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Developing a Patient-Centered Community-Based Model for Management of Drug Resistant Tuberculosis in Rural Eastern Cape: A Collaborative Approach of Health Care Facilities, Diagnostic Laboratories and Research Institutions

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Abstract: Infectious illnesses have always posed a threat to human health, with tuberculosis (TB) being a major concern. The use of various medications and antibiotics in the fight against such illnesses has led to the emergence of drug-resistant infectious diseases, which have become increasingly difficult to manage as medical and scientific research has advanced. Inadequate medical infrastructure, incorrect treatment practices that exacerbate resistance patterns, and transmission within communities and healthcare facilities are the main factors contributing to the spread of drug-resistant TB. Though treating individuals with multiple drug resistance (MDR) and extreme drug resistance (XDR) strains is challenging, early identification of resistance and the implementation of a well-designed treatment regimen can result in a cure. Community-based interventions that address socioeconomic barriers to adherence can also enhance treatment outcomes. While there have been few studies and proposed conceptual models on how to manage and prevent various drug-resistant TB mutations and lineages, a model aimed at limiting and controlling such mutations has been developed. This paradigm seeks to bridge the gap by facilitating the exchange of knowledge among healthcare professionals (HCP) in healthcare facilities (HCF), diagnostic laboratories (DL), and research institutes (RI), particularly for underprivileged communities in the Eastern Cape. The model guide will also monitor and evaluate TB management plans.

Keywords: model; drug resistance TB; collaboration and intergration

1. Introduction

TB remains a concern for public health worldwide, with drug resistance tuberculosis (DR-TB) adding to the danger. The initial treatment for TB is based on Isoniazid (INH) and rifampin (RIF)medications [1–4]. The largest concern for TB control worldwide is now drug-resistant tuberculosis (DR-TB). DR-TB is defined as tuberculosis that is resistant to the two most effective and commonly used first-line drugs, INH and RIF [5–8]. Resistance to first-line drugs for TB has been linked to various gene mutations, including *rpoB, katG, and inhA* [6]. Ensuring adherence to TB treatment is a vital concern due to its severe health consequences. It is important to determine the factors that contribute to such adherence. Failure to comply with therapy can lead to relapse, continued transmission, and an increase in drug resistance caused by widespread gene mutations. Globally, smoking is the cause of more than 20% of all tuberculosis cases [7–10]. The spread of tuberculosis (TB) infection is heavily influenced by smoking, which also leads to worsened outcomes and prognosis for TB treatment. Usage of tobacco and smoking are factors that promote the spread of tuberculosis and increase its morbidity and mortality rates [8–13]. The negative effects of smoking

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on TB are substantial and hinder successful treatment. Studies have shown that smoking is a contributing factor to poor adherence and a higher rate of default in TB care settings. These findings have been established for some time now [9]. Smoking in this location continues to be associated with lower cure rates, worse treatment outcomes, and a higher likelihood of rapid disease progression and severity [9–17], It is crucial to intensify health education. Those who fail to complete their treatment are at the highest risk of developing drug resistance and spreading TB in the community. Research conducted in other places has shown that interventions are needed to enhance treatment compliance among TB patients. Overcoming the challenge of improving compliance among TB patients who smoke requires the involvement of families and social organizations, as well as the provision of smoking cessation interventions [18–22]. All TB patients who are receiving DOTS treatment while smoking should be educated on the importance of smoking cessation to prevent the development of antitubercular drug resistance. Public awareness programs should be implemented to address this issue [23–30]. This model has the potential to effectively address the high prevalence of MDR TB, co-infections, and limited human resources in Eastern Cape [31–37]. Previous discussions have taken place regarding the community-based model for multi-drug resistant tuberculosis (MDR-TB) in South Africa, particularly in the Eastern Cape. However, this is the first attempt to comprehensively analyze the operational challenges of MDR-TB using a collaborative approach involving research, laboratory, and clinical stakeholders. The model aims to manage and control the spread of MTB mutations and strains [38–47]. Delaying the progression of the disease, reducing its intensity, and preventing antitubercular drug resistance can be achieved through this approach. The approach involves sharing knowledge between healthcare professionals (HCP) in healthcare facilities (HCF), diagnostic laboratories (DL), and research institutes (RI). The dissemination of health education and counseling to the community will follow the collection of information. Dealing with the intricate healthcare needs and the limited knowledge of TB transmission in rural areas necessitates a comprehensive approach that integrates primary healthcare, diagnostic services, and research services. An information system should be established to facilitate data storage as part of the strategy. Data quality is determined by data completeness, which is associated with the completeness of data entry by collaborating organizations in the information system. Insufficient completeness makes it difficult to evaluate the actions taken and the epidemiological profile of affected areas, making it challenging to make decisions and develop disease control plans.

