Does "Latent Tuberculosis Infection (LTBI)" Really Exist? Genealogy of a Medical Nosology

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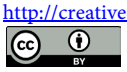


Abstract

Introduction: The diagnosis of latent tuberculosis infection (LTBI) is based on secular ways: chest radiography and tuberculin skin test (TST). In front of a recent enthusiasm for LTBI, this paper reports a historical perspective of this concept. **Method:** Bibliometric analysis and literature review from medical databases, using the terms "latent tuberculosis infection (LTBI)", "primary tuberculosis", "tuberculin skin test", "tuberculosis", and from reference books on tuberculosis. **Results:** In the PubMED/MEDLINE search for LTBI, a total of 7787 articles were found between 1901 and 2020, 95% from 2000 to 2020. In the first part of the 20th century, LTBI term was used for sub-clinical tuberculosis disease, the latency being also called "*primary tuberculosis*" or "*abortive tuberculosis infection*". From 1960, randomized prospective therapeutic studies mentioned "*tuberculosis chemoprophylaxis*". By the end of the 20th century, the epidemic of AIDS impeded tuberculosis decrease, making LTBI search more efficient. In 2000, the *American Thoracic Society* and the *Centers for Disease Controls and Prevention* proposed the systematic used of LTBI, relayed through public health policies. A significant higher scientific production about LTBI was noted, supported by IGRA tests commercialization. **Conclusion:** In the recent years, health public policies, combined with epidemiologic and economic factors, strengthened the use of LTBI terminology.

Keywords

Tuberculin Skin Test, Latent Tuberculosis Infection, IGRA Tests, Medical History

1. Introduction

Latent tuberculosis infection (LTBI) was defined in 2015 by the WHO "*as a state of persistent immune response to stimulation by Mycobacterium tuberculosis an-*

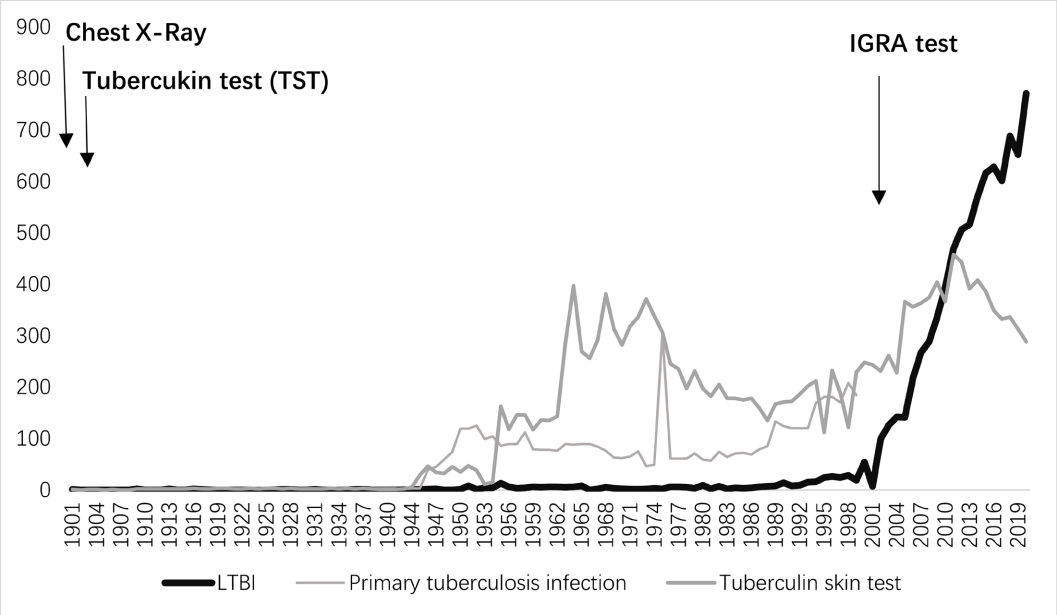
tigens without evidence of clinically manifested active TB" [1]. Thus, LTBI diagnosis relies on secular means: normal chest radiography and positive tuberculin skin test (TST). However, the nosology of "LTBI" is recent. In front of that recent enthusiasm, this paper reports a historical perspective of LTBI concept, to study the forces of production and dissemination of that medical nosology.

2. Method

We used a bibliometric analysis and literature review, referenced in the PubMed/MEDLINE and OldMEDLINE databases between 1879 and 2020, using the terms "latent tuberculosis infection (LTBI)", "primary tuberculosis", "tuberculin skin test", "tuberculosis", and from reference books on tuberculosis and phthysiology. Particular attention was given to the writings of George Canetti (1911-1971), physician and microbiologist, who was interested in the study of "*prehistory of consumption*", and a pioneer in tuberculosis prophylactic treatment [2] [3].

