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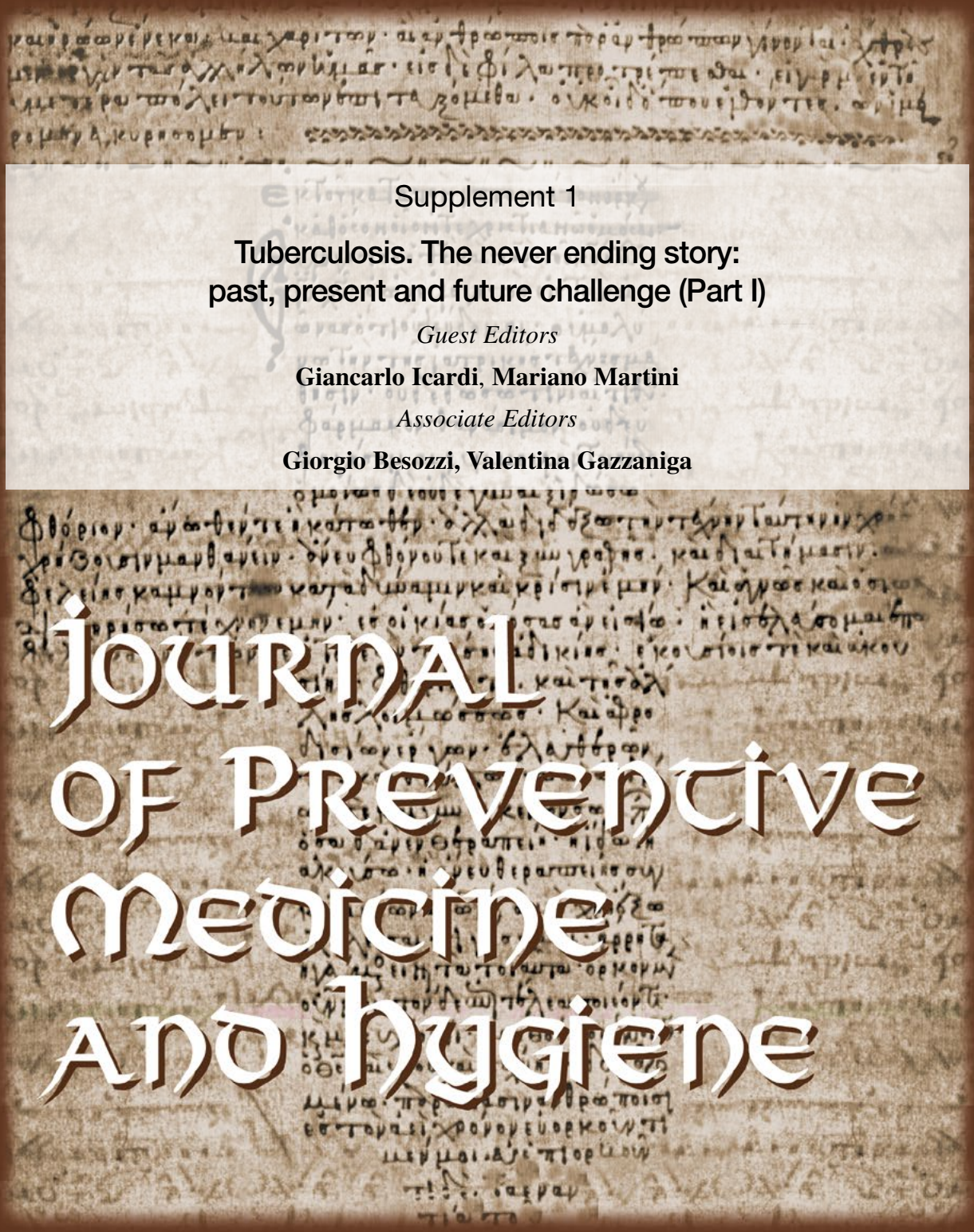

Supplement 1

Tuberculosis. The never ending story: past, present and future challenge (Part I)

Guest Editors

Giancarlo Icardi, Mariano Martini

Associate Editors

Giorgio Besozzi, Valentina Gazzaniga

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Tuberculosis. The never ending story: past, present and future challenge (Part I)

GUEST EDITORS

Giancarlo Icardi

Department of Health Sciences, University of Genoa, Italy

Mariano Martini

Department of Health Sciences, University of Genoa, Italy; Section Chief of "Liguria-StopTB Italia Onlus", Genoa, Italy

ASSOCIATE EDITORS

Giorgio Besozzi

Villa Marelli Insitute, Niguarda Ca' Granda Hospital, Milan, Italy; President of "StopTB-Italia Onlus", Milan, Italy

Valentina Gazzaniga

Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Italy

CONTENTS

EDITORIAL

The fight to end tuberculosis: a global challenge in strong partnership

M. MARTINI[1], I. BARBERIS[1], V. GAZZANIGA[2,3], G. ICARDI[1]
[1] Department of Health Sciences, University of Genoa, Italy; [2] Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Italy; [3] President of Italian Society of Human Sciences in Medicine (SISUMed), Rome, Italy

Keywords

Tuberculosis • Global challenge • Partnership

Since 1982, one century after the discovery of *Mycobacterium tuberculosis* as the causal agent of the disease by Robert Koch in Berlin, on March 24th each year the World Health Organization (WHO) celebrates the World TB day.

This event aims to raise people awareness about the burden of tuberculosis (TB) and the status of TB prevention and to spur social and political stakeholders to make further efforts and work together in strong partnerships to stop TB at all levels [1].

The global end TB strategy 2016-2035 and the WHO global TB programme develop policies, strategies and standards, assess national programme performances and facilitate partnerships and communication to advance universal access to TB prevention, care and control.

The global TB report 2019 showed that the world didn't reach 2019 goal in stop TB, and that multidrug resistant TB is still spread in many countries in the world.

TB is one of the top 10 causes of death worldwide, killing over 4.500 people every day [2]. In 2018, there were an estimated 10 million new TB cases worldwide.

There were an estimated 1.2 million TB deaths among HIV-negative people in 2018, and an additional 251.000 among HIV-positive people; 57% of all TB cases were in men in 2018.

Geographically, most TB cases in 2018 were in the WHO Regions of South-East Asia (44%), Africa (24%) and the Western Pacific (18%) [2].

Moreover, the social and economic impacts of tuberculosis worldwide are devastating, including poverty, stigma and discrimination.

On 26 september 2018, the first hig-level meeting of the United Nations General Assembly (UNHLM) on the fight against tuberculosis brought together Heads of State under the theme "United to end tuberculosis: an urgent global response to a global epidemic", with support of WHO and other international organizations.

The meeting resulted in an action-oriented political declaration, builds on previous commitments in the Moscow declaration to End TB, that will strenghten action and investments towards the end TB response [3].

The end TB strategy adopted by the WHO in 2014 aims to end the global TB epidemic and to remove catastrophic costs for TB-affected households by 2030, to reduce deaths about 90% and TB incidence of 80%.

The 2020 theme for stop TB day, "It's time!", highlights the timely need for action in scale up, research, funding, human rights and accountability [4].

Main goals are:

- improve access to prevention and treatment of tuberculosis;
- grant for research;
- stop discrimination of illness people.

In 2018, 484.000 people developed a drug-resistant tuberculosis; in these cases treatment success rate was low globally, with a mean of 56% [2].

Drug resistant TB remains a public health problem with gaps in detection and treatment: in 2016 490.000 people developed a multi-drug resistant TB worldwide, and other 110.000 people were affected by rifampicin-resistant TB and required second-line treatment [5].

From 2000 to 2016, however, about 53 million people were saved, also thanks to a great effort organized and carried out worldwide, that permitted to reduce the mortality rate by 42%.

Every year, during the World TB Day, WHO together with the Global Fund and Stop TB Partnership highlights to governments, communities, civil society organizations, health care providers and national / international partners the need to join forces under the slogan "*Find. Treat. All. #EndTB"* to guarantee assistance to millions of people who do not have access to quality care.

United Nations member states committed to fulfilling the following key targets by 2022: successfully treat 40 million people with TB, including 3.5 million children (under 15 years of age), successfully treat 1.5 million people with multidrug-resistant TB, including 115.000 children, provide TB preventive therapy for at least 30 million people, including 4 million children under the age of 5, 20 million other household contacts of people affected by TB, and 6 million people living with HIV [6].

Moreover, stakeholders will try to increase global investment in TB prevention, diagnosis, treatment and care to US$ 13 billion annually [4].

A strong support for research, innovation and development is needed by 2025, in order to reach an annual decline in the global TB incidence rate of 17% per year.

Principal targets are to discover a vaccine to lower the risk of infection, or new drug treatment to cut the risk of TB disease in the 1.7 billion people already latently infected [2]. Only by reinforcing a joint response, it is possible for the world to reach the commitments established by the End TB strategy, WHO and Stop TB Global Plan.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

GI and MM conceived the study, IB, MM, drafted the manuscript, GI, VG revised the manuscript, GI,VG,MM,IB performed a search of the literature, GI, VG,MM,IB revised critically the manuscript. All authors read and approved the last version of the manuscript.