2. Materials and Methods

We set out to illustrate the primary factors contributing to the spread of DR-TB and how medical systems may be made more effective at managing resistance patterns brought on by ineffective treatment, transmission in communities, and usage in healthcare settings. Patients with multidrug-resistant TB (MDR-TB), and extensively drug-resistant TB (XDR-TB) strains can be difficult to treat, but with early resistance detection and the administration of a well-planned regimen, a cure is frequently achievable. By letting patients receive care in their homes and eliminating socioeconomic barriers to adherence, community-based programs can enhance the effectiveness of therapy. Promoting the expansion of TB (MDR and XDR) management services, exposing the difficulties in managing TB services at scale, and contributing to the creation of this model as a suggestion for policy revision in South Africa. This study was carried out in rural Eastern Cape, South Africa, at the study's healthcare facilities, which included 5 general hospitals and 1 referral hospital. These hospitals were chosen from Eastern Cape Province districts that are served by or fall within the boundaries of the Nelson Mandela Academic Hospital National Health Laboratory Services TB Laboratory and are overburdened by TB. The Eastern Cape Province has the third-largest population in the nation, with 6,498,700 people, or 12% of the total population, according to mid-population projections for 2017 that were published in July 2017 [48]. In rural regions, almost 60% of the population resides. The province has the highest rates of unemployment (28%) and poverty (48%) in the Country. The two main causes of mortality in the province in 2014 were TB and HIV/AIDS [48]. In addition, to eight decentralized MDR-TB clinics outfitted to handle MDR-TB patients, the province has two specialist DR-TB hospitals that treat both MDR- and XDR-TB patients. The province started decentralizing its

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MDR-TB services in 2011 [49]. The South African DR-TB guidelines state that patients with clinically unstable MDR-TB, patients with extensive disease, and patients with XDR-TB must be admitted for DR-TB treatment while ambulant patients who are in fair to good condition and are smear-negative should begin receiving care in the outpatient setting [50–53].

3. Results

3.1. Phase 1

Gene mutations and the genotypes of DR-TB (mono DR-TB, MDR-TB and XDR-TB) in the rural Eastern Cape Province were identified by using different assays. From patients who were suspected to be having TB, 1157 sputum samples were collected and analyzed. These analytic methods identified regions of DR-TB mutations, heteroresistance, and genetic diversity [45].

3.2. Phase 2

The distribution of M. tuberculosis mutations and spoligotypes identified in part one were investigated to identify transmission hotspots by analyzing a total of 1157 DR-TB and heteroresistant clinical isolates which were isolated from different healthcare facilities as published in our manuscript [46]. Identifying geographical areas with a high incidence of disease was done by analyzing Line probe assay (LPA) and spoligotype results of M. tuberculosis isolates using the QGIS 3.14 software. LPA score and banding patterns were used to determine the type of DR-TB and heteroresistance. Clinics within hospitals with the same coordinates were merged in the analysis [46].

3.3. Phase 3

The investigation of treatment outcomes and associated factors among tuberculosis patients that were conveniently selected from part one was done using the ambidirection method where clinic records from 457 patients with DR-TB were examined for data collection while 101 patients were followed up prospectively until the end of treatment [47]. The data collected included socio-demographics, clinical data, and treatment outcomes data were analyzed using Stata version 17.0. The odds ratio and 95% confidence interval were calculated to check the association between variables where $p \leq 0.05$ was considered statistically significant [47].

3.4. Model key points from parts 1, 2, and 3 of the findings

The model will help to understand the spread of TB and its epidemiological link to HIV in rural areas and to evaluate different intervention strategies as

3.4.1. HIV-TB coinfection

The rate of co-infection of TB and HIV was high with men being mostly infected and resulting in undesirable treatment outcomes. Tuberculosis and HIV/AIDS are the major public health problems in many parts of the world particularly in resource-limited countries like South Africa. It has been a long time ago having proved that the double burden of TB and HIV is one of the major global health challenges [31–33]. TB is the leading immune-suppressing infection and the commonest cause of death among HIV-infected patients [34–45]. For a very longest time, HIV and TB are known to be working together to suppress the immunity of the patients and, thereby, shorten the lifespan if there is no early treatment, WHO estimated that patients living with HIV are at 20 times higher risk of acquiring TB than their counterparts [1–3,40,53].

3.4.2. Smoking

It is argued that this is the case due to behavioral habits usually associated with males: unhealthy habits such as drinking and smoking, and spending time in settings such as bars which are conducive to the transmission of communicable diseases [21]. Smoking is a risk factor for developing tuberculosis and is linked to unsuccessful treatment. Health education needs to be intensified.

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Improving TB treatment and reducing TB transmission requires prompt identification of smoking behavior and smoking cessation. To reduce treatment failure and drug resistance, smoking cessation is a highly successful strategy. By smoking, TB becomes more severe and has a higher mortality rate [4]. It is indisputable that tobacco use and smoking pose a problem in the fight against tuberculosis. Therefore, it is essential that tobacco control initiatives and integration of health education be strengthened and that every chance is used to inform the public by HCPs about tobacco's negative consequences. HCPs should speak with patients and emphasize the detrimental effects of tobacco use. They should also inform patients and their families about the dangers of secondhand smoke and the legal protections for a smoke-free environment in public places [9].

