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Latent tuberculosis: Epidemiology, diagnostic and treatment challenges in Nigeria

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Abstract

Background: Tuberculosis (TB) remains a significant global health challenge, causing considerable morbidity and mortality worldwide. Despite advancements in healthcare, TB continues to prevail, particularly in resource-limited settings. Understanding latent tuberculosis infection (LTBI) is critical for TB control strategies.
Objective: This review aimed to assess LTBI epidemiology together with diagnostic and treatment challenges in Nigeria.
Methods: Search of relevant articles on Latent tuberculosis in Nigeria compared to other countries published between 2008 and 2023 were undertaken mainly using Google scholar and PubMed. Related articles from websites of World Health Organization and Federal Ministry of Health, Nigeria were also retrieved and reviewed.
Results: LTBI represents a substantial reservoir for TB, with one-quarter of the world's population harboring the infection. The epidemiology of LTBI in Nigeria mirrors the global pattern, with a high prevalence observed among vulnerable populations. Diagnosis of LTBI relies on indirect methods, including tuberculin skin tests (TST) and interferon-gamma release assays (IGRAs). Challenges in treating LTBI persist, including poor screening tools, low treatment compliance, and adverse drug reactions. Addressing these issues requires a comprehensive approach, including improved screening, patient education, and healthcare infrastructure strengthening, to enhance LTBI management and contribute to TB control efforts globally and in Nigeria.
Conclusion: Screening and treatment of LTBI remains a crucial preventive intervention for TB eradication. Innovative dedicated policies with augmented research and strategies would be necessary to establish a successful LTBI program in Nigeria.

Keywords: Latent tuberculosis, Nigeria, Tuberculin skin test, IGRA, Treatment compliance

Introduction

Tuberculosis (TB) is one of the most challenging infectious diseases of the human race. In the last 200 years, it has killed an estimated one billion people globally.[1] TB is a major global cause of infectious disease death.[2] In 2022, there were 7.5 million newly diagnosed TB cases and 1.3 million related deaths worldwide.[3]

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TB is caused by *Mycobacterium tuberculosis* (*M. tuberculosis*).[4] This bacillus is transmitted by the inhalation of infected aerosols generated by active TB patients. The inhalation of the bacilli will usually lead to the trigger of an immune response that can have one of three different clinical outcomes: complete clearance of the pathogen, latent TB

infection (LTBI), or progression to primary active disease.[5]

LTBI occurs when the immune response of the host ensures the initial containment of *M. tuberculosis* by developing an encapsulating granuloma. In most cases, the tubercle bacilli remain constrained both physically and immunologically by these encapsulated granulomas throughout the lifetimes of the hosts.[6] Throughout this progression, an endogenous reinfection of tuberculosis has the potential to generate fresh infection focal points, likely subject to similar regulatory dynamics. Nonetheless, even years following initial infection, particularly among immunocompromised individuals such as those with HIV, the regulation mechanism may falter, leading to the onset of active disease in the host. On average, approximately 10% of individuals with latent tuberculosis infection (LTBI) develop active tuberculosis over the course of their lifetimes while patients with cellular immune deficiency as occurs in HIV/AIDS have an increased 10% risk of developing TB disease within one year of LTBI.[6,7]

A latently infected host can be re-infected several times, thereby increasing the load of M. tuberculosis in its body and increasing the risk of progressing to active disease. The diagnosis, treatment and prompt management of LTBI has been implicated as one of the crucial prerequisites in TB elimination.[8] Hence, the aim of this review is to explore LTBI epidemiology, together with diagnostic and treatment challenges in Nigeria while proffering possible intervention strategies.

Epidemiology of Latent Tuberculosis Infection (LTBI)

The global prevalence of LTBI has been commonly represented as approximately one-third of the world's population, with a vast pool of these individuals being in developing countries, and posing a major barrier to global TB control.[9-11] The prevalence of LTBI has also been estimated to be around 24.8% based on IGRAs (interferon-γ release assays) and 21.2% based on TST (tuberculin skin test), representing a huge reservoir of potential TB disease.[12] LTBI is a state of persistent immune response to *M. tuberculosis* without evidence of manifestation of clinical or other symptoms of active TB disease. A weak immune system increases the risk of progression from LTBI to active disease. This is particularly evident in high-risk groups or vulnerable subpopulations such as those with concurrent conditions including HIV/AIDS and diabetes mellitus. The lifetime risk of progressing from LTBI to active disease is 5-10% in non-diabetics compared to 30% in people living with diabetes.[13]

