

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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Article

Mapping a Model for Collaboration of Health Care Facilities, Diagnostic Laboratories, and Research Institutions: Management of Drug Resistant Tuberculosis in Rural Eastern Cape

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Abstract: Infectious illnesses have always posed a threat to human health, with tuberculosis being a major concern. The use of various medications and antibiotics in the fight against such TB has led to the emergence of drug-resistant tuberculosis, which has become increasingly difficult to manage. While there have been a 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 in rural areas burdened with tuberculosis is lacking. This study seeks to map a model that is to be used to bridge the gap by facilitating the exchange of knowledge among healthcare professionals in healthcare facilities, diagnostic laboratories, and research institutes, particularly for underprivileged communities in the Eastern Cape. The model will also serve as a guide to monitor and evaluate epidemiological TB management plans.

Keywords: model; drug resistance tuberculosis; collaboration

1. Introduction

Tuberculosis (TB) remains a problem of concern for public health worldwide, with drug resistance tuberculosis (DR-TB) adding to the problem. 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 DR-TB which is defined as TB 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]. The approach involving sharing knowledge between healthcare professionals (HCP) in healthcare facilities (HCF), diagnostic laboratories (DL), and research institutes (RI) can help to enhance a better understanding of the epidemiology of DR-TB.

According to other studies [9,10], there is increased interest in considering information sharing as a valuable resource for healthcare organizations, and TB management is at the center of this knowledge-sharing among health institutions. Knowledge management is defined by the World Health Organization (WHO) and other sources of evidence as "a set of principles, tools, and practices that enable people to create, share, translate, and apply knowledge to create value and improve effectiveness [11,12]." Knowledge exchange for improved management and the transmission of up-to-date healthcare management information to staff, patients, decision-makers, and other sectors have been the defining characteristics of collaboration across various health stakeholders, including HCP, HCF, and DL, for the effectiveness in TB. Additionally, it is essential to provide health

information and counseling to the community so that HCP who interact with patients will have a better awareness of the condition and be able to provide high-quality medical treatment [9,10]. Studies conducted elsewhere have shown that fostering a culture of information sharing inside companies is crucial for the success of health institutions and the people who use them by boosting intellectual capital, cutting costs, and boosting competitiveness [9–12]. To advance their expertise and deliver evidence-based healthcare, health professionals require current health information from reliable sources. Medical personnel in resource-constrained nations have a history of not sharing their information and experiences with one another, which has led to a variety of medical blunders, hence the idea of mapping this model between these health stakeholders (HCF, HCP and DL). Based on information from HCF, DL, and RI an information system should be established to facilitate data storage as part of the strategy to build TB epidemiological information in rural areas of Eastern Cape. When HCF, DL, and RI work collaboratively there will be a storage of data quality which will be comprised of data completeness, which is the overlooked gap due to not knowing the importance of how completeness of data entry by collaborating organizations in the information system is important. The insufficient completeness of data makes it difficult to evaluate the actions to be taken and the epidemiological profile of affected areas, making it challenging to make decisions and develop disease control plans. A comprehensive strategy that incorporates healthcare facilities, diagnostic services, and research services is required to increase the inadequate understanding of TB transmission in rural parts of the Eastern Cape. The multisectoral cooperation between these parties will also be economically advantageous in terms of resource allocation, staff motivation, and readily available information sources on interventions to enhance the issue of TB management in the research region.

2. Materials and Methods

We set out to map a model for management of drug resistant tuberculosis in rural areas of Eastern Cape using information of gene mutation, genotypes of DR-TB isolates, distribution of *M. tuberculosis* mutations and spoligotypes and factors associated with treatment outcomes of *M. tuberculosis*. Model information is based on three categories:

2.1. Category 1

Gene mutations and the genotypes of DR-TB (mono DR-TB, MDR-TB and XDR-TB) in the rural Eastern Cape Province that were identified by using different assays. From patients who were suspected to be having TB, their 1157 sputum samples were collected and analyzed. These analytic methods identified regions of DR-TB mutations, heteroresistance, and genetic diversity [13].