3.4.3. Gene mutation and regions of mutations

Analysis of the RIF-associated mutations revealed a prevalence of the rpoB gene which is known to be a hot spot of resistance in M. tuberculosis. The region of rpoB S531L was the most prevalent with mutations and is associated with major MDR-TB outbreaks in many parts of the world. Introduction. Most study samples exhibited a pronounced dominance of mutations within the rpoB codon 531 that give RIF resistance. This demonstrates that the mutation in codon 531 is largely responsible for the general resistance to RIF and indicates that it predominates globally [12]. The katG gene's codon 315 mutations are primarily responsible for INH resistance. Numerous investigations conducted all around the world revealed the same pattern of relationship between the S315T mutation and high levels of INH resistance. One of the main mechanisms of INH resistance in MTB is the katG gene mutation [12].

3.4.4. Heteroresistance

Heteroresistance occurs when resistant and susceptible strains of an infection infect a patient at the same time [38,39] and is known as a precursor to full resistance or low levels of drug-resistant TB. Studies by Faye et al., [45] it was observed as it is increasing yearly. Heteroresistance refers to the combination of resistant and susceptible M. tuberculosis isolates from clinical specimens. The results of treatment could be negatively impacted by heteroresistance. Heteroresistance can develop when drug-resistant individuals spread susceptible and resistant M. tuberculosis strains to untreated cases or newly infected patients.

Given that MDR isolates are known to be more likely to carry katG S315T mutation than non-MDR strains [10,11], we discovered that katG S315T had more heteroresistant strains than rpoB and InhA, which can result from mixed infection or clonal heterogeneity and is thought to be the first step toward total resistance, shows that INH in this region is beginning to exhibit full resistance.

3.4.5. Type of lineage

The Beijing family is associated with drug resistance in some parts of the world [37] and is also known to be more transmissible than other families and more prevalent in Eastern Cape and Western Cape [34,35]. In addition, our study findings have confirmed this high prevalence in the rural Eastern Cape as well [45,46]. Other studies elsewhere have also confirmed this high prevalence in other provinces of South Africa such as Western Cape, Limpopo, and Mpumalanga [35,36]. Studies by Ameeruddin and Luke [28], Ano et al. [29], and Gagneux et al. [18], the katG-S315T mutation has a low-fitness cost, spread to Beijing strains and other strains, and is more likely to be clustered. Treatment failure is positively correlated with katG mutations [24].

3.4.6. Treatment outcomes

One of the most efficient and targeted medications for the treatment of the disease brought on by M. tuberculosis is INH. It is a key component of current short-course chemotherapy for tuberculosis and is frequently used to treat latent MTB infection (LTBI) to halt the progression of the infection to active disease and the consequent spread of TB. A typical first stage in the transition to MDR is the development of INH resistance [12]. Treatment success rate (TSR) is a critical factor in the

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global End TB strategy. For this factor, a 90% rate was determined as a standard for all countries to actualize [41]. With 76% national TSR in South Africa, the country still falls short of the standard set by WHO, the global health body [40]. The treatment success rate (65.8%) was lower than the WHO threshold standard with a high proportion of patients being lost to the follow-up. The co-infection of TB and HIV resulted in undesirable treatment outcomes [41].

3.5. Main Findings from the Original Investigations (Phases 1, 2, and 3)

Phase 1: Spoligotyping analysis revealed that the dominant strain was the Beijing strain. The diversity of mutations provided valuable insights into the evolutionary lineages of M. tuberculosis isolates as observed by our study findings [45]. The frequency of rpoB, katG, and inhA mutations in different study areas can aid in determining treatment approaches, whether standardized or individualized, in regions where these mutations are prevalent. The rpoB 531 and katG 315 mutations were the most prevalent regions of a mutation linked to RIF and INH resistance, respectively that are the first-line drugs for the treatment of TB. The prevalence rate of heteroresistance was increasing with time and INH had more heteroresistance cases occurring mostly in the katG gene 315 region. The Beijing family was the most prevalent genotyping lineage among eight lineages identified in SITVIT2 data base as our study demonstrated [45]. The study provides important information about gene mutations and genetic diversity of DR-TB in the rural Eastern Cape Province. These findings offer crucial insights for enhancing tuberculosis treatment strategies in the affected regions.

Phase 2: All three (rpoB, katG, and inhA) genes under investigation had one or more mutations from each isolate with the rpoB gene representing the highest number of mutations, followed by the katG gene then the inhA gene. RIF's resistance is typically thought of as a marker for MDR-TB [46]. The key control for DR-TB is to interrupt its transmission; this was done by identifying hotspots of gene mutations and lineages, especially those that are drivers of DR-TB transmission and mixed infections.

Phase 3: The co-infection of TB and HIV challenges treatment, resulting in undesirable outcomes of TB treatment. The prevalence of HIV co-infection in this study the male gender dominated the study with HIV/TB co-infection [47]. TB was more prevalent in the productive age group both among HIV-positive and HIV-negative TB patients. More patients had successful treatment compared to patients who had unsuccessful TB treatment [47].

