History of Medicine and Ethics

Historical and Social Considerations upon Tuberculosis

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Summary

The present article offers a concise perspective on tuberculosis (TB) ranging from antiquity to the present day and highlights the dangerousness of the disease in the light of its historical manifestations and current antibiotic resistance. Reflections on the social and economic impact of tuberculosis are presented together with notes on TB's interplay with malnutrition and the social stigma linked to this disease in modern times. Different types of evidence from palaeopathological to artistic ones are offered and the need for a more comprehensive understanding on the disease's history and evolution is stressed.

Introduction

Understanding tuberculosis

According to WHO statistics, in 2023 a total of 1.25 million people worldwide died from tuberculosis (TB), which explains how TB has now returned to be the main infectious disease killer, after three years in which it was "replaced" by COVID-19, and ranking higher than AIDS [1]-two of the most significant epidemic diseases in the last 40 years capable of breaking the previous pathocoenosis balance [2-4]. For a long time, TB has been a scourge for humankind and currently its dangerousness is associated with multi-drug-resistant strains of *Mycobacterium* spp. Again, the WHO data indicate that in 2023, only 2 out of 5 people with antibiotic-resistant TB accessed treatment [1]. Moreover, despite an estimated 75 million lives saved from TB since 2000, TB still represents a major hindrance factor in the development of nations [1, 5]. The most commonly prescribed antibiotics include isoniazid, rifampin, pyrazinamide, ethambutol and streptomycin [1, 6]. Such drugs need to be administered every day for a period of 4-6 months and a key to the success of the therapeutic strategy is not to stop taking them too early or without medical advice, since this could let TB *Mycobacteria* to survive and become drug-resistant [1, 7].

Economic and Social Impact

Tuberculosis has enormous economic implications for its hosts and society. The financial consequences of tuberculosis may be of two types. The first one, direct, refers to the costs of medical treatment, including drugs, laboratory tests, physician fees, radiological investigations, and hospitalization. These costs to TB patients are high compared to *per capita* income and have also a major impact on the family economy in low- and middle-income countries. The second type of financial burden, indirect one, is related to illness-induced reduction of the earning capacity of the patient and by reducing the demand for labour as a result of death or disease [8]. TB causes large costs in healthcare systems and hospital budgets as well as increased expenses on welfare. There are also substantial revenues that can be realised if full cost recovery from elements of tuberculosis care such as human resources, laboratory investigations, radiology, drugs, etc. is achieved. A study based on a TB-endemic country like India [9], for example, indicated that approximately 24.3% of TB patients experienced both social and economic reverberations, with 75% patients suffering from at least one of them. In addition, "social impact was perceived by more female patients as compared to males (80.7% *vs* 62%)" and "more patients with extra-pulmonary disease (44.4%) and patients belonging to joint families (40.7%) perceived economic impact" [9].

Stigma and Discrimination

Tuberculosis is stigmatised by most communities mainly due to the fear of transmission during contact with infected person, but second important aspect includes its

link with such factors as: "HIV, poverty, low social class, malnutrition, or disreputable behaviour" [10].
As with leprosy (Hansen's disease), tuberculosis is also almost always associated with stigma. In some societies, this can result in consequences such as being abandoned by family or shunned by a community (*e.g.* co-workers, villagers, etc.). In more extreme cases, losing a job might also be an outcome. The social impact of TB is considerable, due to direct or indirect forms of discrimination [11].
The TB sufferer will endure both the physical pain caused by the disease as well as the social sequelae of stigma and discrimination. Perceptions of TB by society in general include negative, and often ill-informed attitudes about the disease. Because tuberculosis is a disease that has been associated with poverty, squalor, poor hygiene, marginalization of certain groups, and even the disintegration of character, it can result in social disregard for TB patients. Much of the prejudice is due to the lack of awareness about tuberculosis [12]. In some cases, health staff hold their own deeply entrenched biases in addition to misinformation.
The stigma associated with tuberculosis (TB) is not only an obstacle to the social acceptance of patients but also has a direct impact on the quality of care and prevention of the disease, hindering the achievement of the World Health Organisation's global goals for TB elimination. Moreover, stigma in healthcare settings compromises access to diagnosis, adherence to treatment and deteriorates therapeutic response. The most effective solutions require an integrated approach that includes educational initiatives, structural reforms and participatory methodologies, involving patients and health professionals in a common goal of reducing stigma at the individual, societal and institutional levels. Such an approach will ensure more accessible, effective and compassionate healthcare, thus contributing to the global TB elimination goals [13, 14].