Globally, the prevalence of LTBI has been found to be declining but at a slow pace. Over a three-decade period between 1990 and 2019, there was a decrease in prevalence from 30.66% to 23.67% across all six World Health Organization (WHO) regions with that of Nigeria declining from 36.02% to 19.85%.[14] This shows an updated global prevalence from approximately one third of the world population to just under a quarter.[10,12,14] The WHO African, Western pacific and Southeast Asian regions account for four-fifth of the number of people with LTBI.[10,14] Using mathematical modelling to estimate the global burden in 2014, China and India were found to have the highest burden, with Nigeria, Ethiopia and Tanzania being African countries among the top 20 countries by absolute LTBI burden world-wide.[10]

Gender disparity in LTBI has been less clearly defined compared to active TB where male gender has been recognized as an independent risk factor.[15] While some studies have associated the male gender with a higher risk of LTBI,[16-18] other studies have reported insignificant correlation between sex and LTBI.[19,20] Some proposed reasons for increased gender disparity of active TB towards males include the tendency of men to have more social contact than females with attendant increased likelihood of exposure to contagious cases. Possible gender bias in some developing countries that are also TB endemic areas which affect the health-seeking behaviour with attendant under-notification of active TB cases in females have also been postulated.[15] The proportion of persons infected with LTBI has been found to increase in age across all WHO regions.[10] Age as a risk factor could result from being a surrogate marker for accumulated exposure to TB.[12] Besides repeated exposure, elderly persons can be at risk from waning immunity from attendant aging-associated changes in innate and adaptive immune responses, while also having increasing tendency for age-related co-morbidities such as diabetes, chronic respiratory diseases and malignancies, that can result in an increased risk for developing active TB.[21]

A study done in Nigeria on the prevalence of LTBI among healthcare workers by Umo et al in 2016

reported a prevalences rate of 24.8% and 45.8% as assessed using QuantiFERON-Gold In-Tube (QFTGIT) and Tuberculin skin test (TST) respectively.[11] Healthcare workers younger than 30 years had a LTBI prevalence of 9.1% while those greater than 50 years had a prevalence of 51.3%. Advance in age and working for more than 10 years were associated risk factors for LTBI among the participants. Another study carried out in Southern Nigeria by Ajayi et al among people living with HIV (PLWH) in 2022 reported a prevalence of 22.5% compared to 10% in controls using IGRA.[22] Lower CD4+ count was associated with a higher risk of LTBI among the cohorts living with HIV. There is need for more studies to assess the LTBI population in Nigeria.

A mathematical model designed by Ahmad et al in 2018, used a virtual experimental device to evaluate TB burden in Nigeria and provided significant information in explaining why the prevalence of TB in Nigeria has been substantially high for a very long period.[6] His model showed that the latently infected population consistently declines with each increase in notification rate. The increase in notification will affect both the active TB and latently infected population. Contrariwise, a population with a poor case detection program will not have significant progress in reducing new TB cases. Hence, increased screening of individuals at risk of LTBI with an attendant effective case detection program remains potentially the panacea in minimizing the TB burden in Nigeria.

Diagnosis of LTBI

In addition to early treatment of patients with active tuberculosis, early detection of LTBI has become an essential means of controlling TB in low-incidence countries, where the endogenous reactivation of a past infection is the principal source of new cases.[13,22] However, the low tissue bacterial burden associated with LTBI works against any diagnostic strategy focused on the identification of the mycobacteria or its components. The diagnosis of LTBI is rather indirect and relies on evidence of cellular immune response to antigens of Mycobacterium tuberculosis, which does not distinguish between LTBI and active TB.[23] Hence, there is no gold standard test for diagnosis of LTBI.

The most commonly used tests for diagnosis of LTBI are TST and IGRAs. TST involves an intra-dermal inoculation of a purified protein derivative (PPD) in an individual's forearm, for which an induration reaction, read after 48 or 72 hours is considered indicative of past or current mycobacterial infection.[23] The interpretation of the result which is the cut-off representing TB infection, is dependent on the individual's risk of progression to TB disease if infected or the person's risk of recent TB infection.[24] This technique was developed over a century ago and is widely used globally, particularly in developing countries due to its cost efficiency and simple implementation compared to IGRAs.