The recommendation for the findings of Phases 1 to phase 3 are presented in Table 1 and Table 2.

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Table 1. Plan for gene mutations and heteroresistance control in Rural Eastern Cape.

Technical approach	Justification
• Identify gene mutations and regions of mutation • Identify lineages • Identify areas of the prevalence of gene mutation and heteroresistance.	For trend analysis and root course analysis, the significant gene mutation and regions should be documented and shared with TB research institutions. According to Ameeruddin and Luke [19], Ano et al. [20], and Gagneux et al. [18], the *katG*-S315T mutation has a low-fitness cost, spreads to Beijing strains and other strains, and is more likely to be clustered. Treatment failure is correlated with *katG* mutations [24]
• Identify epidemiological trend of heterogeneity of Infecting *M. tuberculosis* strain (single strain or mixed strain).	To stop the spread of these strains, it's crucial to identify critical gene alterations and heterogeneity hot spots. In patients from various geographic backgrounds who had drug-resistant *M. tuberculosis* infections, the prevalence of particular mutations of *rpoB*, *katG*, and *inhA* differed significantly [23]. It may be necessary to develop a diagnostic test specific to each country due to the significant variations in the types of mutations observed. To enhance the management of TB, it is essential to conduct further research on the drug resistance mechanisms of *M. tuberculosis* prevalent in rural Eastern Cape regions, to facilitate rapid assessment of drug resistance.
• Treatment category (New or retreating) • HIV status (Negative or Positive) • Gender (Female or Male) • Age category	To conduct trend analysis and root cause analysis, it is essential to document and engage in discussions with research institutions that specialize in TB. This involves analyzing the prevalence of significant gene mutations and the heterogeneity of strains.
• Phenotypic DST result (INH and RIF susceptible, INH Monoresistance, RIF monoresistance, Multidrug resistance) • Treatment outcome (completed, cured, lost to follow-up, died and failed)	Knowing the type of prevalent DR-TB is crucial for keeping track of *M. tuberculosis* transmission and hot spots. The heterogeneity of strains and their relationship with major gene mutations to improve control measures and identify which affect treatment outcomes that are successful and unsuccessful should be tracked.

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Table 2. Frequency of Poor Treatment Outcomes.

Technical approach	Justification
• Age category i.<21 ii.21–30 iii.31–40 iv.41–50 v.≥51 • Gender i.Female ii.Male • Strain heterogeneity i.Single strain ii.Mixed strain • HIV status i.Negative ii.Positive • Phenotypic DST result i.INH and RIF susceptible INH ii.monoresistance iii.RIF monoresistance	Which demographic and clinical category contributes to poor treatment outcomes? This knowledge will assist in designing informed interventions and targeting the patient category that contributes the most to poor treatment outcomes

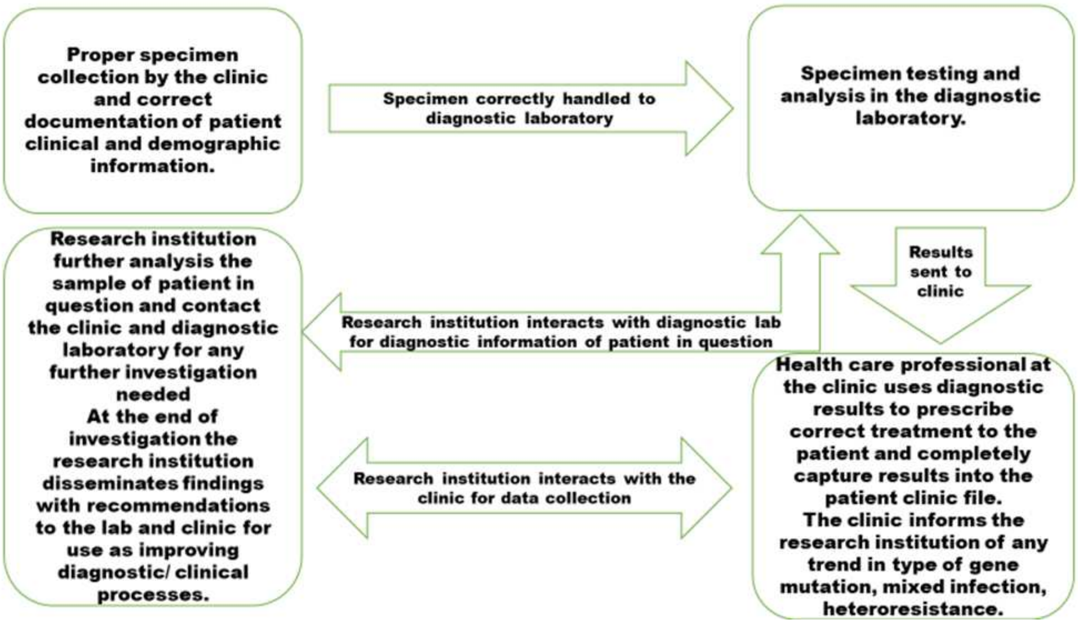

Figure 1. Model creation for management and spread of DR-TB gene mutations and lineages in rural Eastern Cape.

