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Combatting the Obstinate Killer: Tuberculosis

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Abstract:

Tuberculosis (TB) is a highly prevalent disease and a leading global killer, making it an important public health issue. This literature review seeks to evaluate the transmission methods, co-morbidities, treatment delay, issues with compliance to treatments and drug-resistant strains of TB in order to better understand why the prevalence of this disease is still very high, and why it is so challenging to eliminate. The review will also briefly analyses the intricate association between tuberculosis prevalence in poorer populations and how looking at it through a different perspective may help with control and decrease in spread. In addition, some of the issues associated with the current adopted tuberculosis elimination plans will be addressed and ways they can be manipulated for improved future outcomes. Lastly, I will discuss the scope of the problem and propose some solutions for how to combat this disease, in relation to the findings presented in the review.

Key Words: Tuberculosis

Introduction:

Tuberculosis (TB) is a contagious, airborne disease caused by Mycobacterium tuberculosis. M. tuberculosis, although classified as a bacterium, should be viewed as a multifaceted entity. It is composed of several strains that carry an array of virulence factors capable of producing a multitude of responses to the disease [22]. The disease predominantly attacks the lungs, however it can disseminate and attack other parts of the body, such as the brain, spine and kidneys and it is then termed miliary tuberculosis. Interestingly, not everyone infected with the bacteria becomes unwell, as presented in the case of latent TB infection (LTBI). LTBI represents a case in which an individual is in a state of consistent immune response, resulting in the absence of clinical manifestations of the disease, [24]. For this very reason, when describing an individual with LTBI, the term "persister" is more specific because it rejects the idea that disease and latency exist as discrete conditions. During this "latent" period, the disease is in fact taking advantage of the necrotic areas formed by the tissue-damaging host response to hide in biofilms [22]. The bacteria can remain inactive permanently, however can also be made active due to certain conditions such as co-morbidities that weaken the host's immune system. Due to the absence of symptoms, LTBI proves to be a more challenging diagnosis, however the bacteria can still be detected through TB blood tests. Other diagnostic tests include the skin test (PPD, purified protein derivative), which is cheap and easy to administer, thus making it highly accessible, [16]. This is beneficial considering the diverse range of groups that suffer from TB. Some of these high-risk groups include individuals that work in high-risk settings, such as hospitals, prisons and homeless shelters, as well as substance abusers, individuals with weakened immune systems, those who were not treated properly for the disease in the past and people of lower economic status [20]. The PPD skin test, however, cannot distinguish an active TB infection from those who were vaccinated with the BCG, or bacille Calmette-Guerin vaccine, given to non-U.S. born individuals living in high risk countries. Unlike several other infectious diseases, prior exposure of tuberculosis does not exempt a previous infected person from reinfection [8]

Exposure→Infection

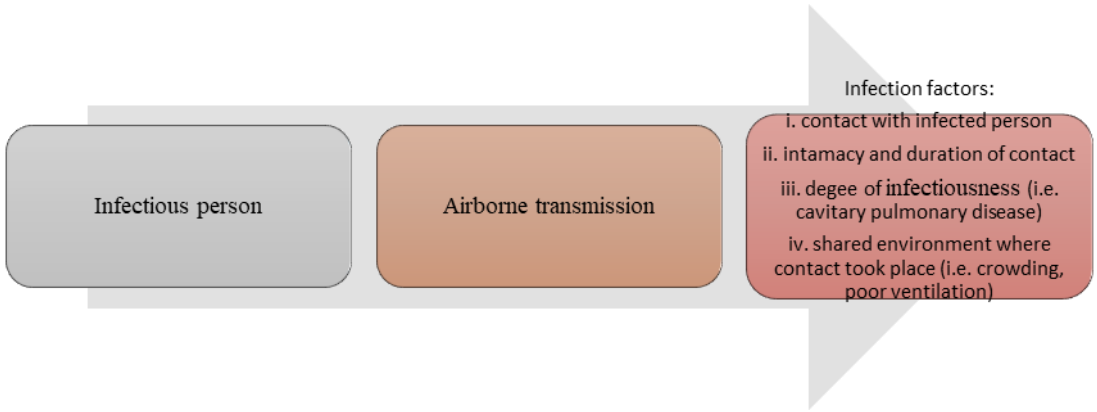

Figure 1: Infection is generally due to exogenous factors [22]

