Chapter

Genealogy of Resistant Tuberculosis in Latin America and the Caribbean until 2020

Onix J. Cantres-Fonseca and Francisco Del Olmo-Arroyo

Abstract

History hallmarks different out brakes events during the last century. Being caught in the in the middle of the catastrophic COVID-19 pandemic, that initiated in 2019 makes possible to forget other causalities. Tuberculosis makes the case. The pathogen has been present more than hundredth years. Relevance rest in worldwide prevalence, pathogen spread, treatment resistance and the need for eradication. Drug treatment resistance is considered as one of the criteria to prioritize a country in the World Health Organization's intention to eradicate tuberculosis infection in the world. For decades in Latin America, including the Caribbean, there have been a persistent high rate of drug resistance with an overall prevalence to one or more drug rounds 13.0%. Approximately 30% of previously treated cases have a multi-drug resistance. In this chapter, we intend to review the epidemiology of resistant tuberculosis, and the causes of resistance associated to the community of people in the Latin American and the Caribbean. We intend to describe the genetic response of *Mycobacterium tuberculosis* from its migratory journey throughout decades from areas of Europa and Asia to Latin America, its genetic transformation secondary to inadequate drug exposure and the characteristics of the infected host, and how a change in the healthcare system and tuberculosis control strategies access are needed to change the surge of multidrug resistance tuberculosis.

Keywords: tuberculosis, treatment, resistance, Latin, America

1. Introduction

More than 100 years have been since the discovery of Mycobacterium tuberculosis (TB) and still continues to be one of the world's leading causes of death by a single infectious organism. Despite extensive knowledge of its pathophysiology and its infectious characteristics, TB continues to cause great morbidity, and continue to be a significant diagnostic challenge. But far from making the diagnosis, the true odyssey occurs when many patients develop an infection with resistance to available therapy.

Mycobacterium tuberculosis is a bacillus shaped, aerobic, slow growing and acid-fast positive staining bacteria. The organism is mostly transmitted through out droplets of particles suspended in the air, and inhalation by the infected host. Deposition of the bacteria in the tissues, especially the lungs, cause the principal manifestations of the disease. Most of the infected people developed a natural immunity by phagocytes which engulf the mycobacteria and form granulomas causing no clinical symptoms. This is known as latent tuberculosis. Differently,

around 10% of exposed people develop active infection, characterized by cavitary and fibrotic lung disease [1]. Immunosuppression can cause that tuberculosis bacilli migrate from the initial lung infection to other sites, causing extra pulmonary disease, which is one of the most lethal sequelae of the infection. TB can virtually invade any organ system and mimic other noninfectious conditions, causing to be a significant source of morbidity and mortality [2]. Early identification and appropriate treatment are the clues to obtain a satisfactory outcome.

The diagnosis of TB is done by identification of the mycobacteria in the affected tissue by culture or polymerase chain reaction. Once the organism is identified, combination antimicrobial drug therapy is started, and continued according to drug sensitivity. Length of treatment is determined by the site of infection and the immunologic status of the host, as well as the drug sensitivity of the organism.

Before the end of the first half of the 20th century, antimicrobial medications for Tuberculosis were discovered, following by the use of combination drug therapy as its principal management [3]. Around 1970s, the use of medications as Isoniazid and Rifampin were established as the principal core of treatment that participates in addition to other drugs for treatment of tuberculosis. The combination with other drugs allowed to decrease length of therapy to around 6 months [3]. After more than 50 years, new drugs for tuberculosis have been approved in 2019. The assemblance of previous known drugs and new ones is the pivotal therapy for the infection, including those with resistance to one or more medications (**Figure 1**).

In between the amaze and current focus in the catastrophic pandemic of Covid-19, we tend to forget that a year before in 2018, *M. tuberculosis* infected more than 10 million people, with 1.5 million people dying from the disease [1]. Despite being TB a well-known disease, it is suspected that more than one third of the cases did not receive adequate treatment due to lack of diagnosis and lack of resources [1]. Besides the direct poor outcome in the individual patient, the absence of an appropriate treatment increase the risk of developing drug resistance, facilitates alterations in the genealogy, and favors poor outcomes in morbidity and mortality. Thus, drug resistance is considered a significant menace to populations of high prevalence of disease, and an important set back to eradicate the infection.