2.2. Category 2

Distribution of *M. tuberculosis* mutations and spoligotypes was investigated to identify transmission hotspots of DR-TB. The identification of 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, gene mutations and heteroresistance. Clinics within hospitals with the same coordinates were merged in the analysis [14].

2.3. Category 3

The investigation of treatment outcomes and associated factors among tuberculosis patients 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 [15]. 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 [15].

2.4. Categories Key Points for Model Mapping

The key points used to map the model for spread of DR-TB are:

2.4.1. 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. Most study samples exhibited a pronounced dominance of mutations within the *rpoB* codon 531 that is known as a marker of RIF resistance [16]. 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 [16].

2.4.2. Heteroresistance

Heteroresistance occurs when resistant and susceptible strains of an infection infect a patient at the same time [17,18], and is known as a precursor to full resistance or low levels of drug-resistant TB. Studies by Faye et al., [13] it was observed as it is increasing yearly in rural areas of Eastern Cape. The results of treatment could be negatively impacted by heteroresistance as it 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 [19,20], it was discovered that *katG* gene had more heteroresistant strains than *rpoB* and *InhA* genes, 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.

2.4.3. Type of Lineage

The Beijing family is associated with drug resistance in some parts of the world [27] and is also known to be more transmissible than other families and more prevalent in Eastern Cape and Western Cape [22,23]. In addition, Faye et al., study findings have confirmed this high prevalence in the rural Eastern Cape as well [13,14]. 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 [34], Ano et al. [25], and Gagneux et al. [33], 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 [27].

2.4.4. HIV-TB Coinfection

According to Faye et al., [15] the rate of co-infection of TB and HIV was high with men being mostly infected and resulting in undesirable treatment outcomes in rural areas of Eastern Cape. 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 [28–30]. TB is the leading immune-suppressing infection and the commonest cause of death among HIV-infected patients [22,23,31] WHO estimated that patients living with HIV are at 20 times higher risk of acquiring TB than their counterparts [1–3,30,31].

2.4.5. Treatment Outcomes

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 in rural areas of the Eastern Cape [15].

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 [16]. Treatment success rate (TSR) is a critical factor in the global End TB strategy. With 76% national TSR in South Africa, the country still falls short of the standard set by WHO, the global health body [30].

The model key points recommended technical approach and justification are detailed in Table 1

Table 1. Recommendations from categories key points of model mapping.

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 cause analysis, the significant gene mutation and regions should be documented and shared with TB research institutions. According to Ameeruddin and Luke [34], Ano et al. [25], and Gagneux et al. [33], the <i>katG</i>-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 <i>katG</i> mutations [27]. 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 <i>M. tuberculosis</i> infections, the prevalence of particular mutations of <i>rpoB</i>, <i>katG</i>, and <i>inhA</i> differed significantly [27]. 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 <i>M. tuberculosis</i> prevalent in rural Eastern Cape regions, to facilitate rapid assessment of drug resistance.
Identify epidemiological trend of heterogeneity of Infecting <i>M. tuberculosis</i> strain (single strain or mixed strain).	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. Knowing the type of prevalent DR-TB is crucial for keeping track of <i>M. tuberculosis</i> 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.
- Treatment category (New or retreating) - HIV status (Negative or Positive) - Gender (Female or Male) - Age category	
- Phenotypic DST result (INH and RIF susceptible, INH Monoresistance, RIF monoresistance, Multidrug resistance) - Treatment outcome (completed, cured, lost to follow-up, died and failed)	
Age category <21 21–30	Which demographic and clinical category contributes to poor treatment outcomes? This knowledge will assist in designing informed

31–40	
41–50	
≥51	
• Gender	
Female	
Male	
• Strain heterogeneity	
Single strain	
Mixed strain	
• HIV status	
Negative	
Positive	
• Phenotypic DST result	
INH and RIF susceptible	
INH monoresistance	
RIF monoresistance	

interventions and targeting the patient category that contributes the most to poor treatment outcomes

3. Discussion

Model mapping for management and spread of DR-TB gene mutations and lineages in rural Eastern Cape needs quality pre analytical and post analytical processes which are well communicated among institutions responsible for TB management, Figure 1.