INFECTION→DISEASE

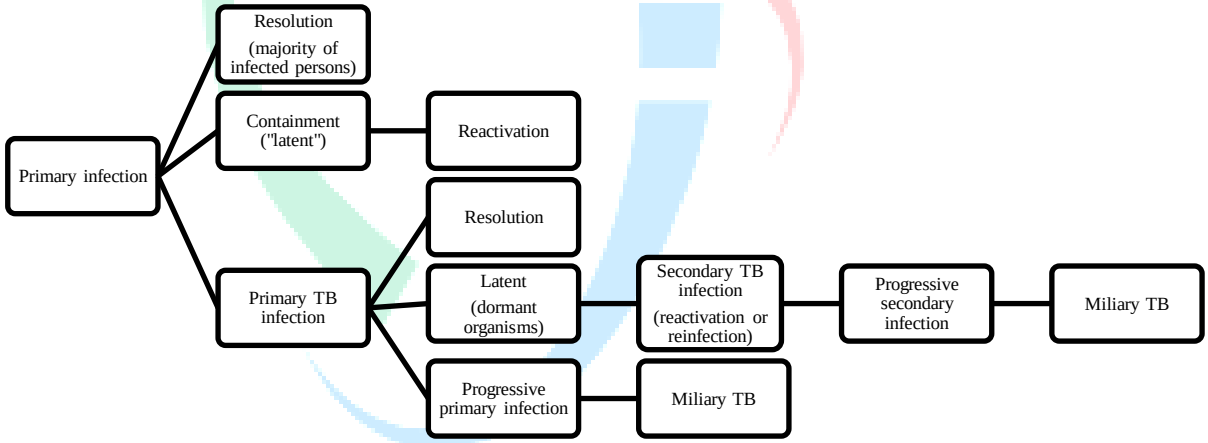

Figure 2: Progression to disease is typically due to endogenous factors [22]

Public Health Significance:

TB is the second leading cause of death from an infectious agent after HIV and is ranked as one of the leading causes of death globally. It affects approximately one third of the world's population [2], and in 2014, there were 9.6 million cases of TB, with 1.5 million deaths, [32]. These figures demonstrate the high prevalence of the disease, and as such show it to be a significant public health issue. It is also one of the oldest killers of humans and has prevailed throughout the ages since ancient times [26], as shown by its presence in the spines of Egyptian Mummies dating back to 5000 B.C. This highlight both the difficulty in its elimination, and its obstinate nature, thus making it an important target for eradication and control efforts. In fact, a major facilitator of TB's prevalence is drug-resistance. Originally, the concern with this disease centred on multidrug resistant (MDR) TB in the many countries faced with the increase in tuberculosis incidence. Recently, extensively drug-resistant tuberculosis (XDR-TB) ("resistance to isoniazid, rifampicin, one fluoroquinolone, and one second-line injectable drug") has taken its place [9]. MDR-TB and XDR-TB strains are present in 105 countries [32]. This is alarming, as it calls attention to how adaptable the bacteria are, how prevalent the disease is, and how challenging it will be to eradicate it, due to the vast number of strains present today. Although

multidrug-resistant and extensively drug-resistant strains of tuberculosis represent a very small proportion of the total tuberculosis case load, it consumes an unreasonable amount of resources when it comes to combating these particular strains, [9]. DOTS or Directly Observed Treatment, Short Course, is a tuberculosis control strategy recommended by WHO in 1994 to approach the growing international tuberculosis problem. It has five principal components: a commitment from the government to monitor and prioritize TB control efforts by providing adequate finances and resources, the use of sputum smear microscopy for diagnosing cases, the use of standardized treatment under observation, adequate and appropriate high-quality medication supply, and a standardized reporting and recording system that allows the assessment of the treatment and progression of the disease [13]. Success rates of the program would most likely be higher if tuberculosis was a standard acute or chronic infectious disease. However, TB is intertwined in a socioeconomic, psychological, and biological web, that it will take more than a vertical approach to eradicate the disease.

