Resistant Tuberculosis: A Comprehensive Health Predicament
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Paleontology researchers detected the presence of tuberculosis (TB) in humans at least nine thousand years ago, i.e., in the neolithic period (8000-10000 years) ¹. TB bacilli were found in the remains of a mother-child buried together in a city named Atlit Yam. The incident can be traced back to 9250-8160 years ago in Atlit Yam ². Atlit Yam was a swampland primeval city belongs the Neolithic community on the coast of the Eastern Mediterranean, currently located under Israel ²,³. Dr. Hermann Biggs took the sole credit for the first published report on TB in New York City in 1893 ⁴. Dr. Biggs influenced and persuaded the Department of Health and Hygiene of New York City that doctors should report TB cases to the respective health authority ⁴,⁵.

The first antitubercular pharmaceutical product that appeared in the market for the management of TB was streptomycin in 1945 ⁶. It has limited pharmacodynamic potential as *Mycobacterium tuberculosis* quickly develops resistance against streptomycin ⁷. In 1945, another antitubercular medication named para-aminosalicylic acid (PAS) was invented ⁶. Interestingly, when these two anti-TB medications are combined, the combination forms better pharmacodynamic efficiency and improves considerable clinical efficacy, which is widespread for TB management. ⁶,⁸ Isoniazid (INH) is a synthetic antimicrobial agent that appeared on the market in 1952 and held efficacious pharmacodynamics in managing TB ⁹,¹⁰. INH possesses minimum adverse drug reactions (ADRs) and is consequently well-tolerated; additionally, the cost of INH is a minimum ⁶. Furthermore, with the availability of INH, overall TB management improved. ⁶. Ethambutol (EMB) was discovered in 1961 and quickly considered a first-line agent for TB infectious disease management ¹¹. EMB was considered safe and well tolerated when replaced with PAS and averted resistance development to a greater extent by TB Bacilli ⁶,¹²,¹³. Rifampicin (RIF) was discovered in 1965 and became available to ordinary people.

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in Italy in 1968. The United States Food and Drug Administration (US FDA) approved it in 1971. The clinical trials for TB management, including the RIF regimen in 1970, revealed good clinical outcomes within nine months of therapy. This regimen contains RIF or pyrazinamide (PZA) in a regimen of streptomycin and isoniazid, considerably bringing down the revert frequency. Although pyrazinamide was discovered in 1954, it was not utilized much practically because it statistically significantly causes hepatic toxicity at doses it was prescribed. PZA-induced hepatoxicity is dose-dependent, principally at daily doses higher than 40-70 mg/kg. PZA was utilized in 1974 in much lower dosages, along with RIF, INH, and EMB. This regimen shortened therapy to six months in 1974.

Multiple studies published in 1946-1951 revealed that although many patients with TB were cured. Nonetheless, a particular portion of TB cases had turned for the worse. Researchers conducted culture sensitivity of *Mycobacterium tuberculosis* isolates from recurrence cases and resistance TB to streptomycin, often called drug resistance TB (DR-TB) and isoniazid resistance (INH-R) usually exists as “mono-resistance (resistance to one first-line anti-TB drug only)” for TB pharmacologic intervention. The US FDA approved INH in 1953 and clinically used in 1954. However, multiple studies reported that INH was published and released for clinical use in 1952. Sulis and Pai, 2020 reported that scientists or researchers commonly believed that isoniazid resistance (INH-R) usually exists as “mono-resistance (resistance to one first-line anti-TB drug only)” for TB pharmacologic intervention.

Antimicrobial resistance is a natural phenomenon of pathogenic microbes through genetic alteration. The World Health Organization (WHO), in 2019, for the first time, reported about the global incidence of INH-R. Worldwide, INH-resistant TB cases were 1.4 million. Among them, 1.1 million were sensitive toward RIF. Globally, INH-R among TB cases without coexisting RIF resistance has been reported in 7.1% and 7.9% of new TB cases and beforehand treated TB cases. It has been revealed by Jenkins et al. 2011 that INH-R was identified among 44.9% and 13.9% of all strains of TB in Eastern Europe and all further territories of Europe from 1994-2009. The study further clarified that 33.5% and 61.4% in Eastern Europe had new cases and relapses, or those patients were treated before for INH-R, respectively. Mittal et al., 2018 reported that in the first Indian national appraisal regarding anti-TB-DR between 2014-2016, the frequency of INH-R TB was 11% among freshly detected cases; nevertheless, it was 25% among those who received anti-TB medication beforehand for therapeutic intervention for TB. Sulis and Pai, 2020 further recommended that health professionals can no longer close their eyes and remain ideal. As INH-R TB is considered as much more dangerous than RR-TB. This study expected that the war of mankind against DR-TB had a strong possibility of being lost. Sulis and Pai, 2020 clarified their comment with another global study by Dean et al. 2020 conducted 156 independent territories and data from 2003-2017. This study reported that INH-R TB has a much higher prevalence than RR-TB. Additionally, pyrazinamide and fluoroquinolones resistance low frequency were observed among INH-R TB cases. Therefore, modification of the TB regime is urgently required, along with improving molecular technology to detect resistant cases. Consequently, it can expect TB control programs by 2030 to have a possibility of hope to succeed.