3. Results

If "*the prehistory of consumption*" [2], a period that separated primary tuberculosis infection from the emergence of the disease in adults, has always interested researchers, the name "*latent tuberculosis infection* (LTBI)" was promoted recently. The interest for this nosology is shown in a bibliometric analysis based on the term "*latent tuberculosis infection*" (Graph 1). A total of 7787 publications were found, of which 6389 (95%) in the period 2000-2020. The limited use in the scientific literature of the 20th century of "*LTBI*" is not due to a lack of interest in this issue, according to the abundance of occurrences for "*tuberculin skin*



Graph 1. Bibliometrics for "LTBI", "primary tuberculosis infection", and "tuberculin skin test" using the PubMed database, 1901-2020.

test" (*TST*) or "*tuberculosis primary infection*" since the 1950s. A historical perspective is required to explain the change in nomenclature (Table 1).

Table 1. LTBI Historiography.

Date	Author	Event	Nosology associated with the concept of LTBI
1839	Schönlein	Designation of tuberculosis	
1882	Koch	Discovery of Koch'sbacillus	
1890	Koch	"Koch's lymph" or "old tuberculin"	
1895	Röntgen	Discovery or radiology	
1896	Bouchard	Description of radiological lesions of pulmonary tuberculosis	
1897	Kelschand Boinon	Description of the radiological anomalies indicative of tuberculosis in asymptomatic carriers	"*LTBI*" *means subclinical tuberculosis*
1907	Von Pirquet	Cutaneous tuberculin test of Von Pirquet (scarification)	
1907	Mantoux	Intradermalreactionto tuberculin	
1909	Mendel and Moro-Hamburger	Test of Mendel and of Moro-Hamburger	
1910	Mantoux	First study of the prevalence of tuberculosis infections in healthy subjects	"*Tuberculosis infection*"
1916	Ranke	Theory of the 3 stages of Ranke	"*Primary tuberculosis infection*"
1926	*Am Journ Public Health*	Performance of tuberculin tests in 51679 heads of cattle	"*Nascent or undevelopped cases*"
1926	Calmette, Valtis and Lacomme	Experimental inoculation of rabbits by BK	"*Sligt or transcient infection*"
1943	Waksman	Discovery of streptomycin	
1946	Canetti	Publication of "T*uberculosis allergy in man*"	"*Tuberculosis allergy*"
1951		Commercialisation of isoniazid	
1952	OMS	Standardization of the production and administration of tuberculin	
1954	Canetti	Publication of "Primary-infection and reinfection in pulmonary tuberculosis»	"*Prior-history of tuberculosis*"
1955	Negre and Bretay	Publication of "*Incompletely evolved Koch's bacilli in tuberculosis infection*"	"*Abortive tuberculosis*»
1961	Mount and Ferebee	First controlled trial, versus placebo, studying isoniazid in a population of children with positive tuberculin test	"*Anti-tuberculosis chemoprophylaxis*"
1965	Comstock and *al*	Double-bind, randomized, control study comparing prophylaxis by isoniazid with a placebo including 7033 residents in Alaska	
1969	Edwards and *al*	Tuberculin survey in the American navy from 1958 to 1965	"*Sensibilityto tuberculin*"
1975	Rust and Thomas	Publication of "*A method for estimating the prevalence of tuberculous infection*"	"*Tuberculosis infection*"
1985	*Am thor Society*	Publication of "*Treatment of tuberculosis and tuberculosis infection in adults and children.*"	"*Tuberculosis infection*"
2000	*Am Thor Society*	Publication of" *Targeted tuberculin testing and treatment of latent tuberculosis infection*"	"*Latent tuberculosis infection*"
2001	Food and Drug administration	Approval of the use of QuantiFERON®	
2015	OMS	Publication of "D*irectives for the treatment of latent tuberculosis infection*"	