Transmission Methods:

TB is an airborne, droplet infection that can be transmitted through methods such as coughing, sneezing, speaking and even laughing. The bacteria infect the lungs via aerosol droplets from an infected individual with pulmonary TB. Other forms of the disease, which can be present in the brain, spine and kidneys are generally not transmissible, with bacteria in the lungs and throat being the most likely to be transmitted to other individuals. The risk of infection is dependent upon several factors, such as the quantity of bacteria inhaled, the immune competency of future hosts, the degree of infectiousness of the bacteria and the distance between individuals [30]. Due to the transmission method, high risk groups tend to be in locations with large numbers of individuals in confined areas, such as in prisons, hospitals or even in certain housing conditions. TB can also undergo congenital transmission and although this is rare, with TB being relatively common in pregnant women, it poses a serious threat with high mortality rates of 50% untreated infants, and 22 % in treated infants [11]. Congenital transmission can also cause a problem when the mother has LTBI, as this will generally go undetected, thus leaving the infant highly vulnerable to the active disease, given that their immune systems may not be strong enough to prevent the rapid replication of the bacteria. In contrast, individuals with strong immune systems will generally be able to combat the infection from two to eight weeks of being infected [29], as the immune system will stop the replication of the bacteria. Nonetheless, TB is a pandemic that affects almost a third of the global population and its success as a disease is perhaps in part, thanks to the method of transmission. Since this droplet infection can be transmitted through infected aerosol droplets, this means that all individuals are susceptible to the disease and with the recent phenomenon of globalization, this has provided a vector for the spreading of the disease more frequently, successfully and to all locations around the world.

Comorbidities:

Weak immune systems due to co-infections are a leading cause in the development of TB disease and the progression of LTBI to active TB disease. Given that the immune system is a major barrier in the development of the disease, other diseases and infections that weaken the immune system inherently increase the risk of developing clinical manifestations of the TB, transmitting the disease and becoming infected with it. Currently, the most prominent example of a comorbidity is the HIV/TB comorbidity, with 1.2 million individuals out of the 9.6 million that were infected with TB in 2014, also having HIV [32]. The risk of acquiring TB when being infected by HIV is increased 20–40-fold [18]. It has been described as the perfect syndemic, due to the fact that HIV specifically attacks the immune system, and the virus-associated immune deficiency increases an individual's vulnerability to TB. This is made evident by the fact that the incidence rate ratio of TB in individuals with HIV was as high as 36.7 in low-level epidemic regions, when compared to individuals without HIV. Other elements that have resulted in the high prevalence of this comorbidity are due to the overlap of several sociographic factors between both diseases [16]. These factors include poverty, low education levels and poor working conditions, as they all facilitate the transmission of these diseases. Another prominent comorbidity involves diabetes mellitus and TB. Diabetes is another highly prevalent disease and it significantly increases the risk of obtaining TB disease. The increased likelihood of obtaining TB when an individual already has diabetes, is shown by the fact that the relative risk of TB in diabetic patients was 3.1, relative to the patients in the study who did not have diabetes [6]. There is an international estimate of almost 50% of diabetes cases underdiagnosed, and greater than 80% are in low income communities with high tuberculosis rates [17]. Diabetes patients often show impaired time to

sputum conversion in smear positive pulmonary TB as well as low cure rates on TB therapy [18]. Therefore, the main contributor to the diabetes-tuberculosis epidemic may have more to do with poorly or uncontrolled diabetes than having diabetes itself [17]. The theory behind this hypothesises that the increased risk is due to the fact that immune response changes are associated with hyperglycaemia, which commonly occurs in those suffering from diabetes mellitus. These immune response changes result in an inconsistency that provides a route for TB disease to manifest and LTBI to progress to active TB disease. As a result, control programs for diabetics include proper glycaemic control, as this can reduce the frequency and severity of symptoms, thus keeping the bacteria under control and inherently resulting in a reduced risk of transmission. Moreover, individuals who are suffering from diabetes/TB comorbidity, as well as the HIV/TB comorbidity, are more likely to have unfavourable treatment outcomes, as the combined exacerbating effects of both diseases acting together prove to be incredibly difficult to treat and as such, are associated with high mortality rates. It is difficult to treat those infected with tuberculosis who have comorbidities, not only due to the number of drugs necessary to treat and or control the diseases and adherence, there's also the issue of adverse reactions between the drugs themselves for each of the diseases. One particular problem among those infected with HIV and TB is the concurrent use of protease inhibitors and rifampicin, one of the 1st line therapy medications for TB. Rifampin is known to induce certain cytochrome P450 enzymes and can therefore substantially decrease the plasma concentrations of serum protease inhibitors thus reducing its antiviral effects. In addition, lifelong antiretroviral therapy puts patients at risk for acquiring metabolic disease., particularly stavudine and zidovudine were greatly associated with diabetes risk. Furthermore, use of protease inhibitors puts patients at a 3-fold risk for acquiring diabetes mellitus [18]. This highlights the importance for the need for integrative programs as these diseases are interconnected not only by socioeconomic environments but by therapy and adherence as well.