Tuberculosis and malnutrition

The latest edition of the *State of Food Security and Nutrition in the World* estimates that nearly 690 million people lived in hunger in 2019, which is an increase of 10 million since 2018 and nearly 60 million in five years. Due to high costs and poor accessibility, billions of people do not have a healthy or nutritious diet (*UN World Food Programme -WFP)* [15].
It is now well established that tuberculosis is related to malnutrition both as a predisposing factor for infection and as an effect of the infection itself. This condition has also been associated with a worse prognosis in tuberculosis patients resulting in increased deaths and in a false negative tuberculin test, thus delaying diagnosis [16]. In fact, malnutrition can cause secondary immunodeficiency that makes the individual more susceptible to contracting infection [12, 16]. Tuberculosis reduces appetite, thus lowers total food intake and prevents absorption of nutrients and micronutrients in the gut as well as alters the individual's metabolism [17]. In particular, patients with a severe form of tuberculosis show significant loss of muscle mass, caused by the body's reduced ability to absorb and metabolise protein. In addition, a deficiency of micronutrients such as zinc, selenium, iron, copper, and vitamins (A, C, D, and E) results in an altered immune system [17].
A correlation between vitamin D deficiency and response to therapy has been sought in several studies [17-22]. Low serum vitamin D was observed in patients with active TB and also in multidrug-resistant tuberculosis (MDR-TB) during treatment, which may be one of the important factors responsible for susceptibility to TB in both groups; however, its significance is still being investigated [17-22].
Even before taking into account the indispensable antitubercular drugs, nutrition plays an important role in the treatment of tuberculosis: proper nutrition and an adequate nutritional supplementation may represent a novel approach for fast recovery in tuberculosis patients. Furthermore, raising nutritional status of population may prove to be an effective way to control tuberculosis in underdeveloped regions of the world.

Medical Advances and Future Outlook

Medical advances have made it possible to treat tuberculosis since the advent of antibiotics in the 1940s [23]. Previously, efforts at developing an effective vaccine for tuberculosis date back to the period just after the bacterium that causes the disease, *Mycobacterium tuberculosis*, was identified by Robert Koch (1843-1910) in 1882 [24] and are still ongoing. Preventing the development of tuberculosis from bacterial exposure is thus the focus of vaccination, while therapy aims to free the human body of the pathogen once an active infection has begun to do harm, although these therapeutic and preventive efforts overlap. One current approach to the elimination of tuberculosis involves primarily detecting and treating active cases of the disease to prevent ongoing transmission. There is also a second approach, in which the search for latent infection precedes caring for active infections, has been suggested. All these efforts, based on antibiotics and vaccine strategies, have always been a balance of risk versus benefit, of which disease and pathology are now much better understood [25].
Several vaccines have been developed to prevent TB. However, while Bacillus Calmette-Guérin (BCG) vaccination is the most widely administered vaccine in the globe, it offers limited protection against the most severe presentations of TB. Bacillus Calmette-Guérin vaccination mainly protects young children from miliary TB and other disseminated forms of TB, but it does not consistently protect against pulmonary TB [26]. Injecting a vaccine directly into the blood (intravenous administration) could provide superior protection against the most severe forms of TB, but it will have other technical/regulatory challenges and potentially other adverse events. Furthermore, no new TB vaccine has received WHO prequalification so far or been endorsed by any national regulatory authorities [27, 28].
Shorter, safer, and simpler regimens for both TB prevention and treatment, with improved effectiveness

against drug-susceptible and drug-resistant TB, would also significantly improve the prevention and hence the management of TB infection. Improving the management of the latter could help prevent progression to TB disease. A regimen of a dose of rifapentine and isoniazid (3HP) weekly for three months for treating late TB infection (LTBI) is recommended by WHO since 2020 to improve compliance and adherence by people getting LTBI treatment [29]. The benefits of such weekly therapy are anticipated to have some impact in reducing TB morbidity, especially in low- and middle-income countries. Tests and regimens for managing TB infection (LTBI) for safety, efficacy, shorter therapy, are a "game changer" for avoiding people progressing from TB infection to TB disease.

