LETTER TO THE EDITOR
https://doi.org/10.4046/trd.2017.0109
ISSN: 1738-3536(Print)/2005-6184(Online) • Tuberc Respir Dis 2018;81:163-165

Bibliometric Analysis of Research Productivity in Latent Tuberculosis: Are We Focusing Our Research Efforts on the Right Areas?

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More than 20 years have passed since the World Health Organization (WHO) recognized the resurgence of tuberculosis (TB) as a global health threat; however, even after intense efforts in the research and public policies areas it remains nowadays a major health problem, reflected in the 10.4 million new cases and the 1.9 million deaths caused by this pathogen globally during 2015[1]. But behind this epidemiological data lies a more worrying picture, as it is estimated that almost one-third of the world's population is infected with the tuberculous bacilli, being this prevalence as high as 73% for prisoners and 57% for health workers in high burden countries[2,3]. Most of these individuals with latent TB infection (LTBI) will not die of the disease; however, this status cannot be underestimated, as the patients in this latency spectrum represent the largest reservoir for potential transmission, being the reactivation and the subsequent spread to close contacts the greatest danger to take into account, especially when the prevalence of immunosuppressive factors as end-stage renal disease, human immunodeficiency virus (HIV) infection and tumor necrosis factor (TNF) inhibitor drugs use, among others, remains rising[4].

Recently published in this journal, the study of Lee[5] highlighted the importance of understanding this spectrum of disease in order to create new alternatives for TB prevention, diagnosis and treatment. However, even with the advances achieved until now, there are still important challenges in latent TB research, in addition, it seems that the research focus in TB has been highly addressed to other topics, being the estimation of the present status of worldwide scientific production in LTBI a relevant need that has still not been fulfilled[6]. For these reasons, we performed this bibliometric analysis in two databases: Scopus and PubMed/MEDLINE (using GoPubmed using the operator "Latent tuberculosis" for the search of articles published in the period 1970–2017. In addition, a secondary search using the term "tuberculosis" during the same years was performed in both databases for estimating the proportion that latent TB research represents.

In the PubMed/MEDLINE search for latent TB a total of 5,494 articles were found, observing an increase in the number of publications in the recent years, being this more evident in the last 10 years with an average of 136 publications per year and a peak during 2016 (Figure 1). Authors from 98 countries contributed to these research documents, being mainly from the United States (10.1%), followed by the United Kingdom (2.7%) and China (2.5%). Remarkably, there was a significant higher scientific production in low TB prevalence regions as Western Europe (12.1%) and North America (11.8%), compared to the 30 WHO TB high burden countries, which represented only the 7,3% of the total scientific production. On the other side, the Scopus search reported 7,021 documents that studied latent TB from various areas as immunology, genetics, pharmacology, and molecular biology, among others. The country which contributed with the larger number of articles was again the United States of America (31%), followed by the United Kingdom (9.6%) and Italy (5.8%).

On the other side, total tuberculosis publications retrieved from the PubMed/MEDLINE search reached 161,345, while Scopus search results accounted for 212,016 documents. With respect to the proportion represented by latent TB research there was observed a low contribution, being just 3.4% for PubMed/MEDLINE results and 3.3% in the Scopus search.

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Received: Sep. 28, 2017
Revised: Oct. 11, 2017
Accepted: Oct. 12, 2017
Published online: Mar. 7, 2018