At the beginning of the 20th century, the nosological outlines of TB and tuberculosis latency were imprecise, following the diagnostic progress of chest X-rays (1895, Röntgen) and TST (1906, Von Pirquet). The term LTBI came first to cover the subclinical stages of TB, while the physiological latency was called "*abortive tuberculosis infection*" [4], "*nascent or undeveloped case*" [5], "*tuberculosis allergy*" [3]. Published in 1916, the theory of Ranke, describing the tuberculosis in 3 stages, was a dominant paradigm in phthisiology [2]. Nonetheless, although the term "*primary complex*" (or Gohn-Ranke complex) and "*tuberculosis primary infection*" are still used, the classification of Ranke is nowadays no longer taught and its author unknown. In the 1950s, TST standardization [6] brought a huge interest for diagnosis of "*tuberculosis primary infection*". Starting in the 1960s, random therapeutic trials examined the benefit of isoniazid in anti-tuberculosis chemoprophylaxis [7] [8] [9] [10]. These original articles are nowadays cited in the current guidelines for the treatment of LTBI; however, they never used the terminology "*LTBI treatment*", but "*chemoprophylaxis of tuberculosis*" [8], or "*tuberculosis preventative therapy*" [11]. From the 1990s, the terminology of LTBI appears in the scientific recommendations of the American thoracic Society (ATS) [11], to denominate a positive TST, but is not often used in comparison with "*primary tuberculosis*" or "*tuberculin skin test*" (**Graph 1**). In 2000, the American Thoracic Society in association with the Centers for Disease Control and Prevention (CDC) proposed to "*change terminology*", and to use "*treatment of LTBI*", rather than "*preventative treatment*" or "*chemoprophylaxis*" [12]. The author argued that nosological change by promotion of tuberculosis antibiotic prophylaxis. It must be noted that this terminology has resonated strongly in scientific publications and public health policies by being immediately adopted by the WHO and the American, Canadian, British, Australian, and French public health agencies. Between 2005 and 2018, several meta-analyses regarding the treatment of LTBI were published [13]. In 2015, the WHO published "Guidelines for the treatment of LTBI" [1] and gives a consensus definition for LTBI, making of a biological phenomenon (immunodiagnosis positivity) the definition of LTBI. This recommendation also aims to make the treatment of LTBI in certain groups at risk one of the pillars of the new fight against tuberculosis, called the "End TB Strategy" [14].

4. Discussion

The nomenclature change for LTBI in the 21th century is not related to usual diagnostic tools (X-Ray and TST). We hypothesize that the success of that terminology is also determined by epidemiological, social, and economic factors.

1) The prevalence of the disease

In the first half of the 20th century, a positive TST was considered to be the norm, and not a pathological condition. Because the risk to develop a TB with a positive TST is very low [15] [16], and depends on many other factors (date from the infection, immunodepression) [17], it was not relevant to characterize an or-

dinary event without therapeutic impact. In the second half of the 20th century, the decrease of the incidence of TB, and the prediction of eradication of TB by the end of the 2nd millennium [18] made LTBI meaningless. However, a new world epidemic has provided it with new relevance: the occurrence of Human Immunodeficiency Syndrome (HIV). Coinfection by an old pathogen (Koch's Bacillus) and a new one (HIV) was responsible for a heightened risk of the disease [19], and an increase in the number of cases and deaths in the world. AIDS elicited a heightened interest regarding immunity in TB, and the search for means of prevention. Identification and preventative treatment for persons living with HIV infected by *M. tuberculosis* became an issue.

2) A public health choice

It was a major change perspective that has displaced the optimism of the previous decades: as of 1993, the WHO has declared tuberculosis to be a "*global emergency*" [20] and wished to "*revisit the elimination of tuberculosis*". A statistical projection estimated that one third of the world's population was "*infected with M. tuberculosis*", and WHO used this argument to strengthen preventive action against tuberculosis. LTBI treatment became in certain groups at risk one of the pillars of the new fight against tuberculosis, called the "End TB Strategy". LTBI definition became hegemonic all over the world, even if it is meaningless in high TB prevalence countries: the need of preventive treatment in front of a positive immunodiagnosis varies according the population studied (risk factors, date of infection) [17] [21], and mainly concerns low TB incidence countries for which recommendations have been written [22].

3) The economic need of a new denomination

Another element influencing the terminology of LTBI was economic, with the emergence of diagnostic tests that revealed the synthesis of gamma interferon (IFN-γ) by T lymphocytes specific for tuberculosis antigens (IGRA tests for "Interferon-γ Release Assays"). These tests were developed in veterinary medicine in the 1990s, with the notion of replacing IDR by a fast test for cattle farms in Australia [23]. As of 2001, two tests have been commercialized: QuantiFERON-TB® and T-SPOT.TB®. In 2001, IGRA tests were approved by the Food and Drug Administration for the diagnosis of LTBI [24] and have been commercialized, that occurred at the same time as greater use of the term "LTBI". Compared to the TST, IGRA tests offer simplicity and better traceability. Nonetheless, IGRA tests, like the TST, do not determinate i) whether the bacillus has been eradicated or whether live bacilli persist, ii) whether the LTBI has progressed toward TB disease and when [25]. The prognosis value of these tests is, therefore, very low [15] [16]. Since then, the commercialisation of IGRA tests influenced nosological evolution, in the sense that it is crucial for the development of a diagnostic test to be able to denominate what relates to its positivity.

