Review Article

Genomic Evolution and Dynamics of Drug Resistance in Mycobacterium Tuberculosis across West Africa- A Systematic Review

ABSTRACT

Background: The continuous evolution of drug-resistant Tuberculosis strains around the globe, particularly in West Africa, continues to be a major public health problem and poses serious threats to the actualization of the "End Tuberculosis Strategy" projected by 2030. Hence, a comprehensive knowledge on genetic variations, lineage distributions and evolutionary adaptations implicated in *M. tuberculosis* drug-resistance could strengthen research efforts in TB control.

Objectives: This review summarizes the genetic mechanisms of drug resistance in mycobacterium tuberculosis and the extent to which they pose threats to public health. It also gives recommendations on managing drug resistant TB in West Africa.

Literature Search: This review assesses available literature relating to the genomic evolution and dynamics of drug resistance in mycobacterium tuberculosis across west Africa. Search for relevant articles in databases such as Google Scholar, PubMed, Scopus and Web of Science was conducted using keywords such as "Genomics", "Evolution", "Drug Resistance", "Mycobacterium tuberculosis" and "West Africa". Sixty articles were found in this search and forty six articles were selected and reviewed.

Results: Multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB), which are common in West Africa, have been linked to the MTBC Lineages 5 and 6 also known as *M. africanum.* The devastating challenges these resistant strains exert on public health justified the urgency for exploring novel therapeutic avenues, improved diagnostic protocol, and robust healthcare systems to curb the disease.

Conclusion: This review maintained a strong advocacy for proper public health education, installation of adequate surveillance systems, and the adoption of alternative therapeutic modalities to tackle drug-resistant *M. tuberculosis,* effectively in West Africa and mitigate the public health burden it poses globally.

Keywords: Genomics, Evolution, Drug Resistance, Mycobacterium tuberculosis, West Africa

1.0. INTRODUCTION

One of the most difficult and oldest known infectious diseases still in existence, with a history dating back up to a century and a half, is tuberculosis (TB), which is caused by the *Mycobacterium tuberculosis* [1]. As a communicable disease TB pose a severe threat to public health and represent major concerns that unevenly affect and decimate vulnerable populations of developing countries [2]. Vulnerable populations are at alarmingly high risk for TB owing to their marginalized or disadvantaged socioeconomic status, which limit their access to adequate healthcare facilities. Although substantial scientific efforts have been leveraged in the combat of TB, the disease continues to rank among the top ten worldwide causes of death [3]. In 2022, 10.6 million new cases of TB and 1.6 million deaths related to the disease were

reported, according to a recent World Health Organization (WHO) report [4]. This puts TB as the 13th most deleterious disease worldwide, ahead of both HIV and AIDS [4]. Africa, with 15.19% of the world's population, accounts for approximately 24% of the worldwide tuberculosis (TB) burden [5]. West Africa is home to all six main MTBC lineages, in contrast with other regions that only have one or a few of these lineages [5]. Furthermore, the global burden of TB is unevenly distributed, with developing countries and middle-income regions particularly in Asia and Africa having the highest burden. In fact, socioeconomic and health-related issues, including HIV co-infection and inadequate healthcare systems, as well as poverty and hunger contribute to this inequality [6]. In addition, the recent appearance and reemergence of different types of tuberculosis, such as extensively drug-resistant TB (XDR-TB) and multidrug-resistant TB (MDR-TB), which continue to counter scientific efforts to curtail the disease, presenting a major threat to public health [7].

Alarmingly high rates of tuberculosis cases are reported in West Africa, where together Nigeria, Ghana, Liberia, Senegal, and Mali account for a sizable share of the world's tuberculosis cases [8]. Notably, the entire West Africa region is faced with substantial challenges in controlling the disease, however, the rate of TB incidence in this region differs across countries. Socioeconomic determinants, like poverty, migration, inadequate reach to healthcare infrastructures, poor disease diagnosis and treatment, particularly in rural areas contribute to a large extent to the spread of TB [9]. Delayed diagnosis and stigma associated with patients constitute the impediments truncating efforts to control TB. Moreover, the high rates of HIV recorded in this region worsens the TB epidemic, and as a co-infection, HIV distorts immune functions and increases risk of TB [10].

