Animal Health

Review

Paradoxes Limiting Real Knowledge of Tuberculosis that May Favor the Spread of the Disease during the COVID-19 Pandemic

Guillermo Barreto Argilagos *⊙, Marcelo Beltrão Molento **⊙, Herlinda de la Caridad Rodríguez Torrens *⊙, Carolina Deuttner Neumann Barroso **⊙

* Faculty of Agricultural Sciences, Ignacio Agramonte Loynaz University of Camaguey, Camagüey, Cuba
** Department of Veterinary Medicine Laboratory of Clinical Veterinary Parasitology Universidade Federal do Parana Curitiba. Brazil.
Correspondence: guillermo.barreto@reduc.edu.cu

ABSTRACT

Background: Tuberculosis is the pandemic causing the highest death toll in humans. **Aim.** To warn on the incongruities that limit an approximation to the real knowledge of tuberculosis, and may favor its spread in the COVID-19 times. **Development:** Six incongruities are hindering real knowledge of the disease: a) underestimation, b) exclusive occurrence in poor settings, c) underestimation of the zoonotic elements of the *Mycobacterium tuberculosis* complex, d) underrating of the animal reservoirs, and f) detachment between the current molecular taxonomy and the previous limitations. The factors that contextualize it can alter its real status, and delayed the decisions necessary for its eradication until 2018. Since 2020, almost the absolute subordination of health systems to COVID-19 interfered with that purpose and it may cause a setback of the advances made in tuberculosis treatment to a situation similar to 2012. Though scarce, studies on possible synergies between the two pandemics predict that coinfected patients are 2.21-2.27-fold more likely to die or develop a serious disease. **Conclusions:** Tuberculosis is the oldest and most lethal pandemic to humanity; it is also the most commonly ignored. It has been caused by overconfidence, underestimation of the least favored areas of the planet, the participation of animals, the environment, and the absence of a proper state-of-the-art taxonomic knowledge to tackle these threats. This situation has been aggravated by the priority demanded by COVID-19. A first step to achieving its eradication in the future would be to assess the incongruities that hindered the existence of more objective knowledge of tuberculosis.

Keywords: *Mycobacterium tuberculosis* complex, pandemic, under notice, tuberculosis, zoonosis (*Source MeSH*)

INTRODUCTION

Tuberculosis is one of the first diseases that affected humans. Some claim that it appeared in the Neolithic, with a zoonotic origin (Sabin *et al.,* 2020). More recent sources have reported a Paleolithic origin, when an environmental bacterium, a predecessor of the later *Mycobacterium tuberculosis* complex (MTC), chose *Homo sapiens* as the exclusive host species (Cardona, Catala, and Prats, 2021). Despite uncertainties, three elements stand out: humans-animals-the environment, though they have not always been weighed in related studies (Katale *et al.*, 2019).

The impact perception of the MTC zoonotic species on human health has been variable, even null in several reviews of this topic (Barberis *et al.,* 2017). Recently, the most accurate taxonomy recommended *M. tuberculosis* as the only species of this group (Riojas *et al.,* 2018). This molecular finding was unquestionable, as it does not respond to the diversity and individuality usually acknowledged for the other members of the complex. This decision would atomize the zoonotic component of the disease and minimize the role of animals in this millenary disease to a larger extent (van de Weg *et al.*, 2020). Again, risking the human-animal-environment trilogy within this phenomenon.

Until the first half of the twentieth century, this disease was considered a lethal pandemic. In the 1980s, in face of the supposed eradication of *M. bovis* in many industrial countries of the northern hemisphere, it was thought to be eradicated (Kleeberg, 1984). The emergence of AIDS and its frequent concomitance with tuberculosis caused a rise in the antibiorresistance of tuberculosis-producing strains. This element triggered its expansion and lethality (Barba, 2020). A decade later, the World Health Organization (WHO), reconsidered it as a global emergency (Candelaria *et al.,* 2014). In 2015, its eradication was decided through the End TB Strategy (World Health Organization, 2015), which did not begin until 2018 (Maciel and Almeida da Silva, 2021).

In 2019, when the first two achievements were evidenced, COVID-19 came into existence. The hegemonic attention demanded by its diagnostic, therapeutics, and control risks the fulfillment of the goals set to eradicate tuberculosis (Maciel and Almeida da Silva, 2021). This issue has been identified as the *ignored pandemic* (Barba, 2020).

Accordingly, this research aims to warn about the incongruities that limit an approximation to the real knowledge of tuberculosis and may favor its spread in the COVID-19 times.

DEVELOPMENT

Tuberculosis, underestimation or excess of confidence, geographic and social determinism

Underrating a disease has unleashed various ancient and lethal conditions, most of which have a zoonotic origin. This trend, along with the reticence to spread the findings of those who study them, has favored its persistence and increase. This perception derives from objective and subjective assessments outside the context that conditions a distorted image of the problem.

Often, the causes of silent effects on a region remain unchangeable until the rest of the world is at risk (Barreto, Rodríguez, and Barreto, 2021). Ebola is a still latent problem (Gates, 2015).

