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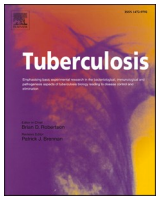

Review

Dynamics of tuberculosis infection in various populations during the 19th and 20th century: The impact of conservative and pharmaceutical treatments

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ABSTRACT

Humans and *Mycobacterium tuberculosis* have co-evolved together for thousands of years. Many individuals are infected with the bacterium, but few show signs and symptoms of tuberculosis (TB). Pharmacotherapy to treat those who develop disease is useful, but drug resistance and non-adherence significantly impact the efficacy of these treatments. Prior to the introduction of antibiotic therapies, public health strategies were used to reduce TB mortality. This work shows how these strategies were able to reduce TB mortality in 19th and 20th century populations, compared with antibiotic treatments.

Previously published mortality data from historical records for several populations (Switzerland, Germany, England and Wales, Scotland, USA, Japan, Brazil and South Africa) were used. Curvilinear regression was used to examine the reduction in mortality before and after the introduction of antibiotic treatments (1946).

A strong decline in TB mortality was already occurring in Switzerland, Germany, England and Wales, Scotland and the USA prior to the introduction of antibiotic treatment. This occurred following many public health interventions including improved sanitation, compulsory reporting of TB cases, diagnostic techniques and sanatoria treatments. Following the introduction of antibiotics, mortality rates declined further, however, this had a smaller effect than the previously employed strategies. In Japan, Brazil and South Africa, reductions in mortality rates were largely driven by antibiotic treatments that caused rapid decline of mortality, with a smaller contribution from public health strategies.

For the development of active disease, immune status is important. Individuals infected with the bacterium are more likely to develop signs and symptoms if their immune function is reduced. Effective strategies against TB can therefore include enhancing immune function of the population by improving nutrition, as well as reducing transmission by improving living conditions and public health. This has been effective in the past. Improving immunity may be an important strategy against drug resistant TB.

1. Introduction

There are numerous definitions of a disease [1–3]. In our understanding, a disease is a situation where the homeostasis of a body is compromised. It can be a result of a number of processes occurring within the body itself or of body's interactions with other organisms. Interactions of the body with other organisms can be symbiotic, commensal, or pathogenic. Pathogens alter workings of the body so that homeostasis is disturbed. Diseases caused by pathogens occur when the body cannot prevent entry of the pathogen, cannot control the pathogen through its immunological processes or has no tolerance for the pathogen [4]. The entry of pathogens is a function of their infectivity (ability to invade tissues of the organism), an individual's exposure to the pathogen (its presence in the immediate environment of an individual) and opportunities for the entry of a pathogen into an individual's body – personal hygiene, quality of food ingested, air breathed, physical contact with others, quality of medical procedures etc. Immunological control of a pathogen depends on how effectively an immune system can eliminate

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the pathogen that has entered the body, or, at least, control it to the level of tolerance. Tolerance depends on individual organism's ability to maintain homeostasis in the presence of a pathogen.

Discoveries of Louis Pasteur and Robert Koch propagated the germ theory of diseases, to the extent that presence of a pathogen in a body of a person commonly defines this person as suffering from a disease caused by this pathogen. The core of this theory is that a pathogen that has been found in individuals displaying signs and symptoms of a particular disease is its cause. The recent example is the shorthand definition of individuals with COVID-19 as those who test positive for the presence of SARS-CoV2 in their bodies. Many of those individuals are asymptomatic. The absence of symptoms means that homeostasis of their bodies has not been affected. Is the fact of infection equivalent to the fact of suffering from a disease? The germ theory of diseases, although underlying the practice of medicine and actually saving countless lives, is a result of too rigorous implementation of the rule of parsimony (Ockham's Razor). The pathogen is considered the one and the only cause of the disease.

