study also confirmed that TB culture compared to the Xpert, detected more active TB in patients that were asymptomatic (Martinson *et al.*, 2017). These significant research findings led to the change from screening to testing of pregnant women in the South African National Department of Health 2019 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy, Adolescents, Children, Infants and Neonates (NDOH, 2019).

A number of studies evaluated the incorporation of different diagnostic tools into the screening framework. However, work performed by Pasipamire (2020) reported the sensitivity of the TB symptom-screening tool increased, when HIV positive pregnant women reported TB contacts. TST and IGRA found to suboptimal screening tools, whereas TB culture performed the best (Pasipamire, 2020).

Subsequently Hamda`s (2020) cross sectional study in Botswana reporting on the contribution of the Xpert MTB/Rif to TB case finding in pregnant women, also supported the shift towards sputum screening test. The study reported a sensitivity and specificity of 100%, for the Xpert (Hamda, 2020). The WHO consolidated guidelines on Tuberculosis Screening Module (2021) supports systematic screening for TB disease. The module also recommends diagnostic tools used for screening for different target profiles (WHO, 2021b). It is however concerning that the finding generated from the Diagnostic accuracy report comparing different screening tools amongst HIV infected pregnant women, reported the Xpert with a sensitivity of 55% and specificity of 99% (WHO, 2021b). See Table 1 in the appendix 1. The report also recommends that further research is required in the HIV subpopulations, as well as the use and placement of molecular rapid diagnostics in antenatal services as opposed to ART services (WHO, 2021b). It is evident that more research is required to review the efficacy of the Xpert as a screening tool.

2.4 Systematic TB screening in South Africa

Apart from Getahun`s (2012) recommendation of strengthening and incorporating TB screening in antenatal and paediatric care services, a gap had also been highlighted in the TB case detection of all patients (irrespective of symptoms) that access PHC facilities (Kweza, 2018). Between 62.9% - 78.5 % of clients with symptoms, receiving care at primary health care institutions are missed (Kweza, 2018). Whilst 89% to 100% of patients that present for other reasons (non-TB complaints) are not screened (Kweza, 2018). A South African cluster randomized study conducted recently, also identified the shortcomings of symptom screening in health facilities. Comparing facilities with Universal TB testing of all high-risk groups to facilities that continued with the traditional symptom screening (Lebina, 2021). Vulnerable groups included

all HIV positive patients, previously TB treated patients (in last two years) and TB close contacts (Lebina, 2021). Findings reported no significant increase in case detection at facilities that performed targeted universal TB testing (TUTT), but found an increase of 17% of cases reported by a difference in difference analysis (Lebina, 2021). As well as a reduction of 8% in TB diagnosis per facility per month, in the clinics, that continued with standard screening (Lebina, 2021).

There is limited information on the implementation of Systematic TB screening, and is used interchangeably with Active case finding (WHO, 2021b). Factors such as lack of capacity in patient communication/education, workforce, epidemiological effect and cost-effectiveness influence active TB case finding significantly (Bierman, 2019). The WHO recommends the successful implementation of six principals prior to undertaking systematic TB screening: Effective TB diagnostic systems, clinical/pharmaceutical management, appropriate capacity and supportive strengthening to intensify the program if case detection increase (WHO, 2021b). It is evident that the estimated losses in the TB cascade reflect a struggling program. Patient losses include 5% of patients who are unable to access testing, 13% loss at diagnosis, 12% initial loss to follow up and 17% unsuccessfully treated (Naidoo, 2017). These estimates are concerning and motivate for further research on the operational feasibility and success of the TUTT in HIV infected pregnant women and other high-risk groups.

There has been limited information on operational research evaluating the efficacy of TUTT in HIV positive pregnant, since implementation in 2019.

Chapter 3: Research Methodology

3.1 Introduction

This chapter describes the research methodology that includes the study aim, objectives, design, study population and sampling. It also includes method of data collection and analysis. The last section includes measures to ensure validity and generalizability, as well as ethical management within the study.

3.2 Study Aim

The study aims to evaluate the uptake of the Universal TB testing in HIV positive pregnant women. It will assess whether the transition from systematic TB screening to Universal TB testing (post policy implementation) at PHC level, has increased the TB case detection. This study also aims to identify whether further intervention is required, that will mitigate serious health implications of TB, due to inefficient TB case finding systems.

3.3 Study Objectives

- To determine the uptake of the implementation of the policy Universal Testing of TB in HIV infected pregnant women, in City of Cape Town PHC facilities. Cape Town.
- To determine if the implementation of the Universal TB testing by GeneXpert at the first antenatal visit, increased TB case detection in HIV infected pregnant women.
- To determine the number of HIV infected pregnant women that had a positive GeneXpert, smear or culture result from June 2018 to May 2019 and June 2020 to May 2021, according to Universal testing of TB policy.

- To describe linkage to care of HIV infected pregnant women with a positive GeneXpert, smear and culture result from June 2018 to May 2019 and June 2020 to May 2021.
- To determine TB treatment outcomes of HIV-infected pregnant women with a positive GeneXpert, smear and culture (taken June 2018 to May 2019 and June 2020 to May 2021).

3.4 Study Design

This was a retrospective and non-experimental before-and-after study design. The study observed changes in a similar group of patients (HIV infected pregnant women) from pre and post periods, after an intervention (policy) had been implemented (Thompson, 2007). The study design included advantages such as minimal researcher input/control (reduced bias), assessed multiple variables (Thompson, 2007) and used routine data, which was low in cost and time. A secondary data analysis was done comparing screening, testing and TB linkage to care in HIV positive antenatal patients in 2018/2019 (prior to Universal Testing policy implementation) and in 2020/2021 after the implementation of this new TB testing policy. It investigated the exposure, which were the time periods that HIV infected pregnant women accessed BANC services and the outcome (TB sputum tested) simultaneously (SOPH, 2020). The assessment of exposures and outcomes increased the efficiency of the study and determined the alignment of service delivery to the policy.

3.5 Study Population

The study population included HIV positive antenatal clients, registered on the electronic Prehmis health information system (periods 01/06/2018-31/05/2019 and 01/06/2020-31/05/2021). These patients accessed 76 PHC facilities rendering BANC

services in City Health PHC facilities, Cape Town. Previously 86 facilities rendered BANC services, but 9 out of the 10 facilities were excluded at the time of data collection, due handover from local municipality to Metro Health service (MHS) and consolidated under one Provincial health authority.

3.6 Study Setting

Fifty-nine percent (59%) of the Cape Metro district (population=4686518) consisted of Female residents, of which 55% ranged between the ages of 15 and 49 years (WCGH, 2020a). Metro Health Service (MHS) and the City Health (local municipality) collectively provided public primary health care to the district`s population. The Cape Town Metro district divided into 8 sub-districts, with 44 MHS primary health care facilities and 76 City Health PHC fixed facilities. MHS provided adult medical management, which includes non-communicable diseases, female screening/diagnostic health, venereal diseases, TB, HIV at all their facilities and paediatric health services to children under 13 years at limited facilities. City Health provided a similar package of care and extended care to children under 13 years. Patient care packages are however subject to the categorization of the facility, determined by pharmacy capacity and other factors. The study evaluated the Universal testing of HIV infected pregnant women in all City Health facilities, which rendered antenatal and TB (screening, testing and treatment) services.