Tuberculosis is a microbial disease that causes the highest death toll in humans. In the 300 years following 1750, a billion people died, mostly between 1760 and 1810. Then, a decline was observed until 1914, then a steep increase in the disease occurred throughout the first World War (Murray, 2015).

Other sources refer to the number of human losses in only 200 years, between the eighteenth and twentieth centuries. The estimates were made according to the first epidemiological records compiled in Europe. They refer to the effects in London, Stockholm, and Hamburg, accounting for 900 deaths/100 000 people (Paulson, 2013). Improvements in the living standards of industrial nations, and the development of antibiotics in the twentieth century reduced the associated mortality (Mondoni, Centanni, and Sotgiu, 2020), a situation that would be reverted after the two world wars (Paulson, 2013).

A century after Koch's contribution, the industrial nations of the north assumed that tuberculosis was under control, thanks to 1) An updated and effective therapy; 2) The adoption of preventive measures, including milk or milk-by-product pasteurization before being sold (Kleeberg, 1984). Hence, a resolution intended to eradicate the many cases of human tuberculosis caused by *M. bovis* was adopted. From that moment on, the MTC species, having a broader range of hosts, was overlooked in the successive control programs (Allen, Ford, and Skuce, 2021).

There were two mistaken decisions: first, inaccurate, local, and illusory provisions that ignored the existence of other scenarios far from that optimism, such as southeast Asia, Africa, the West Pacific, and the east of the Mediterranean Sea. Although there may be other examples, these four regions comprised 95% of cases and 98% of the deaths caused by tuberculosis. This issue persists and continues to grow (Barba, 2020). The second provision favored the uncontrolled diffusion and increase of *M. bovis* in domesticated and wild animals, a disaster inherited by the present century (Allen, Ford, and Skuce, 2021).

In 1993, the General Assembly of WHO declared tuberculosis a "global emergency" due to its re-occurrence in developing and developed countries. Consequently, the fallacy of associating the disease with poverty crumbled (Barba, 2020). The provision responded to several conditions. First, the enormous extent of the AIDS pandemic and the risks to immunodepressed patients posed by the growing emergence of antibioresistant *M. tuberculosis* strains (Mondal *et al.,* 2016). Secondly, the rise of immigration and economic crises, two elements that triggered infectious diseases (Popejoy *et al.,* 2017). Thirdly, the control programs had been neglected, though it was the second cause of death in humans at the time (Barba, 2020).

In May 2012, the member states of the 65ª World Health Assembly demanded the presentation of an analysis of the situation of the disease globally, and the multisectoral strategies and international goals beyond 2015. Two years later, WHO presented its End of TB strategy. The

goals for 2035 included a 95% reduction of associated mortality (WHO, 2015). This proposal was ratified by the General Assembly of the United Nations (UNGA), in 2018 (WHO, 2018).

In 2019, a year following the beginning of the End of TB Strategy, the disease claimed 1.4 million human lives. A more detailed analysis showed that 208 000 of the deaths were co-infected with HIV. As macrophages are the main intracellular niche in the response to the two pathogens, a possible joint modulation of these cells has been thought to produce an ensuing acceleration and progression of both diseases (Santos-Pereira, Magalhães, Araújo, and Osório, 2021). This must be elucidated since interactions of this kind could involve SARS CoV-2 in the present context.

The WHO and the International Union against Tuberculosis and Respiratory Diseases, following the quick expansion of COVID-19 in 2020, expressed their concern over the repercussions for the completion of the strategies laid out to eradicate tuberculosis (Maciel and Almeida da Silva, 2021). These concerns are justified due to the assessment of the current scenario of the least economically favored countries, which coincide with the areas that withstand the highest rates of infection (Barba, 2020).

Despite Canada's industrial development, it is one good example; the appearance of COVID-19 forced the country to adopt quick and efficient control measures of which many were already part of the programs to fight tuberculosis. If they had been implemented strictly, the number of cases and mortality rate would have been lower (Long *et al.,* 2020). The ones who support this information recognize that antituberculosis therapy reduced mortality significantly all over the country in the twentieth century, being close to eradication. The exception was made by the marginal groups (indigenous people, homeless and derelicts, and more recently, migrants). These unfavored and untreated minorities were blamed for the persistence of the diseases. Was it the same case with COVID-19?

Tuberculosis is another pandemic that targets the airways. How many reasons were needed to decide what to do? Underestimation or overconfidence, geographic and social determinism, may have mediated the inexplicable inertia, but they are not the only ones.

The origins of the disease and its setting

Tuberculosis has remained around humans for thousands of years. Where, when, and how it emerged is a controversial topic; multiple sources coincide that, like its host, the site was in Africa (Gutierrez *et al.,* 2005; Wirth *et al.,* 2008). Using Bayesian inference, an ancestor from the ACMTB came out in eastern Africa 40 000 years ago, in the regions where the first modern humans spread. The original ACMTB produced two main lines 10 000-20 000 years later; one was transmitted to animals (Wirth *et al.,* 2008). Gutierrez *et al.* (2005) placed ACMTB around 20 000-35 000 years before the contemporary age, showing the parallelism between the human demographic evolution and the millenary pathogens, some of which were the same for other mammals. These criteria produced a 180-degree turn of the previous theories about the zoonotic origin of the disease (Stead, 1997).