Diagnostic and Treatment Delay:

A crucial component in the control of TB lies in detecting and diagnosing the disease early on and notifying appropriate healthcare authorities. Any interruption in these steps leads to delays in appropriate treatment, increased transmission, severity of the disease, and poorer outcomes [5]. Studies have shown majority of cases reported, regardless of the incidence being low or high, are attributable to recent transmission. This stress the importance of prompt physician visits by the patient and early and correct diagnosis by the physician to initiate appropriate treatment and prevent new transmission, a two-component model [8]. Peru has demonstrated efforts to combat TB through model programs that provide diagnostic, medical, social and pharmaceutical services free of direct charges, however, it still ranks second in the America's for TB incidence and number one in all of America for multi-drug resistant TB. A significant factor is the total time it takes an infected individual to seek appropriate health care, receive a correct diagnosis of TB, and obtain adequate treatment. The duration for this entire process is termed "diagnostic delay", and for Peru the diagnostic delay between treatments averages about 57 days [5]. The national recommendation for time of delay for tuberculosis diagnosis and treatment is 14 days or two weeks to increase the chances of a positive prognosis, however, many countries, for various reasons continue to exceed this recommended time period. A cross-sectional study done in several countries for sputum smear positive pulmonary TB had diagnostic delays ranging from 1 month to almost 6 months. These countries included Afghanistan, Nigeria, Chad, Ethiopia, and Angola. Delay was also associated with rural areas when compared to urban locations of residence. Those living in rural areas had a delay of 8 more days than those living in urban communities, most likely due to accessibility of healthcare facilities. In this particular study, the average delay time was 41. 6 days which is comparable to the study done in Peru [4]. Much of the delay is due to the difficulty of recognizing the signs and symptoms of TB as well as not being diagnosed properly the first time, leading to inadequate treatment by healthcare authorities. The study done in Lima, Peru, recognized a least 5 factors contributing to the delay for treatment in patients diagnosed with TB. The five categories included "(1) material resources and social support available, (2) previous knowledge and experience with illness, (3) threshold of symptom severity, (4) health seeking behaviours, and (5) community and health system reactions to TB disease" [5]. Although the study was conducted in Peru, many common themes can be applied to other countries with high incidence rates of tuberculosis especially the educational aspect of the disease and health seeking behaviours. Self-medication was also a reoccurring theme in diagnostic delays in many of the studies done. According to Bogalel et. al, a significant contributor to diagnostic delay in their study included patients

believing the symptoms will resolve on their own and initially seeking assistance from informal care providers such as a pharmacist before seeking a medical doctor. Even after seeking the care of a physician, it is not always guaranteed an appropriate diagnosis will be made the first time, adding to the duration between diagnoses and adequate treatment measures. Lastly, social factors seem to play a vital role in seeking treatment as well. In countries were tuberculosis is endemic, there is a stigma associated with the disease, leading to the desire to hide the disease from those in the community not only contributing to the diagnostic delay, but also putting others at risk of contracting the disease [5]. Regardless of the reason for the delay in diagnosis and/or treatment, it is a contributing factor to the spread and acquisition of TB and fruition of drug resistance strains.

Compliance to Medications:

A patient is said to be non-compliant to medications if they miss over 25 percent of their treatment in a month, do not collet their medication for more than one week, or if they miss a daily or intermittent injection for more than one week [2]. When a patient is not compliant with regard to not collecting their medication, they are referred to as defaulters and if a patient then defaults for more than a month, the treatment is then considered abandoned. Many epidemiologists regard obtaining high levels of compliance as an even more important factor than the identification of new cases, [2], due to the fact that non-compliance is one of the major causes of poor treatment outcomes, prolonged duration of the disease and the emergence of drug-resistance strains. This indicates how important compliance to medications and the treatment regimen is, when it comes to controlling the spread of the disease. Standard TB therapy ranges from 6 to 9 months with a combination of at least four drugs; the regimen includes an intensive phase and a continuation phase [34]. Therapy with the four recommended drugs, isoniazid (INH), rifampin (RMP), pyrazinamide (PZA) and ethambutol (EMB)/SM, generally have a 95% success rate, leaving little space for relapse. This is due to the fact that all play a crucial role in the elimination of the bacteria from the body. For instance, INH plays a role in eliminating the active TB replication, while RMP works as a bactericidal, killing both active and inactive strains of TB. PZA is important in abolishing persistent strains, thereby shortening the treatment time by $\geq$ 3 months and lastly EMB is used to prevent TB emergence [33]. Therefore, if resistance is developed for at least one of these drugs, the effectiveness of the treatment will dampen, and poorer treatment outcomes is expected. Some of the major reasons for non-compliance include socioeconomic issues, a prolonged duration of the treatment, drug toxicity, the need for several drugs, a lack of social support and a lack of counselling, [3]. Depending on the strain or strains of M. tuberculosis an individual is infected with will determine the course of the treatment, some lasting as long as two years. The issue of a prolonged duration of treatment compounds the issues regarding a lack of social support and counselling. Given that the recommended minimum duration for treatment is 6 months [2], and prevention strategies involve isolation from others, this treatment regimen can place a large psychological burden on a patient and even their family and friends. Many programs created to combat TB have recognized the important aspect of social support. The Peruvian National TB Program (NTP) has secured strict guidelines for the diagnosis and treatment of TB patients to assist in the eradication of this public health burden with the inclusion of psychosocial support. However, many of the steps cannot be followed thoroughly as there is insufficient resources. For instance, shortage of healthcare specialty support from psychologists to help with the mental and social aspect of fighting the disease, [5]. Nonetheless, internationally recognized programs such as DOTS has prioritized medical treatment for those infected with TB with little emphasis on social support. With the lack of support, a greater chance of nonadherence is expected as this can be an arduous treatment process. In fact, in a survey, 30.94 percent of participants listed the main reason for non-compliance to be a lack of social support, highlighting how important this factor is in creating a successful treatment process. Moreover, socioeconomic issues and the number of drugs a patient may be required to take also tie in together, as medications can be expensive and may even be difficult to access, [29]. This results in several people taking certain medications and not others, or simply abandoning their treatments all together once they start to feel better. Of course, this results in an incomplete treatment, thus potentially causing them further health issues in the future, such as a resurgence of the TB disease. The medications can also be fairly toxic, resulting in negative side effects such as permanent hearing loss and kidney damage. This can dramatically reduce the quality of life for patients, with the issues being exacerbated by the long duration of their treatment. Due to this, they are likely to stop taking their medications when their symptoms start to clear, which of course results in non-compliance, and the development of drug-resistant strains. This is conceivably the major

consequence of non-compliance, unfortunately implying that multi-drug-resistant TB is perhaps a man-made phenomenon.

Drug-resistant TB:

Drug-resistance is the phenomenon, whereby a drug is made ineffective due to gene mutations in the bacteria [12], which result in the development of the resistant strain. Zhang et al. has recognized several notions for the acquisition of resistant strains of tuberculosis. Primarily, resistance emerges as naturally occurring chromosomal mutations. The wild strains of M. tuberculosis can undergo spontaneous mutations; however, it is through poor compliance, inadequate treatment, and transmission attributable to diagnostic delay, that aid in the progression from a spontaneous mutation to a drug resistant strain, to an acquired resistant strain and finally an overall primary resistant strain. Drug-resistance is perhaps the main threat that is preventing the achievement of TB control, and is progressively getting worse, with a 14 percent increase from 2013 to 2014 [32]. In fact, in 2014, there were 480,000 cases of MDR-TB with 190,000 deaths, and this form of TB only has a 50% survival rate, [32] highlighting the gravity of its threat on a global scale. A study in South Africa has demonstrated that the number of drugs that a particular strain of M. tuberculosis is resistant to has a significant influence on mortality [9]. MDR-TB is defined as being resistant to isoniazid, rifampin and at least two of the most powerful first-line drugs, while XDR-TB is defined as being resistant to all of these drugs, along with any fluoroquinolone and at least one of the second-line drugs [15]. Any type of drug-resistance occurs if the individual is initially infected with a resistant strain, or if resistance is acquired in an individual who is already infected [27]. Previous use of anti-tuberculosis medication has proven to be the greatest risk factor for the development of a multidrug resistant tuberculosis, as well as treatment inadequacy and number of prior drug administration. It was also demonstrated in a study in Iran that second line drugs used in the treatment of other respiratory diseases can contribute to the emergence of totally resistant strains of TB [9]. Besides non-compliance, issues that can lead to inadequate treatment include clinical errors such as an erroneous diagnosis and treatment regarding the specific strain of TB and even organizational errors from disease control planners [3]. In addition, it is possible for an individual to be infected with multiple isolates of M. tuberculosis, adding to the difficulty of adequately treating primary or reactivated tuberculosis infection. It has proven difficult to know the extent of the severity of individuals infected with mixed strains because (1) it is virtually impossible to isolate the bacteria from an individual with latent infection as the bacillary loads are too low, and (2) for individuals with active TB, each sputum sample given may contain different results, and the isolate strains may not be adequately reflected [8]. An important social factor for drug resistance is the diagnostic delay due to the stigma related to the disease, thus leading to a delay in seeking treatment. Common stigmas associated with the disease include those having the disease being associated with inadequate nutrition, lack of physical strength, or alcoholism, again leading to the hesitancy of seeking support when TB is suspected [5]. Other social factors include the individual's level of education, socioeconomic status and social security [12], as these can facilitate the transmission of the disease due to a lack of awareness of transmission methods and treatment practices, as well as being subject to high-risk settings, such as poorly ventilated housing. Moreover, negative treatment outcomes are much more likely in patients with acquired resistance, than those without it. The main reason for this is the use of second-line drugs (SLD) in the treatment process, which are not effective enough, require a long treatment duration, are costly and are also poorly tolerated [14]. In fact, treatment with SLDs can increase the risk for the development of further resistance, which is a major issue due to the fact that there would be very few effective drugs left for treatment and thus may also result in the development of XDR-TB [14]. This phenomenon of drug-resistance poses a major obstacle to any chance of disease eradication and is reflective of the flaws in disease control and treatment programs for TB [12]. The prevalence of TB has made a significant decrease in the past few decades, however the increasing burden of disease-resistance and the current lack of medical, social and pharmaceutical resources, provide a bleak outlook for the future with regard to TB control.