Human beings’ trials and tribulations construct DR-TB. Once, TB was a 100% curable disease. Currently, our planet is confronting catastrophe antimicrobial resistance (AMR). Additionally, DR-TB became rampant around the globe and increased public health terrifying issues, furthermore as first-line anti-TB agents are almost resistant and evolution RR-TB, multi-drug resistant TB [(MDR-TB) first reported resistance 1957], and extreme drug-resistant TB [(XDR-TB) first reported resistance 2006]. This is because the evolution of MDR and XDR-TB second-line anti-TB agents is of absolute clinical necessity. The second line of commonly used medicine for TB management includes - bedaquiline, pyrazinamide, linezolid, moxifloxacin, levofloxacin, clofazimine, cycloserine, para-aminosalicylic acid, ethionamide, prothionamide, delamanid, kanamycin, capreomycin, and amikacin, etc. The second-line anti-TB regimen usually required 18-20 months. Internationally, a total of 186,772 cases were identified with MDR-TB and RR-TB, and 156,071 patients received second-line anti-TB agents in 2018. Nevertheless, only 56% of MDR-TB and RR-TB positive were able to complete the treatment regime efficaciously. Such poor adherence to medication was because of the prolonged treatment regimen of second-line anti-TB medicines and a higher rate of adverse drug reactions (ADRs) in comparison...
with commonly utilized four anti-TB medicines for drug-susceptible tuberculosis \textsuperscript{11,60}. Certain ADRs are often fatal, e.g., cardiotoxicity, nephrotoxicity, central nervous system toxicity, and gastrointestinal toxicity due to fluoroquinolones, aminoglycosides, cycloserine, and ethionamide or para-aminosalicylic acid, respectively \textsuperscript{61}. Several studies additionally revealed that second-line agents frequently cause drug-induced hepatitis, electrolyte disturbance, acute psychosis, acute kidney injury, peripheral neuropathy, and hypothyroidism \textsuperscript{62,63}. The global prevalence rate of significant ADRs was 5.79 per 100 person-month (95% CI: 5.16, 6.49) \textsuperscript{64}. Nonetheless, well-planned and designed as per the patient’s clinical condition and requirement, second-line anti-TB agents’ medical outcome regarding therapeutic intervention is much better has been reported \textsuperscript{65,66}.

DR-TB, through spontaneous chromosomal mutation, happens at a low frequency \textsuperscript{67-69}. Selective pressure caused by inefficient, incompetent therapeutic intervention and poor treatment adherence to TB medications is the principal trajectory that leads the way to DR-TB, consequently ensuring treatment failure and reappearance of TB \textsuperscript{70-74}. Singh and Chibale, 2021 \textsuperscript{75} suggested two ways to fight back with DR-TB. Those are i. chemically altered drug in improving maximum performance, permitting inactivated anti-TB to get away from the resistance procedure, and ii. targeting resistance, thereby resistance appliances targeted by exclusive enzyme deterrent that can desensitize resistant bacteria to the inactive drugs \textsuperscript{75}. Sharma et al., 2020 \textsuperscript{76} suggested to fight back against global DR-TB drugs. We need to work, develop, and implement repositioning medicine. The researcher needs to create new congeners of available anti-TB medicine, and extensive research is required to invent new medicines with a completely different mechanism of action (TB pathogen centrical tactic); TB researchers need to concentrate on producing to evolve novel immunomodulatory medication, developing effective vaccines, immune and cellular treatments approaches (host-centric) and nano-based medicine administration technology should be created and utilized separately as a single medication or multiple agents at a time \textsuperscript{76}.

Kumar et al. (2021) \textsuperscript{77} suggested controlling TB by 2030. Health professionals must ensure the following strategies. Researchers and public health systems should focus on identifying active TB infection and immediately installing anti-TB medication to ensure open case TB and closed TB cases. Subsequently, the spread of infection drastically reduced. Furthermore, government agencies and non-government voluntary working groups in the field must exterminate paucity, improve access to healthcare, ensure adequate protection, and strengthen communities to develop robust policies and systems to stop TB \textsuperscript{77}. Figure 1 depicts history and principal findings of this paper.

**Figure 1:** Depicts the various factors that may lead to Anti-tubercular drug resistance.TB:Tuberculosis; pre-extensively drug-resistant TB (pre-XDR-TB) which is MDR-TB with resistance to a fluoroquinolone; XDR-TB that is TB resistant to rifampicin, plus any fluoroquinolone, plus at least either bedaquiline or linezolid Dihydrofolate Reductase. This figure has been drawn with the premium version of BioRender (https://biorender.com/ accessed on 23rd January 2024) with license number AK267V4SEG. Image credit: Rahnuma Ahmad
Drug resistance is an unavoidable consequence of the use of drugs; however, the emergence of multi-drug resistance can be managed by accurate diagnosis and tailor-made regimens.

Consent for Publication

The author reviewed and approved the final version and has agreed to be accountable for all aspects of the work, including any accuracy or integrity issues.

Disclosure

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