Barreto Argilagos, G., Beltrão Molento, M., Rodríguez Torrens, H.C., Neumann Barroso, C.D.

New evidence, including the African scenario, corroborate that the disease emerged 70 000 years before the common era (BCE) (Cardona *et al.,* 2021).   It was a moment of the Middle Paleolithic Age, when *Homo sapiens* were regarded as primates and were relatively fragile, who organized into small tribes of hunters and gatherers to survive (Miller, 2018). These qualities made them the exclusive hosts of an ancestral line of *Mycobacterium tuberculosis* responsible for non-serious but chronic forms of tuberculosis that could have been the beginning of this interrelation. Later, the changes during the Demographic Transition of the Neolithic Age gave rise to more virulent forms of the pathogen, having no risk of losing their hosts due to the rise in human population density (Cardona *et al.,* 2021).

The above responds to where and when the disease appeared, but not how. The most acceptable variant refers to a time between 73 000 and 70 000 years of BCE when an ACMTB ancestor emerged. It was an environmental mycobacterium, which under ecological pressure, chose the *Homo sapiens* as their reservoir. It was a period inserted in the Mid-Paleolithic Age. The most important event at the moment was the conquest and control of fire. The close contact made around bonfires, and inhalation of the smoke that may have conditioned the occurrence of primary chronic infections, as described (Cardona *et al.,* 2021).

This conception, despite the evidence in favor of the origin in the Neolithic Revolution, demonstrates that it only took an important instant in history. It was a stage that came after a climatic crisis: the last glaciation. The transit to the Neolithic Age had a different setting: an intense fertile area that spread beyond the African limits. This ecosystem favored the transit from a gathering economy to a producing one that developed agriculture and livestocking. It permitted the first humans to settle in larger communities (Diamond and Bellwood, 2003). This population increases conditioned the predominance of more virulent forms of the ACMTB (Cardona *et al.,* 2021). The migrations in Africa, and outside Africa, favored its expansion. A continuous phenomenon (unfortunately unheard of) enhanced in the twenty-first century, was clear evidence of the human-surrounding-disease interdependence (Popejoy *et al.,* 2017).

The links established between livestocking in the Neolithic Age and the *Mycobacterium bovis* (or similar ancestor) interspecies leap (Stead, 1997) did not contradict recent theories; they just added another condition to the already existing ones. *M. bovis* stands out among the MTC components due to its broad range of reservoirs. This element has confirmed its current status as a significant cause of tuberculosis in animals and people (Allen, Ford, and Skuce, 2021). Surprisingly, it is underestimated and overlooked, as other zoonotic members, in the reviews of this disease (Lekko *et al.,* 2020; Arnot and Michel, 2020). This error rules out the animals surrounding humans.

This topic is intended to encourage further research on tuberculosis within the One Health context, which explains why it has reached modern times. A deep review of this issue will show the limited number of investigations that focus on this variant (Katale *et al.,* 2019). [3]

The animal- (domesticated and wild) tuberculosis relationship will be dealt with in detail below. As to the environment (infinite and critical) for *Mycobacterium* spp. activity, it is necessary to

tackle two elements: a) Climate change. *Per se*, it is enough to erase present-day life if new urgent measures are not taken. Any research on the status of tuberculosis should include this element (Harries, Martinez, and Chakaya, 2021). b) The capacity of *Mycobacterium* spp. of producing biofilm. This phenotype is stimulated under ecological stress; the form in which the bacteria prevail (99.9 %), allowing them to have a long-lasting existence (Samal and Das, 2018).

It is worth noting that despite the pile of previous uncertainties, several steps have been taken in the study of the biofilm phenotype of *M. tuberculosis* and *M. bovis*. They explain their resistance to the environment and antimicrobials (Richards *et al.,* 2019). There is no need to abound in the MTC phenotype-pathogeny relationship, a line that has explained its persistence and chronicity in other millenary diseases (Barreto *et al.,* 2021).

Mycobacterium, the Mycobacterium tuberculosis complex, and the molecular taxonomy

Although the focus on the disease has varied, *Mycobacterium* has garnered uninterrupted scientific interest since the late twentieth century. Research performed on pathogeny-host faced a colossal problem: a large number of species. It was ascending in figures along with the increase and sensitivity of the molecular techniques employed. In 2017, a number of 170 species were mentioned (Forbes, 2017); with 188 species the next year (Gupta, Lo, and Son, 2018), and 197 species by December 2019. The estimates for possible increases in 2020 were supposed to have been taken into account (Parrish, 2019).

However, they were not. The technological optimization of taxonomy offered an unexpected solution: gender fractioning into five. Four were unheard of, associated with non-tuberculosis producing mycobacteria (*nontuberculous mycobacteria* -NTM): *Mycobacteroides*, *Mycolicibacter*, *Mycolicibacterium*, and *Mycolicibacillus*. The fifth was named *Mycobacterium* and it inherited the species that caused such disease (Gupta *et al.,* 2018). The proposal was accompanied by the corresponding nomenclature, published in the International Journal of Systematic and Evolutionary Microbiology (IJSEM), the official journal of the International Committee on Systematics of Prokaryotes (Oren and Garrity, 2018). It was such a sudden turn that some still cannot assimilate it, and others are unaware of it (Tortoli *et al.,* 2019).