The institutions shown in Figure 2 have a weak connection, which negatively impacts health programs intended to strengthen TB control and reduce drug resistance. Effective sharing of TB information between diagnostic labs, research institutes, and HCFs can enhance the information that HCPs provide to patients in a way that patients can understand. HCPs in HCFs play a vital role in providing direction, motivation for change, and promoting long-term adherence to medication use. This model also emphasizes the importance of patients being prepared, willing, and able to boost their self-confidence for change through health education provided by HCPs.

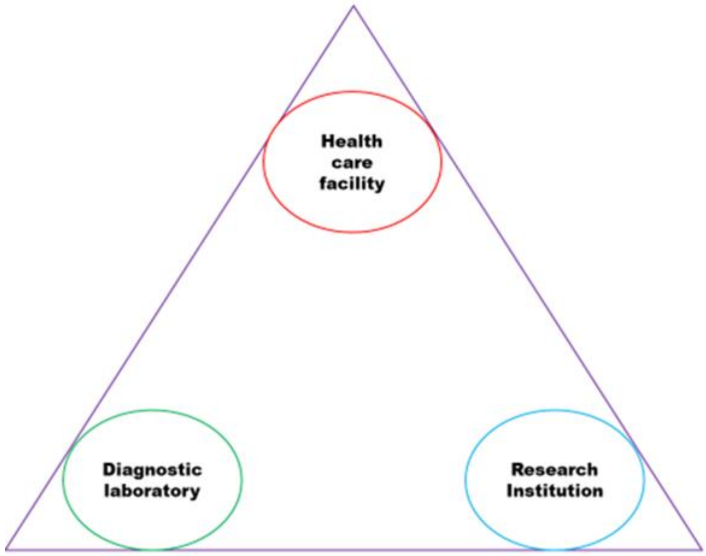

Figure 2. Collaboration and communication motivation model of patient care and disease monitoring institutions.

The increasing number of drug-resistant TB cases, heteroresistance, and treatment failures in the study area is a major concern. This is due to the lack of a collaborative approach to tackling TB. Therefore, it is crucial to establish cooperation between healthcare facilities (HCF), diagnostic laboratories (DL), and research institutions (RI) to address these issues. Unfortunately, there are few effective joint initiatives currently in place, which highlights the need to integrate various approaches in this model to improve the current situation. In low-resource, high-TB burden settings like rural Eastern Cape, it is imperative to have TB-specific governance to enhance TB control programs. This requires multidisciplinary professionals to work together with the institutions depicted in Figure 2 to effectively analyze DR-TB mutations and strains for TB control. To achieve comprehensive TB control, all healthcare organizations (HCFs, DL, and RI) must be included in the effort, as outlined by the World Health Organization's (WHO) Global Report [41]. To continuously monitor the progression of TB in rural areas, institutions need to collaborate. This is demonstrated in Figure 2. The collaborators to ensure that disease updates are precise must establish a strict system for entering data. Failure to provide complete data may result in challenges in accurately characterizing the true epidemiological state of TB [30]. Collaborative efforts are necessary for the development of an Information System that focuses on DR-TB gene mutations and strains, as stated in the passage in Figure 2. To effectively monitor and manage the spread of DR-TB gene mutations and strains, it is necessary to conduct mandatory data completeness and spatial analysis at least every three months. Failure to do so can lead to misinterpretation of the disease's epidemiological situation and case follow-up due to incomplete disease notification instruments and follow-up procedures [30].

The focus is on tackling the risks posed by DR-TB genetic mutations and strains in rural regions. These areas have been pinpointed as the primary sources of the TB epidemic in rural Eastern Cape [45,46]. It is important to regularly evaluate existing systems and note trends in tuberculosis (TB) using key points, as shown in Figure 3. This allows opportunities to refine and adapt to the changing epidemiology of TB, as well as incorporate new advances in TB control. However, collaboration for enhancing TB control has been less emphasized in rural areas. Thus, this model illustrates how collaboration practices can influence the implementation of standardized TB control programs in different locations.

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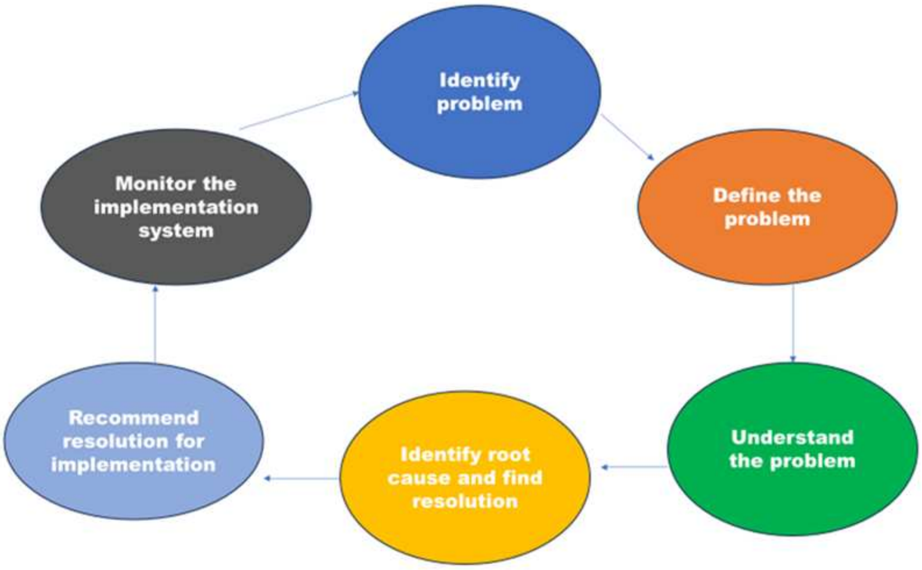