An infectious disease is a result of complex interactions among the invading organism, the body and the environment where the interaction occurs. The body may clear out the invader, it may limit its spread and thus its impact on the body's homeostasis or it may succumb to the invasion and lose its homeostasis. Environment provides the body with more or less support for its homeostatic processes by altering temperatures, humidity, atmospheric pressures, availability of nutrients and the presence of toxic or healing substances and events. Therefore, manipulation of environmental conditions may combat an infectious disease even without antibiotic or anti-viral therapies.

Tuberculosis (TB) is a disease presenting the definitional dilemma. A large proportion of persons with TB (PWTB) microbiologically diagnosed as being infected with the pathogen do not develop signs and symptoms of TB disease [5,6]. The so-called minimal and subclinical TB may become self-cleared [7] in as many as some 73.1% of PWTB [8]. The reason for the ability of human organisms to clear TB infection without antibacterial treatment is the long co-evolution of the *Mycobacterium* and humans. Data extending back for nearly 10,000 years show that the prevalence of skeletal signs of TB, particularly Pott's disease, has declined through time (Fig. 1) [9,10]. Over time, the relationship between *Mycobacterium tuberculosis* and humans has moved towards commensalism, with very few individuals infected with the bacterium showing signs and symptoms of TB disease. Among those with "latent TB" only some 5–10% are at risk of developing an active disease while antibacterial treatments for latent TB take many months, have a risk of side-effects and efficacy of 60–90% [11]. Additionally, individuals infected with drug-resistant strains of TB are very difficult to treat while special pharmacotherapies are expensive, time consuming and not all that efficient [12,13]. Presence of drug resistant TB threatens resurgence of the disease even in populations with well-developed health systems while the reliance on germ theory demanding chemotherapies offers little hope.

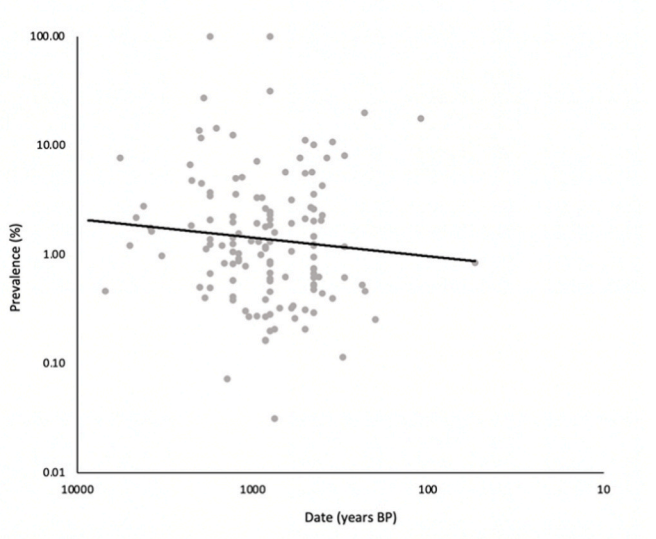

Fig. 1. Prevalence of skeletal signs of tuberculosis (e.g. Pott's disease) in archaeological samples. Both scales logarithmic. Data from Holloway et al., 2011 and Henneberg et al., 2021.

Pharmacological attempts at controlling tuberculosis started with the introduction of the primary Bacille Calmette–Guérin (BCG) vaccination in 1921. It is only partially protective against *Mycobacterium tuberculosis* infecting humans [14,15]. Until the 1940s, there were no known pharmaceuticals that could eliminate the *Mycobacterium tuberculosis* once it infected the human body. The antibiotic streptomycin was first isolated in 1943, but was not available for routine use until 1946 or later. Other pharmaceutical treatments such as para-aminosalicylic acid and isoniazid, appeared later, in the early 1950s.