5. Conclusion

In the recent years, convergent forces like health public policies, combined with

epidemiologic and economic factors, strengthened the use of LTBI terminology as a dominant paradigm. In fact, LTBI nomenclature was driven by the promotion of a new strategy for tuberculosis control. Nevertheless, several acceptances are superimposed under the terminology "LTBI", depending on the point of view of the pathophysiologist (infra-clinical infectious state), public health (positive immunodiagnosis as a risk factor for TB) or patients. Because of diagnostic difficulties, confusion and paradoxes within the same medical category, criticisms have been formulated. The current pathophysiology of tuberculosis infections recognizes a spectrum of subclinical pathological conditions, putting in question the binary categorization of LTBI/tuberculosis [26] [27] [28]. Lee and Al highlight that LTBI nosology could mask certain realities [29], and even stymie fundamental research [30]. The use of a diagnosis for identifying disease processes is crucial in the field of medicine and for therapeutic issues, but it remains essential that the diagnostic noun represent real processes.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

[1] WHO (2015) Guidelines on the Management of Latent Tuberculosis Infection. (Update in 2020). https://apps.who.int/iris/bitstream/handle/10665/136471/9789241548908_eng.pdf;sequence=1

[2] Canetti, G. (1954) Primo-infection et ré-infection dans la tuberculose pulmonaire. Edition Médicales Flammarion, Paris.

[3] Canetti, G. (1946) L'Allergie tuberculeuse chez l'homme. Edition Médicales Flammarion, Paris.

[4] Nègre, L. and Bretey, J. (1955) Les bacilles de Koch incomplètement évolués dans l'infection tuberculeuse. Masson et Cie, Paris.

[5] (1926) The Tuberculin Test. *American Journal of Public Health*, **16**, 823-824. https://doi.org/10.2105/AJPH.16.8.823

[6] World Health Organization (1952) Comité d'experts pour la standardisation biologique. Cinquième Rapport. 7. Tuberculine. *Technical Report Series*, **56**, 6-7.

[7] Mount, F.W. and Ferebee, S.H. (1961) Preventive Effects of Isoniazid in the Treatment of Primary Tuberculosis in Children. *The New England Journal of Medicine*, **265**, 13-21. https://doi.org/10.1056/NEJM196110122651501

[8] Comstock, G.W., Ferebee, S.H. and Hammes, L.M. (1967) A Controlled Trial of Community-Wide Isoniazid Prophylaxis in Alaska. *The American Review of Respiratory Disease*, **95**, 935-943.

[9] Comstock, G.W., Livesay, V.T. and Woolpert, S.F. (1974) The Prognosis of a Positive Tuberculin Reaction in Childhood and Adolescence. *American Journal of Epidemiology*, **99**, 131-138. https://doi.org/10.1093/oxfordjournals.aje.a121593

[10] Thompson, M.J. (1982) Efficacy of Various Durations of Isoniazid Preventive Therapy for Tuberculosis: Five Years of Follow-Up in the IUAT Trial. International Union against Tuberculosis Committee on Prophylaxis. *Bulletin of the World Health Or-*

ganization, **60**, 555-564.

[11] American Thoracic Society (1986) Medical Section of the American Lung Association: Treatment of Tuberculosis and Tuberculosis Infection in Adults and children. *The American Review of Respiratory Disease*, **134**, 355-363.

[12] American Thoracic Society (2000) Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection. *American Journal of Respiratory and Critical Care Medicine*, **161**, 221-247. https://doi.org/10.1164/ajrccm.161.supplement_3.ats600

[13] Stagg, H.R., Zenner, D., Harris, R.J., Munoz, L., Lipman, M.C. and Abubakar, I. (2014) Treatment of Latent Tuberculosis Infection: A Network Meta-Analysis. *Annals of Internal Medicine*, **161**, 419-428. https://doi.org/10.7326/M14-1019

[14] WHO (2016) Global Tuberculosis Report 2016. World Health Organization, Geneva.