More worrisome is the alarming rates of the prevalence of multidrug resistant strains of the bacteria in West Africa, where inadequate diagnostics and surveillance systems often translates to underreporting of cases. Besides, the porosity of the region's borders and inadequate control of cross-border migrations also facilitate TB transmission, including drug-resistant strains across neighboring countries [5]. The majority of drug resistant tuberculosis cases are caused by human intervention. The first documented case of drug resistance in *M. tuberculosis* was linked to the use of streptomycin (S) shortly after its discovery. Combined resistance of Streptomycin with other drugs such as isoniazid, pyrazinamide, ethambutol and rifampin also emerged [11].

In order to stop the worldwide tuberculosis (TB) epidemic, the World Health Organization (WHO) has implemented the "End TB Strategy", which would lower global TB incidence and mortality rates by 90% and 95%, respectively, by 2035 compared to 2015 [12].

The expected number of new TB cases and deaths has continued to fall, a trend that started in the African Region in 2005. TB and TB/HIV therapies are expected to have prevented 16 million deaths in the region between 2000 and 2021. With a 22% decrease in new cases from 2015 to 2021, the African Region of the "End TB Strategy" achieved its 2020 milestone. Additionally, eight nations have achieved a 35% decrease from 2015 [12].

In this review, we discussed the mechanisms of drug resistance in *Mycobacterium tuberculosis*, along with the challenges and implications of the disease for public health. We also highlighted strategies for detecting and controlling drug-resistant tuberculosis in West Africa.

2.0 LITERATURE SEARCH

This review assesses available literature relating to the genomic evolution and dynamics of drug resistance in *mycobacterium tuberculosis* across the west Africa region. Search for relevant articles in databases such as Google Scholar, PubMed, Scopus and Web of Science was conducted using keywords such as "Genomics", "Evolution", "Drug Resistance", "*Mycobacterium tuberculosis*" and "West Africa". Paper selections were gotten by reviewing abstracts and titles. Sixty articles were found in this search and forty six articles, including reports were selected and reviewed. The review discussed studies from 2014 to present.

3.1 Genetic Diversity of Mycobacterium TB in West Africa

Mycobacterium tuberculosis (MTB) is the causative agent of tuberculosis in the lungs of humans. It is composed of seven distinct lineages that are related to geographical regions based on phylogeny [13]. Lineages one through four (1-4) and seven (7) are generally known as *Mycobacterium tuberculosis sensu stricto*, and are widely distributed. On the other hand, lineages five and six (5 and 6), *Mycobacterium africanum* is exclusive to West Africa [14].

Genomic diversity of MTB in West Africa is characterized by the prevalence of lineages 5 and 6 [15]. The lineage five (5) is most common in the eastern part of West Africa, which encompasses Nigeria, Cameroon, the Benin Republic, and Ghana [16] while the western areas in West Africa, which includes Ghana, Senegal Guinea Bissau, Sierra Leone, and Gambia, Lineage six (6) is more prevalent [17]. *M. africanum* is usually known for its slow progression of the tuberculosis disease compared to the progression in other lineages. It has also been established that areas with higher prevalence of *M. africanum* will experience different transmission dynamics and higher disease severity than regions with other lineages [15]. Evolutionary dynamics of tuberculosis in these regions are usually influenced by different factors, including environmental pressures and genetic mutations [18]. The evolution of tuberculosis is driven by genetic mutations that contribute to its adaptation. Mutations linked to drug resistance in tuberculosis have been found in genes such as *katG, inhA* and *rpoB* [19].