References

[1] World Health Organization. Implementing the end TB strategy: the essentials. 2016.

[2] World Health Organization. Global Tuberculosis Report 2019.

[3] United Nations. Political declaration of the high-level meeting of the United Nations General Assembly on the fight against tuberculosis. 18th plenary meeting (10 October 2018).

[4] Stop TB partnership. The Global Plan to End TB 2018-2022 (Geneva. 2019)

[5] Alene KA, Clements ACA, McBryde ES et al. Sequelae of multidrug resistant tuberculosis: protocol for a systematic review and meta-analysis. BMJ Open 2018;8:e019593. https://doi.org/10.1136/bmjopen-2017-019593

[6] Canetti D, Riccardi N, Martini M, Villa S, Di Biagio A, Codecasa L, Castagna A, Barberis I, Gazzaniga V, Besozzi G. HIV and tuberculosis: The paradox of dual illnesses and the challenges of their fighting in the history. Tuberculosis 2020;122:101921. https://doi.org/10.1016/j.tube.2020.101921

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Correspondence: Ilaria Barberis, Department of Health Sciences (DISSAL), University of Genoa, largo R. Benzi, University of Genoa, Italy - Tel./Fax +39 010 35385.02 - E-mail: ilaria.barberis@hotmail.it

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The paleopathological evidence on the origins of human tuberculosis: a review

I. BUZIC[1,2], V. GIUFFRA[1]
[1] Division of Paleopathology, Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Italy; [2] Doctoral School of History, "1 Decembrie 1918" University of Alba Iulia, Romania

Keywords

Tuberculosis • Paleopathology • History • Neolithic

Summary

Tuberculosis (TB) has been one of the most important infectious diseases affecting mankind and still represents a plague on a global scale. In this narrative review the origins of tuberculosis are outlined, according to the evidence of paleopathology. In particular the first cases of human TB in ancient skeletal remains are presented, together with the most recent discoveries resulting from the paleomicrobiology of the tubercle bacillus, which provide innovative information on the history of TB. The paleopathological evidence of TB attests the presence of the disease starting from Neolithic times. Traditionally, it was thought that TB has a zoonotic origin, being acquired by humans from cattle during the Neolithic revolution. However, the biomolecular studies proposed a new evolutionary scenario demonstrating that human TB has a human origin. The researches show that the disease was present in the early human populations of Africa at least 70000 years ago and that it expanded following the migrations of Homo sapiens out of Africa, adapting to the different human groups. The demographic success of TB during the Neolithic period was due to the growth of density and size of the human host population, and not the zoonotic transfer from cattle, as previously hypothesized. These data demonstrate a long coevolution of the disease and its human host. Understanding the changes of TB through time thanks to the advances in the field of paleopathology can help to solve the present problems and understand the future evolution of TB.

Introduction

Tuberculosis (TB) is an infectious disease caused by bacteria of the *Mycobacterium tuberculosis* complex (MTBC), which includes *M. tuberculosis*, *M. bovis*, *M. canettii*, *M. africanum*, *M. pinnipedii*, *M. microti*, *M. caprae*, *M. mungi* and *M. orygis*. The first two strains are most frequently responsible for TB in humans [1]. Despite the efforts to reduce the burden of TB worldwide and the progress in care and prevention, it is still a major global cause of disease and death [2].

Starting from the industrial era, TB became particularly diffused, favoured by the increased population density and the poor living conditions. Thanks to the improvement of health status, alimentation and hygiene during the 20th century in developed countries, the disease began to decrease its incidence; the introduction of the BCG (Bacillus Calmette-Guérin) vaccine in 1921 and the use of chemotherapeutic drugs efficacious against the infection, such as streptomycin and isoniazid in 1943 and 1952 respectively, further decreased the incidence. However, despite being considered in the 80s of the 20th century as a conquered infection [3], TB still remains a plague on a global scale and is the top infectious killer globally by being present today in both developed and developing countries; it is estimated that a quarter of the world population (1.7 billion people) is infected with *M. tuberculosis*, 5-15% of which will develop the TB disease during their lifetime [4]. Statistics show that in 2016 TB was the underlying cause of 1.3 million deaths among HIV-negative people and furthermore was a contributing cause of 374,000 deaths among people with HIV [4]. Due to historical, social and geopolitical determinants, the regions with the highest rates of TB are Sub-Saharan Africa, South-East Asia and East Europe [5, 6]. The only available vaccine (BCG) is obtained from attenuated strains of *M. bovis*, but is not extensively effective; no other vaccines had been produced in the meantime [7]. Finally, the appearance of TB-strains that are resistant to antibiotics, in particular multi-drug and even totally drug-resistant strains, represents a real challenge in the struggle against the disease [8].

Paleopathology, the interdisciplinary field of research that focuses on the development of ancient diseases and their impact and distribution in past populations, together with ancient DNA analyses, can provide important contributions to our knowledge of this major pathogen through the study of how TB evolved through time.

Early paleopathological and biomolecular evidences for TB in ancient skeletal remains

The paleopathological evidence for TB is based on primary sources, such as the analysis of skeletal remains and mummified soft tissues. The diagnosis of TB can be considered reliable on the basis of specific skeletal fea-

tures; these include characteristic changes to the spine, consisting in lytic lesions affecting the vertebral bodies with resulting ankylosis, body collapse and kyphosis (Pott's disease); extraspinal unifocal lytic lesions with absence of new bone formation; single joint ankylosis, specially localised in the hip, knee and wrist; and new bone formation on the internal surface of the ribs [9, 10].
In the last decades, the development of the new field of palaeomicrobiology permitted in several cases further corroboration of the diagnosis through the detection of TB ancient DNA (aDNA); the latest technologies of high-throughput sequencing and metagenomics allowed us to obtain a complete picture of the pathogen in ancient human remains [10].
However, modern clinical data demonstrated that only 1-5% of patients with pulmonary TB develops skeletal lesions [11]; therefore, it should be considered that the detection of TB in paleopathology is largely underestimated [12].
The earliest human skeletal remains with paleopathological changes of TB date back to 8000-10000 years ago, corresponding to the Neolithic revolution, and come from the Near East. Before this period, a single controversial diagnosis of Leptomeningitis tuberculosa, in relation to non specific endocranial changes of the frontal bone of a fossil, has been attributed to a Homo erectus from Turkey dating from the middle Pleistocene (490000–510000 years BP) [13]; this could represent the most ancient example of TB in a human fossil, but this interpretation was questioned by other authors [14].
The most ancient animal case, which was confirmed by morphological and biomolecular analyses, is represented by a ca. 17000-year-old late Pleistocene long-horned extinct bison (*Bison antiquus*) enclosed in sediments from the Natural Trap Cave from Wyoming (United States). This fossil documents that TB was present in North America at least 20000 years BP, long before the domestication [15].
The most notable of the first TB traces in human skeletal remains are concentrated in the Near East and Europe.
As for the Near East, five cases from two sites located in the Fertile Crescent belonging to the Pre-Pottery Neolithic B (PPNB) period provide evidence for the presence of human TB. Four individuals with lesions consistent with TB were brought to light from Dja'de el Mughara, situated on the Euphrates river in Northern Syria and dating to the pre-domestication phase (8800-8300 BC). An individual from Tell Aswad from Southern Syria, belonging to the early domestication phase (8200-7600 BC), displayed features typical of Hypertrophic Pulmonary Osteoarthropathy (HPOA), that is caused by chronic pulmonary diseases such as TB. In addition to the morphological features, multidisciplinary analyses such as morphological examination, MicroCT scan, lipid biomarkers and molecular analyses were also performed with positive diagnostic results on selected specimens from these archaeological sites, confirming the presence of human TB in the pre-domestication and early domestication phases of the Neolithic [16].
Another three cases evoking skeletal human TB were reported in the Neolithic village of Ain Ghazal in Jordan, dated to 7250 BC and also located in the cradle of agriculture; these cases, whose diagnosis was only morphological as no molecular analyses were performed, suggest the presence of human TB before and/or during the introduction of agriculture and animal domestication [17].
From the same geographical area, in the ancient Levantine village of Atlit-Yam now submerged (Israel), there is a report of two cases of TB on the basis of scarce paleopathological changes involving an adult individual and an adolescent, presumed to be mother and son, as they were buried together. The site is dated from 6200-5500 BC, corresponding to the last phase of the Pre-Pottery Neolithic period, when the transition to agriculture and animal domestication was fully accomplished. Lipid biomarkers and molecular analyses confirmed the presence of TB in the two individuals [18, 19]. Lipid biomarkers examination consists in the extraction, derivatisation and high-performance liquid chromatography (HPLC) analysis of mycobacterial cell wall mycolic acids [18, 19].
As for Europe, among the earliest cases of TB in skeletal evidence there are cases of tuberculous spondylitis (Pott's disease) in two individuals from the Early Neolithic belonging to the Linear Pottery culture (5400–4800 BC) from three sites (Halberstadt, Derenburg and Karsdorf) from Saxony-Anhalt in central Germany. Molecular analyses detected the presence of pathogens belonging to the MTC in skeletal remains from all the three sites taken in examination [20].
Other cases with morphological evidences of TB were unearthed from several Neolithic sites dated back to 5000 BC, including Heidelberg, Germany [22], Zlota, Poland [20], Hódmezővásárhely-Gorzsa, Hungary (confirmed by lipid biomarker analyses and ancient DNA analysis) [23], Alsónyék-Bátaszék, Hungary (confirmed by molecular analyses) [24, 25], attesting to the diffusion of the infection in different areas of Europe.
A particular concentration of TB was observed in the Finalese area in Liguria (Northwestern Italy) belonging to the Middle Neolithic period (4000-3500 BC), where three cases were discovered in three important caves that are in close proximity to each other: Arene Candide [26], Arma dell'Aquila [27], and Pollera [28] caves. The diagnosis was based on typical skeletal lesions; biomolecular analyses using polymerase chain reaction (PCR) were performed on the Pollera case, but did not confirm the presence of the MTBC ancient DNA.
As for Africa, 13 cases from the Upper Egyptian site of Nagada (4500-3000 BC) suggest that the earliest evidence of TB in Egypt could be dated back to 4500 BC [3]. The first Egyptian cases of TB confirmed by molecular analyses date back to the predynastic period (3500-2650 BC) and suggest that infection with *M. tuberculosis* was relatively recurrent in this period [29-33].
Outside the European landscape, a possible Neolithic case of TB was observed in an adult individual from Shanghai, China, associated with the Songze culture