Interferon gamma release assays involve the use of in vitro immunodiagnostic techniques, more recently introduced in clinical practice compared to TST, that allows tuberculosis infection to be diagnosed using laboratory tests.[23] These techniques involve in-vitro stimulation of T-cells circulating in the blood, using antigens specific to the M. tuberculosis complex.[23,25] Prior to 2015, only two types of assays were commercially available: QuantiFERON-TB Gold In-Tube test (QFT-GIT; QIAGEN, Hilden, Germany) and the T-SPOT.TB(T-SPOT; Oxford Immunotec, Abingdon, UK).[26] Both tests utilized long peptides derived from ESAT -6 (early secretory antigenic target-6) and CFP -10 (culture filtrate protein-10), which are M. tuberculosis antigens.[23] They rely on the measurement of interferon-gamma released via CD4+ T-helper cells mediated responses following stimulation of whole blood or peripheral blood mononuclear cells with the above antigens derived from the region of difference 1 (RD1) of the M. tuberculosis genome.[26] A newer version of QFT-GIT, released by Qiagen in 2015, named QuantiFERON-TB Plus (QFT-Plus), now includes both long peptides derived from ESAT 6 and CFP – 10 designed to induce specific CD4+ T-cell responses and shorter peptides in an additional tube, to induce interferon gamma production by CD4+ and CD8+ lymphocytes mediated responses.[23,26] The inclusion of peptides for stimulation of CD8 T-cells has been reported to improve discrimination of LTBI from active disease and is theoretically envisaged to improve performance in conditions with immunocompromise that affect CD4+ T cell responses.[23]

Challenges in the Diagnosis of LTBI

The approach to diagnosis of LTBI varies according to local settings, which is dependent on available resources in terms of diagnostic equipment,

consumables and trained manpower. Tests for the diagnosis of LTBI vary in sensitivity, specificity, speed and cost. The newer diagnostic test for LTBI is the T-cell-based Interferon Gamma Release Assays (IGRAs) with higher specificity and sensitivity over TST but shows variable results with repeated testing in low risk of infection populations and individuals with results around the cut-off point.[24] Generally, TST results are affected by a complex array of factors such as age, malnutrition and immunological status, the time interval between antigen exposure and the test performance, BCG vaccination, immunocompromise, genetic background, and cross-reactivity with environmental non-tuberculosis mycobacteria.[23] The need for patients to return after 48-72 hours for the result to be read can be associated with some level of attrition.. However, false-positive results in individuals vaccinated with Bacille Calmette Guérin (BCG) or infected with Nontuberculous Mycobacteria (NTM) and low specificity hinder its global usage.[27]

Given that TST has been in use for more than 100 years, it is more accessible in developing countries and represents one of the useful tools in the management of LTBI. There are logistical considerations with TST since a patient is expected to return for a further visit, within 48 -72 hours to obtain results. This leads to some patients' results not being read due to failure to return, compared to IGRA testing, where sample are taken once for in-vitro immunologic analysis. Screening guidelines for the use of TST or IGRAs in LTBI diagnosis are generally not fully implemented in Nigeria as a result of financial barriers to program implementation and prioritization of active TB control interventions.[9]

Unlike TST, neither the BCG vaccine nor infection by non-tuberculous mycobacteria interferes with the IGRA test.[23] However, the use of IGRAs involves higher cost and the need for specialized trained personnel. In addition, the handling and transport of blood samples especially for T-SPOT.TB is both temperature and time sensitive. Hence, making the performance of IGRA logistically more difficult in resource-constrained settings.[28] Nonetheless, even with these limitations, IGRAs have been shown to significantly improve the diagnosis of tuberculosis infection.[12] By comparison, IGRA has been found to be more specific than TST, while TST has been found to be more sensitive than IGRA due to the higher possibility of false-positive results.[29]

Generally speaking, both TST and IGRA exhibit similar limitations. For instance, they have low precision in immune-compromised individuals being screened for LTBI. This is a serious constraint as these individuals are the ones at higher risk of developing active TB. Apart from QTF-Plus which looks promising in predicting progression to active TB, neither TST nor QTF-GIT are particularly useful in predicting progression to active TB. However, there is need for further validation of QTF-Plus in high- and low-risk populations.[23] Another vital consideration is the budgetary constraints bedeviling diagnostic assays and treatment plans in developing countries like Nigeria. Expensive requirements for laboratory infrastructure, equipment, and supplies to perform IGRA, make it challenging for low-resource high-burden countries. For instance, a cost-effective analysis carried out in Brazil, comparing strategies for LTBI diagnosis among primary health care workers concluded that the most cost-effective approach was TST.[30]