During the 19th and early 20th centuries many countries, especially those with advanced medical sciences and public health systems, introduced a number of policies and procedures aimed at limiting TB burden. They consisted of improvements in living conditions of potential and actual PWTB and in interrupting chains of pathogen transmission. PWTB with clinical signs were treated by regimes of rest, high protein diet and limited exercise, often organised in special establishments called sanatoria. Sanatoria were preferably located in areas with clean air. Combined effects of general public health policies and sanatoria treatments lowered TB mortality many times over (about fivefold) during a century before 1945 in Switzerland, New York, England and some other European countries [16]. We aimed to assess efficiency of those undertakings on reducing the TB burden independent of pharmacotherapies. Therefore, this study investigated the extent that public health strategies were able to reduce mortality in 19th and 20th century populations and compare them with the impact of the introduction of pharmacological treatments.

2. Data and methods

This study used previously published data obtained from historical records which described mortality from TB in nine countries during the 19th and 20th centuries. These were divided into two groups based on their status at the time as "high-income" or "low-and-middle income" countries. High-income countries included Switzerland, Germany, England and Wales, Scotland and the United States of America. Low-and-middle income countries included Japan, Brazil and South Africa. Table 1 shows the details of data used in this study.

Curvilinear regression fitting was used to examine the reduction in mortality before and after the introduction of the first antibiotic treatment for tuberculosis. The curve fitted by the least squares method was that of the logistic regression that is characteristic for evolutionary processes such as co-adaptation of pathogen and host (e.g. Ref. [17]). In the Excel notation: Mortality = a/(1 + 10(t*c)) where a – the range of change, t – time, c – rate of change.

3. Results

In all high income countries TB mortality rate declined over time, prior to the introduction of pharmacotherapies around 1946 (Fig. 2). The regression line shows that the TB mortality rate would have continued to decrease after 1946, however, the introduction of pharmacotherapies increased the speed of this decline.

Fig. 3 shows TB mortality rates for both high-income and low-and-middle income countries. In the low-and-middle income countries, mortality rates were not declining before 1945, they declined primarily due to pharmacotherapies. The TB mortality rates in high-income and low-and-middle income countries reached similar levels by the 1980s.

Table 1
Details of the data sources used in this study.

High-income Countries	Year range	Reference details
Switzerland (whole country)	1867–2005	Holloway et al., 2014 [16]
Canton Zürich	1840–1933	Holloway et al., 2014 [16]
City of Zürich	1893–1933	Holloway et al., 2014 [16]
Bern	1855–1950	Zürcher et al., 2016 [29]
Germany	1892–1940	Zürcher et al., 2016 [29]
England and Wales	1838–2006	Blower et al., 1995 (1851–1938) [43] Wilson, 1990 (1838–1850 & 1939–1964) [44] WHO[a], 2012 (1979–2006) [45]
London (inner London)	1913–1964	Hermans, 2015 [25]
Scotland	1855–1964	McFarlane, 1990 [46]
United States of America (New York)	1804–2012	Drolet & Lowell, 1952 (1804–1950) [47] WHO[a], 2012 (1951–2012) [45]
Low-and-middle income Countries	**Year range**	**Reference details**
Japan	1886–2006	Johnston, 1995 (1886–1970) [48] WHO[a] (1971–2006) [45]
Brazil	1900–1990	Antunes & Waldman, 1999 [49]
South Africa (Cape Town)	1910–2012	Hermans, 2015 [25]

[a] World Health Organization.

However, the data for South Africa (Cape Town) showed a sharp increase around the year 2000, which was due to an increase in HIV.

4. Discussion

In this study, we compared TB mortality rates from multiple countries in the 19th and 20th centuries. In high-income countries, the TB mortality rate declined well before the introduction of pharmacotherapies. In low-and-middle income countries, the TB mortality rate declined primarily as a result of antibiotic use. In both groups TB mortality reached similar rates by late 20th century, indicating that both public health strategies and pharmacotherapies can be effective at reducing the burden of TB. Multiple strategies can reduce morbidity and mortality from TB by educating the population about the disease and ways of avoiding infection, reducing exposure to the bacteria through isolation of PWTB, improving hygiene and nutrition.