The advantages of molecular taxonomy are undeniable due to its accuracy and promptness, two reasons for the publication of related news. Besides, the proposal did not affect MTC, whose number of species has varied in time. At the moment of assessment, it included *M. tuberculosis*, *M. africanum, M. canettii, M. bovis, M. microti, M. orygis, M. caprae, M. pinnipedii, M. suricattae*, and *M. mungi*. All have a common denominator: they cause tuberculosis in humans and/or animals. To some, the former are their exclusive reservoirs (*M. tuberculosis*, *M. africanum,* and *M. canettii*). Meanwhile, others affect both thanks to their zoonotic character (Thapa *et al.,* 2017). Among them, *M. tuberculosis* causes the highest percentage of human deaths. The deaths caused by the other members in little-favored areas are underestimated or overlooked (Arnot and Michel, 2020). A bias that alters the global mortality figures.

Barreto Argilagos, G., Beltrão Molento, M., Rodríguez Torrens, H.C., Neumann Barroso, C.D.

By 2018, an unexpected event would occur. As happened with the genus, a new proposal that denied MTC validity was presented; it relied on the results achieved by next-generation sequencing (NGS), digital DNA–DNA hybridization (dDDH), and average nucleotide identity (ANI). Accordingly, the proverbial species were qualified as strains (*M. canettii, M. orygis,* and *M. mungi*) or varieties anew (the rest) of *Mycobacterium tuberculosis* (Riojas *et al.,* 2018).

MTC species' genetic homogeneity (99.9%) was known, but its singularity was respected given their pathogenic differences, geographic distribution, host preference, biochemical behavior, and nutritional requirements (Thapa *et al.,* 2017; van de Weg *et al.,* 2020). Will tuberculosis disappear as a zoonosis, or is it a taxonomic game?

The significance of the genus *Mycobacterium* for public health, not only in developing countries, has rested on its zoonotic component (Katale *et al.,* 2019). It is the main reason why several researchers have ignored the proposal of Riojas *et al.* (2018). In 2018, MTC was responsible for the death of 1.2 million people. This figure was low, considering that only 16 countries referred to *M. bovis* behavior in patients with tuberculosis. Most deaths took place in southeast Asia and Africa (Lekko *et al.,* 2020), as has been the case since the 1980s (Barba, 2020). Therefore, the techniques for diagnostic in cattle, goats, and pigs demand improvements (Sánchez-Carvajal *et al.,* 2021). In that sense, the studies based on the One Health approaches state that every animal species must be considered as possible MTC reservoir (One Health input paper for the GF strategy development by the Germany Constituency, 2021).

MTC-caused zoonosis in cattle, sheep, and goat reservoirs, with milk as the main form of transmission. The disease follows a slow course, so there may be years until the infected individuals die. One of them is sufficient to transmit it in the community before the symptoms are observed. Simultaneous infections with *Fasciola hepática* are frequent; the trematode interferes with the inflammatory response during the tuberculin intradermic test, producing false negatives (Barreto and Rodríguez, 2019). Overall, 90% of the more than one billion goats live in the poorest countries that do not have the resources for proper diagnosis. and most farmers make their cheeses from raw milk (Barreto and Rodríguez, 2018).

The impact of MTC on health is dramatic in southeast Asia and Africa, but it does not exclude Australia, New Zealand, the UK, Europe, and even the US (Thapa *et al.,* 2017; Barreto and Rodríguez, 2018; van de Weg *et al.,* 2020). Only the One Health approach could unveil the true causes of this phenomenon (Byrne *et al.,* 2021). Otherwise, the millenary disease will subsist, regrettably.

Rather than questioning the modern taxonomy, the objective is to use it to correct the previous shortcomings when addressing this issue, regardless of species, strains, varieties, or serovars. The multivariate reality that surrounds tuberculosis from its onset must not be ignored. In it, animals (domesticated and wild) and the environment are critical.

COVID-19 and tuberculosis

The infectious diseases that affect the respiratory tract (RTD) are responsible for most morbidity and mortality cases in the world. Until December 2019, three pathogens were the priority of the WHO project for research and development: The Severe Acute Respiratory Syndrome-Coronavirus (SARS-CoV), the Middle East Respiratory Syndrome-Coronavirus (MERS-CoV), and *Mycobacterium tuberculosis* (WHO, 2020). A novel coronavirus appeared in China this month: SARS-CoV-2. It spread out as the COVID-19 pandemic since December 2020, and attracted the attention of health institutions (Maciel and Almeida da Silva, 2021).