The clinics and community day centres selected for this study were a true reflection of the services and patient profile at the primary care level. These facilities render basic antenatal, HIV, TB screening and treatment services. They are predominantly nurse driven with medical officer support. All City health facilities had integrated TB symptom screening into their programs. However, prior to policy implementation in

2019, the BANC services were only limited to systematic TB screening versus universal TB screening and testing of all HIV infected pregnant women.

3.7 Sampling

HIV infected antenatal clients remain a smaller subgroup of facility total patient counts and inclusive sampling therefore performed. All HIV infected pregnant women from the HTS (HIV Testing Service) antenatal report that attended their first antenatal visit for the two specified times, were included.

Inclusion criteria:

1) All pregnant women with a known HIV status (from HTS data element or antenatal patient category: Known Positive or Known Positive on ART) or tested HIV positive at their first antenatal (booking) visit in PHC.

2) Clients between 15 and 50 years old, that presented for their first antenatal visit from 01/06/2018-31/05/2019 and 01/06/2020-31/05/2021. All data captured and reported in the Antenatal HTS report.

Exclusion criteria:

1) Known existing TB diagnosis, as captured at booking visit or reported on the electronic TB register (ETr), where duration of TB treatment episode coincided to the booking visit date.

2.) Patients that had a TB sputum sample (with results) taken 7 days prior to their booking visit date. PACK clinical guidelines stipulate that results should be available after 2 days (KTU, 2021). An extension to 7 days also accommodated for weekends and any operational delays that could have affected the turnaround time for results.

3.) Women that were newly diagnosed with HIV at their 20 and 32 antenatal visits, as the policy stipulates TB testing to be performed at first antenatal visit (booking visit).

3.8 Data Collection

This study used records from all HIV positive pregnant women that accessed BANC services at their first antenatal visits for the periods 2018/2019 and 2020/2021. All routine patient data and encounters from the PHC file were captured onto Prehmis (Electronic health information system used in the City of Cape Town), which were linked to different programs of City Health. Data extraction occurred in October 2022, from the back end of Prehmis electronic database.

The extracted data provided by the City Health information office, consisted of four separate Excel datasets that were password protected. The first three accessed from the HTS Antenatal register with different data elements and the fourth set extracted from ETr. The researcher captured and managed all extracted data into a data collection tool, prior to analysis. See details below:

Dataset 1 included all patient records with either *HIV positive status* at first antenatal visit and records where client category was *Known HIV POS or Known HIV Positive on ART* at first antenatal visit. Clients that tested positive throughout pregnancy for HIV at antenatal visit 20 and 32 weeks were also included in this provided dataset. Elements of interest that were included: ART initiation episode date, intake date of first antenatal visit, patient category, and first visit gestational age in weeks, facility name and sub district name.

Dataset 2 included all antenatal clients (HIV positive and negative) at their first antenatal visit, with TB screening elements (TB screening result and TB symptoms status) and event dates. TB screening elements captured differently were subject to the type of service that the client received on the day. Therefore, one client might have had two different screenings captured on one day. Concatenation used for double or different screening elements, will be discussed the pre-analysis cleaning section.

Dataset 3 consisted of all (HIV positive and negative) antenatal patient records at their first antenatal visit (extracted from the HTS antenatal register) for specified periods (June 2018 - May 2019 and June 2020 - May 2021) and all their laboratory sputum type of tests and results (extracted from the Presumptive TB register).

Dataset 4 (extracted from ETr) included records of all patients diagnosed and initiated on Drug sensitive TB treatment in City Health facilities. The reported period was from January 2018 until December 2021. All notified TB cases were captured monthly directly onto this register, at facility level. The dataset included TB registration number, personal identifiers (name, surname and DOB), laboratory sputum results and variables of interest: treatment start date, TB type, patient category and System generated treatment outcome.

3.8 Pre-Analysis Data Cleaning

The first three datasets (described above) cleaned, as described above. Followed by linkage of the combined dataset (1-3) to the ETr dataset. The researcher created a patient identifier consisting of the name and date of birth (linked to report year) for all four datasets. As some women were pregnant in both cohorts and ETr data did not include a PHC folder number. See data collection tool (Appendix 2).

Dataset 1 (per specified year period) became the main member data list and matched to all other remaining datasets. Initially the PHC folder number, report year and intake date of first antenatal visit was grouped per line, as some women presented in both cohorts. Followed by a unique patient identifier consisting of first name and DOB was added and 201 duplicates were removed. Initial 7851 records.

As per City Health research approval, the researcher excluded 43 patients (2018/2019 period) and 29 patients (2020/2021) from 9 facilities. These facilities were in the process of being

consolidated under one Provincial health authority. Thereafter followed the removal of Patients that tested HIV positive at antenatal 20 and 32 weeks (total 72 patients). As the aim of the study was to evaluate policy implementation at the first antenatal visit.

The researcher matched the main member list to Dataset 2 and excluded patients that were not on Dataset 1. Thereafter, standardized the TB Screening elements, by adding two columns. TB screening had different element data types that were subject do different encounters. Screening that took place at HTS services were captured as, *TB symptoms identified.* Followed by yes/no in the TB symptom data value. Whereas TB screening in other services were captured as *TB pos* (positive) or *TB neg* (negative) and left blank in the TB symptom data value. Therefore, one patient could have had two different TB screenings on one day and appear as a duplicate. One line per patient remained, after concatenation.

Additional columns as follows:

- TB screened with dropdown: One (yes) = TB pos, TB neg and TB Symptoms identified

  Zero (no) = Null/ Unknown

- TB symptom status with dropdown:

  Yes = TB pos and TB symptoms identified Yes

  Known TB = Known TB

  No = TB neg and TB symptoms identified No

  Unknown = Unknown

As dataset 3 included all sputum tests and results that had been done for all antenatal clients from the HTS antenatal register, a reporting period of 6 weeks from the last antenatal visit of each 2018/2019 and 2020/2021 period was set and all other tests and results outside of the reporting periods were removed. Subsequently the main member data list matched to dataset 3 and removed all other members.