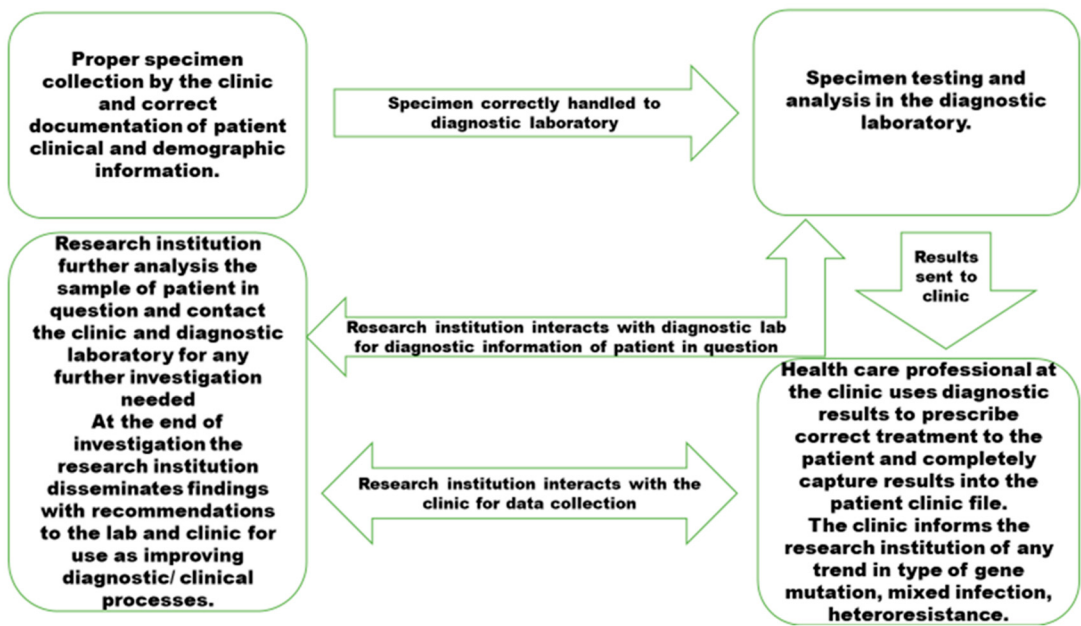


Figure 1. Model mapping for management and spread of DR-TB gene mutations and lineages in rural Eastern Cape.

The institutions shown in Figure 2 were involved in the three categories of this study and have been observed to have a weak connection, which negatively impacts health programs intended to strengthen TB control and reduce drug resistance. Effective sharing of TB information between DL, RI, and HCF through collaboration can enhance the information that HCP provide to patients in a way that patients can understand.