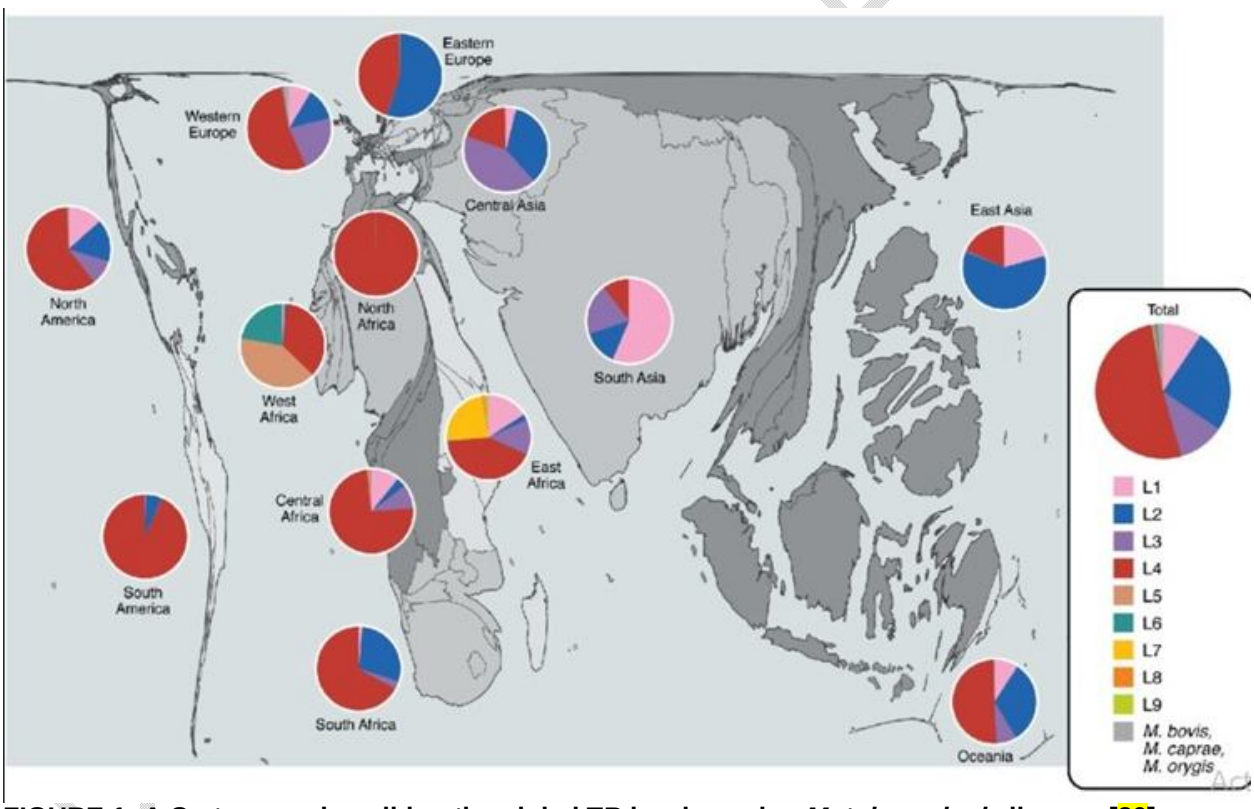

FIGURE 1: A Cartogram describing the global TB burden using *M. tuberculosis* lineage [20].

3.2 Genetic Mechanisms of Drug Resistance

There are different types of drug-resistant tuberculosis disease.

Resistance to just one tuberculosis treatment drug is known as Mono-resistant TB disease. Poly-resistant TB disease is caused by tuberculosis bacteria that are resistant to at least two TB drugs (other than isoniazid and rifampin) [21].

The resistance to more than one drug is defined as Multi-drug resistance and in tuberculosis, it is explained as the minimum resistance to both isoniazid and rifampin [22].

Pre-extensively drug-resistant TB (pre-XDR TB) disease is a type of multidrug resistant tuberculosis caused by TB bacteria that are resistant to isoniazid, rifampin(MDR-TB), a fluoroquinolone and at least one of the three second-line injectables (amikacin, capreomycin, and kanamycin) [21].

Rifampicin resistance (RR) is the resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, in the form of mono-resistance, poly-resistance, MDR or XDR [21].