Some historical remarks

Historically, tuberculosis has been known by various names, ranging from the *White Plague* to *Phthisis*, *Consumption* or *The Great Killer*. Since the discovery of its aetiologic agent in 1882, over one billion people have succumbed to it. Much greater numbers could be hypothesised from previous eras, yet no comprehensive statistics on the disease's prevalence can be collected from the palaeopathological record [30-35], which consists of lesions detected in osteological and mummified remains, data recovered through biomolecular tests as well as literary and artistic sources [33-35]. Nevertheless, as highlighted by other infectious diseases in the past [36, 37], unless a combination of phenotypic and genetic information can be collected (or at least a convincing proportion of such data), no definitive inferences about the actual prevalence of tuberculosis can be effectively made. Hence, the process of tracing back its antiquity must be accompanied by a careful scrutiny of the available sources and greater caution should be used when making strong statements about this aspect. For example, while it was previously thought that no evidence of ancient tuberculosis was present in Sicily [38], recent discoveries effectively pushed the disease's history on the island to the potentially as far back as the 7th-5th centuries BC [39].

Indeed, tuberculosis, together with other infectious lung diseases, represented the leading cause of death in the 18th and 19th centuries, in the pre-antibiotic era, with a peak around 1850 [31], with a 35-40% mortality. It is a disease that develops most in crowded cities due to contagion via the respiratory route showing its most critical periods in the Middle Ages and, above all, during the Industrial Revolution. Despite scientific advances, in 1993, the World Health Organisation (WHO) declared TB a global emergency [31]. A watercolour (ca. 1912) (Fig. 1) by the artist Richard Tennant Cooper (1885-1957) portrayed TB as the angel of death, showing the shape of a human skeleton clutching a scythe and an hourglass, visiting a sickly pale young woman who is sitting on a balcony. Such an image powerfully points to the devastating effects of a disease at the time certainly considered to be a death sentence.

Moving on, in the 20th century, as the nature of TB's aetiologic agent and transmission methods were scientifically clarified, it is worth mentioning a poster (Fig. 2) entitled *Tuberculosis Don't kiss me!: Your kiss of affection - the germ of infection*, which focuses on the disease's impact on the paediatric population. Parents' kisses to their children, though an obvious manifestation of parental love, could turn into a powerfully effective transmission route for *Mycobacteria*, hence parents were advised to show greater caution. The disease was still extremely dangerous, and the first antibiotic strategies were *de facto* in their infancy. Hence, in order to contain

Fig. 1. A sickly young woman sits covered up on a balcony; death (a ghostly skeleton clutching a scythe and an hourglass) is standing next to her; representing tuberculosis. Watercolour by R.T. Cooper, ca. 1912. Attribution 4.0 International (CC BY 4.0). Source: Wellcome Collection. https://wellcomecollection.org/works/vktusgk3

Fig. 2. Tuberculosis Don't kiss me!: Your kiss of affection - the germ of infection / / JD. Poster about tuberculosis in children and methods of transmission, showing a child wearing a bib. [New York]: WPA Federal Art Project, District 4, [between 1936 and 1941]. No known restrictions on publication. https://catalog.loc.gov/vwebv/search?searchCode=LCCN&searchArg=98516354&searchType=1&permalink=y.

Fig. 3. Healthy looks can hide tuberculosis: the x-ray will show it before you know it. Images from the History of Medicine (IHM). [S.l.]: Christmas Seals, [193-?]. https://collections.nlm.nih.gov/catalog/nlm:nlmuid-101451864-img.

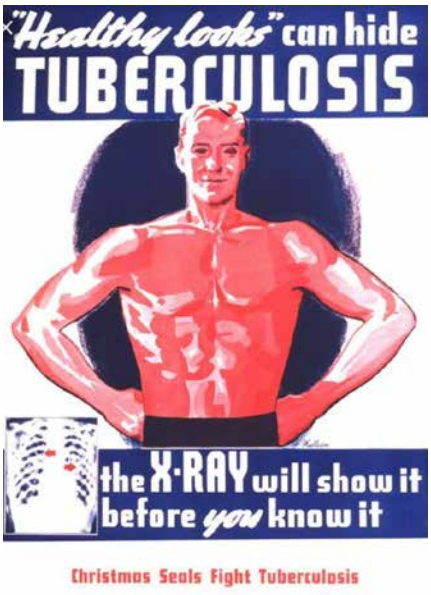
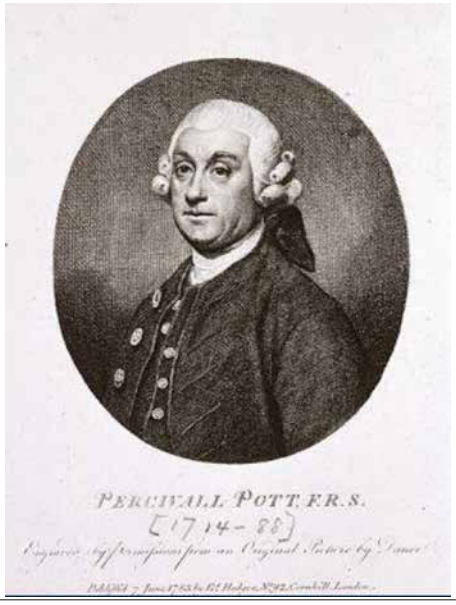