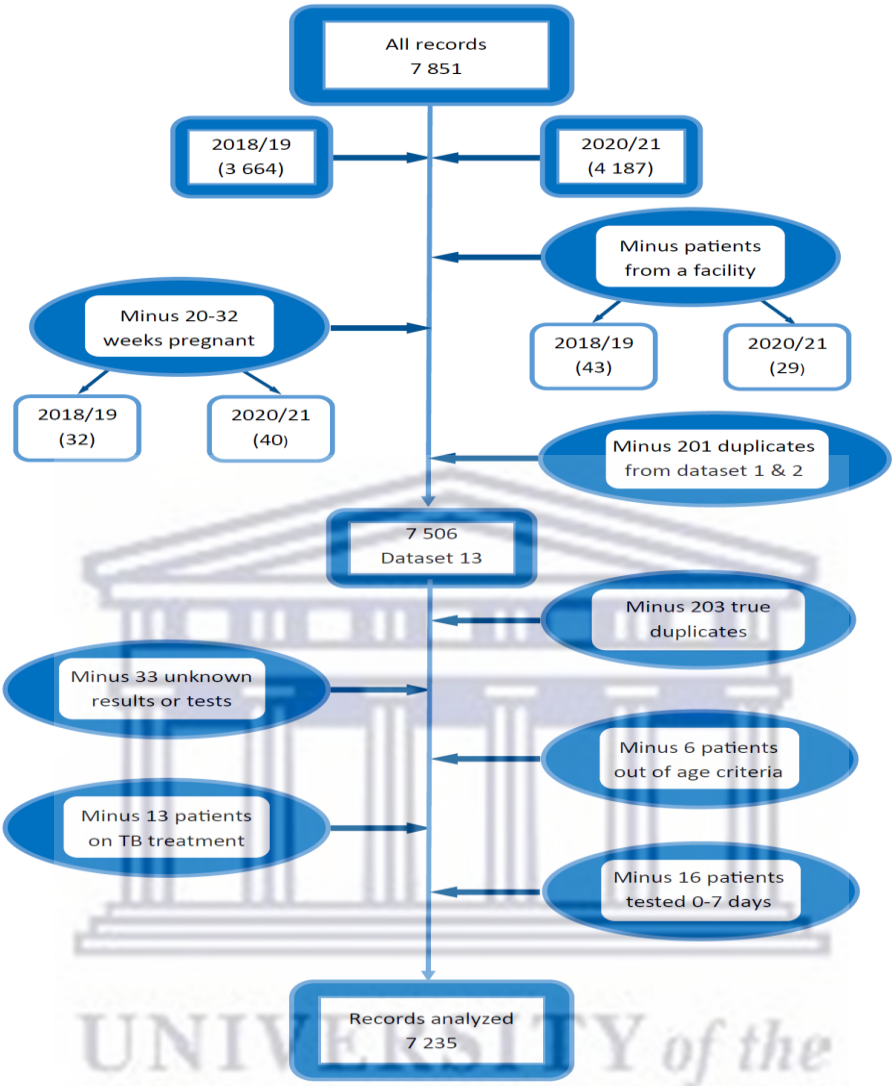
After conditional formatting, the researcher identified a second round of duplicates. Several clients had three lines, as different test types with results were in separate lines. All results from the same date moved into one line. Thereafter the researcher selected the closest date to the booking visit, where patients had more than one result. Followed by excluding 33 patient records that had a date for TB sputum testing, but no record and results were unverified or not found. After filtering the report year, I removed 203 true duplicates.

The researcher created a time period window of 0 days (booking visit) to 42 days (6 weeks). This 6-week window accommodated for operational challenges/variances such as staff shortage, delayed laboratory collection times or patients that tested positive in a non-antenatal section of facility. Example. Patient presented with a positive pregnancy test towards the end of the day, in the Family planning section/ outreach. The clinician performed a comprehensive antenatal assessment to establish gestation and excluded any immediate complications. All laboratory investigations delayed until the second visit at the Antenatal section. Hence forty-two (42) days used, based on the test performed on the first (performed possibly outside of the antenatal program) or second antenatal visit. All tests done prior to booking (that were not included in other exclusion groups) and past 42 days (from antenatal visit), grouped as not done according to the policy. The purpose of the study was to evaluate whether Universal TB sputum testing were performed at entry point into the BANC service, irrespective of TB symptoms.

Linkage of the merged dataset to the ETr dataset, took place through index matching. Followed by the removal of true duplicates through various exclusion exercises. Secondly, the researcher excluded all clients with positive sputum results (prior to booking) from the cohort that commenced treatment 6 months and less from the booking visit. As well as clients, that were still on TB treatment at their booking visit.

The following exclusions included patient records captured as *Known TB*, patients younger than 15 and older than 50 years. As well as patients with tests done 7 days prior to booking and results available. This 7-day time window was in alignment with PACK guidelines, requiring patients to return after 2 days for their results (KTU, 2021) and accommodating 5 days for weekends and operational delays. Once all datasets merged in one excel sheet, the researcher assigned a unique identifier to each client and removed all personal identifiers.

Figure 1: Data cleaning flow chart



3.9 Data Analysis

A descriptive analysis compared clinical characteristics of the two patient cohorts for June 2018 to May 2019 (3664 patients) and June 2020 to May 2021 (4187 patients). Categorical variables were summarised as proportions. A contingency coefficient tested for differences in ratios over the two periods. The total number and proportions were used to demonstrate and compare the HIV infected antenatal patients that were TB screened, tested, diagnosed and treated at Basic antenatal care (BANC) services in PHC facilities.

The researcher conducted the Statistical analysis using SPSS. Associations between individual patient characteristics (cohort period, age, gestation and ART) and tested patients were determined by using a multivariate analysis. The Hosmer-Lemeshow goodness-of-fit test was used for the logistic regression model. Odds ratios and 95% confidence intervals were calculated. The p-value less than 0.05 and contingency coefficient test measured the statistical significance.

3.10 Validity

The study design by nature reduced selection bias, by using all appropriate HIV positive pregnant women at their first antenatal visits. Pre-defined data elements (variables) reduced selection bias, as well establishing clearly defined inclusion and exclusion criteria (SOPH, 2021).

Data fields entered by different facility data capturers could potentially have introduced measurement bias. However, the use of Prehmis health information system mitigated this bias, through standardized data fields and sequenced actions. Differently captured TB screening elements for various programs, also potentially introduced measurement bias. This was resolved through creating a separate column and concatenating different types of screening elements and follow up elements. ETr data were captured monthly directly at the facilities. Routine verification took place at various sub district, provincial and national reporting levels. Patients in City facilities were all screened using similar prompting stationery ex. TB screening, HTS screening forms, and management guidelines. All facilities used the same method in collecting TB sputum and laboratory stationery. One regional laboratory processed all specimens and used standardized testing algorithms. Secondary data did not require active patient participation and therefore excluded participation error and bias.

3.11 Generalizability

The patients of whom the records were included in this study were not only representative of patients that accessed public health care sectors, but also of the population across the City of Cape Town Metro. The policy of Universal Tuberculosis sputum testing by GeneXpert Ultra in HIV infected pregnant women aligned with both provincial and national guidelines and the findings of this study will be relevant to the management of TB screening and testing at PHC facilities with similar HIV burden of disease.

3.12 Ethical Considerations

This study involved the use of confidential HIV information of patients, which required anonymization of the data. All data were extracted from Prehmis in excel format. Original password protected datasets were requested with names, surnames, DOB/age, gender, and age. After data sets were linked, a unique identifier was assigned to participants and identifying information removed. The original data sets have been saved in the main researcher`s device with password protection and will be saved for three years.

Consent had been waivered, due to the use of retrospective routine data. No interventions took place and patients were not harmed or at risk, adhering to the non-maleficence principle. The researcher will provide a report of Sub-district performance in aligning to the Universal testing policy.

Ethics approval was obtained from the University of Western Cape`s Biomedical Research Ethics Committee. The City of Cape Town Health department granted permission to access and report routine data.

Chapter 4: Results

4.1 Introduction

This chapter presents findings on the operational uptake of the Universal TB testing policy in HIV positive women in Cape Town Metro by comparing two cohorts – pre and after policy introduction. It includes reporting of microbiologically confirmed TB results, linkage to care and treatment outcomes, as well as multivariable logistic regression determining association between testing and various individual factors.

This study reports extracted data for the periods of 01/06/2018 to 31/05/2019 and 01/06/2020 to 31/05/2021, of 74 PHC facilities. A total of 7235 records of HIV infected pregnant women at their first antenatal visit have been included for analysis, which consists of 3332 patient records for 2018-2019 period and 3903 records for 2020-2021 period.