Figure 3. Collaboration oversight.

Despite the availability of effective treatments since the 1980s, tuberculosis remains a significant global public health concern. By integrating communication into this model, medication adherence and treatment success can be improved. This is because healthcare professionals will gain a better understanding of the disease's epidemiology through deep learning and data analysis, while patients will receive a more comprehensive education. In Figure 4, there is a communication plan that emphasizes the importance of gaining knowledge together to increase self-confidence in adhering to TB treatment. This plan should be considered by healthcare professionals when creating motivation programs for treatment adherence. By doing so, patients can communicate their treatment barriers to healthcare professionals and engage in collaborative discussions. This is the first step in developing a health education program that will increase the patient's ability to carry out the recommended course of action [1,3]. When individuals fail to take their anti-tuberculosis medications as directed, their chances of treatment failure increase. One of the reasons behind patients losing track of their treatment regimen and the disease spreading is the difficulty they face in following the prescribed guidelines, coupled with a lack of interest in the lengthy therapy course [31,32]. When an HCP conducts a motivational interview with a patient, the patient can freely communicate while being directed by the HCP's well-informed information. This type of interaction can inspire patients to overcome their ambivalence which is often a barrier to understanding the importance of adhering to treatment. Health education for patients can help them to understand the challenges that arise from treatment side effects and other social problems, leading to a greater likelihood of long-term medication adherence. Patients who are more optimistic about treatment and understand the need for support from within and their social environment are more likely to be ready and willing to make the necessary changes [23]. Understanding the patient's perspective on TB treatment and self-management is crucial to preventing the disease and predicting treatment success. Communicating about TB-HIV co-infection varies across communities due to differing factors. It is important to avoid using information from one community to address the issue in another community, as it can lead to ineffective strategies and poor collaboration. The collaborative approach presented in Figure 4 is recommended for controlling TB-HIV co-infection transmission in rural areas of the Eastern Cape. This model is specific to the study area and has been studied extensively. Stigma has been linked to negative mental health outcomes, lower self-esteem, reduced self-efficacy, and poor treatment adherence [16]. Effective health education that fosters good communication between patients and healthcare professionals can help to reduce stigmatization and discrimination associated with HIV and TB infections. This, in turn, can support public health efforts aimed at tackling this dual epidemic.

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The educational health programs should be tailored to the specific needs of the community, taking into account the latest information on DR-TB gene mutations and strains.

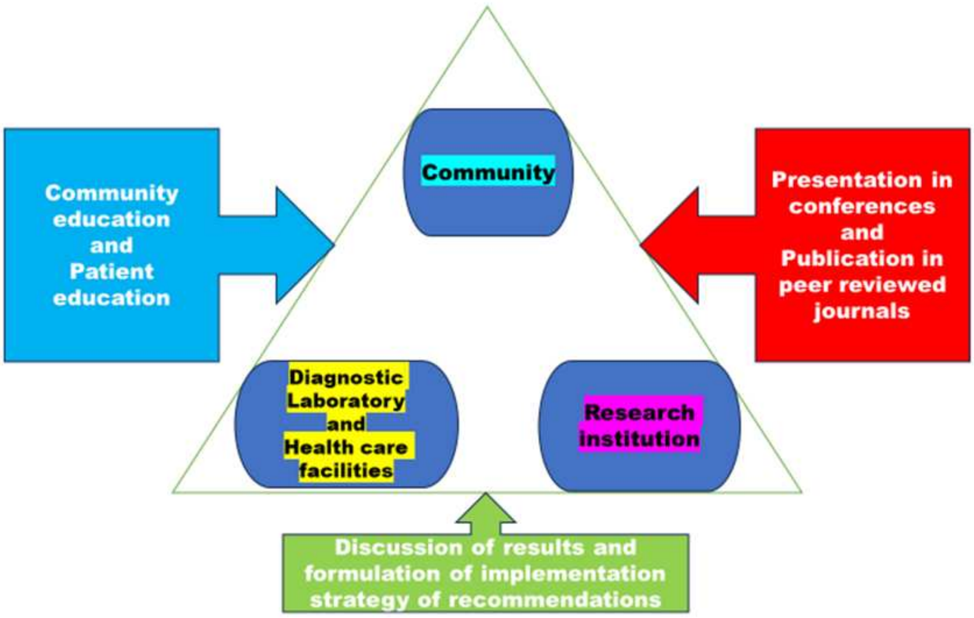

Figure 4. Intervention Plan to manage DR-TB gene mutations and strains.