Fig. 4. Sir Percivall Pott, engraving based on an original picture by Nathaniel Dance-Holland, National Library of Medicine. Image in the public domain from Wikimedia Commons: https://en.wikipedia.org/wiki/Percivall_Pott#/media/File:PercivallPottb026992.JPG.



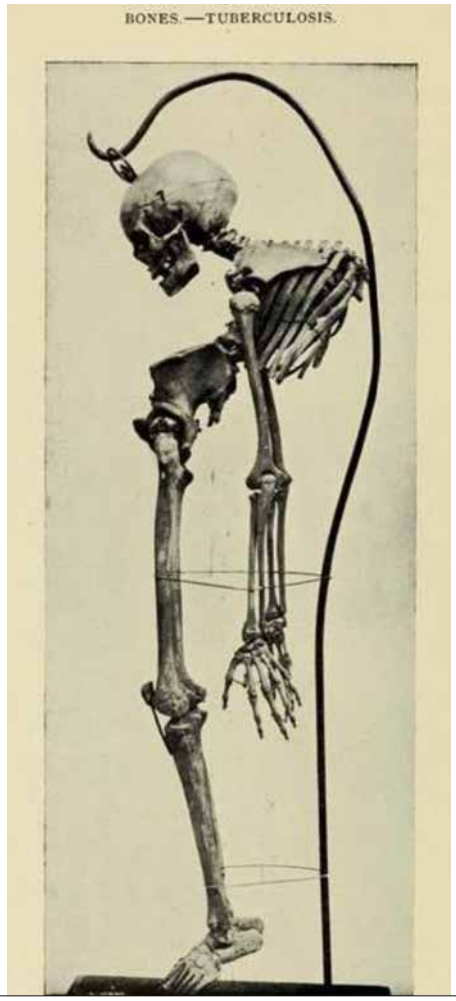
the advancing infectious disease, a disruption of social and family conventions was deemed a necessary sacrifice in order to safeguard the general populace.

Another poster (Fig. 3), *Healthy looks can hide tuberculosis: the X-RAY will show it before you know it*, testifies the advancing preventive strategies to stop the disease and to inform the population about the risks of tuberculosis. After the introduction of X-rays in 1895, chest radiographs started to play a role in the identification of individuals with pulmonary lesions, who, then, since the 1940s onwards, would be selected as candidates for treatment [40]. Indeed, by identifying TB patients who may have not yet developed the typical consumptive external phenotype but who may already have active lung TB, it was possible to detect positive cases and to implement the necessary therapies [40].

As the disease's pathophysiology teaches, when the TB *bacterium* enters the human organism through the respiratory system, it reaches the pulmonary alveoli. Macrophages attempt to counter it and the result of this fight between immune cells and the mycobacteria determines the formation of the characteristic tubercle. In the central portion of the tubercle, caseous necrosis takes place where some *Mycobacteria* persist being dormant [31, 32]. The infection can then, through the haematogenous route, spread from the lungs to the skeletal system, in some cases causing skeletal TB, the spinal column being the most commonly involved district (over 50% of cases). Through the vertebral arteries, the *Mycobacteria* reach the central portion of the vertebral bodies, causing it to be eroded so that a reduction in size and a collapse of the vertebral body's anterior portion ensues. This phenomenon ultimately results in a skeletal condition known as Pott's disease (angular gibbus), most frequently affecting the first lumbar vertebra [32-34]. This specially hyperkyphotic spine is named after Sir Percivall Pott (1714-1788), who, being a surgeon at St Bartholomew's Hospital in London, first described it in 1779 (Fig. 4) [34, 41].

