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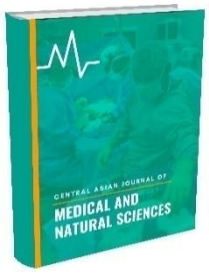

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Tuberculosis Diagnostics with Modern Solutions (Literature Review)

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Annotation: Every year, 3 million people die of TB worldwide, and another 8 million fall ill. Over the past few years, domestic doctors have recorded an explosion of this disease in our camp. Every year the number of patients increases by 25-30% and, which is especially alarming, children and adolescents often become victims. Inflammatory processes are generally very similar regardless of their cause. Modern solutions have been emerging in the past decade, seeking to overcome many of the inhibiting issues in this field by utilising recent advances in molecular biology, genetics and sequencing or even completely 'reinventing the wheel', by developing novel and unprecedented diagnostic techniques. In this mini review, the issues and challenges arising from the historical methods of diagnosing tuberculosis are discussed, followed by outlaying their particular lack of appropriateness for regions of the world where tuberculosis still remains endemic. Subsequently, more recent developments of new methods and technological advancements as 'modern weapons' in the battle to defeat this disease and associated challenges are reviewed, and finally an outlook is presented, highlighting the future of the modern solutions under development, which are envisioned to lay the platform for improvements in delivering timely intervention, reduce immense expense and burden on healthcare systems worldwide, while saving millions of lives and eventually, may enable the eradication of this ancient disease.

Keywords: new methods, diagnostics, tuberculosis.

Introduction

Tuberculosis (TB) is an ancient bacterial disease, which is believed to have been infecting humans for over 40 000 years and understood to have originated from the domestication of animals. Its primary causative agent, *Mycobacterium tuberculosis* (*Mtb*), is thought to infect approximately 1 in 3 people worldwide, according to the World Health Organisation (WHO); accounting for ~90% of TB

infections and as such, this review shall primarily focus on *Mtb*. Other causative agents of TB in humans, include *Mycobacterium bovis* and *Mycobacterium africanum* amongst others and these form the *Mycobacterium tuberculosis* complex (MTBC) . The WHO estimates that TB has claimed the lives of over 1.4 million people in 2019 alone. Infection establishes itself following inhalation of an exhaled droplet from a patient with an active infection. Upon being inhaled, the bacilli travel to the lungs, where they are engulfed by macrophages, replicate and eventually form a granuloma. At this time point, an infection has established itself within the lungs. For most people (*circa.* 90%) , this is where the infection stays; the replication of the bacteria is kept in equilibrium and the infection is latent (Latent Tuberculosis Infection (LTBI)), unable to infect others . For the remaining 10%, due to a litany of factors, the resulting caseous granuloma ruptures and the infection can proliferate and disseminate through the individual's airways to infect other people. In some cases, the bacteria can exfiltrate the lungs and establish an infection elsewhere in the body, causing extra pulmonary TB in ~15% of cases. Treatment requires a lengthy course of a range of antibiotics. Generally consisting of rifampicin being taken in combination with isoniazid over the course of 6 months, as per recommendations from the National Institute for Health and Care Excellence (N.I.C.E.). According to WHO, pneumonia is the leading cause of infant mortality worldwide. Among the causes of mortality in children under 5 years of age, it accounts for 17.5%, which annually accounts for about 1.1 million deaths in the world (this is more than AIDS, malaria and measles combined). At the same time, 99% of fatal cases from pneumonia in children under 5 years of age occur in poorly and medium-developed countries of the world. A global study found that in 2010, mortality due to severe acute lower respiratory tract infections in hospitalized children under the age of 5 in developing countries was almost 4 times higher than in developed countries (2.3% and 0.6%, respectively)Findings indicate that adverse reactions can be observed in over 75% of patients during rifampicin treatment. Specifically, this can include gastrointestinal disturbances, arthralgia, peripheral neuropathy and drug-induced hepatitis . Additionally, hepatotoxicity can present in up to 28% of patients . Due to these side effects and the duration of the antibiotic course, it is vital to ensure the most appropriate antibiotics are used by correctly identifying drug-sensitive and drug-resistant *Mtb*. This will also bolster patients' compliance and improve the overall prognosis. Multi-drug resistant TB (MDR-TB) has been emerging as a major cause for concern. Whilst predominantly emerging from the former USSR, apprehensions around the emergence of drug resistance in Africa and Asia are also prevalent amongst the WHO and researchers. It is estimated that MDR-TB was the cause of death in around 182 000 people in 2019, with many countries reporting continued rises in the proportion of MDR-TB cases and extensive drug resistant TB (XDR-TB) also being more frequently reported. This is further exacerbated by the co-infection of Human Immunodeficiency Virus (HIV) and TB, particularly in certain areas of South Africa, where up to 36% of the population is known to be infected with HIV. HIV poses a key co-morbidity in TB; being a component in a third of all TB deaths in 2019. HIV also increases the risk of a latent infection becoming either an active infection or a pulmonary infection becoming extra pulmonary. Diagnosis is typically underpinned by a combined use of molecular detection methods, immunological based assays and direct culture and observation. These methods however, do have known limitations such as, being less effective in individuals infected with HIV (due to their reduced immune response), those with a latent infection, and in children unable to produce significant sputum containing *Mtb*. Furthermore, these methods often require a steady supply of electricity, well-trained personnel and lab modules, which are seldom available in the often under-resourced laboratories in low- and middle-income countries (LMIC). In terms of diagnosing extra pulmonary TB, diagnosis often remains the same as with pulmonary or latent TB, though it is often combined with the use of invasive biopsies taken from the suspected site of infection. Timely and effective diagnosis for combatting and eradicating TB is at the heart of WHO guidelines with management of latent infections being considered a key component in eradication. However, this goal is poorly supported by current technologies which fall short of the portable diagnostic needs, exhibiting poor-sensitivity, special-handling requirements and complicated,