[15] Auguste, P., Tsertsvadze, A., Pink, J., Court, R., McCarthy, N., Sutcliffe, P. and Clarke, A. (2017) Comparing Interferon-Gamma Release Assays with Tuberculin Skin Test for Identifying Latent Tuberculosis Infection That Progresses to Active Tuberculosis: Systematic Review and Meta-Analysis. *BMC Infectious Diseases*, **17**, Article No. 200. https://doi.org/10.1186/s12879-017-2301-4

[16] Diel, R., Loddenkemper, R. and Nienhaus, A. (2012) Predictive Value of Interferon-Gamma Release Assays and Tuberculin Skin Testing for Progression from Latent TB Infection to Disease State: A Meta-Analysis. *Chest*, **142**, 63-75. https://doi.org/10.1378/chest.11-3157

[17] Fox, G.J., Dobler, C.C., Marais, B.J. and Delhom, J.Y. (2016) Preventive Therapy for Latent Tuberculosis Infection—The Promises and the Challenges. *International Journal of Infectious Diseases*, **56**, 68-76. https://doi.org/10.1016/j.ijid.2016.11.006

[18] Raviglione, M.C., Sudre, P. and Rieder, H.L. (1993) Secular Trends of Tuberculosis in Western Europe. *Bulletin of the World Health Organization*, **71**, 297-306.

[19] Daley, C.L., Small, P.M., Schecter, G.F., Schoolnik, G.K., McAdam, R.A., Jacobs, W. Jr. and Hopewell, P.C. (1992) An Outbreak of Tuberculosis with Accelerated Progression among Persons Infected with the Human Immunodeficiency Virus. An Analysis Using Restriction-Fragment-Length Polymorphisms. *The New England Journal of Medicine*, **326**, 231-235. https://doi.org/10.1056/NEJM199201233260404

[20] WHO (1993) Tuberculosis: A Global Emergency. *World Health*, **46**, 3-31. https://apps.who.int/iris/handle/10665/52639

[21] Winje, B.A., Grøneng, G.M., White, R.A., Akre, P., Avistland, P. and Heldal, E. (2016) Immigrant Screening for Latent Tuberculosis Infection: Numbers Needed to Test and Treat, a Norwegian Population-Based Cohort Study. *BMJ Open*, **9**, Article ID: e023412. https://doi.org/10.1136/bmjopen-2018-023412

[22] Ochoa, S. and Chio, B. (2018) Bibliometric Analysis of Reserch Productivity in Latent Tuberculosis: Are We Focusing Our Efforts on the Right Areas? *Tuberculosis and Respiratory Diseases*, **81**, 163-165. https://doi.org/10.4046/trd.2017.0109

[23] Rothel, J.S., Jones, S.L., Corner, L.A., Cox, J.C. and Wood, P.R. (1990) A Sandwich Enzyme Immunoassay for Bovine Interferon-Gamma and Its Use for the Detection of Tuberculosis in Cattle. *Australian Veterinary Journal,* **67**, 134-137. https://doi.org/10.1111/j.1751-0813.1990.tb07730.x

[24] Food and Drug Administration, Center for Devices and Radiological Health (2002) QuantiFERON®-TB-P010033. Food and Drug Administration, Rockville.

[25] Zellweger, J.P., Sotgiu, G. and Block, M. (2015) Risk Assessment of Tuberculosis in Contacts by IFN-Gamma Release Assays. A Tuberculosis Network European Trials Group Study. *American Journal of Respiratory and Critical Care Medicine*, **191**, 1176-

1184. https://doi.org/10.1164/rccm.201502-0232OC

[26] Barry, C.E., Boshoff, H.I., Dartois, V., Dick, T., Ehrt, S., Flynn, J., Shnappinger, D., Wilkinson, R.J. and Young, D. (2009) The Spectrum of Latent Tuberculosis Rethinking the Biology and Intervention Strategies. *Nature Reviews Microbiology*, **7**, 845-855. https://doi.org/10.1038/nrmicro2236

[27] Delogu, G. and Goletti, D. (2014) The Spectrum of Tuberculosis Infection: New Perspectives in the Era of Biologics. *The Journal of Rheumatology*, **91**, 11-16. https://doi.org/10.3899/jrheum.140097

[28] Ling, L.P. and Flynn, J. (2010) Undertsanding Latent Tuberculosis: A Moving Target. *The Journal of Immunology*, **185**, 15-22. https://doi.org/10.4049/jimmunol.0903856

[29] Lee, S.H. (2016) Tuberculosis Infection and Latent Tuberculosis. *Tuberculosis and Respiratory Diseases*, **79**, 201-206. https://doi.org/10.4046/trd.2016.79.4.201

[30] Young, D.B., Gideon, H.P. and Wilkinson, R.J. (2009) Eliminating Latent Tuberculosis. *Trends in Microbiology*, **17**, 183-189. https://doi.org/10.1016/j.tim.2009.02.005