4.2 Demographic and Clinical characteristics for HIV infected pregnant women

Table 1: Baseline demographic and clinical characteristics comparing two cohorts, 2018/2019 and 2020/2021

Characteristics	2018/2019 Cohort	2020/2021 Cohort	Total
	%(n)	%(n)	%(n)
Age in years at first antenatal visit			
15 – 19	0%(4)	1%(28)	0%(32)
20 – 24	6%(210)	11%(424)	9%(634)
25 – 29	23%(769)	25%(987)	24%(1756)
30 – 34	31%(1026)	30%(1165)	30%(2191)
35 – 40	29%(957)	26%(1025)	27%(1982)
41 – 45	10%(318)	7%(254)	8%(572)
45 years and above	1%(48)	1%(20)	1%(68)
Total	*100%(3332)*	*100%(3903)*	*100%(7235)*
Gestation at first antenatal visit			
< 20 weeks	65%(2175)	67%(2491)	64%(4666)
≥ 20 weeks	29%(964)	33%(1221)	30%(2185)
Unknown	6%(193)	5%(191)	5%(384)
Total	*100%(3332)*	*100%(3903)*	*100%(7235)*

ART initiated			
Yes	89%(2971)	91%(3535)	90%(6506)
No	11%(361)	9%(368)	10%(729)
Total	*100%(3332)*	*100%(3903)*	*100%(7235)*
TB Symptom screened			
Yes	17%(561)	16%(621)	16%(1182)
No	83%(2771)	84%(3282)	84%(6053)
Total	*100%(3332)*	*100%(3903)*	*100%(7235)*
Sputum Results: GeneXpert result			
Positive	12%(10)	3%(17)	4%(27)
Negative	85%(69)	95%(578)	94%(647)
No definitive result	2%(2)	2%(13)	2%(15)
Total	*100%(81)*	*100%(608)*	*100%(689)*
Sputum Results: Culture Result			
Positive	0%(2)	0%(5)	0%(7)
Negative	0%(12)	4%(145)	2%(157)
No Culture done	100%(3243)	96%(3274)	98%(6517)
Specimen contaminated	0%(0)	0%(1)	0%(1)
Total	*100%(3257)*	*100%(3425)*	*100%(6682)*
Sputum results: TB Smear Result			
Positive	0%(3)	0%(1)	0%(4)
Negative	0%(7)	1%(20)	0%(27)
No Smear	100%(3243)	99%(3274)	100%(6517)
Total	*100%(3253)*	*100%(3295)*	*100%(6548)*

The baseline demographic and clinical characteristics comparing HIV infected antenatal patients of periods 2018- 2019 and 2020- 2021 are included in Table 1. The cohort includes 46% (n=3332) of the 2018/2019 group and 54% (n=3903) of the 2020/2021 group, which represents relative equal sampling. The highest age proportion of patients for both groups were between the ages of 25 and 40 years, with 84% and 81% respectively. The median age was 33 years (IQR: 29, 37) in the 2018/2019 cohort and 32 years (IQR: 27, 36)) for the 2020/2021. Sixty-eight percent (n= 4666) of women presented before 20 weeks for their first antenatal visit, with 69% and 67% respectively for the 2018/2019 and 2020/2021 groups. Gestations at the first antenatal visit ranged from 1 week to 42 weeks, with the 2018/2019 cohort reporting

a median of 15 weeks (IQR: 10, 21) and cohort 2020/2021 a median of 16 weeks (IQR: 11, 22). Both median and mean were similar, indicating a normal distribution. There were 384 patient records did not have gestational age captured at the first antenatal visit.

The greatest proportion of patients (90%) commenced on ART at their first antenatal visit, with an increase from 89% in 2018 (n= 2971) to 91% in 2020 (n = 3535).

Overall, staff screened 16% of patients for TB. The 2018/2019 cohort reported TB screening for 17% of the 3332 patients and 16% of 3903 patients of the 2020/2021 cohort.

4.3 Policy uptake on Universal testing of TB among HIV infected pregnant women at their first antenatal visit.

4.3.1 TB screening and sputum testing

Table 2: A comparison of TB sputum screening and testing at first antenatal visits in 2018/2019 and 2020/2021 cohort.

TB testing	2018/2019 Cohort %(n)	2020/2021 Cohort %(n)	Total	Contingency coefficient	P value
Proportion tested for TB on Day 0	0,21% (7)	10,89%(425)	432	0,237	<0.001
Proportion tested for TB within 42 days	0,27%(9)	2,13%(83)	92		
Proportion tested for TB after 42 days	0,78%(26)	1,26%(49)	75		
Proportion screened for TB	16,8%(561)	15,9%(621)	1182	0,012	0,288
GeneXpert test done	2,43%(81)	15,58%(608)	689	0,219	<0.001
TB Culture test done	0,42%(14)	3,87%(151)	165	0,128	<0.001
TB Smear test done	0,30%(10)	0,72%(28)	38	0,041	0,004

Testing of patients during their antenatal period included 3-time categories: Patients that were TB tested at their first antenatal visit (day 0), within 6 weeks (42 days) from their first antenatal period and patients tested after a 6-week (42 days) period from booking. There was an increase from 0.2% patients (n=7) that were tested at their booking visit in 2018/2019 to 11 %(n=425) in 2020/2021. Patients that were tested within 6 weeks after booking, also increased from 0.3% (n=9) in 2018/2019 to 2% (n=83) in 2020/2021. Lastly, reporting on patients that tested after

6 weeks from booking were similar with 1% (2018/2019) and 1.3% (2020/2021). Overall, there was an increase from patients that had been sputum tested from 1.3% in 2018/2019 to 14.3% in 2020/2021 (p-value< 0.001), which is statistically significant.

The proportion of sputum that were GeneXpert tested increased from 2.4 %(n=81) in 2018/2019 to 15.6 %(n=608) in 2020/2021 with p-value less than 0.001. The proportion of sputum TB culture tests also increased from 0.4 %(n=14) to 3.9 %(n=151), which was also statistically significant. The TB smear tests increased significantly (p-value =0.004) from 0.3% (n=10) to 0.7% (n=28).

Table 3: Multivariate logistic regression of patient predictors associated of Sputum tested amongst HIV infected pregnant women

Predictor	Odds ratio	95% Confidence Interval	P-value
Cohort	0.949	0.805-1.119	0.533
ART initiated	0.937	0.717-1.225	0.634
Screened for TB symptoms	1.089	0.879-1.350	0.436
Gestation age at first antenatal visit	1.001	0.841-1.192	0.993
Age group	0.996	0.927-1.070	0.916

There is no association between clients that are sputum tested and clinical/demographic characteristics. Characteristics include reporting year, patient initiated on ART, Screened for TB symptoms, patient's gestational age at booking visit and age of the patient. The 95% confidence interval crosses 1 and the p-value is more than 0.05, which is statistically insignificant.

Table 4: A comparison of proportion of patients screened, symptom screened positive and tested for TB across sub-districts for 2018/2019 and 2020/2021

2018 Cohort														
Sub-district	HIV+ pregnant patients		Facilities		Screened for TB symptons		Positive TB status		GeneXpert Test		TB Culture test		TB Smear test	
	No	Percent	No	Percent	No	Percent	No	Percent	No	Percent	No	Percent	No	Percent
Eastern	747	22%	11	16%	136	24%	3	18%	24	30%	1	7%	2	20%
Khayelitsha	676	20%	8	12%	102	18%	6	35%	12	15%	3	21%	1	10%
Klipfontein	184	6%	7	10%	31	6%	0	0%	4	5%	1	7%	1	10%
Mitchells Plain	590	18%	8	12%	116	21%	5	29%	11	14%	2	14%	3	30%
Northern	395	12%	6	9%	54	10%	1	6%	11	14%	1	7%	2	20%
Southern	142	4%	13	19%	34	6%	1	6%	3	4%	1	7%	0	0%
Tygerberg	192	6%	6	9%	28	5%	0	0%	10	12%	4	29%	1	10%
Western	406	12%	8	12%	60	11%	1	6%	6	7%	1	7%	0	0%
Total	**3332**	**100%**	**67**	**100%**	**561**	**100%**	**17**	**100%**	**81**	**100%**	**14**	**100%**	**10**	**100%**