(3900-3200 BC), at the beginning of the wet rice agriculture [34].
From the late Neolithic onward the paleopathological evidence of TB becomes more frequent.
Finally, in the prehistoric New World, macroscopic and molecular analyses suggest that the earliest evidence of human TB in skeletal remains and mummified soft tissues is attested in prehistoric South America in Peru by 700 AD, while in North America it is attested by 900 AD in the Southwest, where large permanent agricultural settlements are concentrated [35, 36].

The biomolecular advancements on the origins of TB

As highlighted in the previous section, the paleopathological evidence of human TB attests the presence of the disease starting from Neolithic times; no sure skeletal cases are dated before this period [37]. However, absence of evidence does not mean evidence of absence. Did TB affect humans in more ancient times? When did TB become a human pathogen? Did human TB originate from animal TB? The new next-generation sequencing technologies tried to answer these questions [38, 39].
According to the traditional theory, formulated before the advent of the biomolecular studies, humans acquired TB from cattle during the Neolithic revolution due to the zoonotic transfer from the newly domesticated animals [40-42]. As several infectious diseases have a zoonotic origin, it was thought that TB was also transferred to humans from animals; in particular, *M. bovis* would have infected humans, then adapting and evolving into *M. tuberculosis*. This theory was supported by the fact that the oldest human remains presenting paleopathological changes of TB were found in the Neolithic period, while the findings in animal remains have suggested a more ancestral existence of TB in cattle [15].
The evolutionary history of TB was dramatically changed by recent biomolecular studies that challenged the old theory, proposing an African origin for the MTBC long pre-dating the Neolithic [43, 44].
Phylogenetic studies have clarified that within MTB seven lineages, associated with different areas of the world, can be identified [46]: the Lineage 1 (East Africa, Philippines), the modern Euroasian lineages 2 (which includes the Beijing family), 3, 4 that are in close phylogenetic relationship, African lineages 5 and 6 with *M. africanum* phylogeographically distributed in West Africa, and finally, the newly described lineage 7 [47] collected from patients with TB from Ethiopia. Animal species, including *M. bovis*, *M. microti* and *M. pinnipedii*, represent monophyletic lineages, and *M. canettii* has an ancestral position in the MTBC. The chronological positions of the lineages are determined by the presence or absence of an MTB-specific deletion (TbD1); the presence makes them ancestral ($TbD1^+$), the absence makes them modern ($TbD1^-$) [48, 49]. On this basis, lineages 1, 5, and 6, the animal lineages and *M. canettii* represent the ancestral MTBC group, whereas lineages 2, 3 and 4 are defined as modern from an evolutionary point of view, because they are thought to have diffused more recently; lineage 7 resulted as intermediate between ancient and modern MTB lineages. These findings suggest that the animal lineages and *M. africanum* have diverged from the progenitor of the ancestral MTB lineages and that the tubercle bacillus was originally a human pathogen [49], confirming previous studies which suggested that animal adapted MTBC strains diverged from the major MTBC strains [48, 43-45]. Therefore, the new evolutionary scenario proposed that the human TB did not derive from *M. bovis*, but that, on the contrary, MTB has a human origin.
Furthermore, a recent work seems to confirm this theory with phylogenetic studies based on whole-genome data of MTCB. This study is based on the sequencing of a global collection of 259 MTBC modern clinical strains representative of the diversity of the global MTBC for reconstructing the phylogenetic relationship between them [50]. The overall results of three independent phylogenetic analyses for the determination of the most recent common ancestor of TB using a Bayesian approach suggested East and West Africa as the most probable geographic origin of MTBC. The results of this research would show the common origin in Africa of Homo sapiens and MTBC and that TB was present in the early human populations of Africa at least 70000 years ago, then infecting humans for thousands of years [50].
The study of Comas and colleagues [50] also would demonstrate that MTBC evolved in parallel with its human host. The disease expanded in correspondence with the migrations of *Homo sapiens* out of Africa. It has been hypothesized that the two *M. africanum* lineages, *M. canettii* and lineage 7 might have remained in Africa, whereas the others could have reached Europe and Asia, following the colonization of these areas, and finally becoming endemic worldwide. This work would suggest that the different lineages have adapted to different human groups. On the basis of this study a correlation between the divergence of the Lineage 1 of MTBC about 67000 years ago and the first human wave of migration out of Africa that was directed around the Indian Ocean was observed. Another split of MTBC that would have occurred 46000 years ago corresponds instead to the second great migration of *Homo sapiens* from Africa, which was directed to Eurasia [50]. With the rise of Neolithic Demographic Transition 10000 ± 2000 years ago, TB raised its rate of diffusion together with the increase in the human population density following the advance of agriculture and animal domestication. These results would suggest that the demographic success of TB during the Neolithic period was due to the growth of density and size of the human host population, and not to the zoonotic transfer from cattle, as previously hypothesized [50].
Also, of interest is the study of the dispersal of the modern Lineage 2, which includes the "Bejing" strains that have an increased virulence and transmission potential, a shorter latency phase than ancient lineages, furthermore being particularly successful in geographical dif-

fusion, and are associated with antibiotic resistance [8]. The study has evidenced that the dating of Lineage 2 in Asia coincides with the arrival of the anatomically modern humans in East Asia about 42000-32000 years ago confirmed by the archaeological evidence. This lineage presents a first expansion about 11000-6000 years ago corresponding to the development of agriculture in China about 8000 years ago and, later, a further expansion about 5000-3000 years ago, when agriculture was introduced in the regions near China [50]. These results seem to show that tuberculosis had various moments of expansion other than the increase during the Neolithic in the Mediterranean region.

Furthermore, these data could explain why TB presents an adaptation to both low and high host population densities. In fact, the high level of asymptomatic latency that allows reactivation of TB and the slow progression to disease are an indication of adaptation to low host population density that is consistent with the ancestral emergence of MTBC in Africa before the Neolithic revolution. On the other hand, the modality of aerosol transmission and the high virulence in order to guarantee the maximum level of transmission are typical of a high-density population environment. This double adaptation would have ensured to the bacterium a large diffusion in both high- and low-density areas, resulting in the fact that one-third of the human population is infected but remains asymptomatic, representing an extraordinary reservoir for the bacterium [8].

The study of the origins and patterns of change in the evolution of MTBC would demonstrate that migration and demography of the anatomically modern humans affected the evolution and spread of TB. The major recent molecular studies on the evaluation of its demography and timing of propagation seem to show a long coevolution of the disease and its human host, demonstrating that TB represents an exemplary model of adaptation to humans [8]. They also suggest that the palaeomicrobiology of TB can be fully understood through an integrated approach in correlation-association with the human host genome sequencing, considering the relation between the evolution of TB genomes and their human hosts.

Conclusions

TB was traditionally thought to be a zoonosis, but the advancements of biomolecular analyses performed by various teams of researchers seem to suggest that *M. tuberculosis* did not evolve from *M. bovis*, but has a complex evolutionary history that reflects human evolution. In order to understand the evolution of the bacterium and the current epidemiology of TB it is necessary to investigate the history of the disease in parallel with that of humans. In fact, MTBC has evolved with humans during thousands of years, influencing reciprocally their evolution. Understanding the changes of TB through time thanks to the advent of the next-generation sequencing technology can aid the problems of the present and future evolution of TB in relationship with its human host.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

IB performed the bibliographic research and wrote the text; VG conceived the design, partially wrote the text and revised the manuscript. All authors critically revised the manuscript. All authors have read and approved the latest version of the manuscript.