Genealogy is described as the study of the history of a specific descendance and how we can follow the different lineages of a family or group. Throughout exposure to drugs, TB has developed the capability of resist antimicrobial therapy, which have evolved in strains that survive beyond those which are sensitive to medications, creating those drug resistant populations of mycobacteria. Current technologies, allow the identification of TB strains with drug resistance using DNA tests which detect genetic mutations to different drugs is less than 48 hours [4]. Also, gene sequencing studies have allowed to follow the lineage of TB in different areas of Latin America. Using specific "gene markers" and mutations detected by

Group	Drugs
First line oral agents	izoniazid (INH) , rifampicin (RIF)
A:Fluoroquinolones	levofloxaxin, gatifloxaxin , moxifloxacin
B:Injectable agents	Streptomycin, amikacin, kanamycin
C: Oral core second line agents	cycloserine, linezolid, ethionamide, protionamide, clofazimine
D: Add on agents	D1: pyrazinamide (PZA), ethambutol (EMB) D2: bedaquiline , delamanid D3: p-aminosalicylic acid, imipenem-cilastin, meropenem, thioacetazone, amoxillin-clavunolanate

Figure 1.
2016 WHO Drug Therapy Groups Tuberculosis.

polymerase chain reactions, the populations of mycobacteria are identified and characterized in different territories [5]. Those genetically identified strains are compared to TB strains in Europa and other continents, and are studied along with migration patterns from those regions, establishing familiar origins.

2. Definition of drug resistance and causes

As mentioned above, the most common therapy for tuberculosis originated from 1970s, which consist in a combination of Isoniazid (INH) and Rifampin (RIF). Adding Ethambutol (EMB) and Pyrazinamide (PZA) can shorten the length of therapy. The first two drugs are considered as the firs line therapy for tuberculosis (**Figure 1**). These are the basic definitions of drug resistant TB:

- **Drug-resistant tuberculosis** is when TB remains unaffected to at least one anti-tuberculosis drug.

- **Mono drug resistance** refers to an infection with resistance to one of the first line agents.

- **Poly-drug resistant TB** occurs when there is resistance to two or more anti-TB drugs but not to both INH and Rifampicin simultaneously.

- **Multidrug-resistant tuberculosis (MDR-TB)** occurs when resistance occurs in more than one antimicrobial drug, or at least isoniazid (INH) and rifampin (RIF).

- **Extensively drug resistance tuberculosis (XDR-TB)**: The extreme case of resistance, in which TB is resistant to at least one drug in each group in the second line therapy groups (see **Figure 1**, groups A to D), besides being resistant to first line therapy.

- For the purpose of this chapter, we will refer and discuss mainly to the multi-drug resistant tuberculosis (MDR-TB).

3. Drug resistance

The development of drug resistance of tuberculosis seems to be secondary to a mutation process of a chromosome that can cause that a specific population of mycobacteria develops a "phenotypic resistance" to a certain drug. That mutation can be cause an alteration in the drug transport in the cell membrane of the mycobacteria, or the increase in production of an enzyme that metabolize and cause incapacity of the treatment drug. When those mycobacterias are exposed to either inappropriate antimicrobial therapy, inappropriate length of treatment, poor quality or low dose of medications, or lack of combination therapy, confers to the resistant bacteria a survival advantage that allows a "genetic" transformation which is transmitted over other nonresistant strains [6].

The common use of more than one drug to treat TB resulted from initial studies that showed a progressive increased in mycobacterial populations with resistance in sputum cultures from patients treated only with streptomycin. Combining para-aminosalicylic acid with streptomycin in a clinical trial showed a more than 7 to 8 times decrease in the rate of resistance to streptomycin [7]. With the eventual

discovery of the efficacy of other antimicrobial drugs against tuberculosis, multiple other combination therapy studies were done, until current regimes were obtained. When done adequately, many countries have been able to eradicate tuberculosis using direct observe therapy programs monitoring adequate compliance with medications including dosing and regimes.