The predictive models since early 2020 evidenced that the global response to COVID-19 might create serious constraints on the diagnosis, treatment, and prevention of tuberculosis. An analysis of 20 countries with a high burden of the disease (approximately 54% of the world's occurrence), revealed that the annual cases would undergo an additional rise of 6.3 million, as a prediction. Meanwhile, mortality between 2020 and 2025 would add 1.4 million deaths more than the mean observed in the five years before 2020. These results matched the ones disclosed in 2012 (Kasaeva, 2020). The WHO and the International Union against Tuberculosis and Respiratory Diseases expressed their concern over the impact of the new pandemic repercussions on the completion of the goals of the End TB campaign (Maciel and Almeida da Silva, 2021).

In China, the epicenter of the pandemic, the notifications of patients with tuberculosis dropped dramatically following the first week of the viral epidemic onset. The attempt to rescue these services in 2020 was unsuccessful. In the short term, the new pandemic deteriorated the report frequency of cases of tuberculosis and the follow-up cases in the country. Consequently, 9% of patients put off or missed their follow-up exams because of the restrictions or quarantine, or the fear of acquiring COVID-19 (Fei *et al.,* 2020).

In Italy, one of the most stricken European countries, Di Gennaro *et al.* (2021) pointed out that the pandemic had a negative effect on the patients with tuberculosis due to a sensitive reduction of diagnostic and hospitalization capacities. Meanwhile, there was a spike in the severity of the cases detected. The authors concluded that the consequences were still unknown.

In Cuba, the experience was driven according to the strategies laid out to eradicate tuberculosis before 2035. In March 2020, the first SARS CoV-2 positive cases were confirmed. The compelling polarization of this fight damaged the rhythm of the tuberculosis control required. A comparison of 2020 and 2019, revealed a reduction in the number of clinical samples (sputum) sent. There was also a reduction in the samples of surveillance of *M. tuberculosis* resistance (Díaz Rodríguez *et al.,* 2020).

Tuberculosis did not trigger the viral pandemic emergency. Both have a time association and a synergic socio-economic impact globally. There are few studies on the possible synergies. These are cases involving a single patient. However, the people with COVID-tuberculosis were deemed to have a 2.21-2.27-fold more probability of dying or developing a serious disease. The former, in the critical cases, trigger a spectrum of immunological responses among which the cytokine

response stands out, with a lethal outcome. The immunosuppression strategies, including steroids, may affect the reactivation of tuberculosis in the future (Visca *et al.,* 2021).

In short, "... people never learn from their errors. In the last five years, tuberculosis, a respiratory disease, remained the main cause of deaths given the fact that in the corresponding agenda, it was less visible than other priorities". "... Today, governments face a windy road through the imminent disaster of COVID-19 and the long-lasting plague of tuberculosis. However, ignoring tuberculosis anew would at least erase half a decade of advance in the fight against the most lethal infection in the world, and more millions could get infected" (Zumla *et al.,* 2020). The publication of this paper would be fully justified if it created the proper awareness.

CONCLUSIONS

Tuberculosis is the oldest and most lethal pandemic faced by humanity, while it has also been the most commonly ignored one, resulting from overconfidence, underestimation of the least favored areas of the planet, the involvement of animals (domesticated and wild), the environment, and the absence of the proper state-of-the-art taxonomic knowledge to tackle previous shortcomings. This situation has been aggravated by the hegemonic priority demanded by COVID-19, which is not an excuse to not create consciousness, and assume that other diseases are lethal as well. The first step for the future eradication of tuberculosis is to assess the factors that biased proper control of the disease in its real dimension.

REFERENCES

Allen, A. R., Ford, T., & Skuce, R. A. (2021). Does *Mycobacterium tuberculosis var. bovis* Survival in the Environment Confound Bovine Tuberculosis Control and Eradication? A Literature Review. *Veterinary medicine international*. https://doi.org/10.1155/2021/8812898

Arnot, L. F., & Michel, A. (2020). Challenges for controlling bovine tuberculosis in South Africa. *Onderstepoort Journal of Veterinary Research*, *87*(1), 1-8. https://hdl.handle.net/10520/EJC-1e8c7738f4

Barba, J.R. Tuberculosis. (2020) ¿Es la pandemia ignorada? *Rev Mex Pato Clin Med Lab*., *67* (2), 93-112. https://dx.doi.org/10.35366/95554

Barberis, I., Bragazzi, N. L., Galluzzo, L., & Martini, M. (2017). The history of tuberculosis: from the first historical records to the isolation of Koch's bacillus. *Journal of preventive medicine and hygiene*, *58*(1), E9. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5432783/

Barreto Argilagos, G., Rodríguez Torrens, H., & Barreto Rodríguez, H. (2021). Brucelosis, aspectos que limitan su justa valoración. *Revista de Salud Animal*, *43*(1).

http://scielo.sld.cu/scielo.php?pid=S0253570X2021000100001&script=sci_arttext&tlng=pt

Barreto, G., & Rodríguez, H. (2018). Capítulo 11. Enfermedades bacterianas frecuentes en las cabras. *Adela Bidot y Juan J. Paretas. La Habana.*

Barreto Argilagos, G., & Rodríguez Torrens, H. de la C. (2019). Dos zoonosis ancestrales reemergen y se complementan. *Revista de Producción Animal*, *31*(1), 58-60. https://revistas.reduc.edu.cu/index.php/rpa/article/view/e2679