One strategy to tackle the diagnostic challenges of current TST and IGRA is to explore other testing modalities. One such approach is the C-TB test, a hypersensitivity skin test that utilizes recombinant ESAT-6 and CFP-10 proteins. This test tries to combine the high specificity of IGRA and the low cost of TST.[31] This may come in handy in resource-constrained high TB-burden settings. Another example is the use of different mycobacterial antigens such as the Esx-1 substrate protein C (EspC; Rv3615c), to improve the IGRA test. It is an ESAT-6-like protein that can identify M. tuberculosis-infected individuals who do not react to ESAT-6 or CFP-10.[32]

The diversity of factors that can affect TST and IGRA, including individual genetic background, highlights need to explore alternative strategies for LTBI diagnosis.[23] One such strategy that has been utilized in PLWH due to the high burden of TB among them has been to use the absence of symptoms suggestive of active TB to screen out active TB and thereby commence such individuals on LTBI treatment in resourced-constrained settings.[33] To be eligible for TPT (Tuberculosis Preventive treatment), the Nigerian national guidelines for HIV Prevention, Treatment and Care stipulates that a person living with HIV must have no symptoms of active tuberculosis and should be counselled and motivated on the need to adhere to the treatment program.[34] Using a WHO approved clinical algorithm, adults

and adolescents living with HIV who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are offered TPT as part of a comprehensive package of HIV care.[35] For children living with HIV, the absence of poor weight gain, fever, current cough or contact history with a TB case are used as possible screening tools for active TB. Tuberculosis Preventive Treatment (TPT) is an effective treatment regimen for preventing the development of active TB.[34] However, it is not a treatment for active TB. Therefore, TB disease should be excluded, with or without the presence of HIV, before commencing a patient on TPT.

Treatment Options for LBTI

TPT entails using one or more anti-tuberculosis drugs to treat persons with latent TB infection who are at high risk of progressing to TB disease. Scaling up TPT uptake in a TB endemic country like Nigeria is a public health necessity. LTBI treatment regimens regardless of HIV status include daily isoniazid for 6-9 months, once-weekly isoniazid plus rifapentine for 3 months, daily rifampin for 3-4 months, and daily isoniazid plus rifampin for 3–4 months. Isoniazid monotherapy have efficacy in preventing active TB disease, but the rifamycin-based regimens are shorter with similar efficaciousness, higher treatment completion rates and adequate safety.[36,37] For PLWH in settings with high HIV and TB prevalence and transmission, continuous administration of isoniazid for at least 36 months probably outweighs the risk of increased adverse events compared with isoniazid regimen for 6 months and has been recommended as a treatment option.[38]

Challenges Treating LTBI in Nigeria

Despite several existing evidence and the existence of WHO guidelines since 1998 recommending TPT, there has been very limited scale-up of IPT especially in high-burden countries including Nigeria.[39] Some of the reasons for the low uptake in these countries have been reported to be concerns about poor screening tools to exclude active TB disease before starting TPT, poor adherence and completion of preventive therapy, risk of adverse events such as hepatotoxicity and perceived risk of acquiring drug resistance which has been found to be unfounded from available evidence.[40] Adherence is an important determinant of programmatic success of the LTBI treatment. The reasons for drug non-adherence have been documented to include adverse drug reactions, longer duration of treatment, long distance from the health facility, absence of perception of risk, presence of stigma, alcohol and drug use, unemployment, time lag between diagnosis and treatment.[41] In a systematic review of randomized controlled trials, it was reported that in LTBI patients, shorter regimens and directly observed treatment effectively improved treatment completion.[42] In addition, it is crucial to monitor adverse drug reactions during treatment especially for individuals taking self-administered therapy via monthly or more frequent assessments by a healthcare provider and patient education.[40]

Conclusion

Screening and treatment of LTBI remains a crucial preventive intervention for TB eradication. A reliable diagnosis and successful treatment of individuals with LTBI is an essential step in the control of TB globally. It is therefore expedient for policymakers to consider effective, integrated, multidisciplinary programs addressing LTBI as an important step towards TB eradication in Nigeria. Innovative dedicated policies with augmented research and strategies would be necessary to establish a successful LTBI program in the country.

Recommendations

Despite progress in techniques used in diagnosing LTBI, the search for a reliable screening tool and evaluation of drug therapy for LTBI patients remains open. In this circumstance, health education becomes especially important. This should involve upscaling awareness campaigns and sensitization to improve preventive and adherence culture for both the healthy and people diagnosed respectively. We also recommend that screening exercises should be extended to other at-risk populations beyond people living with HIV/AIDS. Lastly, adherence control is an essential measure if LTBI treatment is to be successful. In this regard, the use of shorter regimens and closer monitoring of clients including via directly observed treatment will be beneficial.

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