References

[1] Brites D, Gagneux S. Co-evolution of Mycobacterium tuberculosis and Homo sapiens. Immunol Rev 2015; 264:6-24. https://doi.org/ 10.1111/imr.12264

[2] Donoghue ED. Palaeomicrobiology of tuberculosis. In: Raoult D, Drancourt M, eds. Paleomicrobiology – Past Human Infections. Berlin/Heidelberg: Springer-Verlag 2008, p. 75-97.

[3] Roberts CA, Buikstra J. The bioarchaeology of tuberculosis: a global view on a reemerging disease. Gainesville, Florida: University Press of Florida 2003.

[4] Glaziou P, Floyd K, Raviglione MC. Global epidemiology of tuberculosis. Semin Respir Crit Care Med 2018;39:271-85. https://doi.org/10.1055/s-0038-1651492

[5] Riccardi N, Alagna R, Motta I, Ferrarese M, Castellotti P, Nicolini LA, Diaw MM, Ndiaye M, Cirillo D, Codecasa L, Besozzi G. Towards ending TB: civil community engagement in a rural area of Senegal: results, challenges and future proposal. Infect Dis (Lond) 2019;51:392-4. https://doi.org/10.1080/23744235.2019.1572920

[6] Lönnroth K, Jaramillo E, Williams BG, Dye C, Raviglione M. Drivers of tuberculosis epidemics: the role of risk factors and social determinants. Soc Sci Med 2009;68:2240-6. https://doi.org/10.1016/j.socscimed.2009.03.041

[7] Kaufmann SH. Tuberculosis vaccines: time to think about the next generation. Semin Immunol 2013;25172-81. https://doi.org/10.1016/j.smim.2013.04.006

[8] Bañuls A-L, Sanou A, Anh NT, Godreuil S. Mycobacterium tuberculosis: ecology and evolution of a human bacterium. J Med Microbiol 2015;64:1261-9. https://doi.org/10.1099/jmm.0.000171

[9] Waldron T. Palaeopathology. Cambridge: Cambridge University Press 2009.

[10] Donoghue ED. Paleomicrobiology of human tuberculosis. Microbiol Spectr 2016;4. https://doi.org/10.1128/microbiolspec.PoH-0003-2014

[11] Resnick D, Niwayama G. Diagnosis of bone and joint disorders. 4th ed. Philadelphia: Saunders 2002.

[12] Aufderheide A, Rodriguez-Martin C. The Cambridge encyclopaedia of human palaeopathology. Cambridge: Cambridge University Press 1998.

[13] Kappelman J, Alcicek MC, Kazanci N, Schultz M, Ozkul M, Sen S. First Homo erectus from Turkey and implications for migrations into temperate Eurasia. Am J Phys Anthropol 2008; 135:110-6. https://doi.org/10.1002/ajpa.20739

[14] Roberts CA, Pfister LA, Mays S. Letter to the editor: was tuberculosis present in Homo erectus in Turkey? Am J Phys Anthropol 2009;139:442-4. https://doi.org/10.1002/ajpa.21056

[15] Rothschild BM, Martin LD, Lev G, Bercovier H, Bar-Gal GK, Greenblatt C, Donoghue H, Spigelman M, Brittain D. Mycobacterium tuberculosis complex DNA from an extinct bison dated 17,000 years before the present. Clin Infect Dis 2001;33:305-11. https://doi.org/10.1086/321886

[16] Baker O, Lee OY, Wu HT, Besra GS, Minnikin DE, Llewellyn G, Williams CM, Maixner F, O'Sullivan N, Zink A, Chamel B, Khawam R, Coqueugniot E, Helmer D, Le Mort F, Perrin P, Gourichon L, Dutailly B, Palfi G, Coqueugniot H, Dutour O. Human tuberculosis predates domestication in ancient Syria. Tuberculosis (Edinb) 2015;95:S4-S12. https://doi.org/10.1016/j.tube.2015.02.001

[17] Al-Sarie I, Al-Shiyab A, El-Najjar M. Cases of tuberculosis at 'Ain Ghazal, Jordan. Paléorient 1996;22:123-8.

[18] Hershkovitz I, Donoghue HD, Minnikin DE, Besra GS, Lee OY-C, Gernaey AM, Galili E, Greenblatt CL, Lemma E, Bar-Gal GK, Spigelman M. Detection and molecular characterization of 9000-year-old Mycobacterium tuberculosis from a Neolithic settlement in the eastern Mediterranean. PLoS One 2008;3:e3426. https://doi.org/10.1371/journal.pone.0003426

[19] Hershkovitz I, Donoghue HD, Minnikin DE, May H, Lee OY, Feldman M, Galili E, Spigelman M, Rothschild BM, Bar-Gal GK. 2015. Tuberculosis origin: the Neolithic scenario. Tuberculosis (Edinb) 2015;95(Suppl 1):S122-6. https://doi.org/10.1016/j.tube.2015.02.021

[20] Nicklisch N, Maixner F, Ganslmeier R, Friederich S, Dresely V, Meller H, Zink A, Alt KW. Rib lesions in skeletons from early neolithic sites in Central Germany: On the trail of tuberculosis at the onset of agriculture. Am J Phys Anthropol 2012;149:391-404. https://doi.org/10.1002/ajpa.22137

[21] Bartels P. Tuberkulose in der jüngeren Steinzei. ArchAnthropol 1907;6:243-55.

[22] Gladykowska-Rzeczycka JJ. Tuberculosis in the past and present in Poland. In: Pálfi G, Dutour O, Deák J, Hutás I, eds. Tuberculosis: past and present. Budapest/Szeged: Golden Book Publishers and Tuberculosis Foundation 1999, pp. 561-573.

[23] Masson M, Molnár E, Dononghue HD, Minnikin DE, Lee OY, Besra GS, Bull ID, Pálfi G. 7000-year-old tuberculosis cases from Hungary: osteological and biomolecular evidence. Tuberculosis (Edinb) 2015;95(Suppl 1):S13-7. https://doi.org/10.1016/j.tube.2015.02.007

[24] Köhler K, Pálfi G, Molnar E, Zalai-Gaál I, Osztás A, Bánffy E, Kirinó K, Kiss KK, Mende BG. A late neolithic case of Pott's disease from Hungary. Int J Osteoarchaeol 2012;24:697-703. https://doi.org/10.1002/oa.2254

[25] Pósa A, Maixner F, Mende BG, Köhler K, Osztás A, Sola C, Dutour O, Masson M, Molnár E, Pálfi G, Zink A. Tuberculosis in Late Neolithic-Early Copper Age human skeletal remains from Hungary. Tuberculosis (Edinb) 2015; 95(Suppl.1): S18-22. https://doi.org/10.1016/j.tube.2015.02.011.

[26] Canci A, Minozzi S, Borgognini Tarli S. New evidence of tuberculousspondylitis from Neolithic Liguria (Italy). Int J Osteoarchaeol 1996;6:497-501.

[27] Formicola V, Milanesi Q, Scarsini C. Evidence of spinal tuberculosis at thebeginning of the fourth millennium BC from Arene Candide cave (Liguria,Italy). Am J Phys Anthropol 1987;72:1-6. https://doi.org/10.1002/ajpa.1330720102

[28] Sparacello VS, Roberts CA, Kerudin A, Müller R. A 6500-year-old Middle Neolithic child from Pollera Cave (Liguria,Italy) with probable multifocal osteoarticular tuberculosis. Int J Paleopath 2017;17:67-74. https://doi.org/10.1016/j.ijpp.2017.01.004

[29] Crubézy E, Ludes B, Poveda JD, Clayton J, Crouau-Roy B, Montagnon D. Identification of Mycobacterium DNA in an Egyptian Pott's disease of 5,400 years old. C R Acad Sci III 1998;321:941-51.

[30] Zink A, Haas CJ, Reischl U, Szeimies U, Nerlich AG. Molecular analysis of skeletal tuberculosis in an ancient Egyptian population. J Med Microbiol 2001;50:355-66. https://doi.org/10.1099/0022-1317-50-4-355

[31] Nerlich AG, Rohrbach H, Zink A. Paleopathology of ancient Egyptian mummies and skeletons. Investigations on the occurrence and frequency of specific diseases during various time periods in the necropolis of Thebes-West. Pathologe 2002;23:379-85.

[32] Zink AR, Sola C, Reischl U, Grabner W, Rastogi N, Wolf H, Nerlich AG. Characterization of Mycobacterium tuberculosis complex DNAs from Egyptian mummies by spoligotyping. J Clin Microbiol 2003;41:359-67. https://doi.org/10.1128/JCM.41.1.359-367.2003

[33] Lalremruata A, Ball M, Bianucci R, Welte B, Nerlich AG, Kun JF, Pusch CM. Molecular identification of falciparum malaria and human tuberculosis co-infections in mummies from the Fayum depression (Lower Egypt). PLoS One 2013;8:e60307. https://doi.org/10.1371/journal.pone.0060307

[34] Okazaki K, Takamuku H, Yonemoto S, Itahashi Y, Lakuhari T, Yoneda M, Chen J. A paleopathological approach to early human adaptation for wet-rice agriculture: the first case of Neolithic spinal tuberculosis at the Yangtze River delta of China. Int J Paleopathol 2019;24:236-44. https://doi.org/10.1016/j.ijpp.2019.01.002

[35] Roberts CA, Buikstra JE. The history of tuberculosis from earliest times to the development of drugs. In: Davies PDO, Gordon SB, Davies G, eds. Clinical Tuberculosis. London: CRC Press 2014.