costly procedures. There is, therefore, an urgent need to develop diagnostic methods that can accurately, rapidly, and cheaply diagnose TB particularly, in the rural areas of the Global South. In this article, current diagnostic methods and their limitations are overviewed. Contemporary technological developments and the future direction of these advancements is further discussed aiming to cover the more recent, novel methods that could be utilized to address the challenges associated with TB in rural areas, such as HIV-TB co-infection, MDR-TB and LTBI. The 'gold-standard' for positive diagnosis of TB is the use of traditional plate culture, typically conducted in a high containment laboratory, due to the inherent risk associated with working with *Mtb*. The culturing of *Mtb* raises several issues, mainly relating to the growth rate of *Mtb*, which is substantially slower than other pathogenic organisms, most probably due to a selective pressure at which faster growing *Mycobacterium spp*. induces a greater immune response. Mycobacteria growth indicator tubes (MGIT) seek to overcome this using a fluorescent probe, which is quenched by dissolved oxygen within a selective medium. Upon successful cultivation of *Mtb*, the oxygen is depleted, causing the probe to be activated. This is subsequently detected using a light sensor. MGITs have been shown to reduce the mean detection time from 38.6 days to 21.4 days. It is worth noting that to successfully culture the organism requires a high level of expertise and MGIT only offers a rather minor advantage over traditional culture methods Since, *Mtb* is a group 3 Hazard according to the Advisory Committee on Dangerous Pathogens , defined as a biological agent, which '*…can cause severe human disease and may be a serious hazard to employees…may spread to the community…'* , it requires the corresponding containment facilities to be safely handled. However, this is not always possible within LMICs and, even less so within the more rural settings. Any such facility would also require the relevant expertise and logistics to be run, which is not possible in many of these circumstances. Furthermore, sampling methods of *Mtb* can be inconsistent, with the subsequent sensitivity varying between 16–60%. Sampling methods can involve for instance, a patient producing sputum and ejecting it into a sterile container, or more invasive methods such as, bronchoalveolar lavage and bronchial washing. Both exhibiting a significant difference in their sensitivity of 85.7% *vs* 50.0%, respectively. This can consequently have an impact on the detection rate in local settings, and consideration must also be given to the impact the lavage or washing methods may have on the patients themselves. The use of smear microscopy is often used in tandem with culture, especially in resource poor settings. The method requires the use of the Ziehl-Neelsen stain that dyes *Mtb* and can often result in low sensitivity (56%) in early active cases. Whilst both culture and smear microscopy can be very useful when used together, their efficacy drops significantly in children [and HIV or immunocompromised patients due to the lower levels of *Mtb* in the sputum as well as a weakened ability to produce sputum. Further methods have been combined with culture to successfully diagnose TB including, the chest X-ray and the Tuberculin skin test. Nevertheless, their efficacy was found to be relatively poor when compared with other more modern methods, which utilize molecular or immunological techniques. The diagnostic flaws of these methods are often attributed to the effect of the human error in interpretation of the results. To overcome this, several companies are developing computational algorithms and the use of Artificial Intelligence (AI) to better interpret chest X-ray results (discussed later). Historically, the above described direct detection methods have formed the basis of TB diagnostics. However recently, a shift has occurred towards, either molecular or immunological methods. These rely on the detection of molecules or compounds associated with *Mtb* (as opposed to the entire organism) or the detection of components of the immune system reactive to *Mtb* (*e.g.* antibodies). There is currently a growing number of products on the market utilizing these approaches. The two most prominent widely used assays are the molecular/Polymerase Chain Reaction (PCR)-based, GeneXpert MTB/RIF® assay and the immunological-based, QuantiFERON-TB gold® assay. GeneXpert first pellets bacteria from sputum and then uses PCR to test for the presence of *rpoB*, a gene in *Mtb* responsible for producing RNA polymerase B. It also tests for resistance to rifampicin, a first-line antibiotic. Gamma interferon release assays (*e.g.* the QuantiFERON-TB gold®) have been developed to test for TB infection by analysing