Mycobacterium tuberculosis resistance is caused by genetic mutations which are usually single nucleotide polymorphisms (SNPs), small deletions or insertions, and in a few instances larger deletions or inversions. These mutations can appear suddenly, usually spread by replication inside of the host and subsequent transfer between bacteria resistant hosts [23]. Three primary ways by which *Mycobacterium tuberculosis* can develop resistance to drugs include efflux pump modulations, enzyme inactivation and target-based mutations. Efflux pumps expel drugs from bacterial cells reducing drug concentrations and contribute to resistance while target-based mutations are scenarios in which the drug target undergoes mutation preventing binding of drugs [23].Other drug resistance mechanisms include, prevention of drug penetration, target overproduction, target mimicry [24].

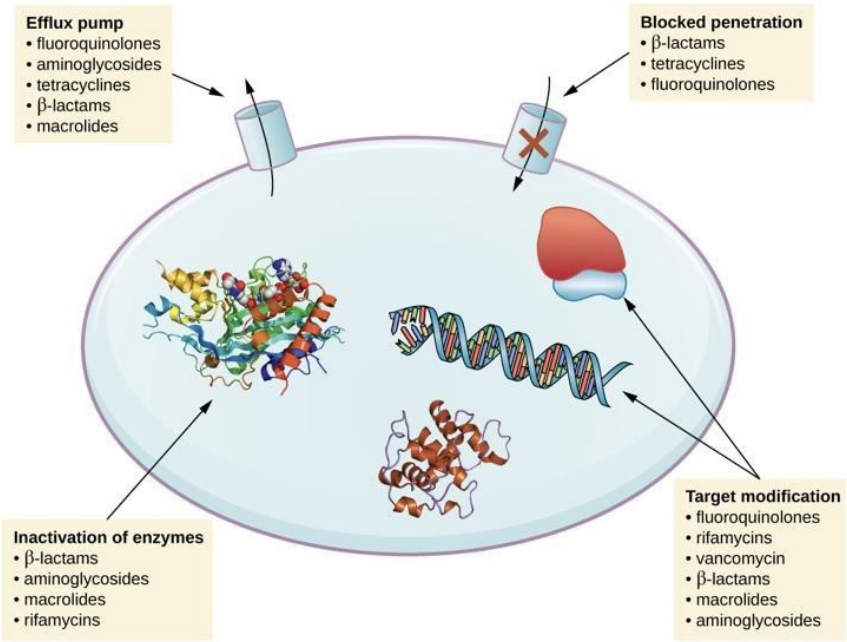

FIGURE 2 Methods of drug resistance mechanisms [24].

3.3 Mechanisms of First Line Drug Resistance

Isoniazid

When treating tuberculosis, isoniazid is frequently used as a medication. The catalase-peroxidase enzyme, which is encoded by the *katG* gene, activates it. Isoniazid resistance is caused by the most prevalent mutation, the katG mutation, which primarily occurs at codon 315. Further mutations that result in resistance can occur within the *inhA* gene and promoter region [25]. 7.1% and 7.9% of newly diagnosed and previously treated TB patients were identified worldwide, according to global data on isoniazid resistance [26].

Rifampicin

Rifampicin, another first-line drug, RNA polymerase encoded by *rPOB* gene which reduces the rifampicin binding and leads to bacterial resistance. The codons 516 and 529 are the sites of the most frequent mutations [25]. 2018 saw a global prevalence of rifampicin resistance in 3.4% of newly diagnosed cases and 18% of patients of tuberculosis that have already received treatment [27].

The frequency of multidrug resistance (MDR) was examined in isolates from eight West African nations: Gambia, Nigeria, Mali, Togo, Ghana, Guinea-Bissau, Senegal and Burkina-Faso. The study was conducted by Gehre *et al*.[16]. According to the study, 39% of the patients who underwent testing had firstline medication resistance. Nigeria has the greatest prevalence, with 30% in Ibadan and 59% in Lagos. Ghana followed closely with MDR prevalence of 26%.The percentages of MDR prevalence in Guinea Bissau and Gambia were low at 7%. In previously treated cases, Mali's prevalence was at 59% while Nigeria (Lagos and Ibadan) had 66% and 39% respectively. Multidrug resistance TB cases were found to be more prevalent in these three locations. With 13%, Gambia had the lowest.