[36] Bos KI, Harkins KM, Herbig A, Coscolla M, Weber N, Comas I, Forrest SA, Bryant JM, Harris SR, Schuenemann VJ, Campbell TJ, Majander K, Wilbur AK, Guichon RA, Wolfe Steadman DL, Cook DC, Niemann S, Behr MA, Zumarraga M, Bastida R, Huson D, Nieselt K, Young D, Parkhill J, Buikstra JE, Gagneux S, Stone AC, Krause J. Pre-Columbian mycobacterial genomes reveal seals as a source of New World human tuberculosis. Nature 2014;514:494-7. https://doi.org/10.1038/nature13591

[37] Holloway KL, Henneberg RJ, de Barros Lopez M, Henneberg. Evolution of human tuberculosis: a systematic review and meta-analysis of paleopathological evidence. Homo 2011;2011:402-58. https://doi.org/10.1016/j.jchb.2011.10.001

[38] Rivera-Perez JI, Santiago-Rodriguez TM, Toranzos GA. Paleomicrobiology: a snapshot of ancient microbes and approaches to forensic microbiology. Microbiol Spectr 2016;4(4). https://doi.org/10.1128/microbiolspec.EMF-0006-2015

[39] Barbier M, Wirth T. The evolutionary history, demography, and spread of the Mycobacterium tuberculosis complex. 2016. Microbiol Spectr 4. https://doi.org/10.1128/microbiolspec.TBTB2-0008-2016

[40] Steinbock RT. Paleopathological Diagnosis and Interpretation: Bone Diseases in Ancient Human Populations. Springfield, Illinois: Charles C. Thomas 1976.

[41] Manchester K. Tuberculosis and leprosy in antiquity: an interpretation. Med Hist 1984;28:22-30.

[42] Clark GA, Kelley MA, Granje JM, Hill CM. The evolution of mycobacterial disease in human populations. Curr Anthropol 1987;28:45-62.

[43] Gutierrez MC, Brisse S, Brosch R, Fabre M, Omaïs B, Marmiesse M, Supply P, Vincent V. Ancient origin and gene mosaicism of the progenitor of Mycobacterium tuberculosis. PLoS Pathog 2005;1:e5. https://doi.org/10.1371/journal.ppat.0010005

[44] 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. Origin, spread and demography of the Mycobacterium tuberculosis complex. PLoS Pathog 2008;4:e1000160. https://doi.org/10.1371/journal.ppat.1000160

[45] Hershberg R, Lipatov M, Small PM, Sheffer H, Niemann S, Ho-

molka S, Roach JC, Kremer K, Petrov DA, Feldman MW, Gagneux S. High functional diversity in Mycobacterium tuberculosis driven by genetic drift and human demography. PloS Biol 2008;6:e311. https://doi.org/10.1371/journal.pbio.0060311

[46] Gagneux S, Small PM. Global phylogeography of Mycobacterium tuberculosis and implications for tuberculosis product development. Lancet Infect Dis 2007;7:328-37. https://doi.org/10.1016/S1473-3099(07)70108-1

[47] Firdessa R, Berg S, Hailu E, Schelling E, Gumi B, Erenso G, Gadisa E, Kiros T, Habtamu M, Hussein J, Zinsstag J, Robertson BD, Ameni G, Lohan AJ, Loftus B, Comas I, Gagneux S, Tschopp R, Yamuah L, Hewinson G, Gordon SV, Young DB, Aseffa A. Mycobacterial lineages causing pulmonary and extrapulmonary tuberculosis, Ethiopia. Emerg Infect Dis 2013;19:460-3. https://doi.org/10.3201/eid1903.120256

[48] Brosch R, Gordon SV, Marmiesse M, Brodin P, Buchrieser C, Eiglmeier K, Garnier T, Gutierrez C, Hewinson G, Kremer K, Parsons LM, Pym AS, Samper S, van Soolingen D, Cole ST. A new evolutionary scenario for the Mycobacterium tuberculosis complex. Proc Natl Acad Sci U S A 2002;99:3684-9. https://doi.org/10.1073/pnas.052548299

[49] Gagneux S. Host-pathogen coevolution in human tuberculosis. Philos Trans R Soc Lond B Biol Sci 2012;367:850-9. https://doi.org/10.1098/rstb.2011.0316

[50] Comas I, Coscolla M, Luo T, Borrell S, Holt KE, Kato- Maeda M, Parkhill J, Malla B, Berg S, Thwaites G, Yeboah-Manu D, Bothamley G, Mei J, Wei L, Bentley S, Harris SR, Niemann S, Diel R, Aseffa A, Gao Q, Young D, Gagneux S. Out-of-Africa migration and Neolithic coexpansion of Mycobacterium tuberculosis with modern humans. Nat Genet 2013;45:1176-82. https://doi.org/10.1038/ng.2744

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Correspondence: Ileana Buzic, MA, Doctoral School of History, "1 Decembrie 1918" University of Alba Iulia, 5 G. Bethlen St., 510009 Alba Iulia, Romania. Tel. +40 258806130 - Fax +40 258812630 - E-mail: ileana.buzic@uab.ro

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The evolution of a neglected disease: tuberculosis discoveries in the centuries

N. RICCARDI[1,2], D. CANETTI[1,3], M. MARTINI[2,4], M.M. DIAW[5], A. DI BIAGIO[2,6], L. CODECASA[2,7], I. BARBERIS[2,4], N.L. BRAGAZZI[4], G. BESOZZI[2]

[1] Clinic of Infectious Diseases, IRCCS San Raffaele Scientific Institute, Milan, Italy; [2] StopTB Italia Onlus, Milan, Italy; [3] Vita-Salute San Raffaele University, Milan, Italy; [4] University of Genoa, Department of Health Sciences, Genoa, Italy; [5] Région Médicale de Thies, Thies, Senegal; [6] Clinic of Infectious Diseases, IRCCS AOU San Martino-IST, Genoa, Italy; [7] Regional TB Reference Centre and Laboratory, Villa Marelli Institute/ASST Niguarda Ca' Granda, Milan, Italy

Keywords

History • Infectious disease • *Mycobacterium tuberculosis* • Phthisis

Summary

Tuberculosis (TB) and humans have coexisted for more than 40,000 years. The word "tuberculosis" derives from "tubercle", the histological lesion which appears in the organs, described by Pott in the late Eighteenth century and found, by molecular biology, in human skeletons dating back to 5000 BC. Early description of TB can be found in the writings of ancient India and China and in the Bible.

In ancient Greece tuberculosis was not considered contagious, but Aristotle recognized the contagious nature of the pig's and ox's scrofula. The suspicion that phthisis is a contagious disease and that isolation can reduce the risk of transmission was expressed for the first time by the Arabian Avicenna, in his work "The canon of medicine". In 1699, the Health Council of the Republic of Lucca founded the "sanatorium" concept as place of care and isolation. In 1865 Villemain inoculated tubercular material from a human lymph node into a rabbit, obtaining for the first time the typical tubercular lesions. Some years later, on March 24, 1882, Robert Koch announced to the Berlin Society of Physiology the discovery of Mycobacterium tuberculosis. In the same period Virchow improved awareness of risk factors and correct behaviours among the general population.

In 1952 Waksman won the Nobel Prize for the discovery of the first active drug against TB: streptomycin. Nevertheless, drug resistance appeared rapidly some years later and it is still a great challenge in TB fight nowadays.

Tuberculosis (TB) and humans have coexisted for more than 40,000 years, since *Mycobacterium prototuberculosis*, supposed ancestor of the *Mycobacterium tuberculosis complex* (MTBC), reached the Fertile Crescent. Then, evolving and differentiating into various lineages, it followed the main human migration routes to the present day [1] (Fig. 1).

The word "tuberculosis" derives from "tubercle", the histological lesion which appears in the organs affected by the infection, first described by Sylvius in 1650.

The disease was christened "tuberculosis" by J. Schoenlein in 1839 and later it was observed in the bone by Pott in the late eighteenth century [2]. Tuberculous lesions attributable to Pott's disease were found, by molecular biology, in human skeletons dating back to 5000 BC, as well as in Egyptian mummies of 4000 BC [3].

Oddly enough, despite the high incidence demonstrated by paleo-infectious studies, TB has never been reported in Egyptian papyruses, unlike urinary schistosomiasis and in the same way of smallpox [2, 4]. A description of TB can be found in the writings of ancient India and China, respectively dated around 3300 and 2300 years ago [5, 6].