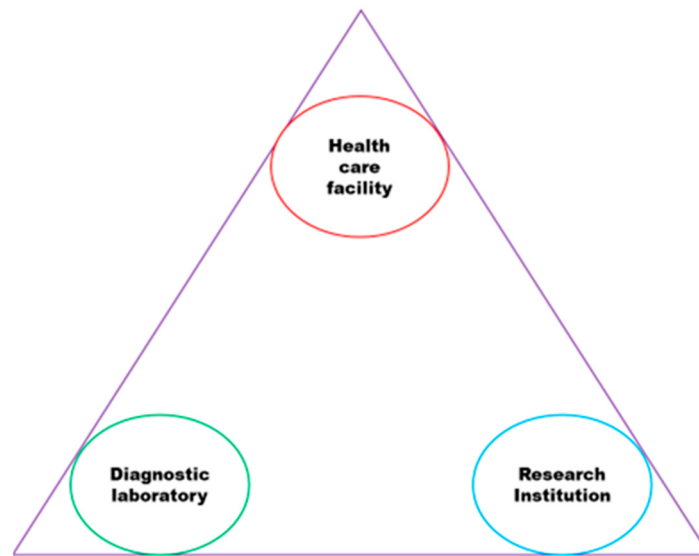


Figure 2. Collaboration and communication motivation model of patient care and disease monitoring institutions.

The increasing number of drug-resistant TB cases, heteroresistance, and treatment failures in the study area is a major concern. This is likely to be due to the lack of a collaborative approach to tackling TB among HCF, DL, and RI. Therefore, it is crucial to establish cooperation between HCF, DL, and RI to address these issues as it 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 (HCF, DL, and RI) must be included in the effort, as outlined by the World Health Organization's (WHO) Global Report [30]. The collaborators to ensure that disease updates are precise must establish a strict system for entering quality data as the failure to provide complete and quality data may result in challenges in accurately characterizing the true epidemiological state of TB [32–37]. To effectively monitor and manage the spread of DR-TB gene mutations and strains, it is necessary to do spatial analysis at least every three months using data entered by the collaborators in the system. 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 [32–37]. Lesson learnt from Covid-19 pandemic is that there is a need of collaborative TB management preparedness for any pandemic that can be experienced so that interruption on TB control and management is not compromised. Before the emergence of SARS-CoV-2, tuberculosis (TB) was the biggest infectious killer of humans. An projected 1.6 million persons died from TB worldwide in 2021, with the majority of deaths taking place in low- and middle-income nations. (LMICs) [38]. An estimated 10 million people contracted TB before the COVID-19 epidemic in 2019. Among them, 7.1 million people received diagnoses and notifications, leaving 2.9 million people without diagnoses. The pandemic had a terrible impact on TB services, increasing the diagnosis gap to 4.2 million cases [39]. Only 6.4 million of the estimated 10.6 million TB cases were diagnosed and notified to national TB programs globally in 2021.

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 [13–15]. It is important to regularly evaluate existing systems and note trends in DR-TB using key points, as shown in Figure 3. This allows opportunities to refine and adapt to the changing epidemiology of DR-TB, as well as incorporate new advances in DR-TB control. However, collaboration for enhancing DR-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.

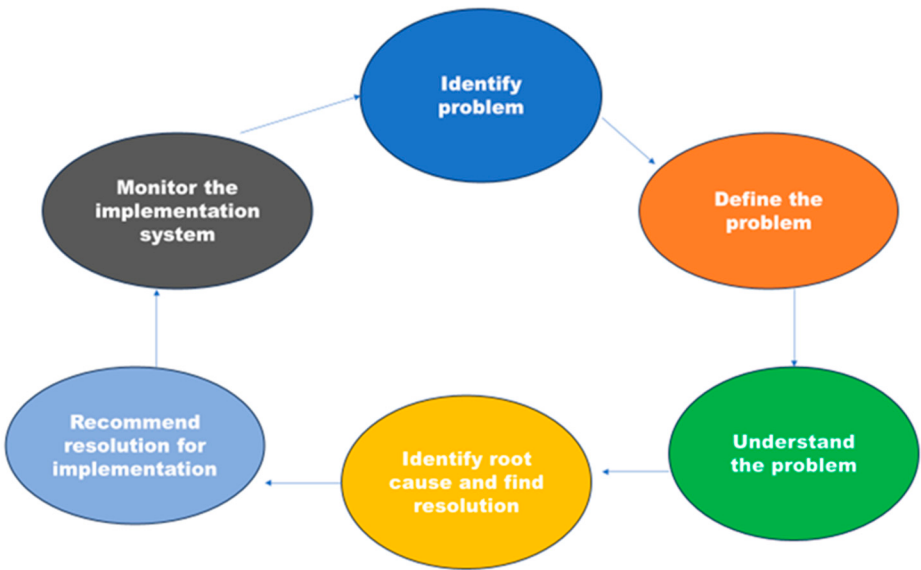


Figure 3. Collaboration oversight.