Each drug against TB has a specific mechanism to cause the bactericidal or bacteriostatic effect on the microorganism. In the case of INH, a specific enzyme is activated by the antibiotic inside the cell to inhibits the production of mycolitic acid, which is integral part of the mycobacterial cell wall [8]. For example, Rifampin inhibits the proliferation of ribonucleic acid, which inhibits genetic material replication and bacterial proliferation.

Mutations that impede Rifampin to inhibit the synthesis of RNA cause drug resistance. In the case of IZH, the drug needs an activation of its initial pro-drug state. A defect in the enzyme that metabolize IZH to its active state will cause resistance to IZH. Rifampin resistance is considered rare and usually occurs concomitantly with resistant of other drugs. This makes the resistance of Rifampin a marker of multiple drug resistance (MDR-TB) [8]. Other drugs as PZA and EMB also function inhibiting the formation of other components of the cell wall, and resistance occurs by mechanism similar to IZH and RIF.

The characteristics of the infected host also can influence in the developing of drug resistance. Immunosuppression allows the mycobacteria to survive the host immunological reaction and proceed to active disease. This can cause population spreading of disease and further dissemination of mycobacterial strains. Immunosuppression include the use of chemotherapy, immunotherapy and anti-inflammatory medications, patients with severe and uncontrolled diabetes mellitus and human Immunodeficiency virus infection (HIV).

Human Immunodeficiency virus infection have been particularly linked to the development of MDR-TB. In patients with HIV there are many factors contributing to the development of drug resistance. Those factors include: the rapid progression of HIV with concomitant tuberculosis infection, poor absorption and interactions between HIV and tuberculosis drugs, and exposure to high risk of resistance populations as other resistant tuberculosis patients, intravenous drug and alcohol users and other patients with poor compliance to medications [9].

Data regarding Diabetes mellitus and development of drug resistance to tuberculosis have been variable. However a recent metanalysis published in 2018, showed significant association between DM and MDR-TB, which was not linked to the degree of economic development of the country. Again, the degree of immunosuppression secondary to uncontrolled diabetes is related to the possibility of developing active disease and infection spreading in the population. The same case occurs with other type of chronic immunosuppression as patients of chemotherapy, immunosuppressive therapy for autoimmune diseases and the chronic use of systemic steroids in patients with respiratory conditions as chronic obstructive pulmonary disease (COPD) and asthma. A publication in 2015 suggested a strong association of MDR-TB with COPD patients with advanced stage disease, severe airway obstruction and long term use of corticosteroids [10]. Also, the multiple use of antibiotics to treat COPD exacerbations, including fluoroquinolones, contribute to the risk of developing drug resistance [10].

4. Epidemiology of drug of drug resistant tuberculosis

It is known that around 4% of newly diagnosed tuberculosis patients are multidrug resistance [11]. From those previously treated, MDR-TB have been reported in

more than 20% worldwide [11]. The Global Tuberculosis Report of 2019 recognize more than 400,000 patients with drug resistance TB [1]. In 2019, before Covid-19 became the global threat that we have been seen now, MDR-TB continued to be a public health crisis with 206,030 patients reported with MDR-TB around the world, a 10% increase from numbers reported in 2018 [12]. According to the World Health Organization, the countries with more MDR-TB burden are India, China and Russia.

In America, Center and South American as the areas with more MDR-TB burden. Around 3% of the total tuberculosis cases reported in the world are from American territories [5]. South America was the region with more incidence of tuberculosis with 46.2 per 100,000 of population, mostly from areas of the Caribbean and Central America [5]. The data regarding each region has been variable, but Brazil, Peru, and Mexico have almost half of the cases of Latin America [13]. Costa Rica, Cuba, Jamaica, Puerto Rico, and Trinidad and Tobago reported an incidence close to the threshold for tuberculosis elimination [5].