4. Discussion

Policymakers can utilize this model as a concept demonstrator to aid in making decisions based on analytical evidence when managing the spread of DR-TB gene mutations and lineages in rural areas of the Eastern Cape. Customized models are crucial for representing individual communities due to unique factors that influence disease spread within them. This emphasizes the significance of having tailored models for the effective management of the disease. The HCF provides clinical care for a large number of tuberculosis patients, while research facilities continue to study, the disease and diagnostic results provide information on Mtb diagnosis. While all three teams will participate in the same intervention, their ability to exchange knowledge and implement improvements to integrate services will vary. The evaluation of integration's impact, as well as the broader policy context, should consider environmental uncertainty that remains throughout the model implementation period, as demonstrated by other studies elsewhere [23]. Research conducted in different locations has shown that incorporating a collaborative knowledge translation framework, along with providing resources like facilitation and distributed leadership, within a transdisciplinary team consisting of research institutions, healthcare workers, and laboratories, can enhance collaboration and aid in achieving transdisciplinary research goals [31]. Collaborating with researchers across different fields can enhance the applicability and adoption of research findings on TB and HIV issues in the province through integrated knowledge transfer [52]. Involving stakeholders in healthcare systems can be a powerful way to bridge the gap between research and practical implementation, leading to desired transformations. This approach emphasizes exchanging knowledge among the three parties, which portrays a shift towards active participation and considering perspectives that may not fit within the boundaries of disciplinary expertise. It has the potential to enhance the understanding of partnership expectations and their related effects or consequences [52]. Our research has found that some patients have developed resistance to TB medication, while also being affected by HIV. Studies have shown that Sub-Saharan Africa (SSA) has been the region most impacted by both TB and HIV epidemics. To address this issue, numerous nations have implemented policies based on recommendations from the World Health Organization

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[41]. Incorporating interventions for both TB and HIV involved HIV screening for TB patients, administering co-trimoxazole preventive therapy, and providing antiretroviral therapy to eligible HIV-positive patients. However, low-income countries such as South Africa faced challenges such as staff shortages, poor documentation, inadequate resources, irregular drug supply, and insufficient infrastructure. On the other hand, direct supervision, standardization, and mutual adjustment were identified as ways to facilitate integration [41]. The Eastern Cape is facing difficulties in managing resistance to TB, such as incorporating TB and HIV programs into other disease prevention efforts [53]. To ensure that individuals with pulmonary TB adhere to their treatment plan, a holistic approach that considers behavior adjustment, transformation, and sustainability is required. This approach should prioritize individual-centered care that balances patients' rights and needs while also acknowledging their responsibility for their recovery. One effective model for understanding health behavior and TB treatment adherence is the Health Belief Model (HBM), which has been studied and utilized in various locations [1,3]. The motivational interviewing (MI) communication approach is based on the Health Belief Model (HBM) and focuses on increasing intrinsic motivation and encouraging self-initiated change. By addressing ambivalence between current behaviors and future goals and values, individuals can become more internally motivated to make positive changes. Studies have shown that individuals are more likely to adhere to treatment if they perceive themselves as vulnerable, view the disease as severe, believe in the effectiveness of prevention measures, and acknowledge potential difficulties or barriers to recovery as studies indicated elsewhere [1,2]. Research conducted in other locations has demonstrated that utilizing the motivational interviewing communication model, which is founded on the Health Belief Model, can have a significant impact on medication adherence, particularly regarding treatment outcomes, among individuals with pulmonary tuberculosis [12–14]. According to [14], factors such as information, attitudes, beliefs, and perceptions are covered by the Health Belief Model (HBM). These factors have an impact on patients' behavior, including treatment adherence. Treatment adherence is generally significant for controlling diseases. TB is an important disease to model for identifying intervention strategies, especially in vulnerable communities like rural areas where the disease is burdensome. [14]. It is important to note that models on TB transmission are specific to certain geographic areas and should not be generalized. Therefore, a model must be developed for this particular study setting. This will allow policymakers to determine which aspects to focus on and which intervention strategies are most likely to be successful in a specific area. As there have been unacceptable levels of *M. tuberculosis* spread in this study setting, renewed attention must be given to reducing its spread. To provide healthcare to our expanding multiethnic world, various service delivery models have been created, including one that ensures ongoing collaboration among healthcare organizations to understand the epidemiology of TB in rural areas of the Eastern Cape. Preventing drug resistance in *M. tuberculosis* involves drug susceptibility testing, surveillance, and ensuring the completion of adequate treatment regimens and patient follow-up. Through the integrated collaboration under this model, a multidisciplinary approach can be applied to address the ongoing issue of TB spread. It has been observed that there is a deficiency in TB awareness, which can lead to non-adherence to medication due to a lack of comprehension. Furthermore, the province has experienced a considerable number of patients abandoning TB treatment before completing the full course of medication [44–46]. Extensive literature suggests that patients who received health education and counseling before and during their TB treatment have higher rates of adherence and completion, and lower rates of loss to follow-up [40–51,53]. All TB patients should receive health education and counseling on the disease and its treatment. The primary objective of health education is to provide patients with accurate information so that they can make informed decisions about their health. Education can be delivered through various means, such as face-to-face discussions, written materials, videos, or artistic performances involving individuals affected by TB. Patients must be informed about the disease, its treatment, and the services available to them. Moreover, health education should be provided multiple times during TB treatment to reinforce previous information and communicate new information regarding changes in treatment. Educational sessions can be conducted by different healthcare professionals or pharmacists and can include the patient alone or