A clear description of the clinical presentation of TB, "schachepheth" in ancient Hebrew, is found in the books Deuteronomy and Leviticus of the Bible [10]

In ancient Greece, the "phthisis" was a well-known disease described in written testimonies of Herodotus (5th century BC) and in the Hippocratic "Corpus" (III century BC), both characterized by representing with great precision the clinical outset of the disease.

Furthermore, writings were rediscovered that meticulously describe tubercular lesions, the destruction of the lung tissue and the subsequent chronic process accountable for the progressive consumption of patients affected [7].

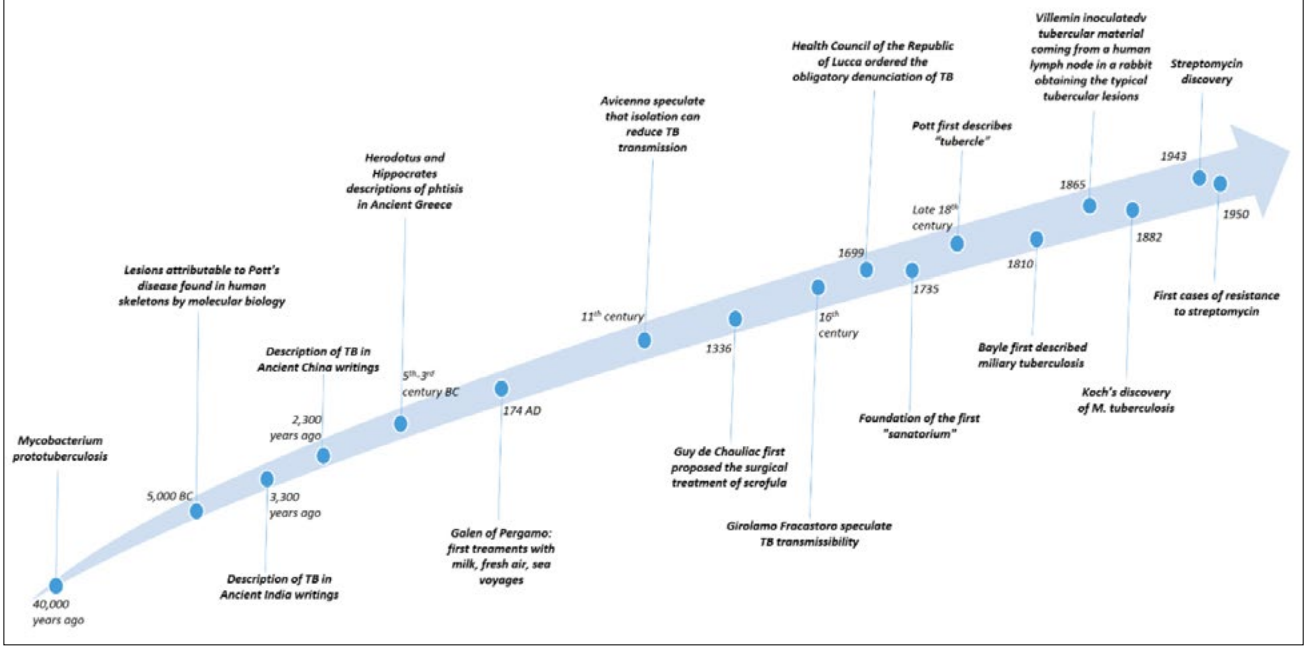
Although at that time the disease was not yet considered contagious, in a passage from his writings Isocrates (4th century BC) wrote about some doubt creeping into the minds of scientists, while Aristotle still recognized only the contagious nature of the pig's and ox's scrofula.

In Roman times, TB is mentioned by Celso, Areteo of Cappadocia and Celio Aureliano. In the complete works of Galen of Pergamum, personal physician of the Roman emperor Marcus Aurelius since 174 AD, a first attempt to treat TB based on milk, fresh air and sea voyages is reported [8].

The Authors of the classical age did not come to understand that even the extrapulmonary manifestations of the disease, such as scrofula, Pott's disease, and tubercular lupus, were to be ascribed to a single etiological agent.

In the following centuries, the Byzantine physicians Alessandro di Tralles, Ezio di Amida and Paolo di Egi-

Fig. 1. Timeline of the main events that characterized tuberculosis' history since its first appearance until the discovery of streptomycin.



na, also described the pulmonary and glandular forms of TB in their treatises. In the Arab world, Avicenna, in his "The canon of medicine", spoke about TB as an "ulcerative, excavating, and summary" disease, and expressed the suspicion that phthisis is a contagious disease. Avicenna was the first to suppose that diabetes was a risk factor for the development of TB and to suggest that the isolation of patients with overt pathology could reduce the risk of transmission [9].

In medieval times, 1336, the French surgeon Guy de Chauliac first proposed the surgical treatment of scrofula by the "myrtle leaf" incision [11].

TB etiology was not known and also therapy was not so clear. In the Middle Ages, it was widely believed that the kings of England and France could cure scrofula simply by touching those affected. To have a clear definition of TB as a contagious disease, we have to wait until the 16th century, when Girolamo Fracastoro, father of the "doctrine of contagion", hypothesized its transmissibility.

The spread of this news created panic among people who began to treat persons with scrofula in the same way as lepers [12]. In 1699, the Health Council of the Republic of Lucca ordered the obligatory denunciation of "persons of any sex and condition affected by etisia" and, in 1735, ordered the isolation and treatment of the consumptives, but forbade their hospitalization in common hospitals, laying the foundation of the "sanatorium" concept as place of care and isolation [13].

In 1671, Franciscus de La Boe recognized the same nature for pulmonary tubercles and scrofula, and he attributed the condition of "tisi" to the suppuration of tubercles in the lung parenchyma, with the formation of caves.

In 1761, Leopold Auenbrugger refined the semiotics of the chest with his treatise on percussion "Inventum novum", facilitating the diagnosis of pulmonary TB [14].

Between the eighteenth and nineteenth centuries in England, due to the increasing incidence of the pathology during the industrial revolution, a great scientific fervour led authors like Willis, Morton, Marten to spread the knowledge of TB [15].

At that time it also became known as the great white plague and the white death, called "white" because of the extreme anaemic pallor of those affected. This term could be also due to its association with youth, innocence and even holiness. Consumptive patients were more frequently affected by TB in case of malnutrition, unsanitary environment and living conditions, that were common risk factors.

In 1810, Bayle was the first to distinguish several anatomopathological entities, describing the presence of tubercles in organs other than the lung and recognizing their possible dissemination to the whole organism, defining it as "miliary tuberculosis".

Louis, supported by 167 autopsies, showed that the tubercles were a specific reaction, where inflammation had only an accessory role [16]. However, Virchow denied the specific nature of the tubercle and, due to his scientific authority and credibility, he delayed the acceptance of a unitary conception of tuberculosis according to what Laennec affirmed.

There was no lack of those who believed in the hereditary character of the disease, such as Linnaeus, who however also argued that pulmonary phthisis was caused "by a real invisible germ of contagion".

A further step forward in thoracic semeiotics was made by Laennec with the invention of auscultation mediated

with the stethoscope, further refining the semiology of the thorax. On December 5, 1865, Villemin informed the French Academy that TB is the effect of a specific causal agent, which he called "virus"; he supported his assertion by the inoculation into a rabbit of tubercular material coming from a human lymph node, obtaining, after some weeks, the typical tubercular lesions in the rabbit [17].

On March 24, 1882, Robert Koch announced to the Berlin Society of Physiology the discovery of *Mycobacterium tuberculosis* and described it with the following words: "Thin, whose length is half-a-quarter of the diameter of a red blood cell, very similar to the lepers' bacillus, but sharper". Once again, Virchow advanced some perplexity on the discovery as the sole explanation for the disease, correctly proposing a larger panel of factors such as poverty, malnourishment, scarce hygiene etc as relevant factors for the development of the disease.

Two German doctors, the bacteriologist Franz Ziehl and the pathologist Friedrich Neelsen first introduced Ziehl-Neelsen stain, demonstrating the typical appearance of acid-fast bacilli.

In the following years, Koch's discovery of the causal agent of TB opened the chance both for the Pasteurian prevention based on the attenuation of the germ and for the search for therapy through the serum of sick people [16], while Virchow's opinions generated also large public health campaigns to improve awareness of risk factors and correct behaviours among the general population.

In 1908, the French scientists Albert Calmette and Camille Guerin grew Koch's bacillus in several mediums to decrease their virulence and increase the capacity to produce immunity.

The BCG vaccine was first used in humans in 1921 when it was given to a child in Paris by Dr Weil-Hale. The baby's mother and grandmother, who had tuberculosis, died just after the baby was born. The baby was given 6 mg. of BCG orally, and he grew in a good health status.

The first active drug against TB to be discovered was streptomycin in 1943, thanks to Waksman who won the Nobel Prize for Physiology and Medicine in 1952 [18]. Unfortunately, since the first streptomycin trial carried out in London in 1950, it became evident that the emergence of drug-resistance appeared rapidly and constituted a contraindication to antibiotic monotherapy [19-21].