3.4 Geographic Distribution and Epidemiology of drug-resistant TB in West Africa

Very little information is known about drug resistant tuberculosis in West Africa [28]. A rising public health challenge for many West African Countries is drug-resistant tuberculosis, which consists of multidrug resistant and extensively drug resistant strains with varying frequency over time [4,29]. According to WANETAM (West African Network for Tuberculosis, AIDS and Malaria), collaborative surveillance on drug-resistant tuberculosis in nine West African countries was reported. Figure 3 shows the estimates provided by the World Health Organization (WHO) often fall short of the actual incidence [4]. For instance, the study conducted by WANETAM reported that 39% of patients were resistant to at least one specific tuberculosis drug, but the WHO indicated that the prevalence of multidrug resistant tuberculosis was 2% in new cases and 17% in cases that had previously received treatment. Highly noted was the presence of pre-extensive drug resistant tuberculosis cases in all the eight countries that participated [16]. The World Health Organization recently released data on tuberculosis cases which showed that the prevalence of multidrug resistance/rifampicin resistant tuberculosis varied widely among West African nations, ranging from 54% in Guinea-Conakry to 0.67% in Togo. This is summarized in Figure 4 below [30].

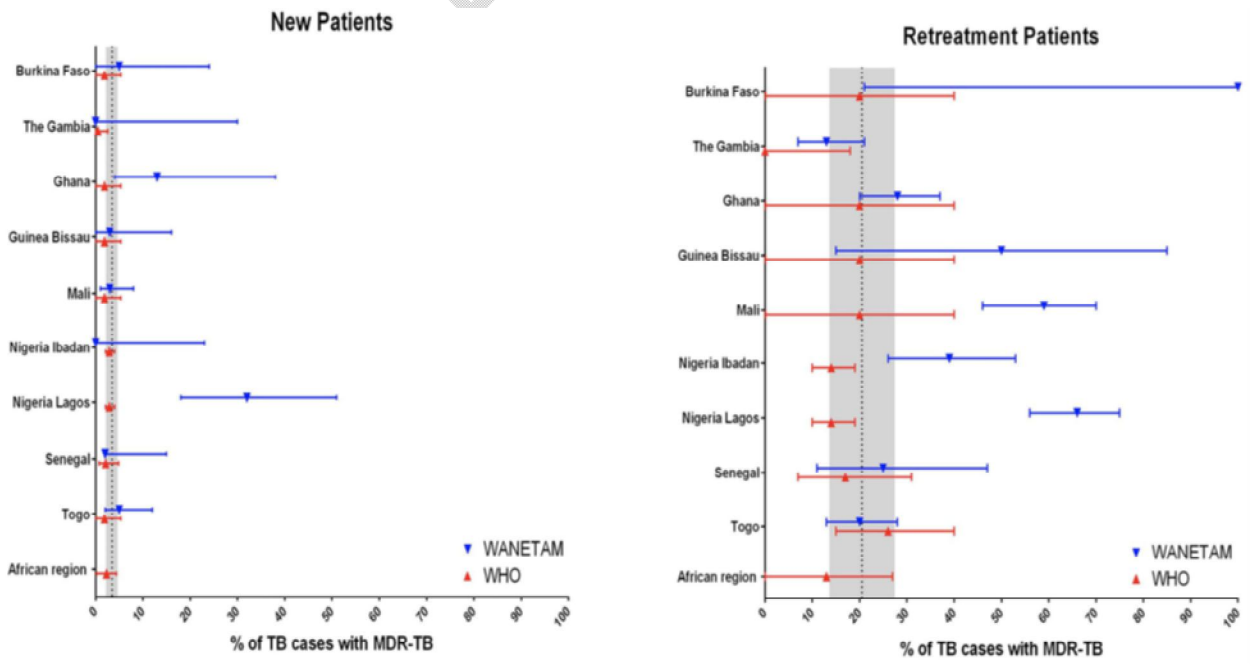

FIGURE 3 The 2016 WHO estimates of Multidrug Resistant Tuberculosis compared with reports from nine West African countries [4].

