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Tuberculosis, an Ancient and Reemerging Disease Full of Contradictions

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Abstract

Tuberculosis (TB) is one of the most ancient diseases and is the infection that has cost humanity the most lives. Unexpectedly, TB has fall into the category of "ignored pandemic". This article advice about inconsistencies that have limited the information of the real TB data and its persistence. The factors that have limited the eradication of TB are multiple and diverse. In this regard, we want to highlight the disease underestimation, the poor attention to the impact of the anthropozoonotic species of *Mycobacterium tuberculosis* Complex (MTC), the several integrated ecological factors, and the gap between the advances of the current and the past molecular taxonomy. Moreover, in addition to distorting its real importance, these facts have contributed to the delay of the campaign for its global eradication until 2018. Since 2020, the almost absolute subordination of health systems to COVID-19 has aggravated TB condition worldwide. The unquestionable priority demanded by COVID-19 pandemic have critically reduced the control of TB and their adequate treatment to the point of causing a possible regression to scenarios similar to those confronted in 2012. At this moment, considering the factors that have hinder TB control they could have caused a decisive condition towards the difficulties for its future eradication. We consider that TB situation took a few steps back and we need to recuperate our multifactor approach as a One Health priority.

Keywords: Diagnostic; *Mycobacterium Tuberculosis* Complex; Pandemic; Sub-Notification; Zoonosis

Abbreviations: TB: Tuberculosis; MTC: *Mycobacterium Tuberculosis* Complex; RTI: Respiratory Tract Infections; NGS: Next-Generation Sequencing; DDDH: Digital DNA-DNA Hybridization; ANI: Average Nucleotide Identity.

Introduction

Respiratory tract infections (RTI) are responsible for the highest morbidity and mortality in the world. In December 2019, three RTI-causing agents were the priorities of the World Health Organization - WHO Research and Development Project (Severe Acute Respiratory Syndrome - Coronavirus - SARS-CoV, Middle East Respiratory Syndrome Coronavirus - MERS-CoV and *Mycobacterium tuberculosis*) [1]. At that moment, a new phenomenon emerged in China that captured the attention of health institutions worldwide [2].

Currently, it is very difficult to accept that any disease could have claimed more lives for humanity than COVID-19. However, it not only exists, but tuberculosis (TB) has caused the death of millions of humans since ancient times – a pandemic that has accompanied *Homo sapiens* since its

distant origins [3]. Despite its lethality, which even in 2019 ranked among the highest causes of RTI prioritized by the WHO, it was not until 2018 that the institution launched a global campaign for its eradication [2]. The inexplicable delay of such a measure was due to the incomprehensible underestimation that has been made of TB as well as other factors that distort its true impact. All of which will be discussed below.

Objective: To advise about inconsistencies that has limited the information of the real TB data and its persistence.

Mini Review

Tuberculosis is one of the first human diseases. Its origin dates back to the Paleolithic, when an environmental *Mycobacterium* spp., predecessor of the *Mycobacterium tuberculosis* Complex (MTC), chose *Homo sapiens*, still a relatively fragile primate, as its hosts. Thus, an ancestral lineage of *M. tuberculosis* initiated a long relationship, causing a chronic and non-lethal form of the disease. Much later, during the Neolithic demographic transition, the virulence of the pathogen increased according to the human population growth. The domestication of animals, mainly sheep and goats, added other anthropozoonotic species to the problem [3]. From the origins, three elements are involved in TB: humans-animals-environment. An indissoluble relationship rarely taken into account in studies on the subject, despite the successful results of those investigations in which the concept of One Health is applied [4]. Perhaps the original error that biases the approximation to the real behavior of tuberculosis. A factor that also contributes to its persistence in the 21th century.

Another element that has most limited the TB eradication is its incomprehensible underestimation. A factor that has made possible the disease to transcend to the present and some identify it as "the ignored pandemic", despite being the deadliest that humanity has suffered [5]. An infection that in 200 years (between the 18th and 20th centuries) caused the death of a billion people [6]. A forgotten disaster, especially due to the advances in health after the advent of antibiotics in the 20th century. A fact that significantly reduced mortality from this cause [7]. Therefore, in 1984 assumed that the deadly disease was under control. A decision taken from the epidemiological reports of the most developed countries, mainly influenced by the reduction of cases caused by *Mycobacterium bovis* [8]. From that moment, *M. bovis* and the additional anthropozoonotic species conforming the MTC, no longer appeared in the surveillance programs of tuberculosis [9].

What happened in the less favored countries in economic and health terms was not considered at all. In this way, subjectivity, overconfidence, geographical fatalism and neglect of the risks imposed on human health by the anthropozoonotic species of the MTC, were added to the list of errors that delayed the start of the campaign End of TB to eradicate this ignored pandemic until 2018 [5,10].

Parallel to the development of the End of TB campaign, Riojas, et al. [11] proposed to the scientific community the dissolution of the MTC. A proposal based on the results obtained by: next-generation sequencing (NGS), digital DNA-DNA hybridization (dDDH), and average nucleotide identity (ANI). They concluded that the species of this group reclassify as strains (*M. canettii*, *M. orygis* and *M. mungi*) or varieties of *Mycobacterium tuberculosis*. A proposal that, despite the known genetic homogeneity (99.9%) of these members, until then their individuality had been respected due to their differences in pathogenicity, geographic distribution, host preferences, biochemical behavior and nutritional requirements [12,13].

No one discards the validity of the techniques used, the basis of this proposal. What is worrying is that in addition to the scant attention paid to cases of tuberculosis caused by anthropozoonotic variants, there is an opinion that questions their existence. In other words, that unfortunate bias according to which tuberculosis disappears as a zoonosis becomes official. Debatable criteria when credence assume publications recognizing that in 2018 the MTC caused 1.2 million human deaths. A much lower figure than the real one given that only 16 countries reported the behavior of *M. bovis* in patients with tuberculosis. Most of the deaths were concentrated in Southeast Asia and Africa [14]. Just as it has happened since the 80s of the last century [5], when in the other side of the world thought TB was absolutely under control [8].

In the midst of such surprising contradictions, those who opt for research from the perspective of One Health, make a call to improve the techniques for the diagnosis of TB in cattle, goats and pigs [15]. Moreover, claimed for all animal species to be valued as possible reservoirs of the MTC [16].

A new catastrophe arrives and complicate even more the analyzed and unsolved problem. COVID-19 has spread to the world since January 2020 as a pandemic and captures the attention of health institutions [10]. The predictive models showed that the global response that it demanded would impose serious limitations on the services of diagnosis, treatment and prevention of TB. Therefore, mortality during 2020 - 2025 would add 1.4 million deaths to the average achieved in the five years prior to 2020. These results are equivalent to going back to 2012 [17].

Conclusion

Tuberculosis has been the oldest and deadliest pandemic in humanity. Also the most ignored due to overconfidence, and underestimating: what happens in the less favored areas of the planet, the participation of animals (domestic and wild), and the environment. Moreover, not adapting advanced taxonomic knowledge in its solution. All of which is aggravated by the hegemonic priority demanded by COVID-19. Which does not prevent preparing minds and assuming that diseases like TB are also lethal. Assuming the factors that delayed its eradication objectively could be the first step for its future eradication.

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