Strategies to improve the immune status of individuals include addressing poor nutrition and air quality. A recent study in India [18] reported that high levels of food insecurity often occurred in households with TB cases. Another recent study [19] reported that nutritional supplementation would be highly cost effective, could avert 81% of TB cases and 88% of deaths over 5 years for Indian people without access to adequate nutrition. The effects of air quality and pollution have also been studied in contemporary populations. One study [20] reported on a TB outbreak that occurred in a poorly ventilated university building in Taiwan. Improving ventiliation within the building reduced the incidence of TB in close contacts by 97%, and ended the TB outbreak. A meta-analysis [21] reported that both indoor air pollution and second-hand tobacco smoke increased the risk of contracting TB.

Many PWTB were able to recover from TB disease while being treated in sanatoria. Rucker & Kearny [22] studied the success rates of sanatorium treatment of at least four weeks for PWTB from 1905 to 1911. They reported that for PWTB with early stage, advanced and very advanced disease, 95%, 85% and 62% improved, respectively. Additionally, PWTB treated in sanatoria were more likely to return to work activities compared to those who were not treated at sanatoria (79% vs 39%). Another study [23] also used archive data from the Sanatorium *Carlos Vasconcelos Porto* (Portugal) to examine differences in length of stay and mortality from before (1931–1944) and after (1955–1961) the introduction of antibiotics. There were no differences in length of stay between the two time periods, however, mortality was higher in the first time period (1931–1944). This observation may reflect improvements in TB treatment using antibiotics, but importantly during the second period (1955–1961), Portugal was undergoing an epidemiological transition, characterised by improved nutrition and healthcare. Additionally, during this time there were a number of specific TB public health measures including BCG vaccination and routine micrographs screenings which would have also contributed to the reduction in TB mortality. The use of antibiotics may also have altered the manifestation of the disease, allowing PWTB to survive for a longer period of time. This has been shown in a study by Steyn et al. [24], where presence of skeletal lesions corresponding to TB increased across three time periods; before 1950, 1950–1985 and after 1985.

A reduction of immunity even with the availability of pharmacotherapies can result in a higher mortality rate. In Cape Town, South Africa, pharmacotherapy reduced mortality rates, however, prevalence

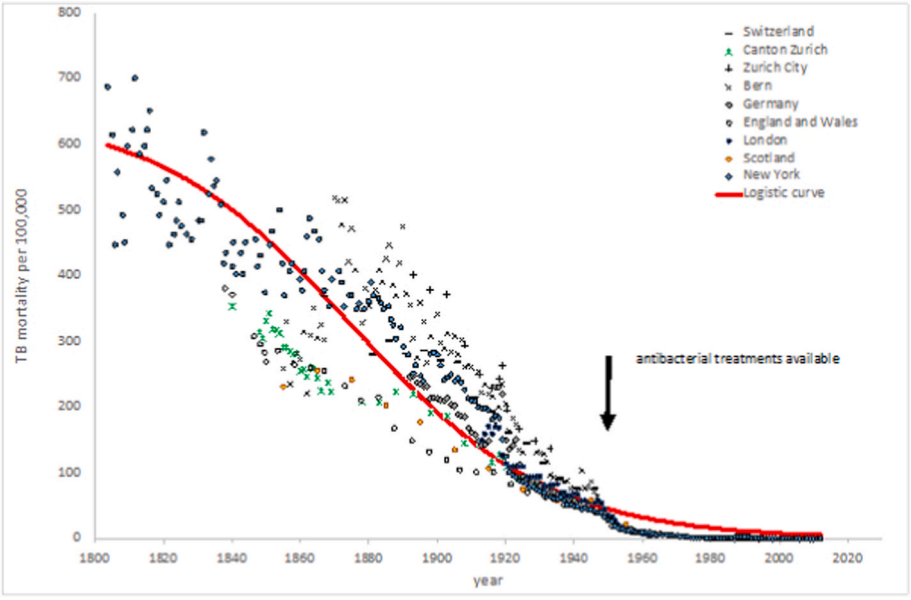

Fig. 2. Changes in the mortality of tuberculosis in populations with developed environmental methods of disease control. The curve is a logistic curve of the form: *mortality= 650/(1 + 10((Date-1875)*0.015))* fitted to the pre-1946 data with r = 0.87.