Discussion:

TB represents over a quarter of the preventable deaths world-wide [12] and to date, no other disease compares to TB, in relation to the magnitude of morbidity and mortality it has inflicted upon the human race [26]. This makes a strong case for greater efforts towards control and eradication, as despite great knowledge of this disease for several decades, it is still a leading killer on a global scale. A major contributor to a recent resurgence of the disease, is drug-resistance, with the WHO stating that control-efforts are off-track with regard to disease

management, [15]. A potential reason for this is the fact that risk factors, rates and patient outcomes are not well defined for acquired resistance [15], thus providing a large hurdle to research regarding new drugs. As such, funds should be allocated to research programs in order to identify issues such as risk factors, so that advances can be made in finding treatments, and policies can be set on societal, community and organizational levels to control the issue [12]. In addition, further research to target factors that facilitate the development of resistance, such as long treatment regimens should be promoted, as by decreasing drug-exposure times, the likelihood of resistance developing decreases [31]. Moreover, TB is primarily a poverty-related disease, as demonstrated by its uneven distribution among populations. Quite a few countries such as the Americas and Europe, are experiencing a decline in their incidence of tuberculosis. However, in other parts of the world (e.g. Africa), this disease is responsible for almost 2 million deaths annually [9]. Additionally, if the focus is placed on disease prevalence in countries such as America and Europe, it is highly widespread in areas of low socioeconomic status and confined areas, such as prisons and low-income housing. WHO has recognized the disparities existing between the wealthy and poor regarding the occurrence and prognosis of those infected with TB. They called for a focus to eliminate barriers for the poor relating to treatment options and healthcare. Yet, little emphasis has been put on the impact socioeconomic focused strategies may have on the reduction and elimination of the disease. In addition, the precise implication poverty has on tuberculosis epidemics and the emergence of multidrug resistant to totally drug resistant strains must also become a priority when it comes to combating TB in these settings. Much of the research that has been done on tuberculosis risk factors focuses on individual level risk factors such as diabetes, HIV, intravenous drug use, living conditions, etc. and it has also been shown that many of these risk factors are disproportionately distributed among the poor. However, it does not fully explain the disparities existing for the progression and incidence of the disease when compared to wealthier areas of a country. It has not been entirely established if whether the association related to the disease and the poor is primarily due to variances of risk of exposure to tuberculosis in particular settings relating to social interaction patterns and crowding, or is poverty related risk factors leading to the differential risk of infection, re-infection, and activation of latent TB [1]. Andrews et. al recognizes three important factors widen the gap between the prevalence of TB between the wealthy and poor. These include length of the disease due to healthcare disparities, the crowding and poor ventilation associated with the living conditions among the poor that allow for more contact time and frequency when compared to the wealthy, and lastly, those with similar socioeconomic statuses tend to "mix" with each other on a social basis. These are potential targets when revisiting programs catered to certain environments when treating TB. Furthermore, tuberculosis spread, like the spread of sexually transmitted infections has a uniqueness when it comes to the spread and control of the disease in certain parts of the world. There is what is said to be a "core" population, and a "bridging" population in the spread of STI's. When it comes to controlling and/or combating the disease, targeting the core population is key. This prevents the gradual outward diffusion of the disease of those coming in contact with the core population. The same model can be applied to tuberculosis when it comes to epidemics in several countries. The core population, in the case of TB is the poor. The disproportionate distribution of this disease in poverty-stricken areas may be one of the many reasons the TB is still such a huge public health burden in so many parts of the world and the efforts of global rollout of Directly Observed Treatment, Short Course (DOTS) programs have not have the impact that was anticipated [1]. Due to this, high-risk groups in populations should identified and intervention programs should be targeted at these groups, as they may be the source of the epidemic in certain regions, [28]. Strategies for these intervention programs should include increased screening, the provision of more accessible health care and education regarding disease prevention strategies. The education regarding prevention strategies is imperative, as due to the method of transmission of TB, it is easily spread between individuals. Educating individuals on prevention, will thus reduce morbidity and mortality rates in the population, as they could protect themselves better in high-risk settings. In fact, education can also facilitate a decrease in patient non-compliance rates, [28]. This is due to the fact that providing further information and following the ethical principle of patient autonomy, allows the patient to make a more educated decision with regard to treatment compliance, thus improving treatment outcomes and reducing the risk of disease-resistance. Other factors that increase the prevalence of TB are comorbidities. A major factor resulting in increasing prevalence of comorbidities, is that traditional approaches, which are disease-specific, do not generally recognize