2020 Cohort														
Sub-district	HIV+ pregnant patients		Facilities		Screened for TB symptons		Positive TB status		GeneXpert Test		TB Culture test		TB Smear test	
	No	Percent	No	Percent	No	Percent	No	Percent	No	Percent	No	Percent	No	Percent
Eastern	844	22%	11	16%	134	22%	4	21%	36	6%	1	1%	5	18%
Khayelitsha	805	21%	8	12%	104	17%	1	5%	55	9%	22	15%	6	21%
Klipfontein	229	6%	6	9%	42	7%	0	0%	8	1%	0	0%	0	0%
Mitchells Plain	598	15%	8	12%	96	15%	5	26%	155	25%	58	38%	5	18%
Northern	499	13%	7	10%	82	13%	4	21%	215	35%	39	26%	3	11%
Southern	283	7%	15	22%	58	9%	1	5%	21	3%	2	1%	0	0%
Tygerberg	221	6%	5	7%	47	8%	3	16%	33	5%	11	7%	3	11%
Western	424	11%	9	13%	58	9%	1	5%	85	14%	18	12%	6	21%
Total	**3903**	**100%**	**69**	**100%**	**621**	**100%**	**19**	**100%**	**608**	**100%**	**151**	**100%**	**28**	**100%**

There was a wide disparity across all eight Sub districts (SD) for both 2018/2019 and 2020/2021. Eastern SD symptom screened the highest proportion of patients (24% and 22%) for 2018/2019 and 2020/2021 respectively. However, it had the most significant reduction in GeneXpert testing from 30% (2018/2019) to 6% (2020/2021), despite reporting an increased proportion of patients that had a positive symptom screen from 18% (2018/2019) to 21% (2020/2021).

In contrast to Northern SD that screened comparatively less over 2018/2019 and 2020/2021 (10% and 13%) but reported a significant increase in patients that had a positive symptom screen from 6% to 21% for 2018/2019 and 2020/2021 respectively. This Sub District also

reported a significant increase of GeneXpert testing from 14% to 35% for 2018/2019 and 2020/2021 respectively.

More than 50% of Sub-Districts reported a reduction in screening, positive symptom screenings and GeneXpert testing from 2018/2019 to 2020/2021, except for Mitchells Plain (14% to 25%), Northern (14% to 35%) and Western (7% to 14%) Sub-districts that reported a doubled increase in testing from 2018/2019 to 2020/2021.

4.4 Microbiologically confirmed TB cases in HIV infected pregnant women

Table 5: A comparison of microbiologically confirmed TB by GeneXpert in 2018/2019 and 2020/2021

Detected TB Cases by GeneXpert	2018/2019		202/2021		Contingency coefficient	P value
	%	n	%	n		
No in the cohort		3332		3903		
GeneXpert test done	2,4%(81)		15,6%(608)		0,219	<0.001
GeneXpert (+) - Rifampicin Inconclusive	0,0%(0)		0,5%(3)		0,222	<0.001
GeneXpert (+) - Rifampicin Resistant	1,2%(1)		0,2%(1)			
GeneXpert (+) - Rifampicin Sensitive	11,1%(9)		2,1%(13)			
GeneXpert positive (Total)	12,3%(10)		2,8%(17)			
Prevalence of GeneXpert+ TB	12%		3%			

Although there was a significant increase of 2.4% (2018/2019) to 15.6% (2020/2021) of GeneXpert TB tests done, there was a reduction of confirmed positive GeneXpert prevalence from 12.3% in 2018/2019 to 2.8% in 2020/2021 (p-value less than 0.001). A proportion of 11.1% (2018/2019) and 2.8 %(2020/2021) were Rifampicin sensitive (susceptible to the first line TB regimen), whilst 1.2% and 0.2% were Rifampicin resistant respectively for 2018/2019 and 2020/2021. All differences are statistically significant.

Table 6: A comparison of microbiologically confirmed TB by sputum TB culture in 2018/2019 and 2020/2021

Detected TB Cases by Culture	2018/2019		2020/2021		Contingency coefficient	P value
	%	n	%	n		
No in the cohort		3332		3903		
TB Culture test done	0,4%(14)		3,9%(151)		0,128	<0.001
TB Culture positive	14,3%(2)		3,3%(5)		0,129	<0.001
Prevalence of TB Culture + TB	14%		3%			

The proportion of TB culture tests performed increased from 0.4% (n=14) in 2018/2019 to 3.9% (n= 151) in 2020/2021, which was statistically significant. Positive TB culture prevalence however reduced from 14.3% (2018) to 3.3% (2020).

Table 7: A comparison of microbiologically confirmed TB by Smear microscopy in 2018/2019 and 2020/2021

Detected TB Cases by Smear	2018/2019		2020/2021		Contingency coefficient	P value
	%	n	%	n		
No in the cohort		3332		3903		
TB Smear test done	0,3%(10)		0,7%(28)		0,041	0,004
TB Smear positive	30,0%(3)		7,1%(2)		0,052	0,001
Prevalence of TB smear +TB	30%		7%			

There was a statistically significant difference (p-value =0.004) in the proportion of sputum tests done between the two years, with 0.3% in 2018/2019 and 0.7% in 2020/2021. As well as a statistically significant reduction (p-value=0.001) in positive TB smear results from 30% (2018/2019) to 7.1% (2020/2021)

4.5 Linkage to care amongst HIV infected pregnant women positive TB sputum results from 2018/2019 and 2020/2021

Table 8: A comparison of anti-TB treatment initiation rate of microbiologically confirmed TB by GeneXpert, culture and smear for 2018/2019 and 2020/2021.

TB Test Type	Total confirmed cases	TB treatment commenced			
		2018/2019		2020/2021	
		Started %(n)	Not started %(n)	Started %(n)	Not started %(n)
GeneXpert (+)	27	27% (3)	73% (8)	56% (9)	44% (7)
TB Culture (+)	7	0% (0)	100% (2)	0% (0)	100% (5)
TB Smear (+)	4	67% (2)	33% (1)	0% (0)	100% (1)

Thirty-seven percent (37%) of microbiologically confirmed TB sputum cases commenced on treatment, for both combined cohorts. GeneXpert diagnosed patients were linked to care as follows: 27% (n=3) in 2018/2019 and 56% (n=9) in 2020/2021. None of the Culture diagnosed patients' commenced treatment. Sixty-seven percent (67%) of smear positive patients linked to care in 2018/2019.

4.6 TB treatment outcomes of HIV-infected pregnant women with positive GeneXpert smear and culture results

Table 9: A comparison of TB treatment outcomes of patients with microbiologically confirmed TB, that started anti-TB treatment in 2018/2019 and 2020/2021

TB Treatment Outcome	Year		Total	Contingency Coefficient	P value
	2018/2019	2020/2021			
	%(n)	%(n)			
GeneXpert (+)	**37%(10)**	**63%(17)**	**27**	0.538	0.027
Treatment completed/Cured	20%(2)	80%(8)	10		
LTFU	33%(1)	67%(2)	3		
ILTFU	50%(7)	50%(7)	14		
Culture	**29%(2)**	**71%(5)**	**7**	0.092	<.001
ILTFU	29%(2)	71%(5)	7		
Smear	**75%(3)**	**25%(1)**	**4**	0.5	0.513
Treatment completed/Cured	100%(1)	0%(0)	1		
LTFU	100%(1)	0%(0)	1		
ILTFU	50%(1)	50%(1)	2		
Total	15	23	38		

Table nine reports on the comparison of TB treatment outcomes between cohorts 2018/2019 and 2020/2021. There was an increase in GeneXpert positive diagnosed cases that completed their treatment from 20 %(n=2) in 2018/2019 to 80 %(n=8) in 2020/202. However, GeneXpert positive patients with a LTFU outcome also increased from 33 %(n=1) to 67 %(n=2), whilst patients with ILTFU outcomes remained the same at 50 %(n=7). These differences were all statistically significant, as their p-value was 0.027.