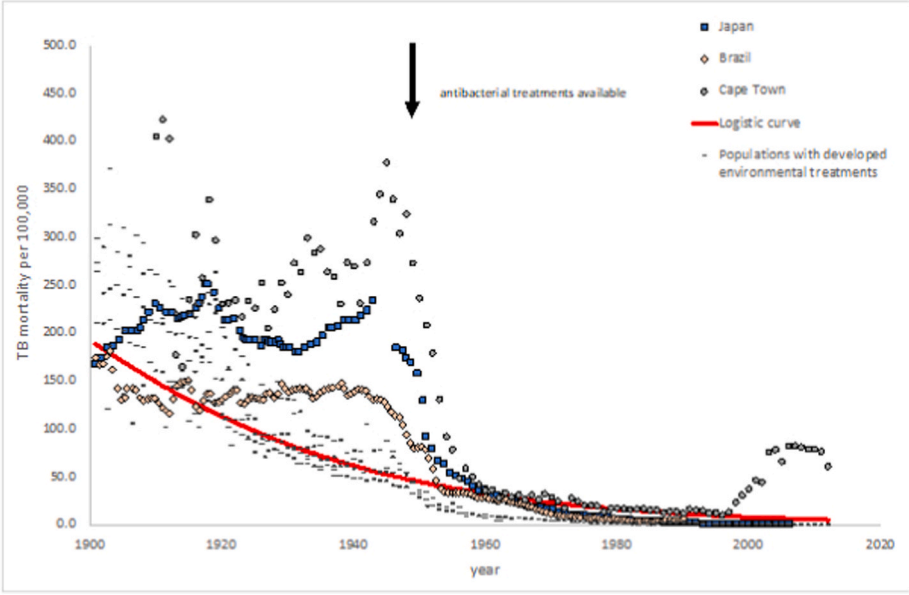

Fig. 3. Changes in tuberculosis mortality in populations without effective environmental methods of disease control pre-1946, compared to the logistic curve fitting changes in populations with developed environmental methods of disease control before introduction of chemical therapy for TB (see Fig. 2 extended beyond 1946).

of TB remained high [25]. This was primarily due to the HIV epidemic resulting in reduced immune function, increasing the likelihood of developing active disease, affecting treatment outcomes and increasing mortality [26]. The HIV epidemic in South Africa was a result of multiple factors, including overcrowding, migrant labour, poor health services and inequality [27]. Recent modelling has shown that 55% of adult TB cases and 69% of TB mortality during 1990–2019 in South Africa were due to HIV [26]. Poor TB control measures and drug resistance have also resulted in increased TB cases and mortality [27], however, antiretroviral therapy for HIV and increased TB screening has shown success in reducing TB incidence [26]. Although HIV is the most important risk factor for TB in South Africa, modelling of a scenario where HIV is excluded showed that a high TB burden remained [26], indicating that other factors are also important.

One example is the reduction of transmission of the bacterium. Historical studies have reported on the effects of two factors influencing transmission, occupation and accommodation, on TB mortality. A study from Tromsø, Norway during 1878–1920 [28] showed that individuals in the working classes had higher rates of TB mortality compared to the upper and middle classes. Zürcher et al. [29] studied specific components of living spaces in Bern (Switzerland) during 1856–1950, reporting that higher TB mortality rates were associated with a lower percentage of rooms without sunlight, fewer windows per apartment and a higher number of persons per room. These factors have been recognised in the World Health Organization's "End TB Strategy" [30].