Amongst the most ancient attestations of tuberculous infection, a recent study has proposed that it may have affected Neanderthal individuals from the Subalyuk Cave (Hungary – earliest individual: 39,732-39,076 cal. BP) [42] Moreover, TB in *Homo sapiens* can be traced back to 9,000 years ago in Atlit Yam, off the coast of Israel [43]. Palaeopathological evidence of tuberculosis has been consistently reported from Predynastic Egypt (6000-3150 BC) and has long been described in Ancient Egyptian mummified remains. DNA evidence has also been adduced from the Predynastic era, the Old, Middle and New Kingdoms and has been found in the young and old, from high- and low-status burials [44]. According to Crubézy et al. [44], as well as Zink et al. [45], tuberculosis existed in Ancient Egypt over 5,400 years BP, with a particularly high prevalence in the Predynastic and Late Periods. The scarcity of TB lesions in bioarchaeological material from this region of the planet is, nonetheless, probably attributed to the poor state of preservation of the affected bones. In addition, one should not ignore the fact that, even in contemporary TB patients, skeletal tuberculosis merely accounts for 3-5% of untreated cases. This may thus lead to the conclusion, as introduced aboved, that the true prevalence of TB in the past may be underestimated. In the Italian Peninsula, a very ancient attestation of skeletal TB is represented by the male adolescent skeleton (aged approx. 15 years at the moment of death) from the Neolithic site of Arene Candide (4,000-3,500 BC, Liguria Region). This prehistoric individual's spine

Fig. 5. 19th century skeleton of an unknown young adult woman with Pott's disease, or spinal tuberculosis. John Collins Warren Collection, OnView, accessed September 5, 2024, https://collections.countway.harvard.edu/onview/items/show/13129.



presents pronounced thoraco-lumbar hyperkyphosis with formation of a 90-degree angular gibbus [46]. This type of morphological deformation has preseved its appearance over time and can be appreciated in modern times, as highlighted by a 19th century skeletal preparation of an unidentified young adult female exhibited in the John Collins Warren Collection (Fig. 5, Harvard University).

Finally, once more the figurative arts – as seen in a number of pathological entities, both infectious and non-infectious ones [47, 48] can offer a valuable source of data on the antiquity and morphology of TB infection. As previously reported by some of the author of this article [35], Ancient Egyptian figurines can show the typical morphology seen in Pott's disease. Out of many such representations, one from the National Archaeological Museum of Naples (MANN) stands out (Fig. 6). Belonging to the erotic objects of the MANN's Borgia Collection, it is currently exhibited in the museum's *Secret Cabinet*, potentially an ithyphallic representation of god Harpocrates. The MANN statuette not only shows an angulate morphology of the

Fig. 6. Statuette possibly representing Harpocrates, the Greek god of silence. Ptolemaic Era, 4th-1st century BC, inventory number: #2767, National Archaeological Museum of Naples (MANN).

Photo credits: National Archæological Museum of Naples (MANN).

gibbus but also pectus carinatum, hence indicating a combination of highly incapacitating multiple muscolo-skeletal abnormalities affecting the individual(s) who served as a morphological inspiration for this artistic representation [35].

Conclusions

The antiquity of TB needs to be investigated further if an adequate understanding of its historical trajectory and evolutionary path is to be achieved. In the process, several sources of information should be used, not limiting the investigation only to skeletal remains or historical written sources. Artworks should also play a role in the process and, together with other typologies of information such as the palaeogenetic one, should actively contribute to a comprehensive reconstruction of the pathology's history. This will provide clinicians with a much better-informed background on TB and may catalyse new preventive and therapeutical strategies aimed at terminating this perilous infectious disease [49]. Even in current days we must always detect and highlight that infection prevention, contagion and control measures are crucial in public health services because there is a risk of transmission of the bacterium *Mycobacterium tuberculosis*; the World Health Organization (WHO) developed recommendations according to the methods defined in the WHO handbook for guideline development [50].

Moreover, we should always consider and reflect on one of the most important aspects in this long pathway: a real and successful vaccine. We still have to remember today

that only a really efficacious vaccine will enable us to eradicate TB [51].
Especially at a time of great societal scepticism about and misunderstanding of vaccinations and medical treatments, paradoxically in an era in which the abundance of information should produce, instead, the opposite effect [52].

Note

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Informed consent statement

Not applicable.

Data Availability Statement

Not applicable.

Conflict of interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' contributions

EV: conceptualisation, original draft-writing, supervision. MM, MV, VV, JMS, RG, FMG and VP: original draft-writing. FMG and VP: supervision.
All authors have read and approved the latest version of the paper for publication.

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