Despite the availability of effective treatments since the 1980s, tuberculosis remains a significant global public health concern which requires proper management of information regarding DR-TB. Proper dissemination of information from laboratories and healthcare professionals will assist HCP to 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 managing knowledge between three collaborators.

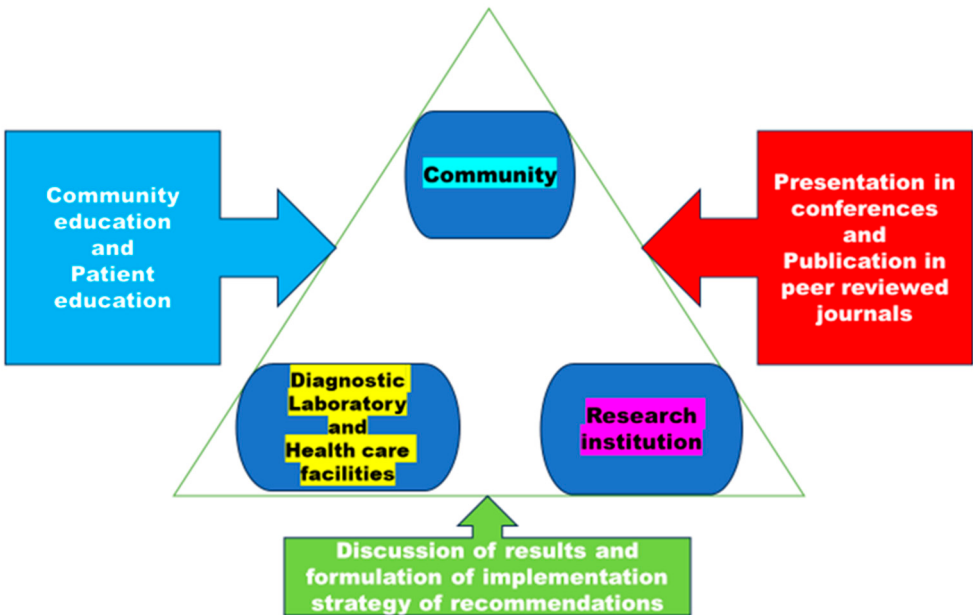


Figure 4. Plan to manage information on DR-TB gene mutations and strains.

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, lineages and treatment outcomes in rural areas of the Eastern Cape. Mapping a customized models is 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 TB in rural

areas of Eastern Cape. The HCF provides clinical care for a large number of tuberculosis patients, while research facilities continue to investigate the provide information on *M. tuberculosis* received from DL. While all three collaborators will participate in the same intervention, their ability to exchange knowledge and implement improvements to integrate services will vary. 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 [35]. TB is an important disease to model for identifying intervention strategies, especially in vulnerable communities like rural areas of Eastern Cape where the disease is a burden [30]. It is important to note that models on TB transmission are specific to certain geographic areas and should not be generalized. Therefore, this model is developed for this particular study setting with the idea that it 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 services tailored to each community, 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. The objective is to have a good model on DR-TB.

4. 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 rural areas of Eastern Cape research. The fact that the study's findings may be used to create and enhance intervention methods in the rural areas of Eastern Cape Province and other contexts is one of its strengths.

5. Conclusions

Collaboration among clinicians, researchers, and laboratories is crucial to benefit patients. The model for collaboration between HCF, DL and RI will enhance educational health programs which are to be tailored to the specific needs of the community, taking into account the latest information on DR-TB gene mutations and strains.

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