When talking about MDR-TB in America, previous publications signaled Countries as Peru, Ecuador and Brazil for most of the cases reported [14]. The overall prevalence of MDR-TB according to a metanalysis published in 2020 [15] was 13%, but it reached 28% in those patient populations previously treated cases for tuberculosis. The reported prevalence have been increased when studied from period ending in 2010 to 2018 [15]. Colombia, Mexico, and Dominican Republic, in data published in 2020, have a reported overall prevalence of MDR-TB of around 20% [15], with more of 30% of attributed to a previous failed or inadequate treatment. In the United States, data reports around 1% of MDR-TB of the total of tuberculosis patients identified [16], being considered a low burden country for MDR-TB.

In the Caribbean, as mentioned above Dominican Republic is the country with more prevalence of MDR-TB reported. However, data regarding the number of cases in many of the territories of the Caribbean is scarce. Haiti was also identified as a high burden MDR-TB area, with around 306 cases per 100,000 of population in 2014 [17].

5. Causes of drug resistant in Latin American and the Caribbean territories

Phenotypic resistance of the mycobacteria due to lack of appropriate treatment is considered one of the reasons for which the rate of MDR-TB has not decreased through the years. However, throughout genetic sequencing studies, the genealogy of tuberculosis origin in Latin America has been study. In the case of MDR-TB, considering data that suggest that horizontal gene transfers are nonexistent between *M. tuberculosis* bacteria [5], is genetic transformation probably the cause of widely spread of resistance between the above mentioned populations. In this case, genetic transformation refers to the survival advantage of those strains of mycobacteria with acquired resistance to certain drugs over others more sensitive bacterial population. This occurs when mycobacteria are exposed to inadequate therapy, including low quality and dose of medications, the lack of use of combination therapy, intermittent use of medications or inadequate length of therapy. Data from Peru during the 90's decade, where they stablished Direct Observe Therapy (DOT), showed a significant decrease in the prevalence of MDR-TB [14], consistent with this theorem of phenotypic resistance that culminate in genetic transformation of the mycobacteria in the population.

A recent publication about the genetic epidemiology of tuberculosis in Latin America discuss how the migratory patterns from Europa and Asia have define

the genealogy of the mycobacteria in those territories [5]. For example, Peru showed a large number of tuberculosis strains very similar to those found on Beijing, compatible with a well-known historical Chinese migration to that country. Those genetic origins allow the mycobacteria to have different virulence, increasing its capability to survive and being transmitted between hosts. Those mycobacteria have developed the capability to survive the immune response of the host, the external environment in the droplet and particles transmitted, and an increase capability to cause active disease, increasing the probability of population spread. This environmental resistance conferred to those genetically more fitted strains has been associated with an increased risk of developing drug resistance [5].

Again, data is scarce in the specific prevalence of MDR-TB in all regions of the Caribbean. However extremely high incidence of tuberculosis in territories such as Haiti and Dominican Republic have overlap with a high rate of co-infection with Human Immunodeficiency Virus (HIV). The degree of immunosuppression contribute to the developing of active disease, population spreading of infection, and dissemination of selected tuberculosis strains, including those which are drug resistant. High prevalence of other conditions such as COPD and diabetes also contribute to the tuberculosis spread and the development of drug resistant infection. In addition, the limited access and poor quality of health care services, malnutrition, poverty and underprivilege living conditions are associated to the spread of tuberculosis throughout populations [18]. All of those factors are highly prevalent in the Caribbean countries.

6. Conclusion

Limited healthcare and economic resources, inadequate exposure to anti tuberculosis drug regimens and specific characteristics of the infected host, have paved the long way to the genetic inheritance of resistant strains of tuberculosis to develop and propagate in this side of the world. Migratory patterns from Europa and Asia to the Latin American territories have brought tuberculosis strains with genes capable of resists specific drugs, but it has been the inadequate use of medication and the exposures in these lands that have allowed the genetic transformation of bacteria in the populations. As Peru did in decade of 1990, establishing direct observation therapy programs help significatively to decrease the prevalence of MDR-TB strains in the population [14]. Also, prevention of TB spread with rapid diagnosis and screening in high risk populations is a pivotal way to decrease the surge of new cases. The global use of the new genetic rapid tests for detecting drug resistant strains of TB [4] is another way for eradication of MDR-TB. Most important, is to increase population's access to appropriate therapy for those with sensitive and resistant TB infections.

