Advancing global programmatic management of latent TB infection for at risk populations

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Background:

In this issue of the ERJ, Erkens[1] et al present experience and results of long term data (1993-2013) in the recording and reporting of latent tuberculosis (TB) infection (LTBI) management from the Netherlands. The authors report a high rate of initiation (77%) among the 37,729 eligible persons and a high rate of treatment completion (82%). Valid and complete data were available on almost all (96%) persons who started treatment due to the use of a technically sound notification system supported by a legal framework and standardized indicators[1]. These findings are important additions to the renewed focus and call to address LTBI, which is considered as the reservoir for virtually all TB cases[2,3]. Other renewed efforts include the establishment of a WHO Global Task Force to raise the profile of programmatic management of LTBI, including monitoring and evaluation of implemented activities, as well as promoting research.

The management of LTBI is a key component of the WHO End TB Strategy[4], which is critical to the advancement of TB control, particularly when TB elimination efforts are pursued[5]. Modelling showed that protection of 8% of persons with LTBI each year from developing active TB disease could result in 14 fold decrease of the global incidence of TB in 2050 compared to the incidence in 2013[6].

Two-prong global approach:

WHO has issued global recommendations on the treatment of LTBI for people living with HIV[7] and for children aged less than 5 years old who are close contacts of a pulmonary TB case[8]. Additionally, WHO recommends the management of LTBI among at risk populations in upper-middle and high-income countries with an estimated TB incidence rate of less than 100 per 100 000 population[9]. In these countries, systematic LTBI testing and treatment is strongly recommended for a wider range of clinical risk groups: patients with silicosis, patients initiating anti-tumour necrosis factor (TNF) treatment, patients on dialysis, and patients preparing for organ and hematologic transplantation. This two-prong approach and the tailored recommendations on diagnosis and treatment are presented in table 1.

Barriers for programmatic management:

The programmatic management of LTBI should consider the underlying epidemiology of TB, the burden of LTBI among risk groups, the availability of national policies and surveillance as well as effective health service delivery system and resources[10]. However, there is a gap between the existence of a policy and the actual implementation of diagnosis and treatment of LTBI[11]. Furthermore, recommendations contained in national guidelines from low TB incidence countries differ in selection of risk groups and test methods as well as on treatment options,[12] while in some high TB burden countries restrictive national policies impede the implementation of treatment for LTBI[13]. Among people living with HIV in high TB burden settings significant barriers were present at different levels. In particular, at programme level negative attitudes of managers and prominent opinion leaders - primarily due to a concern about development of

drug resistance[13] - prevented implementation of LTBI treatment, while at service delivery level lack of experience, knowledge and clarity on the benefits of preventive therapy and existing guidelines by health workers hampered its utility[14]. Increased risk of development of drug resistance following treatment for latent TB has not been established [9,15].

The lack of a gold standard for LTBI diagnosis and imperfection of the acceptable tests to predict progression to active TB [16,17], and long-winded treatment[12] are key elements in compromising programmatic management of LTBI. The tuberculin skin test is widely used and inexpensive but it has poor sensitivity in immunocompromised people[18], and is subject to cross reactivity with environmental non-tuberculosis mycobacteria[16]. Interferon-gamma release assays measure *in-vitro* effector T-cell responses to two immunogenic *M. tuberculosis* antigens [6-kDa early secretory antigenic target (ESTA-6) and 10-kDa culture filtrate protein (CFP-10)], which are not found in BCG and most non-tuberculous mycobacteria. However, these tests are expensive, requiring equipment and infrastructure [19]. A novel *M. tuberculosis* specific skin test, C-Tb, that contains ESAT-6 and CFP-10 antigens has been developed and shown to have improved specificity [20] and sensitivity[21] than tuberculin skin test. However, the utility of this novel skin test has yet to be investigated for the diagnosis of latent TB infection.