Although there were no culture positive cases that completed treatment, there was a statistically significant increase of patients with an ILTFU outcome, from 29 %(n=2) in 2018/2019 to 71 %(n=5) in 2020/2021 (p-value less than 0.01).

Smear positive cases that completed their treatment and that had a LTFU outcome were reduced insignificantly from 100% (n=1) in 2018/2019 to 0% in 2020/2021 (p-

value=0.513). Patients that were never linked to care, remained the same for both cohorts at 50% (n=1) respectively.

Chapter 5: Discussion

5.1 Introduction

The purpose of this study was to assess the uptake of the policy on Universal Tuberculosis sputum testing by GeneXpert Ultra in HIV infected pregnant women, at all City Health PHC facilities in Cape Town. This chapter discusses findings on clinical and demographic characteristics of the two respective cohorts of 2018/2019 and 2020/2021, that accessed care at their first antenatal visits. Further discussions include the programmatic uptake of the Universal TB testing policy at PHC level, the comparison of microbiological confirmed TB test results between the two cohorts, as well as relevance against other data and research. The chapter also explores the findings of linkage to care and TB treatment outcomes of the patients that had a positive sputum test. Lastly, it highlights limitations of the study.

5.2 Description of clinical and demographic characteristics of patient records

This is a unique study as it assessed the real life setting in determining the success of the policy roll out, without any researcher intervention or additional resources. The two cohorts of 2018/2019 and 2020/2021 are relatively equal (45% and 56%) in size and therefore do not represent skewed results or introduced measurement bias. The increase from 3332 pregnant women at booking visits to 3903 patients in the 2020/2021 cohort aligns to Pillay`s (2021a) descriptive analysis on the impact of COVID-19 on PHC health services with focus on reproductive health, HIV and TB. The study reported similar numbers of antenatal visits before and after the pandemic started, which was most likely due to the drastic reduction in family planning uptake a couple of months prior to the COVID-19 pandemic, as well as at the start of lock down (Pillay, 2021a).

The two comparative cohorts in this study are similar in descriptive characteristics. They share similarities to other significant studies such as Martinson's (2017) RCT of Universal testing vs symptom screening in HIV positive pregnant women, Hoffman`s (2013) cross sectional study

on TB prevalence in HIV infected pregnant women and Gounder`s (2011) cross sectional research in ACF in Pregnant women. The median age of participants in both cohorts of this study, were similar to Martinson (2017) and Hoffmann`s study (Hoffmann *et al.,* 2013). However, this study included patients from 15-year-old, as opposed to 18 years in the mentioned studies, as this age group at present is classified as high risk for unwanted pregnancies and HIV with an incidence rate 1.25% in 2021(Barron, 2022). Both spectrums of the age group (15 - 50 years) were potentially impacted by the COVID-19 disruption, as both injectable and longer duration contraceptives such as subdermal implants and IUCDs were negatively affected (Andeleker, 2021).

This study reported that overall, 68% of women booked before 20 weeks of gestation, with 69% and 67% for 2018/2019 and 2020/2021 respectively. These figures are in line with the South African National data reporting antenatal care before 20 weeks at 68% in 2019 (NDOH, 2020). Pillay (2021) also reported a reduction of 3% in the Western Cape`s antenatal visits before 20 weeks in 2020 (Pillay, 2021a). It is however encouraging to find that the median gestational weeks of this study were 15 and 16 weeks for 2018/2019 and 2020/2021 respectively. This significantly improved from that reported in 2017 by Martinson and Hoffman`s 2013 studies (both 24 weeks), illustrating the return investment of strengthening antenatal and integrated care over the last couple of years (Hoffmann *et al*., 2013; Martinson *et al*., 2017).

The sum of both cohorts in this study reported that 90% (n=6506) of pregnant patients were on ART at their first antenatal visit, aligning to the National strategic goal of 2020 (NDOH, 2020), as well as Martinson`s study (Martinson *et al.*, 2017). Apart from the increase of 89% to 91% (from 2018-2020), both years exceeded 2019 national performance of 76% overall, as well as 71% for males and 76% female on ART (NDOH, 2020). A large proportion of women were already on ART and possibly still on / completed TPT at the entry point of their antenatal care.

This in turn could have influenced clinicians testing for TB and led to suboptimal uptake of sputum testing.

5.3 Universal TB testing uptake

5.3.1 Screening

Prior to the implementation of the Universal TB testing policy in 2020, facilities were following systematic TB screening. This was the intensified symptom screening of a high/vulnerable group and testing once the patient had a positive symptom (WHO, 2021b). Therefore, integral to case detection in the 2018/2019 group and anticipating a drastic reduction (of screening) once universal testing rolled out. However, there was an overall screening rate of 16 % over the two periods, with minimal reduction once Universal testing was implemented, which was statistically insignificant (p=0.288). This poor result is in keeping with the 21% TB screening of patients that reported to health facilities for non-TB related problems (Kweza, 2018). Combined for both cohorts, this study reported that 3% of patients had positive TB symptoms of the 16% patients screened. This is a reduction from previous studies: Martinson's (2017) study reported 17% of patients in the Universal testing arm screened positive and 22% in the symptom screening arm, whilst Hoffman's TB prevalence study reported 16% (n=226) of 1451 HIV infected patients screened positive (Hoffmann *et al.*, 2013). The low positivity of the TB symptoms screening can be attributed to the masking of TB symptoms due to pregnancy physiological changes (Hamda, 2020). This is concerning in view of the latest TB prevalence survey in 2021, that reported 58% of asymptomatic people had TB disease (Pillay, 2021b). However, this reduction in symptomatic clients could be the result of placing 90% of patients on ART and minimizing their risk of developing active TB disease.

The evaluated facilities in this study reported an increase of 17% in booking visits of HIV infected pregnant women. In contrast, to the Western Cape that reported a reduction in antenatal visits before 20 weeks of 5% from 2019 to 2020 (Pillay, 2021a). National department

of health data on antenatal first visits remained unchanged from 2019 to 2020 (Pillay, 2021a). Eastern and Khayelitsha Sub-Districts reported the highest increase in headcount (13% and 19% respectively) and symptom-screened patients, however reported the greatest reduction in GeneXpert and TB cultures performed. Whilst smaller Sub-Districts reported an increase in sputum tests done proportionally, this is most likely also a reflection of additional workload in larger facilities due to COVID-19, which translated into shortage of staff (illness or task shifting) and compromise of routine services (Pillay, 2021a).

