

Why Has the Management of Latent Tuberculosis Been Relegated in High Burden Countries? An Ounce of Prevention is Worth A Pound of Cure

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Conflict-of-interest statement: The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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Received: June 8, 2018

Revised: June 23, 2018

Accepted: June 26, 2018

Published online: November 3, 2018

ABSTRACT

Latent tuberculosis infection (LTBI) is defined as the persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifest active tuberculosis (TB). The lifetime risk of reactivation TB for an immunocompetent person with documented LTBI is estimated to be 5-15%. The most recent estimates of global latent tuberculosis infection (LTBI) is that approximately 1.7 billion people are infected worldwide, of which 10% are infected with an isoniazid-resistant strain. Prevention of new infections of *Mycobacterium tuberculosis* and their progression to active disease is critical to reduce the burden of disease and death caused by TB. Several high-risk groups, including individuals living with HIV and household contacts regardless of their age will benefit

with treatment of LTBI. Unfortunately, according to the literature, globally, the proportion of LTBI subjects *initiating* treatment ranges from 24% to 98%, while the proportion of people *completing* LTBI treatment varies from 19% to 90%. Treatment of LTBI, as part of an integral approach to TB control, will facilitate the achievement of the targets of the WHO End TB strategy and eventually contribute to the elimination of TB.

Key words: Latent; Tuberculosis; Infection; Management

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Laniado-Laborín R. Why Has the Management of Latent Tuberculosis Been Relegated in High Burden Countries? An Ounce of Prevention is Worth A Pound of Cure. *Journal of Respiratory Research* 2018; **4(1)**: 134-136 Available from: URL: <http://www.ghrnet.org/index.php/jrr/article/view/2359>

EDITORIAL

Latent tuberculosis infection (LTBI) is defined as the persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifest active tuberculosis (TB). Although this is not a transmissible condition, subjects are at risk of developing active TB and become infectious. The lifetime risk of reactivation TB for an immunocompetent person with documented LTBI is estimated to be 5-15%, with most of the cases arising within the first 5 years post-infection. However, the likelihood of progression to active TB will depend on various factors including the host immunity status^[1].

The most recent estimates of global latent tuberculosis infection (LTBI) is that approximately 1.7 billion people are infected worldwide, of which 10% are infected with an isoniazid-resistant strain. Prevention of new infections of *Mycobacterium tuberculosis* and their progression to active disease is critical to reduce the burden of disease and death caused by TB^[2]. If LTBI is not diagnosed and treated efficiently, it will be impossible to reach the End TB Strategy of the World Health Organization (WHO) goal for the year 2035 of 90% global reduction in TB incidence (< 10 cases/per 10⁵)^[3].

The most recent WHO guidelines for programmatic management of LTBI are mainly directed at countries with TB incidence rates < 100 per 10⁵. In general, any country regardless of its TB rate could benefit from the systematic management of LTBI, however the guidelines are targeted to high and middle income countries since, according to the document, these countries are more likely to benefit from programmatic management of LTBI based in their current epidemiology, the availability of resources^[4] and the fact that many cases of active TB result from reactivation of LTBI in these epidemiological settings^[3].

The current guidelines list several high risk groups, including individuals living with HIV and household contacts regardless of their age. Also, WHO recommends that patients initiating anti-TNF treatment, patients receiving dialysis, patients preparing for an organ or hematological transplant and patients with silicosis should be systematically tested and treated for LTBI. In countries with a low TB incidence, the guidelines recommend that systematic testing for and treatment of LTBI may be also considered for prisoners, health workers, immigrants from countries with a high TB burden, homeless people and people who use illicit drugs. For countries with incidence rates > 100 per 10⁵, the WHO recommends that LTBI should be treated in children < 5 years-old and subjects living with HIV (the benefit of isoniazid preventive treatment in patients co-infected with TB and HIV is additive to the benefit of antiretroviral therapy^[5]), and that LTBI in children ≥ 5 years-old and household contacts *may* be given preventive treatment^[11].