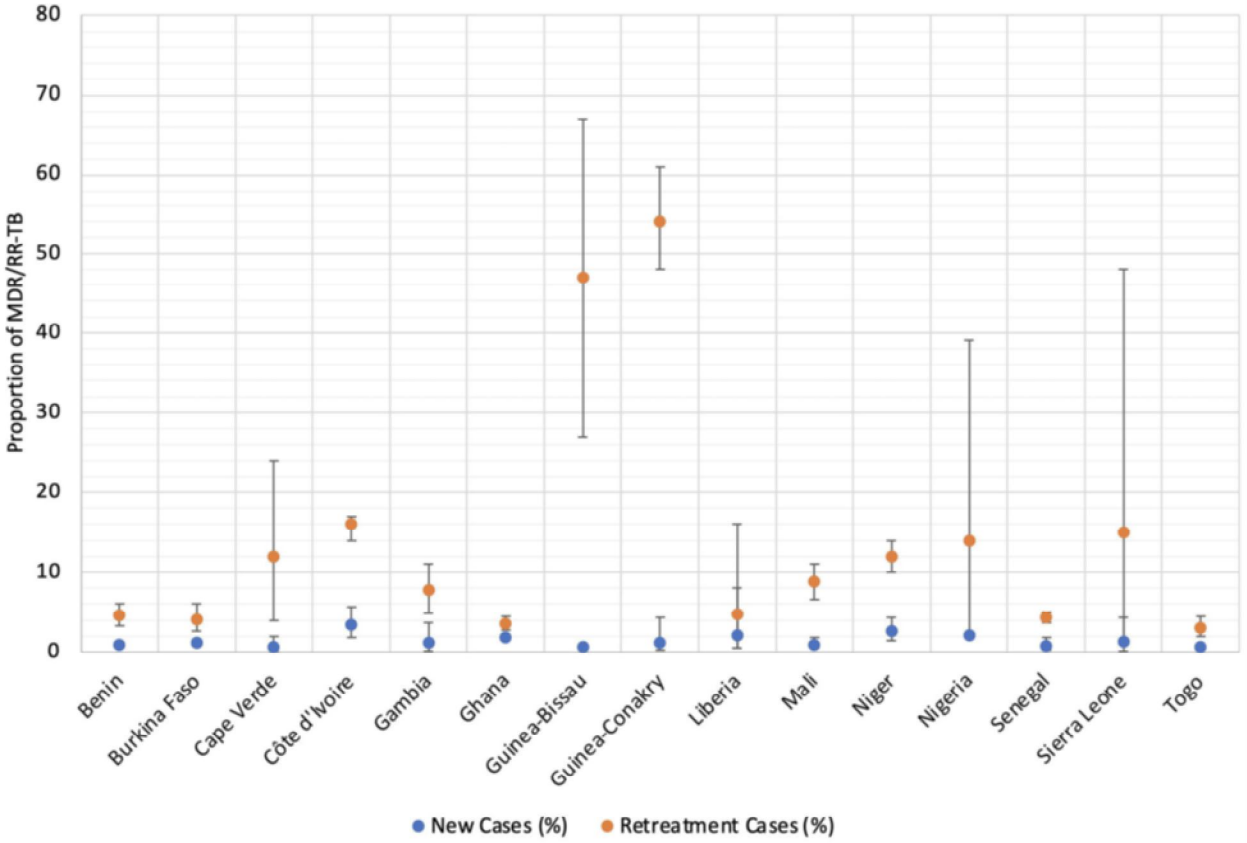

FIGURE 4 The Global Tuberculosis Report on the estimates of multidrug resistant/rifampicin resistant tuberculosis among newly diagnosed and recurrent cases of tuberculosis in West Africa as of 2022 [30].