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with their family and friends. Sessions could be scheduled before or at the beginning of treatment, after the intensive therapy phase, or during follow-up care [5–7,12,13,53]. The goal of health education is to provide individuals with appropriate knowledge, while counseling assists them in implementing that knowledge by altering their attitudes and actions. "Counseling" refers to a dialogue between the patient and the healthcare provider in which both parties participate [40,41]. The process of communication between a patient and a healthcare provider with counseling skills is interpersonal and dynamic. This involves a contractual agreement where the healthcare provider assists the patient in making decisions and developing disease control plans without any moral or personal judgement. It can be a difficult and concerning process for both parties [40,41]. To do this, healthcare professionals need to learn how to develop relationships with patients and how to communicate effectively with them to deepen their understanding of TB. The objective is to provide the patients with the confidence they need to carry out the necessary actions for the treatment of their TB condition [40,41].

5. Definition of operational concepts

Collaboration- joint management between HIV programs and TB-control programs for delivering integrated TB and HIV services preferably at the same time and location [41]

MDR TB- Multidrug-resistant TB (MDR TB) is caused by an organism that is resistant to at least isoniazid and rifampin, the two most potent TB drugs [41].

HIV- HIV (human immunodeficiency virus) is a virus that attacks cells that help the body fight infection, making a person more vulnerable to other infections and diseases [41].

Transdisciplinary research- is a research strategy that crosses many disciplinary boundaries to create a holistic approach [52].

Multiethnic- made up of or relating to people of several ethnic groups [52].

Ambivalence- simultaneous and contradictory attitudes or feelings (as attraction and repulsion) toward an object, person, or action [3]

Gene mutations and lineages- A mutation refers to a single change in a bacterial genome (genetic code). Mutations happen frequently, but only sometimes change the characteristics of the bacteria. Lineage: A lineage is a group of closely related bacteria with a common ancestor [45–47].

TB strains- *M. tuberculosis* complex (MTBC) causes tuberculosis (TB) in humans and various other mammals. The human-adapted members of the MTBC comprise seven phylogenetic lineages that differ in their geographical distribution [46].

Genetic diversity- is the total number of genetic characteristics in the genetic makeup of a bacteria, it ranges widely from the number of species to differences within species and can be attributed to the span of survival for a species [45].

Lineage- a term used to describe cells with a common ancestry, that is developing from the same type of identifiable immature cell [47].

Spoligotyping analysis- is a PCR-based method allowing the analysis of strain-dependent polymorphisms observed in spacer sequences present within the direct repeat (DR) genomic region of *M. tuberculosis* complex strains. Spoligotyping provides some important advantages over other genotyping techniques [47].

Hetoresistance- Heteroresistance of *M. tuberculosis* (MTB) is defined as the coexistence of susceptible and resistant strains to anti-tuberculosis (TB) drugs in the same patient [47].

Mixed infections- when a patient is infected by two or more different *M. tuberculosis* strains at the same time [47].

Heterogeneity- variation between *M. tuberculosis* strains [47].

6. Study Limitation

The fact that the outcomes of this study are all dependent on those that have been published in manuscript parts 1, 2, and 3 is one of its limitations. These conclusions also have limited generalizability because they are exclusively based on data from the Eastern Cape research. The fact that the study's findings may be used to create and enhance intervention methods in the Eastern Cape Province and other contexts is one of its strengths.

7. Conclusions

Collaboration among clinicians, researchers, and laboratories is crucial to benefit patients with the early initiation of medication, proper management of side effects, and monitoring of medication adherence while researching to generate new evidence on TB. Integration of HIV with TB is also necessary. In the Eastern Cape, community-based treatment for MDR-TB can be implemented within the existing TB control program and scaled up where resources allow. To prevent DR-TB development and management, a functional TB program is necessary for patients in this province. Resource availability to mitigate the costs of accessing care for socioeconomic factors in this poor province requires additional support. It is vital to provide health education on smoking cessation for TB patients to promote cure rates. Consistent testing for TB in HIV patients and HIV in TB patients should be upheld as stipulated in the World Health Organization collaborative guide for low-income provinces like Eastern Cape. Constant monitoring and evaluation of the care model's feasibility, as well as conducting studies to determine the effectiveness of our preferred patient care model, is essential.

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