the levels of gamma interferon released by immune cells (taken from a blood sample) in the presence of TB antigens. If the level of release is found to be above a specified threshold, a patient is considered positive for TB. There are several additional diagnostic methods for diagnosing TB, though their uptake is not as prevalent . Notably, this includes loop-mediated isothermal amplification (LAMP), which uses an isothermal amplification procedure, in contrast with PCR's multiple, cycling reactions, to produce a result that can be visualised by the naked eye. Molecular or immunological approaches can produce results in considerably shorter times than conventional culture. These tests are known to be prone to false positives, and thus a combined use with culture methods enables a more accurate diagnosis. Though limitations become prominent when used in HIV, immunocompromised, pediatric or latent patients. Additionally, molecular or immunological assays are costly to deploy and require a good level of expertise and suitable infrastructure to be implemented as evident by their high uptake in high-income countries, such as the United Kingdom yet, almost negligible uptake in countries such as India, which often lack such infrastructure. Overall, the inherent weaknesses of the current diagnostic methods as well as the reasons for their failings are broad and various. Summarises the methods and their principle with the corresponding benefits as well as drawbacks. Briefly summarising the limitations of the current repertoire of TB tests include being highly time-consuming (in either acquisition or generation of results), requiring specialist laboratory equipment and well-trained personnel, being open to wide interpretation, exhibiting low specificity, which is further exacerbated in HIV and immunocompromised patients as well as children, or infrastructure issues within LMICs. Therefore, recent developments have been sought to overcome many of these limitations by both reducing the equipment and infrastructural requirements and by utilizing different sample types. Recent developments more recent developments have started utilizing some of the newly emerging technologies such as, digital droplet PCR (ddPCR). ddPCR is a more recent innovation which partitions the amplification reaction seen in PCR; this way, it provides an absolute quantification of gene expression rather than a relative one. Due to this, its sensitivity is higher than qPCR, and this method is capable of detecting single copies of DNA. This technique has already been used to monitor mixed populations of cells to better understand drug-resistance. Whilst ddPCR offers a greater amount of sensitivity than quantitative or qPCR methods and can be used to test for *Mtb* infection in both sputum and blood samples, and therefore useful in cases of pulmonary, extra pulmonary, LTBI and active TB, though its main drawback is that it can be prohibitively expensive.

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