3.5 Public Health Implications and Challenges

To effectively treat drug-resistant tuberculosis, there is a need for correct and timely diagnosis. It is possible to detect diseases using a variety of diagnostic techniques that combine both DNA and culture-based (phenotypic) testing [31]. The disadvantages of drug susceptibility testing (DST) procedures based on culture include the need for specialized laboratories, a high level of expertise, and the fact that results can take weeks to obtain. In contrast, DNA based techniques, like polymerase chain reaction (PCR), give a more rapid alternative for testing [32]. Treating drug resistant tuberculosis is challenging as it demands longer use of drugs lasting between 6 to 9 months. This long period can lead to several difficulties. Firstly, side effects such as liver and gastrointestinal problems may develop as a result of combining drugs and cause treatment failures [33]. Though the treatment rate was among the highest in West Africa, it still fell below the WHO recommended target of 90% registration. Limited access to these essential medications can cause inadequate treatment plans , which may undermine treatment results and lead to the progression of drug resistance further [34].

3.6 Managing Drug Resistant TB in West Africa Public Health Sector

In West Africa, managing DR-TB has proven to be a complex issue that needs careful solution. Firstly, the inadequate access diagnosis which then causes delayed diagnosis and less effective therapy needs to be tendered to and controlled [35]. Secondly, the delayed diagnosis of this drug-resistant TB then results in an extended infectious period which then increases the risk of further transmission to others that did not

have the disease [36]. This solidifies the need for prompt diagnosis and appropriate treatment as these are very important for improving treatment results and stopping transmission [37].

4.0 Future Directions and Recommendations

Early detection of DR-TB is dependent on surveillance systems, and it is necessary that they should be improved. By improving better surveillance systems, healthcare professionals will be able to identify and respond to cases of emerging resistance faster [38]. The Government also has a role to play in improving health outcomes. Governments in countries in West Africa should reduce their dependence on foreign aid and should focus on building healthcare systems in the country to be more responsible and resilient [39, 40].

Contact tracing and monitoring of individuals that have been exposed to DR-TB patients should be effective. This, in addition with regular testing of patients will facilitate the detection of new cases early, it will prevent secondary transmission and improve treatment outcomes in the country [41, 42].

There should be more research on TB in West Africa to advance our understanding and also aid in the creation of more effective control measures. There are several medicinal plants in West Africa, for treating different diseases including tuberculosis. Investing in this plant-based field is necessary as it contains promising potential leads for new anti-tuberculosis drugs [43]. Plant species such as *Zanthoxylum leprieurii, Lantana camara, Cryptolepsis sanguinolenta* have been reported to exhibit antimycobacterial action against drug-resistant strains of *Mycobacterium* TB [44].

Finally, educating the public is the first and most important step in addressing the growing threat of drug-resistant TB in these regions. Even healthcare workers are not excluded in education as a good number of them are ignorant on causes, symptoms and management of drug-resistant tuberculosis. Targeted educational programs can help address misconceptions about the disease and increase early diagnosis and treatment [45]. A combination of different communication platforms such as social media, mass media, print materials e.t.c should be used to reach a wide audience with consistent and accurate information [46].

5.0 CONCLUSION

This review demonstrated that the genomic diversity and emergence of DR-TB in *Mycobacterium tuberculosis* in West Africa instigate tremendous threats to public health and contributes to the alarmingly high rate of tuberculosis cases in this region, caused by *M. africanum* lineages (5 and 6). The advent of MDR-TB strains endangers public health, necessitating the active search for innovative therapeutic modalities against drug-resistant tuberculosis, as well as the implementation of enhanced diagnostic paradigm, effective treatment regimen, and resilient healthcare facilities. To address the several challenges of drug-resistance in TB, we recommend the design of multidimensional and comprehensive strategies for the propagation of public health education against disease management, enhancement of surveillance systems, and the adoption of alternative remedies such as phytotherapeutics against TB and DR-TB. It also behooves the collaboration of governments agencies and other relevant stakeholders to strengthen the healthcare systems and promote timely and proper TB diagnosis, prevention and management, to minimize the spread and lethal impacts of tuberculosis in the developing countries. In addition, appropriating public funds to improve public health education programs and the installation of adequate healthcare facilities in rural and remote areas is quintessential to improving TB control and realizing better health outcomes among vulnerable populations in West Africa.

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