Byrne, A. W., Barrett, D., Breslin, P., Madden, J. M., O'Keeffe, J., & Ryan, E. (2021). Future Risk of Bovine Tuberculosis (Mycobacterium bovis) Breakdown in Cattle Herds 2013–2018: A Dominance Analysis Approach. *Microorganisms*, *9*(5), 1004. https://doi.org/10.3390/microorganisms9051004

Cardona, P. J., Català, M., & Prats, C. (2021). The Origin and Maintenance of Tuberculosis is Explained by Its Subclinical Course, the Neolithic Revolution Being the Trigger for Its Devastating Deadly Drift. https://doi.org/10.21203/rs.3.rs-437338/v1

Di Gennaro, F., Gualano, G., Timelli, L., Vittozzi, P., Di Bari, V., Libertone, R., Cerva, C., Pinnarelli, L., Nisii, C., Ianniello, S., Mosti, S., Bevilacqua, N., Iacomi, F., Mondi, A., Topino, S., Goletti, D., Vaia, F., Ippolito, G., Girardi, E., & Palmieri, F. (2021). Increase in tuberculosis diagnostic delay during first wave of the COVID-19 pandemic: data from an Italian infectious disease referral hospital. *Antibiotics*, *10*(3), 272. https://doi.org/10.3390/antibiotics10030272

Diamond, J., & Bellwood, P. (2003). Farmers and their languages: the first expansions. *Science*, *300*(5619), 597-603. https://www.science.org/doi/abs/10.1126/science.1078208

Díaz Rodríguez, R., Lemus Molina, D., & Martínez Romero, M. R. (2020). La tuberculosis en Cuba en tiempos de COVID-19: ¿retroceso en su plan de eliminación?. *Revista Cubana de Medicina Tropical*, *72*(3). http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S0375-07602020000300014

Fei, H., Yinyin, X., Hui, C., Ni, W., Xin, D., Wei, C., Tao, L., Shitong, H., Miaomiao, S., Mingting, C., Keshavjee, S., Yanlin, Z., Chin, D. P., & Jianjun, L. (2020). The impact of the COVID-19 epidemic on tuberculosis control in China. *The Lancet Regional Health-Western Pacific*, *3*, 100032. https://doi.org/10.1016/j.lanwpc.2020.100032

Forbes, B. A. (2017). Mycobacterial taxonomy. *Journal of clinical microbiology*, *55*(2), 380-383. https://doi.org/10.1128/JCM.01287-16

Gates, B. (2015). The next epidemic—lessons from Ebola. *New England Journal of Medicine*, *372*(15), 1381-1384. https://www.nejm.org/doi/full/10.1056/NEJMp1502918

Gupta, R. S., Lo, B., & Son, J. (2018). Phylogenomics and comparative genomic studies robustly support division of the genus Mycobacterium into an emended genus Mycobacterium and

Barreto Argilagos, G., Beltrão Molento, M., Rodríguez Torrens, H.C., Neumann Barroso, C.D.

four novel genera. *Frontiers in microbiology*, *9*, 67. https://doi.org/10.3389/fmicb.2018.00067

Gutierrez, M. C., Brisse, S., Brosch, R., Fabre, M., Omaïs, B., Marmiesse, M., Supply, P., & Vincent, V. (2005). Ancient origin and gene mosaicism of the progenitor of Mycobacterium tuberculosis. *PLoS pathogens*, *1*(1), e5. https://doi.org/10.1371/journal.ppat.0010005

Harries, A. D., Martinez, L., & Chakaya, J. M. (2021). Tackling climate change: measuring the carbon footprint of preventing, diagnosing and treating TB. *Public health action*, *11*(1), 40. https://doi.org/10.5588/pha.20.0076

Kasaeva, T. (2020). Coping with TB in the time of COVID-19. https://www.who.int/docs/default-source/documents/tuberculosis/tbcovid-webinar-presentation.pdf?sfvrsn=1377b5b1_8

Katale, B. Z., Mbugi, E. V., Keyyu, J. D., Fyumagwa, R. D., Rweyemamu, M. M., Van Helden, P. D., Dockrell, H. M., & Matee, M. I. (2019). One Health approach in the prevention and control of mycobacterial infections in Tanzania: lessons learnt and future perspectives. *One Health Outlook*, *1*(1), 1-8. https://doi.org/10.1186/s42522-019-0002-1

Kleeberg, H. H. (1984). Human tuberculosis of bovine origin in relation to public health. *Revue Scientifique et Technique Office International des Epizooties*, *3*(1), 11-32. https://www.semanticscholar.org/paper/Human-tuberculosis-of-bovine-origin-in-relation-to-Kleeberg/2105051790e223acf8abb302b3f5f1228c85eaef

Lekko, Y. M., Ooi, P. T., Omar, S., Mazlan, M., Ramanoon, S. Z., Jasni, S., Jesse, F. F. A., & Che-Amat, A. (2020). Mycobacterium tuberculosis complex in wildlife: Review of current applications of antemortem and postmortem diagnosis. *Veterinary world*, *13*(9), 1822. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7566238/