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

NR and MM conceived the study, NR, DC, MM, GB drafted the manuscript, NR, DC, ADB revised the manuscript, NR, DC, MM, IB performed a search of the literature, LC, MMD, NR, GB, IB, NLB and ADB revised critically the manuscript. All authors read and approved the last version of the manuscript.

References

[1] 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. Origin, spread and demography of the Mycobacterium tuberculosis complex. PLoS Pathog 2008;4:e1000160. https://doi.org/10.1371/journal.ppat.1000160

[2] A.J.E. Cave, Arnott Demonstrator. The evidence for the incidence of tuberculosis in ancient Egypt. British Journal of Tuberculosis 1939;33:142-52. https://doi.org/10.1016/S0366-0850(39)80016-3

[3] Nerlich AG, Haas CJ, Zink A, Szeimies U, Hagedorn HG. Molecular evidence for tuberculosis in an ancient Egyptian mummy. Lancet 1997;350(9088):1404. https://doi.org/10.1016/S0140-6736(05)65185-9

[4] Di Bella S, Riccardi N, Giacobbe DR, Luzzati R. History of schistosomiasis (bilharziasis) in humans: from Egyptian medical papyri to molecular biology on mummies. Pathog Glob Health 2018;112:268-73. https://doi.org/10.1080/20477724.2018.1495357

[5] Morse D. Tuberculosis. In: Brothwell D, Sandison AT, eds. Diseases in antiquity. A survey of the diseases, injuries and surgery of early populations. Springfield, IL: Charles C. Thomas 1967.

[6] Brown, Lawrason and Brown, Martha Lewis Harris, Mrs.(ed.) The story of clinical pulmonary tuberculosis. Baltimore, Md: The Williams & Wilkins Company 1941.

[7] Daniel VS, Daniel TM. Old Testament biblical references to tuberculosis. Clin Infect Dis 1999;29:1557-8. https://doi.org/10.1086/313562

[8] Meachen GN. A short history of tuberculosis. John Bale Medical Publications Ltd 1936.

[9] Galien C, Gottlob Kühn K. Claudii Galeni opera omnia. Medicorum Graecorum Opera Quae Extant. Lipsiae: Libraria Car. Cnoblochii 1821.

[10] Sharma OA. Avicenna's description of tuberculosis. Bull Indian Inst Hist Med Hyderabad 1981;1-4:83-6.

[11] Barberis I, Bragazzi NL, Galluzzo L, Martini M. The history of tuberculosis: from the first historical records to the isolation of Koch's bacillus. J Prev Med Hyg 2017;58:E9-E12.

[12] Hieronymi Fracastorii. De sympathia et antipathia rerum liber vnus De contagione et contagiosis morbis et curatione libri III. 1546.

[13] Martini M, Gazzaniga V, Behzadifar M, Bragazzi NL, Barberis I. The history of tuberculosis: the social role of sanatoria for the treatment of tuberculosis in Italy between the end of the 19th century and the middle of the 20th. J Prev Med Hyg 2018;59:E323-E327. https://doi.org/10.15167/2421-4248/jpmh2018.59.4.1103

[14] Smith JJ. The Inventum Novum of Joseph Leopold Auenbrugger. Bull N Y Acad Med 1962;38:691-701.

[15] Keers RY. Richard Morton (1637-98) and his Phthisiologia. Thorax 1982;37:26-31. https://doi.org/10.1136/thx.37.1.26

[16] Astruc P. Louis (Pierre-Charles-Alexandre). Les Biographies médicales. Les Maîtres du passé. Paris: J-B Ballière et fils: 245-60. 1933.

[17] Daniel TM. The history of tuberculosis. Respir Med 2006;100:1862-70. https://doi.org/10.1016/j.rmed.2006.08.006

[18] Selman A. Waksman, Winner of the 1952 Nobel Prize for Physiology or Medicine H. Boyd Woodruff. Appl Environ Mibrob Dec 2013;80:2-8. https://doi.org/10.1128/AEM.01143-13

[19] Pyle MM. Relative numbers of resistant tubercle bacilli in sputa of patients before and during treatment with streptomycin. Proc Staff Meet Mayo Clin 1947;22:465-73.

[20] Mitchison DA. Development of streptomycin resistant strains of tubercle bacilli in pulmonary tuberculosis; results of simultaneous sensitivity tests in liquid and on solid media. Thorax 1950;5:144-61. https://doi.org/10.1136/thx.5.2.14

[21] Canetti D, Riccardi N, Martini M, Villa S, Di Biagio A, Codecasa L, Castagna A, Barberis I, Gazzaniga V, Besozzi G. HIV and tuberculosis: The paradox of dual illnesses and the challenges of their fighting in the history. Tuberculosis 2020;122:101921. https://doi.org/10.1016/j.tube.2020.101921

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Correspondence: Ilaria Barberis, Department of Health Sciences (DISSAL), University of Genoa, largo R. Benzi, University of Genoa, Italy - Tel./Fax +39 010 35385.02 - E-mail: ilaria.barberis@hotmail.it

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Tuberculosis in Iran: a historical overview from al-Tabari, Rhazes, Avicenna and Jorjani to Abolhassan Ziyā-Zarifi. Old and new pioneers in the fight against tuberculosis: challenges, pitfalls and hopes

Ma. BEHZADIFAR[1], M. MARTINI[2,3], Me. BEHZADIFAR[4], N.L. BRAGAZZI[2,3,5,6]

[1] Health Management and Economics Research Center, Iran University of Medical Sciences, Tehran, Iran; [2] Department of Health Sciences (DISSAL), University of Genoa, Italy; [3] UNESCO Chair, Health Anthropology Biosphere and Healing Systems, University of Genoa, Italy; [4] Social Determinants of Health Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran; [5] Postgraduate School of Public Health, Department of Health Sciences (DISSAL), University of Genoa, Italy; [6] Department of Mathematics and Statistics, Laboratory for Industrial and Applied Mathematics (LIAM), York University, Toronto, Canada

Keywords

Tuberculosis • History of tuberculosis • Iran • History of medicine

Summary

Tuberculosis is a serious respiratory infectious disease, caused by Mycobacterium tuberculosis bacteria. It has always represented a permanent, serious public health challenge over the course of human history, because of its severe epidemiological, clinical and societal implications. The present review aims at over-viewing the contributions of the Iranian medicine to the control, management and treatment of tuberculosis, from the glorious past of the eighth-ninth centuries to the present, from Ali Abu al-Hasan Ahmad ibn Sahl-e Rabban al-Tabari to Rhazes, Avicenna, Jorjani and Abolhassan Ziyā-Zarifi. However, despite the efforts, tuberculosis and, in particular, multidrug-resistant tuberculosis still represent a great public health concern in Iran. On the other hand, this country can capitalize on its millennial, incredibly rich story of major achievements in the battle against tuberculosis to develop and implement ad hoc public health programs for the control of the disorder, including targeted and specialized interventions.

Introduction

Tuberculosis is a serious respiratory infectious disease, caused by *Mycobacterium tuberculosis* bacteria. It has always represented a permanent, serious public health challenge over the course of human history, because of its severe epidemiological, clinical and societal implications [1]. The present review aims at overviewing the contributions of the Iranian medicine to the control, management and treatment of tuberculosis, from the glorious past of the eighth-ninth centuries to the present.

Tuberculosis and the glorious past of the Iranian medicine

The Iranian medicine has a rich, glorious millennial past. Ali Abu al-Hasan Ahmad ibn Sahl-e Rabban al-Tabari (born in Merv, in the Khorasan, or in Toranja, in the province of Tabaristan in 783, 808, 810 or 838, and dead in Baghdad or in Samarra, in 855, 858, 864 or 870, according to other scholars) was an erudite Persian Muslim scholar, son of a prominent Syrian Christian physician, Sahl ibn Bishr, who was also a mathematician and astronomer. al-Tabari was erroneously considered Jewish by some researchers because of the nickname of the father ("*Rabban*", meaning "master"), whereas other scholars thought he was Christian ("*al-Katib al-Nasrani*", meaning "the Christian writer"). According to other sources, he was Zoroastrian. He was the secretary of the Persian prince Mazyar from the Qarinvand dynasty ("*katib Mazyar*"), who, in 839, guided the rebellion against the Abbasids. This rebellion failed and al-Tabari converted to Islam, serving as personal physician of various Caliphs, including al-Mu'tasim (833-842) and al-Mutawakkil (847-861). He cultivated different medical disciplines and specialties, including pediatrics and pediatric infectious disorders [2-4]. He was the author of one of the first most comprehensive treatises of medical knowledge and pharmacopeia, known as "*Firdous al-Hikmah*" ("The Paradise of Wisdom") or "*al-Kunnash*". A chapter of his seven-volume encyclopedia was entirely devoted to the description of tuberculosis, the etiopathogenesis of which, according to the author, should be attributed to the adoption of unhealthy lifestyle behaviors, characterized by excessive sexual desire and grief. Socio-economic status, such as poverty, could as well be a facilitating condition for an increased risk of development and/or transmission of tuberculosis. Once being infected, the pathogen could erode heart's veins creating cavities. Moreover, al-Tabari described in detail tuberculosis cases affecting the skin (*lupus vulgaris*) as well as involving the lymph nodes (*Khanazir* or scrofula) [4].