5.3.2 Testing

An increase in the proportion of patients tested by molecular sputum testing was observed in HIV infected pregnant patients from 1.26% (2018/2019) to 14.28% (2020/2021) in this study, which was statistically significant with a p-level less than 0.001. This was in stark contrast to the South African national data, which reported an overall decline of 26% from 2019 to 2020 in GeneXpert testing of all patients presumed to have TB (Pillay, 2021a). Specialised management by allocated BANC staff ensured that pregnant women continued to receive care throughout the COVID-19 pandemic. This possibly contributed to the reported difference, together with the specific antenatal visits that are required in BANC service. Therefore, the deferral of this service was not possible. Only 16% of the 2020/2021cohort patients were TB screened and therefor probably not perceived as symptomatic COVID-19 patients. As opposed to the routine symptomatic TB patients that were probably tested for SARS-CoV-2 virus instead. Sierra Leone also reported a decline in testing from 2019 to 2020, with children and women most affected, reporting a reduction in testing of 20% and 25% respectively (Lakoh, 2021).

Apart from a significant increase in tests performed in 2020/2021 (post-policy implementation), this study also reported that 76% of the patients in the 2020/2021 cohort were tested at their first antenatal visits versus the 17% in 2018/2019 (pre-policy). In contrast to 62%

of tests (2018/2019 cohort) conducted, 6 weeks after the first antenatal visit. Therefore, these patients possibly did not receive a test at their second antenatal visit, as programmatically the second visit is scheduled and aligned to 20 or 26 weeks, subject to the gestation of the client (KTU, 2021). This improvement indeed is a step closer to diagnosing TB early enough during the pregnancy and avoiding multiple harmful implications to mother and child (Hoffman *et al.*, 2013). Although testing rates improved in this before and after study, it is still not close to the national treatment TB targets for 2022 of diagnosing 90% of people that require TB treatment (NDOH, 2020).

This study showed that factors such as reporting year (odds ratio=0.95; 95% Cl: 0.805-1.119, p= 0.5333) and ART initiated (odds ratio=0.937; 95% Cl: 0.717-1.225, p= 0.634) had no association to the likelihood of being tested for TB. As well as Screened for TB symptoms (odds ratio=1.089; 95%Cl: 0.879-1.350, p=0.436), gestation (odds ratio=1.001; 95%Cl: 0.841-1.192, p=0.993), and age (odds ratio=0.996; 95%Cl: 0.927-1.070, p=0.916). All 95% confidence intervals crossed one and were more than 0.01. I have found no similar designed studies that have reported on secondary routine data to date.

In this study, GeneXpert tests also significantly increased from 2.43% (n=81) for 2018/2019 to 15.58% (n=608) in 2020/2021. This is in keeping with the 2021 WHO TB Global report aiming to increase the rapid exclusion of Drug resistant TB and ensure effective regimes, through microbiological diagnosis of TB with rapid molecular testing or culture (WHO, 2021a). Globally, the use of molecular TB testing for initial TB diagnosis has also increased from 28% (2018) to 33% (2019) (WHO, 2021a). In this study TB culture tests have increased marginally from 0.4% (n=14) to 3.9% (n=151) in 2020, despite the laboratory performing cultures as a reflex test when HIV status of the patient is indicated on the form. This most likely requires internal training, as TB cultures identify more TB than Xpert in asymptomatic

pregnant women (Martinson *et al.*, 2017). However, significant increase of GeneXpert definitely indicates the operational feasibility of implementing this policy.

5.4 Microbiological confirmed TB sputum tests

There has been an overall significant increase in TB tests from 2018/2019 to 2020/2021 for all pregnant. GeneXpert tests performed the highest. The prevalence of GeneXpert confirmed TB has declined from 12% (2018/2019) to 3% (2020/2021), as well as the prevalence of TB confirmed by TB culture (14.3% to 3.3%). Clearly resulting from the significantly increased testing from 2018/2019 to 2020/2021 and possibly an indication of an improved universal screening program in this high-risk group. It could however also be attributed to 90% of the cohort that had been placed on ART and possible exposure to TPT. The TB prevalence of this study is similar to Martinson`s (2017) work, reporting 3.5% prevalence in HIV positive pregnant women that had been universally tested (Martinson *et al.*, 2017). Overall 3.3% TB prevalence was also reported in Hoffman`s (2013) cross sectional survey, detecting TB through the TB symptom screen and microscopy with culture. The prevalence of microbiologically diagnosed TB by culture was 2.5 %(Hoffmann *et al.*, 2013). Pasipamire (2020) reported a 5% TB prevalence (95%Cl: 2-7) in HIV positive pregnant women, 1% in HIV positive postpartum patients and 2% in HIV neg pregnant women (95%Cl: 0-3(Pasipamire, 2020)). This study also reported a higher prevalence compared to the cross-sectional study, which assessed the contribution of the Xpert in all pregnant women on Botswana (Hamda, 2020). The study reported a prevalence of 1.45% (95%CI: 0.29-2.61) in HIV positive pregnant patients and 0.31 %(95%CI: 0.23-083) in HIV negative patients that had been tested with Xpert and culture (Hamda, 2020).

5.5 Linkage to care

Linkage to care for combined cohort patients remained poor with only 37 % of patients that were sputum investigated, starting treatment. However, the study only reported from one

routine data source and could be under reporting. There was an improvement in patients linked to care from 27% (n=3) in 2018/2019 to 56 % (n=9) in 2020/202. Although an improvement in linkage was reported, this remains concerning as it is far below the national target of linking 90% of patients to care (NDOH, 2020). Also highlighting that not only should the focus of the policy be testing, but also ensuring linkage of HIV positive pregnant women to care.

As opposed to 0% patients starting treatment, that were diagnosed by culture. This is most likely due to the long turnaround time of culture results from four to six weeks, as well as the gap in follow up of these results.

Eighteen (18) patients not diagnosed on TB sputum linked to care across the two reporting periods. In 2018/2019, 9 patients commenced on treatment and included four extra pulmonary TB, 2 unknowns TB types and 3 pulmonary TB patients. Nine patients, which included two extra pulmonary TB, 4 unknowns and three pulmonary TB, reported for 2020/2021 cohort. None of the six patients diagnosed with extra pulmonary TB (4 for 2018/2019 and 2 for 2020/2021) screened or sputum tested for TB, yet their TB treatment start dates ranged from 1-day post first antenatal visit, 18-days post and 175-days post booking. Reiterating the importance of early detection and clinical examination, as HIV positive pregnant women are 5.67 times more likely to have extra pulmonary TB (Bekker *et al.*, 2016).

Globally there was also a reduction in TB case notification of 18% and 2.5% in the WHO African region (WHO, 2021a). Other factors contributing to the decline in testing and case notification in low- and middle-income countries could also be attributed to lack of health education, financial implications of transport and gender-based risks (Lakoh, 2021). Apart from individual level barriers to TB care, COVID-19 contributed through the exacerbation of social determinants such as lockdowns causing low access to health facilities, increased unemployment, stigma due to similar symptom profile and disruption of public transport (Loveday, 2020).

5.6 TB treatment outcomes

The Drug-sensitive TB success rate globally for 2019 was 86% and 77% for PLHIV (WHO, 2021a). This study reported a success rate (combination of treatment completed and cured) of 29% for all the women that were microbiologically diagnosed and commenced on treatment during the specified periods. Twenty percent (20%) for the 2018/2019 and 35% for the 2020/2021 cohort. This is significantly lower than the 2020 treatment success rate in South Africa of 78%, among registered HIV positive people infected with TB (WHO, 2021a). Cape Town Metro District also reported a treatment success of 76% in 2018 (Massyn *et al.*, 2020). The calculated success rate of this study used the number of patients diagnosed with TB as denominator, as opposed to the historical method of using the number of patients notified (Naidoo, 2018). This potentially poses an underestimate, but also highlights the various losses in the TB cascade through a different lens. Eleven percent of combined cohorts were lost to follow-up (LTFU) and 61% were never started on treatment (ILTFU). There was however a reduction from LTFU and ILTFU: 13% (n=2) to 8% (n=2) and 67% (n=10) to 57% (n=13) for the 2018/2019 and 2020/2021 cohorts respectively.