Long, R., King, M., Doroshenko, A., & Heffernan, C. (2020). Tuberculosis and COVID-19 in Canada. *E Clinical Medicine*, *27*. https://doi.org/10.1016/j.eclinm.2020.100584

Maciel, E. L., & Silva, P. E. A. D. (2021). Fighting tuberculosis: from 1993 to 2035 during the COVID-19 era. *Jornal Brasileiro de Pneumologia*, *47*. https://doi.org/10.36416/1806-3756/e20210033

Miller, E. F., Manica, A., & Amos, W. (2018). Global demographic history of human populations inferred from whole mitochondrial genomes. *Royal Society open science*, *5*(8), 180543. https://doi.org/10.1098/rsos.180543

Mondal, M. N. I., Nazrul, H. M., Chowdhury, M. R. K., & Howard, J. (2014). Socio-demographic factors affecting knowledge level of Tuberculosis patients in Rajshahi City, Bangladesh. *African health sciences*, *14*(4), 855-865. https://www.ajol.info/index.php/ahs/article/view/111387

Mondoni, M., Centanni, S., & Sotgiu, G. (2020). New perspectives on difficult-to-treat tuberculosis based on old therapeutic approaches. *International Journal of Infectious Diseases*, *92*, S91-S99. https://doi.org/10.1016/j.ijid.2020.02.039

Murray, J. F. (2015). Tuberculosis and World War I. *American journal of respiratory and critical care medicine*, *192*(4), 411-414. https://doi.org/10.1164/rccm.201501-0135OE

One Health input paper for the GF strategy development by the Germany Constituency. (2021). Integration of the One Health approach into the work of the Global Fund to Fight AIDS, TB and Malaria. https://www.theglobalfund.org/media/10617/strategydevelopment_2021onehealthapproach_inputpaper_en.pdf

Oren, A., & Garrity, G. (2018). List of new names and new combinations previously effectively, but not validly, published. *International journal of systematic and evolutionary microbiology*, *68*(7), 1411-1417. https://www.microbiologyresearch.org/content/journal/ijsem/10.1099/ijsem.0.002711

Parrish, N. (2019). An update on mycobacterial taxonomy, 2016–2017. *Journal of clinical microbiology*, *57*(5), e01408-18. https://doi.org/10.1128/JCM.01408-18

Paulson, T. (2013). Epidemiology: a mortal foe. *Nature*, *502*(7470), S2-S3. https://doi.org/10.1038/502S2a

Popejoy, M. W., Gasana, J., & Ravikumaran, R. (2017). The pandemic nature of reemerging tuberculosis and the role of population migration in its spread. *MOJ Public Health*, *6*(4), 383-392. https://medcraveonline.com/MOJPH/the-pandemic-nature-of-reemerging-tuberculosis-and-the-role-of-population-migration-in-its-spread.html

Popejoy, M. W., Gasana, J., Ravikumaran, R., Westphal, D., Mendy, A. (2017). The pandemic nature of reemerging tuberculosis and the role of population migration in its spread. *MOJ Public Health, 6*(4). https://medcraveonline.com/MOJPH/the-pandemic-nature-of-reemerging-tuberculosis-and-the-role-of-population-migration-in-its-spread.html

Riojas, M. A., McGough, K. J., Rider-Riojas, C. J., Rastogi, N., & Hazbón, M. H. (2018). Phylogenomic analysis of the species of the Mycobacterium tuberculosis complex demonstrates that Mycobacterium africanum, Mycobacterium bovis, Mycobacterium caprae, Mycobacterium microti and Mycobacterium pinnipedii are later heterotypic synonyms of Mycobacterium tuberculosis. *International journal of systematic and evolutionary microbiology*, *68*(1), 324-332. https://www.microbiologyresearch.org/content/journal/ijsem/10.1099/ijsem.0.002507?crawler=true

Candelaria, S. R., Llanes, L. G., & Ranero, V. M. (2015). Evaluación del Programa Nacional de Control de la Tuberculosis en Bauta. *Revista Cubana de Higiene y Epidemiología*, *52*(1), 98-105. https://www.medigraphic.com/cgi-bin/new/resumen.cgi?IDARTICULO=56204

Barreto Argilagos, G., Beltrão Molento, M., Rodríguez Torrens, H.C., Neumann Barroso, C.D.

Sabin, S., Herbig, A., Vågene, Å. J., Ahlström, T., Bozovic, G., Arcini, C., Kühnert, D., & Bos, K. I. (2020). A seventeenth-century Mycobacterium tuberculosis genome supports a Neolithic emergence of the Mycobacterium tuberculosis complex. *Genome biology*, *21*(1), 1-24. https://doi.org/10.1186/s13059-020-02112-1

Das, P. K., & Samal, S. (2018). Microbial biofilms: pathogenicity and treatment strategies. *PharmaTutor*, *6*(1), 16-22. https://doi.org/10.29161/PT.v6.i1.2018.16