The reach for better healthcare systems, population awareness, programs for better screening and assurance of adequate treatment for tuberculosis patients will be the only infallible tool to decrease the rate of MDR-TB infections and the way to achieve eradication.

IntechOpen

Author details

Onix J. Cantres-Fonseca* and Francisco Del Olmo-Arroyo
VA Caribbean Health System, San Juan, Puerto Rico

*Address all correspondence to: onixcantres@gmail.com

IntechOpen

References

[1] Maiolini M, et al. The War against Tuberculosis: A Review of Natural Compounds and Their Derivatives. Molecules. 2020 Jul; 25(13): 3011

[2] Cantres-Fonseca O, et al. Extra Pulmonary Tuberculosis: An Overview. Role of Microbes in Human Health and Disease. Intech Open 2019.

[3] Iseman MD. Tuberculosis therapy: past, present and future. European Respiratory Journal. 2002; 20: 87S-94s, DOI: 10.1177/0022219410391190

[4] WHO: Rapid diagnostic test and shorter, cheaper treatment signal new hope for multidrug-resistant tuberculosis patients. May 2016

[5] Woodman M, et al. Tuberculosis Genetic Epidemiology: A Latin American Perspective. Genes (Basel). 2019 Jan; 10(1): 53.

[6] Lallungawi J, et al. Drug resistant Tuberculosis: A review. Comparative Immun Microb and Infect Dis 74. Sept 2020.

[7] Kerantzas CA, et al. Origins of Combination Therapy for Tuberculosis: Lessons for Future Antimicrobial Development and Application. Am Soc for Microbiol; March/April 2017 Volume 8 Issue 2 e01586–e01516

[8] Kurz SG, et al. Drug Resistant Tuberculosis: Challenges and Progress. Infect Dis Clin North Am. 2016 Jun; 30(2): 509-522.

[9] Singh A, et al. Drug-Resistant Tuberculosis and HIV Infection: Current Perspectives. HIV AIDS (Auckl). 2020; 12: 9-31, DOI: 10.2147/HIV.S193059.

[10] Zhao J, et al. Multidrug-Resistant Tuberculosis in Patients with Chronic Obstructive Pulmonary Disease in China. PLoS One. 2015; 10(8): e0135205, DOI: 10.1371/journal.pone.0135205.

[11] Dean AS, et al. Epidemiology of Drug-Resistant Tuberculosis. Strain Variation in the *Mycobacterium tuberculosis* Complex: Its Role in Biology, Epidemiology and Control. pp. 209-22

[12] WORLD HEALTH ORGANIZATION: TUBERCULOSIS

[13] Pan American Health Organisation. Tuberculosis in the Americas 2018. Pan American Health Organisation; Washington, DC, USA: 2018. WHO., DOI: 10.1080/23802359.2018.1483754

[14] Battista Migliori G, et al. Emerging epidemic of drug-resistant tuberculosis in Europe, Russia, China, South America and Asia: current status and global perspectives. Curr Opin Pulm Med 16:171-179, DOI: 10.2471/BLT.14.030514

[15] Tengan FM, et al. Prevalence of multidrug-resistant tuberculosis in Latin America and the Caribbean: a systematic review and meta-analysis. Europen Journal of Tropic & Intern Health, Volume 25, Issue 9; September 2020.

[16] CDC. Fact Sheet: TB Drug Resistance in the U.S. ww.cdc.gov/nchhstp/newsroom/docs/factsheets/tb-drug-resistance-factsheet.pdf. Published October 2015. Accessed June 19, 2017

[17] Millet J, et al. A First Assessment of *Mycobacterium tuberculosis* Genetic Diversity and Drug-Resistance Patterns in Twelve Caribbean Territories. Biomed Research Intern. Volume 2014 |Article ID 718496

[18] Bergonzoli G, et al. Determinants of tuberculosis in countries of Latin America and the Caribbean. Rev Panam Salud Publica 39(2), 2016