common features of management between different diseases and there is not enough knowledge on the combined effects of the diseases, [19]. Due to this, it is imperative to further research these combined effects and how they affect treatment outcomes, as this could provide alternative treatment methods, as well as identifying potential risk factors that could then be controlled. In addition, there is a need for integrated healthcare systems for those with comorbidities. The direction of tuberculosis treatment in those with comorbidities should be one with a broader integration focus. This includes both communicable and non-communicable diseases, a direction that has been overlooked by conventional vertical methods. It is crucial to the control of the spread of TB and related deaths. Potential advantages of such programs include ensuring continuity of care, reciprocal screening programs, poverty alleviation, cohesive recording and reporting system, and community education and engagement to name a few (17, 18).

Conclusion:

Tuberculosis is a leading killer globally and is one of the most challenging diseases to eliminate. Its success as a disease is multifaceted, with its high mutability and survivability resulting in the development and high prevalence of multi-drug resistant and extreme-drug-resistant strains. Compounding this, the method of transmission facilitates its development as a pandemic and is exacerbated by comorbidities, which further increase mortality. Thus, factors that facilitate the worsening of this pandemic such as compliance to medications must be addressed. Many of the public issues in the past have been solved by a linear approach, label the problem, then prevent, remove, or treat it. Yet when it comes to combating TB, it's clear that a more complex method will be needed to control and eradicate the disease. Although TB is a communicable disease, the global burden and increasing resistance has given it more qualities of a non-communicable disease in terms of treatment. This is an important step in the care of those infected with TB. Similarities between chronic communicable disease and non-communicable disease include both requiring long term management, issues with adherence, and lifestyle changes. If the burden of TB with a chronic communicable disease and/or chronic non-communicable disease is added, it's no wonder that TB continues to be a leading cause of death globally [18]. TB spread has escalated on a global scale and much of it is due to human behaviours such as diagnostic delay and non-adherence to medications leading to MDR, XDR and TDR strains of TB. Because of its interrelations to other diseases and socioeconomic factors, there is an intricate game of balance that must be played when it comes to "fixing" the components of an infected individual. For instance, when it comes to adverse drug reactions or drug interactions leading to other disease. HIV and TB are often called twin epidemics, and about ¼ of TB related deaths occur in individuals infected with HIV, usually in those who test "negative" in a sputum culture. Hence the need for more sensitive diagnostic techniques for those with minimal immune response to the TB infection to prevent spread and initiate suitable treatment options, [7]. The importance of early diagnosis and the need for new antibiotics for the emerging resistant TB strains has been recognized. Many efforts have been put in to detect the specific resistance mechanisms for available TB antibiotics in several TB isolates to develop new anti-TB. drugs. Once these newer molecular diagnostics techniques are available to all, there will be quicker diagnoses and recognition of specific drug resistance to provide efficient and individualized drug treatment for those infected with TB [22]. There has also been a refocus on vaccinations. The efficacy of BCG has been the emphasis for many clinical trials. It has been agreed that there is a 60-80% protective efficacy of the BCG vaccine against severe form of the disease in children, mainly meningitis. However, it is known that the vaccine serves no purpose for those who have already been infected or exposed to mycobacteria [24]. Thus, the understanding of how this vaccination works and how it can be manipulated to help a greater population should be revisited. It has been debated whether the BCG vaccine protects an individual against acquiring the disease or prevention from progression of infection to disease. This is because of the limitation of the PPD skin test in detecting whether the positive results were caused from the vaccine or a non-TB mycobacterial infection, but this problem can be solved by using an interferon gamma release assay. This is useful in determining the actual mechanism of action of the vaccine and its potential use in immunization programs. [24]. Besides the vaccine itself, it's particularly important to pay attention to the individual host response to the vaccine and/or disease. Although extensive research has been done to understand the host interaction and immune response to TB, there has not been many advances in the development in new vaccines because the specific immunological responses to induce for maximal protection remains uncertain. Much of the focus of TB vaccines have been focused on eliciting