Sánchez-Carvajal, J. M., Galán-Relaño, Á., Ruedas-Torres, I., Jurado-Martos, F., Larenas-Muñoz, F., Vera, E., Gómez-Gascón, L., Cardoso-Toset, F., Rodríguez-Gómez, I. M., Maldonado, A., Carrasco, L., Tarradas, C., Gómez-Laguna, J., & Luque, I. (2021). Real-Time PCR validation for Mycobacterium tuberculosis complex detection targeting IS6110 directly from bovine lymph nodes. *Frontiers in Veterinary Science*, *8*, 231. https://doi.org/10.3389/fvets.2021.643111

Santos-Pereira, A., Magalhães, C., Araújo, P. M., & Osório, N. S. (2021). Evolutionary Genetics of Mycobacterium Tuberculosis and HIV-1: "The Tortoise and the Hare". *Microorganisms*, *9*(1), 147. https://doi.org/10.3390/microorganisms9010147

Stead, W. W. (1997). The origin and erratic global spread of tuberculosis: how the past explains the present and is the key to the future. *Clinics in chest medicine*, *18*(1), 65-77. https://doi.org/10.1016/S0272-5231(05)70356-7

Thapa, J., Nakajima, C., Gairhe, K. P., Maharjan, B., Paudel, S., Shah, Y., Mikota, S. K., Kaufman, G. E., McCauley, D., Tsubota, T., Gordon, S. V., & Suzuki, Y. (2017). Wildlife tuberculosis: An emerging threat for conservation in South Asia. In *Global exposition of wildlife management*. IntechOpen. https://www.intechopen.com/chapters/52794

Tortoli, E., Brown-Elliott, B. A., Chalmers, J. D., Cirillo, D. M., Daley, C. L., Emler, S., Floto, R. A., Garcia, M. J., Hoefsloot, W., Koh, W. J., Lange, C., Loebinger, M., Maurer, F. P., Moimoto, K., Niemann, S., Richter, E., Turenne, C. Y., Vasireddy, R., Vasireddy, S., Wagner, … & van Ingen, J. (2019). Same meat, different gravy: ignore the new names of mycobacteria. *European Respiratory Journal*, *54*(1). https://erj.ersjournals.com/content/54/1/1900795.short

van de Weg, C. A., de Steenwinkel, J. E., Miedema, J. R., Bakker, M., van Ingen, J., & Hoefsloot, W. (2020). The tough process of unmasking the slow-growing mycobacterium: case report of Mycobacterium microti infection. *Access Microbiology*, *2*(1). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7525059/

Visca, D., Ong, C. W. M., Tiberi, S., Centis, R., D'Ambrosio, L., Chen, B., Mueller, J., Mueller, P., Duarte, R., Dalcolmo, M., Sotgiu, G., Migliori, G. B., & Goletti, D. (2021). Tuberculosis and COVID-19 interaction: a review of biological, clinical and public health effects. *Pulmonology*, *27*(2), 151-165. https://doi.org/10.1016/j.pulmoe.2020.12.012

Wirth, T., Hildebrand, F., Allix-Béguec, C., Wölbeling, F., Kubica, T., Kremer, K., van Soolingen, D., Rüsch-Gerdes, S., Locht, C., Brisse, S., Meyer, A., Supply, P., & Niemann, S. (2008). Origin, spread and demography of the Mycobacterium tuberculosis complex. *PLoS pathogens*, *4*(9), e1000160. https://doi.org/10.1371/journal.ppat.1000160

World Health Organization. (2018). UN General Assembly adopts modalities resolution for the UN High-Level Meeting on TB, 26 September 2018. https://www.who.int/news/item/04-04-2018-un-general-assembly-adopts-modalities-resolution-for-the-un-high-level-meeting-on-tb-26-september-2018

World Health Organization. (2018). WHO Updates Blueprint List of Priority Diseases. https://globalbiodefense.com/2018/02/12/who-updates-blueprint-list-of-priority-diseases/

World Health Organization. The End TB Strategy. Geneva, Switzerland: World Health Organization; 2015. Available at: https://www.who.int/tb/strategy/ end-tb/en/

World Health Organization. (2015). The End TB Strategy. Geneva, Switzerland: World Health Organization; 2015. *Contract No.: WHO/HTM/TB*. https://www.who.int/tb/End_TB_brochure.pdf

Zumla, A., Wang, F. S., Ippolito, G., Petrosillo, N., Agrati, C., Azhar, E. I., Chang, C., El-Kafrawy, S. A., Osman, M., Zitvogel, L., Galle, P. R., Locatelli, F., Gorman, E., Cordon-Cardo, C., O'Kane, C., McAuley, D., & Maeurer, M. (2020). Reducing mortality and morbidity in patients with severe COVID-19 disease by advancing ongoing trials of Mesenchymal Stromal (stem) Cell (MSC) therapy—Achieving global consensus and visibility for cellular host-directed therapies. *International Journal of Infectious Diseases*, *96*, 431-439. https://doi.org/10.1016/j.ijid.2020.05.040

AUTHOR CONTRIBUTION

Research conception and design: GBA, MBM, HRT, CDNB; data analysis and interpretation: GBA, MBM, HRT, CDNB; redaction of the manuscript: GBA, HRT.

CONFLICT OF INTEREST

The authors declare the existence of no conflicts of interest.