5.7 Limitations of the study

Although the use of routine secondary data minimizes researcher bias, it limits the control of the researcher in adding any other variables of interest, as data was pre-selected. Verification of monthly data takes place at various levels of the health system; however, the data was still subject to the quality of capturing at facility level.

One of the major limitations to this study was the use of a single data source: Prehmis health information system. Variables such as linkage to care and TB treatment outcomes could possibly have been under-reported, as patients present to MHS health facilities for TB treatment. Verifying against sources from Provincial health data centre and National Health laboratory could potentially have mitigated this limitation.

The extension of these specified periods of interest can accommodate for expected inter - seasonal variation, which the study has not considered.

In view of the impact of the COVID-19 pandemic, which started in 2020, the study could possibly have benefited from a longer post policy period to assess implementation of sputum testing by GeneXpert.

Chapter 6: Conclusion and Recommendation

6.1 Conclusion

The key objective of this study was to determine the operational uptake of the Universal TB testing of HIV infected women by GeneXpert, outside the research environment. The significant increase of TB testing, especially of GeneXpert tests, amidst low screening is indeed an indication that universal testing is operationally feasible. This positive finding carries more weight amidst the height of the COVID-19 pandemic and the disruption that it has caused in routine services at the primary health platform. However, the scale up of testing and the use of rapid molecular testing must be elevated, to meet the 90/90/90 strategic target for TB. "Great effort will also have to be applied to catch up to the projected setback of 5-8 years in TB incidence and estimated deaths by 20% "(Loveday, 2020: 1161).

A concerning finding was the high rate of TB LTFU, in this group of patients that require multiple health facility visits for safe and efficient antenatal care.

Although there was an overall increase of TB testing at the assessed facilities, the concerning poor performance of sub districts that service higher headcounts will have to be investigated to ensure that additional support is given, when they are exposed to disrupted services or unexpected increase in burden of disease.

6.2 Recommendation

- In-service training will be required at Sub district level by HAST coordinators, to improve correct requested tests and laboratory forms. It is imperative that the BANC clinician follows up TB Results and that verification takes place monthly, at facility level.
- Access to Single patient viewer, the Provincial health information system that provides a comprehensive clinical picture of the patient at any public health facility, to all appropriate staff that render BANC, immunization, HIV and TB care. It ensures

seamless care, mitigates unnecessary tests and allows the clinician to monitor treatment initiation and adherence (especially in TB and HIV care). Access to all staff will have to be expedited and supported by City Health information and Information technology department at both area and central level. The City Health Training department must incorporate the use of SPV, with the on boarding of new clinicians.

- Historically, TB management is isolated to TB rooms. However, the high rate of LTFU requires integrating care across health facility programs. The same clinician that provides BANC care can facilitate care of uncomplicated TB patients in continuation phase of treatment. This is however subject to the prioritization of sufficient TB training. Therefor ensuring continuity in care and mitigating the in-facility factors that contribute poor adherence.
- Point of care molecular TB testing at PHC BANC sites with large HIV headcounts could potentially assist with rapid results, higher linkage to care and reduction in ILTFU.
- Strengthening the Community health care workers in household contact screening, identifying and linking pregnant women to facilities. Therefor expediting earlier TB testing and management.

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Appendix 1: Diagnostic accuracy of different screening tools among HIV infected pregnant women compared with culture as reference standard

Screening tool	No of studies No of participants	Sensitivity (95% Cl)	Specificity (95% Cl)
WHO recommended four symptom screens (WRFSS)	8 (1937)	0.61 (0.39-0.79)	0.58 (0.39-0.75)
C-reactive protein, using cut-off > 5mg/L	2 (62)	0.70 (0.12-0.97)	0.41 (0.12-0.78)
WRFSS combined with Chest X-ray	1 (8)	0.75 (0.11-0.99)	0.56 (0.24-0.84)
WHO recommended rapid diagnostics (Xpert MTB/Rif	4 (473)	0.55 (0.33- 0.75)	0.99 (0.97- 0.99)

Appendix 2: Data Collection Tool

Patient Identifier	Year	Age	ART initiated	Date of 1st Ante- natal visit	Intake Year	1st visit gestation age	Facility name	Sub District name	TB screen	TB status	TB sputum tested	1st visit TB test	GeneXpert test	Culture test	Smear test	GeneXpert result	Culture result	Smear result	TB type	TB category	TB treatment started	TB treatment start Date	TB treatment year	TB treatment month	Outcome

Appendix 3: Permission City Health

CITY OF CAPE TOWN
ISIXEKO SASEKAPA
STAD KAAPSTAD

CITY HEALTH

Dr Natacha Berkowitz
Epidemiologist: City Health

T: 021 400 6864 F: 021 421 4894
E: Natacha.Berkowitz@capetown.gov.za

Ref: 9510 2022-03-14

RE: Evaluating the implementation and uptake of the Universal Tuberculosis sputum testing by GeneXpert Ultra in HIV infected pregnant women in the City Health PHC facilities, Cape Town.

Dear Kay Joseph

Your research request has been approved as per your protocol. Please refer to the subsequent pages for the approval of any facilities or focus areas requested. Approval comments on any proposed impact on City Health resources are also provided.

Please contact Dr Kevin Lee for assistance with data extraction.

Please note the following:

1. All individual patient information obtained must be kept confidential.
2. Access to the clinic and its patients must be arranged with the relevant Manager such that normal activities are not disrupted.
3. A copy of the final report must be uploaded to https://web1.capetown.gov.za/web1/mars/ProjectClosure/UploadReport/0/9510, within 6 months of its completion and feedback must also be given to the clinics involved.
4. Your project has been given an ID Number (9510). Please use this in any future correspondence with us.
5. No monetary incentives to be paid to clients on the City Health premises
6. If this research gives rise to a publication , please submit a draft before publication for City Health comment and include a disclaimer in the publication that "the research findings and recommendations do not represent an official view of the City of Cape Town "
7. As the research is approved as per submitted protocol, any changes to the protocol need to be submitted and approved by City Health prior to implementation.
8. We are currently not approving research for joint authority facilities (Dirkie Uys, Durbanville, Heideveld, Kasselsvlei, Nolungile, Nyanga, Parow, Ravensmead, Scottsdene) as they are in the process of being consolidated into one authority.

Thank you for your co-operation and please contact me if you require any further information or assistance.

Kind Regards
Dr Natacha Berkowitz Epidemiologist: City Health

Natacha Berkowitz Digitally signed by Natacha Berkowitz Date: 2022.04.08 10:16:21 +02'00'

Appendix 4: Ethics Approval

UNIVERSITY of the WESTERN CAPE

50 YEARS of hope, action & knowledge

29 November 2021

Dr K Joseph
School of Public Health
Faculty of Community and Health Sciences

Ethics Reference Number: BM21/10/20

Project Title: Evaluating the implementation and uptake of the Universal Tuberculosis sputum testing by GeneXpert Ultra in HIV infected pregnant women in the City Health PHC facilities, Cape Town.

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

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

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

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

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

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

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

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

NHREC Registration Number: BMREC-130416-050

FROM HOPE TO ACTION THROUGH KNOWLEDGE.