a Th1 response. Recently, there has been interest in mimicking clinical latency of the disease, having long lasting reactivity against M. tuberculosis antigens in the absence of clinical symptoms. It is estimated that about a third of the world's population is infected with TB. Infection, however, does not always lead to disease. Therefore, a key to controlling the spread of infection and activating a latent TB is through controlling the risk factors that lower an individual's immunity that predisposes them to active TB infection. For instance, HIV, diabetes, and malnutrition may all contribute to the high incidence of TB, but if these areas can be controlled, LTBI can remain latent [20]. Nevertheless, there is still a great need for research and development of new drugs and strategic changes as more drug resistant strains are emerging. Research should focus on alternative drugs, risk factors and high-risk groups, with an ultimate goal of policy changes to establish control. Through these policy changes, regulations regarding treatment methods and drug prescribing can be monitored to ensure the maintenance of proper clinical procedure, therefore minimizing the risk for drug-resistance. Moreover, protocols must be put into place to reduce the risk of transmission in high-risk settings, such as prisons and hospitals, with the aim of restricting and eventually eliminating reservoirs for the disease. One of the most challenging issues however, is patient non-compliance. The best solution to combat this issue is the integration of education into the treatment process, in order to enable patients to fully understand the potential consequences due to non-compliance. As we look toward the future in controlling and eventually eradicating TB, we must not forget the current problem with patients with limited medical therapy options. There is adequate data for the standard therapy for patients with TB, but there are challenges to strategies and limited options when it comes to those with XDR and TDR strains of TB. There have been a few cases studies on resectional surgery for those with these pharmaceutical limited options for TB therapy. In a study done in Latvia, 17 patients with MDR underwent differing surgical procedures to decrease the burden of the isolates by removal of areas of the lung where the tissue was ridden with cavities or abnormal lung tissue that was most likely poorly penetrated by antibiotics to treat the disease. The surgical options ranged from pneumonectomy, lobectomy, to segmental resections. Although the success and evidence of better prognosis from surgery for XDR and TDR has not been established due to the small number of procedures done, it can be an option for those who have run out of pharmaceutical opportunities in the meantime as new drug are being developed [10]. By tackling each issue directly, through methods that are educated by intensive research, the establishment of greater control over TB disease may be achievable. There should not be a competition between resources for communicable and noncommunicable diseases. The reason being is that there is a significant amount of overlap, especially when it comes to certain demographics and environments. It will be nearly impossible to and cure/manage an individual with more than one disease as if they do not coexist. There should be a more unified approach, because as we see in the case with TB, it links both types of disease, in addition to some medications from communicable disease putting you at risk for non-communicable disease suggesting a need for integrative and screening programs [18]. It is clear that the road to control TB infection and eventual eradication will take a lot of effort. Many of the current treatment programs will have to revisited, having a combination of targeting core groups as well as individualized treatment regimens for those infected with other diseases or who have acquired MDR or XDR. TB is a unique infectious disease in which a vertical approach will not suffice. With the recognition of the issues discussed in this paper, the future health of those with TB may not have to look so bleak.

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35)