Critical bottlenecks for programmatic management of LTBI include fragmented organization of services for the identification of individuals, for testing and treating of eligible persons, as well as recording, reporting and following up of patients. For example, in most low TB burden countries, LTBI interventions among contacts are usually carried out by Public Health Services while a wide spectrum of clinical services handle LTBI management in clinical risk groups: infectious diseases services for people living with HIV; nephrology units for patients awaiting

dialysis; rheumatology units for candidates for anti-TNF therapy; pneumology units for patients with silicosis; and a variety mix of other specialties for candidates who will undergo transplantation. The lack of standardised indicators and case definitions applicable across these services impedes functional and integrated monitoring and evaluation systems for programmatic management of LTBI. A recent survey performed by the European Respiratory Society (ERS) and WHO among 31 European countries shows that only 6 countries were able to report LTBI treatment completion rates, which ranged between 40 and 88%[22]. The role and feasibility of LTBI management among asylum seekers has also been raised in the face of recent influx of migrants to Europe, presenting another programmatic challenge[23].

Solutions for programmatic management:

The implementation of the programmatic management of LTBI requires establishing national policies and legal frameworks as well as close collaboration and harmonization across the different services[9]. This was illustrated by the experience of Erkens *et al* in the Netherlands that the adoption of the policy and legal framework coupled with the centralized web-based integration of the reporting systems with ongoing evaluation of its performance including clarifying the case definitions has been instrumental for the success of the programme[1]. Their ability to report the management of LTBI in clinical at risk groups such as anti-TNF treatment candidates is particularly encouraging, and reflects the intensified collaboration between the municipality health and clinical services.

While there is no current mechanism to capture the provision of treatment for LTBI globally for at risk populations and child contacts, there has been a burgeoning experience in the global

monitoring of the provision of isoniazid preventive treatment among people living with HIV (Figure 1). This was possible by standardizing the definition of the indicator to measure, the number of adults and children living with HIV who are started on treatment for LTBI expressed as a percentage of the total number newly enrolled adults and children in HIV care during the reporting period[24] and mainstreaming this indicator to the existing HIV monitoring systems of WHO and UNAIDS[25]. This was also enabled by the implementation of a four symptom-based simplified algorithm that has a negative predictive value of more than 98%[7]. It is estimated that half of the people living with HIV who are newly enrolled into HIV care will fulfil this criteria and hence are eligible for TB preventive treatment[26].

It is, therefore, essential to develop standard indicators to accelerate and monitor the global implementation of programmatic management of LTBI particularly for child contacts and other at risk populations. Such efforts should be based on a clear definition of numerators and denominators as well as the source of information and responsible services. Similarly, simplified algorithms should be used and developed to advance the programmatic management of LTBI among at risk populations including child contacts. Estimating targets for eligible candidates for LTBI testing and treatment will be useful for programme management. These efforts will help to monitor the global progress in the implementation of programmatic management of LTBI.

Establishing effective systems for client education on adherence and clinical monitoring of adverse events, as well as supplying diagnostic tests and the drugs are other crucial steps. Furthermore, establishing continuous surveillance and evaluating the impact of the programmatic management is important as well. Programmes should design flexible

interventions that are tailored to respond to the local context and needs of the population to ensure adherence to, and completion of, LTBI treatment.

Operational research efforts to enable the effective delivery of the intervention based on context and disease epidemiology need to be integral part of programmatic management of LTBI.

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Table 1. Summary table of WHO recommendations for LTBI programmatic management based on category of countries

Country groups	Indicated at risk populations (strong recommendations)	Testing algorithm	Treatment options
High-income and upper middle-income countries with an estimated TB incidence rate of less than 100 per 100 000 population (Low TB burden)	People living with HIV Adults and children who are household contacts of pulmonary TB cases. Clinical indications: patients with silicosis; patients initiating anti-TNF treatment; patients on dialysis; patients preparing for organ or haematologic transplantation	Exclude active TB using TB investigations according to national guidelines. A positive IGRA or TST result is required to diagnose LTBI.	6 months daily isoniazid 9 months daily isoniazid 3 months weekly rifapentine plus isoniazid 3 to 4 months daily isoniazid plus rifampicin 3 to 4 months daily rifampicin
Resource-limited and other high and middle-income countries with an estimated TB incidence rate of more than 100 per 100 000 population (High TB burden)	People living with HIV Children under 5 years of age who are household contacts of a pulmonary TB case.	Exclude active TB using TB investigations according to national guidelines An LTBI test is not required prior to LTBI treatment, but is encouraged for people living with HIV. IGRA should not replace TST.	6 months daily isoniazid

Figure 1. Number of people living with HIV initiated on isoniazid preventive therapy globally (blue) and in the Africa region (red) between 2002-2014