Unfortunately, according to the literature, globally, the proportion of LTBI subjects *initiating* treatment ranges from 24% to 98%, while the proportion of people *completing* LTBI treatment varies from 19% to 90%^[6].

There are several factors that affect adherence to LTBI treatment. The most frequent argument expressed by the subjects (these actually are not patients) is the fear of adverse effects^[6] associated to a drug taken to prevent a disease that may never develop. Length of LTBI treatment is another barrier to adherence. The WHO guidelines recommend the following treatment options: 9 months of isoniazid (H), 6 months of H, 3 months of weekly rifapentine (Rp) plus H, 3 to 4 months of H plus rifampicin (R), or 3 to 4 months of R alone^[11].

The 300 mg daily dose of H for 9 months established the gold standard for LTBI treatment success 40 years ago by reducing by 90% the risk of active TB *in those subjects who completed the regimen*^[7]; unfortunately, as mentioned, levels of adherence and completion of prolonged treatment regimens have been consistently suboptimal^[8,9].

It has been proven in a large clinical trial that a 3-month regimen with Rp and H was as effective, had a higher completion rate and a lower rate of adverse effects than a 9-month H regimen^[10]. Moreover, the decision of using rifamycins instead of H is particularly important in regions with high rates of H resistance.

WHAT ARE THE CHALLENGES FOR A SUCCESSFUL LTBI PROGRAMMATIC MANAGEMENT?

There are many financial and non-financial obstacles for a successful management of LTBI, including poverty, stigma, language and cultural barriers. However, the most significant obstacle for the control of the LTBI is that most national TB programs do not consider among their priorities in the strategy for the control of the TB, the programmatic management of LTBI and its implementation^[6].

The BCG vaccine, as a control strategy, only mitigates disease

severity (prevents disseminated and meningeal TB in infants and young children) and despite its widespread application in high burden countries, has not had an appreciable effect on the global incidence of pulmonary TB^[5].

Most control efforts in high burden countries are dedicated almost exclusively to the diagnosis and treatment of active TB and include LTBI management only peripherally^[5], and although this will stop the chain of transmission in the community, it does not have any effect on those that are already infected. The active search of cases and their treatment is an indispensable and vital component in the strategy for the control of the TB epidemic, but this approach by itself, based mainly in the diagnosis and treatment of active cases, will not be able to even stabilize the incidence rate in high burden countries, since more cases will originate from the reservoir of subjects with latent infection than those that the program can detect and treat in a timely manner.

The best approach for the prevention of new cases arising from this enormous pool of 1.7 billion infected individuals is to treat them accordingly, to prevent the progression from latent infection to active disease. LTBI diagnosis and treatment should be an essential component in the strategy for the elimination of TB, for *every* country in the world and not just for low-burden countries. Testing and treating only children < 5 years and HIV co-infected individuals in high burden countries will not be enough to make an impact on active case incidence. Even high burden countries must expand the scope of their LTBI strategy to other high risk groups (e.g. all household contacts regardless of age, prisoners, marginalized populations, etc.).

Although isoniazid has been shown to be effective for decades, it requires longer treatment than regimens containing rifamycins, given the higher sterilizing capacity on the latent forms of *M. tuberculosis* of this class of drugs^[11,12]. Completion of treatment is significantly higher in the 3- 4-month rifamycins treatment regimens compared with the 6-9 month isoniazid treatment and although H is 20 times more economical than R, its prescription will not have any beneficial effect if the infected individual does not adhere to the regimen.

Obviously there is an urgent need for the rapid scale up and investment in TB programs from local, provincial, national and international funders^[13]. Treatment of LTBI, as part of an integral approach to TB control, will facilitate the achievement of the targets of the WHO End TB strategy and eventually contribute to the elimination of TB^[14].

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Peer Reviewer: Maryam Al-Nesf Al-Mansouri