A review by Bhargava et al. [31] explored the social determinants of TB in India and highlighted that the medical strategies implemented were not sufficient to reduce the burden of TB. Many PWTB did not complete therapy and the authors state that both biomedical and social interventions are needed to control and eliminate TB. The review also indicated that in addition to treating latent TB, "improving population health" is another important strategy to help reduce the burden of TB. It may not be feasible to treat all PWTB in sanatoria, however, a study comparing sanatorium and home treatment of TB [32], showed that home treatment of TB is possible. The positive outcomes for the home treatment group in the study were likely due to the strong support network provided to PWTB which included regular home visits, financial and nutritional support. This is important, as the authors reported that it was more difficult to convince PWTB to complete their treatment at the sanatorium than at home and therefore it may be more effective for the PWTB to remain at home.

Although it is difficult to estimate precisely costs of public health and conservative treatments aimed at reducing TB mortality, a simple consideration of the cost of a typical medical treatment of active TB, especially the drug resistant one, may be an indication of the possible savings resulting from non-pharmacological approaches. In 2015 the cost of treating one case of the multi drug resistant TB ranged from 83,365 US$ to 1218 US$ in high income and the lowest income countries respectively [33]. This cost was about five times greater than the cost of treating one drug susceptible PWTB that was still not negligible ranging from 14,659 US$ to 258 US$ in high and low income countries [33]. About half of the large cost is made up of the price of medication and medical diagnostics, most of the rest is the cost of hospitalisation. Compare these costs with the cost of treating one latent TB case that is some 400 US$; from 3 to 452 times less than treating one active case [34]. Public health and conservative measures have a potential to significantly reduce the number of active cases. Application of these measures may optimise allocation of health resources besides reducing suffering of PWTB in long, and not always effective, hospital treatments with expensive medications.

Another important consideration in the control of TB includes differences in the pathogen, *Mycobacterium tuberculosis*, which may have changed over time and its virulence at present may be different. For example, Bottai et al. [35] have reported that "modern" strains of *Mycobacterium tuberculosis*, which have an absence of the *Mycobacterium tuberculosis*-specific deletion 1 region (TbD1), show an increase in virulence compared to the "ancestral" strains which still retain the TbD1 region. Additionally, within the "modern" lineage of *Mycobacterium tuberculosis* known as the Beijing family, there are more recent sublineages, which are more likely to have increased virulence compared to the less recent sublineages [36]. This appears to be driven partially by reduced cytokine production (particularly IL-1β, IL-6, and IFN-γ) in response to infection by more recent lineages [37]. Additionally, drug resistant strains of *Mycobacterium tuberculosis* have been reported to have lower fitness, since some of the mutations that provide drug resistance change essential genes to become "sub-optimal" [38,39]. Much of the work exploring this effect has been done *in vitro*, however, there are several studies that have included human populations. Children (<5yr) from Cape Town who were exposed to drug-resistant TB were more likely to become infected, but less likely to develop active TB

disease than children exposed to drug-sensitive TB [40]. In Armenia [41], only 2% of the children (<15 yrs) who were exposed to drug-resistant TB had TB disease. Another study used stochastic mathematical modelling to estimate the fitness of multiple drug resistant TB in Lima (Peru), in comparison with drug sensitive TB [42], showing that the multiple drug resistant TB had much lower fitness.

One limitation of this study is that we relied on historical records for the data, which may not be accurate. However, we have included data for multiple different countries, and the trends are similar among all of them. The data also include years where TB notification was mandatory. Diagnostic methods and nomenclature for TB have changed over time, however, we did not study TB disease, but rather mortality, which would still be similar regardless of changes in diagnostic methods. The ICD codes for TB were introduced in 1900, and thus changes in nomenclature would only be affected prior to this time.

5. Conclusion

This study has shown that TB mortality was already declining rapidly in high-income countries prior to the introduction of pharmacotherapies. Thus, effective control and management of tuberculosis might be achieved using a combination of improved public health interventions, conservative therapy and less pharmacotherapy. This is especially important in areas where tuberculosis is re-emerging and where drug resistance is developing.

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Ethical approval

Not required.

Data statement

This study used previously published data which are available online.

CRediT authorship contribution statement

K.L. Holloway-Kew: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **M. Henneberg:** Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing.

Declarations of competing interest

None.

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Transparency declaration

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