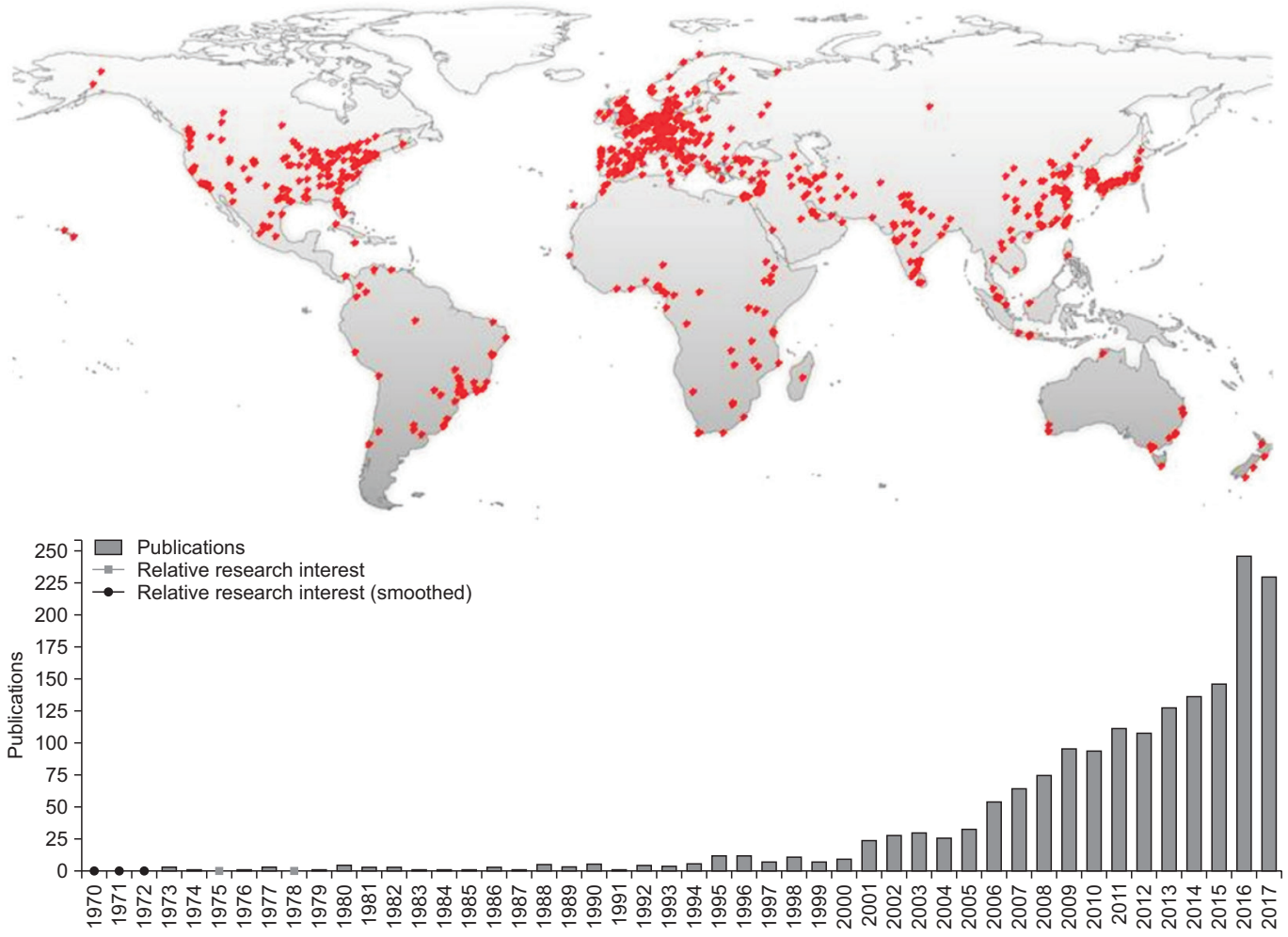

Figure 1. Articles regarding latent tuberculosis infection published per year in the period between 1970 and 2017.

Mycobacterium tuberculosis is a pathogen that has evolved with humanity for thousands of years, adapting and surviving the immune response with the development of hundreds of mechanisms that have given it the ability of manipulating and overwhelming the immune system at a level of complexity that even now is far from being well understood. However, the immune system has still managed to generate a response to overcome this seemingly unstoppable phenomenon, confining the mycobacteria to an adaptive state known as "latency," in which the risk of active disease and its implications drop drastically. Nevertheless, this immunological solution was challenged with the appearance of the HIV epidemic almost 40 years ago, favoring TB resurgence as a new international public health problem which became rapidly the leading killer of HIV-positive individuals[7]. In response, and according to the results found in this and other similar studies, there have been a significant increase in the number of publications in the last years regarding TB research in many areas, being the United States, India, United Kingdom, China and Japan the leaders in TB research, in contrast with the countries with a high prevalence, which had the lesser amount of publications in this area[8].

Specifically, when reviewing the LTBI research, it results evident that there have been significant advances both in the diagnostic and therapeutic areas; however, there are still many challenges, as for example the diagnosis of latent TB in HIV-positive individuals and the development of new model systems that resemble properly the human latent infection. Moreover, multiple questions remain without a clear answer, as the reason why determined individuals without an immunological defect develop the active disease and others do not, why HIV-positive patients remain at increased risk for TB reactivation despite their CD4 T-cell counts, the regulatory pathway that triggers bacterial antibiotic tolerance and growth arrest or the role of efflux pumps in antibiotic tolerance in latency, among many others[9].

Because all of these reasons, the research in bacterial physiology during LTBI and the understanding of the heteroge-

neous stages of this status represent nowadays a critical point for the discovery of new biomarkers (to estimate the risk of reactivation and to monitor the curative effect of the therapy) and the development of novel treatments to target the recalcitrant mycobacterial populations, improving the treatment durations and effectiveness and reducing the negative outcomes, an advance that will lead to a breakthrough in the way TB is addressed. However, to achieve this objective there is a significant need of strengthening the research in LTBI using all the tools available in the lipidomic, genetic, proteomic, metabolomic, immunological and even imaging areas, all of this contributing to the eradication of LTBI and impacting globally the TB phenomenon.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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