Abu Bakr Mohammad Ibn Zakariya Al-Razi, known as "Rhazes" (born in Rey, formerly known as Arsacia, Iran,

in 854/865 and dead in Rey in 925/930 or 932 according to other scholars), compiled a prominent collection of medical case-reports and case-series, termed "*Kitab Al-Hawi Fi Al-Tibb*". In this treatise, the author reported a case of a patient who had bloody sputum (*nafeth-o-damm*), speculating that the most probable cause was pulmonary tuberculosis, in that it rarely occurred in other pulmonary diseases (such as pleuritis or pneumonia). Furthermore, Rhazes was one of the first to describe in detail tuberculosis of the joints [5, 6].

In the "Canon of Medicine" (*al-Qānūn fi al-Ṭibb*), Avicenna, known also as Ibn Sina, Abu Ali Sina or Pur Sina (born in Afshona, Uzbekistan, in 980 and dead in Hamadan, Iran, in 1037), dedicated two chapters to the description of tuberculosis, the fourth and the fifth of his medical encyclopedia addressing, respectively, the etiopathogenesis, the differential diagnosis and the pharmacological treatment and management of this communicable disorder. Avicenna maintained that pulmonary tuberculosis (*sil*) should be differentiated from other respiratory diseases, including pleuritis (*zaat al-janb*), and asthma (*rabv*), because all these disorders may clinically result, for different etiopathogenetic reasons, in cough and shortness of breath. However, tuberculosis is uniquely characterized by symptoms such as chronic fever that is more severe and relevant at night, sweating, sputum that may be bloody (hemoptysis) or contain plaster-like material (lithoptysis), dyspnea, and severe weakness, among others. Avicenna added that in advanced cases of pulmonary tuberculosis, a potential danger would be represented by the insurgence of lung hemorrhage, which may ultimately lead to death. Furthermore, from an etiopathogenetic standpoint, Avicenna believed that tuberculosis has three stages including i) pre-inflammatory, ii) ulcerative, and, finally, iii) cavernous stage. According to the author, some aggravating factors are seasonality (in particular, autumn), and eating garlic. Moreover, Avicenna listed 21 potentially beneficial herbs, including plantain (*Plantago ovata*), grey oak (*Quercus baloot*), almond (*Prunus amygdalus*), dried sponge, oligochaeta (*Volutarella divaricata*), and opium (*Papaver somniferum*).

In another famous Persian medical text, "*Zakhireh-ye Kharazmshahi*" (Treasure of Kharazm Shah), Ismail Jorjani (born in Urganj, Uzbekistan, in 1040 and dead in Chorasmia, Northeastern Iran, in 1136) claimed that tuberculosis was a contagious illness characterized by a rather prolonged and marked fever.

Modernity and the fight against tuberculosis in Iran

During the last decade of the Qajar dynastic period (1789-1925) [5], in 1921, the "Pasteur Institute of Iran" was established for the proper and effective control of tuberculosis. It represented "the most significant medical establishment partly endowed by *waqf*" (in Persian language, a Muslim religious/charitable foundation created by a trust fund) [5]. The first physician who visited tuberculosis patients in his private clinic facility was Dr. Siavash Shaghaghi, a physician trained in Switzerland and an authentic Iranian pioneer in the management and treatment of tuberculosis [6, 7].

Another prominent physician in the battle against tuberculosis was Dr. Masih Daneshvari (born in 1899 and dead in 1976), a pulmonologist that studied in various European countries, especially in France, and who, after a long period of training, returned to Iran in October 1934 and founded the first Iranian tuberculosis sanitarium, known as "Shah Abad Tuberculosis Patients' Hospital". This major healthcare facility, entirely devoted to the treatment of tuberculosis patients, was finally settled in 1937 due to his efforts. However, due to a shortage of healthcare staff, Daneshvari decided in 1939 to write a letter to the Prime Minister, in which he explained the urgent need to strengthen and considerably expand an ambitious tuberculosis control and mitigation program at the Shah Abad Tuberculosis Patients' Hospital. The Prime Minister was convinced by this letter and ordered the responsible authorities of the Ministries of Interior and of Health to provide support to him [6, 7].

Several medical doctors and directors of the Pasteur Institute of Iran have continued these efforts, achieving fundamental results in terms of vaccination coverage against tuberculosis as well as diagnosis and treatment of the disorder. Among these prominent and outstanding professional figures, Dr. Abolhassan Ziyā-Zarifi (born on 20 August 1926 and dead on 4 October 2010) undoubtedly represents the most famous one. He pursued his degree at the School of Pharmacy of Tehran University and he started his professional career in 1952 at the Health Ministry, to later join the academy. His research and clinical interests were mostly represented by communicable disorders, and, in particular, respiratory infectious diseases, including tuberculosis and legionnaires' disease or legionellosis. In 1956, he worked at the First tuberculosis diagnostic laboratory supervised by Dr. Mehdi Zolriassatian, and, later, he decided to go to England in order to strengthen his expertise in the field of the clinics of infectious diseases and microbiology. Once returned to Iran, he managed to settle the "National Reference tuberculosis Laboratory" in 1963. In the same year, Dr. Zia-Zari became a member of the "International Union against Tuberculosis and Lung Diseases" (IUTLD), of which later he was appointed Director. In 1968, Dr. Zia-Zari went abroad to continue his training at the Pasteur Institute of Paris and in 1971 he completed his studies on medical laboratory management at the University of Maryland as well as the Centers for Disease Control and Prevention (CDC) in the USA that had been recently founded in 1942. Between 1975 and 1979, Dr. Zia-Zari was appointed as the Director General of the Laboratories of the Ministry of Health and during these years with the support of the "World Health Organization" (WHO) he was able to establish more than 400 medical laboratories, including facilities in remote, rural, generally underserved regions of Iran, significantly expanding laboratory coverage.

Due to his strenuous efforts and major achievement, he was nominated as a consultant to the WHO in the Middle East, Asia and Africa. Furthermore, he wrote several pa-

pers and books on tuberculosis, including "Bacteriology of Tuberculosis" (1973), "A Short History of Robert Koch" (1984) and "History of Tuberculosis" (1984) [6, 7].

Tuberculosis in Iran: the current situation and future prospects

In Iran, tuberculosis still represents a public health concern, with an incidence rate on the rise, because of different factors, including immigration [8], poor economic-financial conditions, co-morbidities (such as diabetes and HIV/AIDS), high-risk behaviors and unhealthy lifestyles, like drug abuse and smoking [9].

Also the incidence of multidrug-resistant (MDR) tuberculosis is increasing [10, 11]. According to Jimma and coworkers [12], the overall pooled prevalence rate of MDR tuberculosis in Iran and neighboring countries (including Iraq, Turkey and Pakistan) was 16% (with a 95% confidence interval or CI of 11-20%). Having received a previous tuberculosis treatment, being aged less than 45 years and being males were significantly associated with an increased pooled risk of developing MDR tuberculosis with an odds-ratio, OR, of 2.01 [95% CI 1.65-2.36%].

Despite the efforts, tuberculosis and, in particular, MDR tuberculosis still represent a great public health concern in Iran. On the other hand, this country can capitalize on its millennial, incredibly rich story of major achievements in the battle against tuberculosis to develop and implement *ad hoc* public health programs for the control of the disorder, including targeted and specialized interventions.

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Authors' contributions

MaB and NLB conceived the study, MaB and NLB drafted the manuscript, MM and MeB revised the manuscript. NLB performed a search of the literature. All authors critically revised the manuscript. All authors have read and approved the latest version of the manuscript.

References

[1] Barberis I, Bragazzi NL, Galluzzo L, Martini M. The history of tuberculosis: from the first historical records to the isolation of Koch's bacillus. J Prev Med Hyg 2017;58:E9-E12.

[2] Hamarneh S. Contributions of 'Ali al-Tabari to ninth-century Arabic culture. Folia Orient 1970;12:91-101.

[3] Ghaffari F, Naseri M, Asghari M, Naseri V. Abul- Hasan al-Tabari: a review of his views and works. Arch Iran Med 2014;17:299-301.

[4] Khan MS. Ali ibn Rabban at-tabari, a ninth century Arab physician, on the āyurveda. Indian J Hist Sci 1990;25:20-33.

[5] Ebrahimnejad H. Medicine in Iran, profession, practice and politics, 1800-1925. New York, USA: Palgrave Macmillan 2014.

[6] Fallah F, Abdolghafoorian H. The History of tuberculosis and Bacillus Calmette–Guérin vaccine in Iran, Arch Pediatr Infect Dis 2015; 3:e59840.

[7] Azizi MH, Bahadori M. A brief history of tuberculosis in Iran during the 19th and 20th centuries. Arch Iran Med 2011;14:215-9.

[8] Pourhossein B, Irani AD, Mostafavi E. Major infectious diseases affecting the Afghan immigrant population of Iran: a systematic review and meta-analysis. Epidemiol Health 2015;37:e2015002.

[9] Fadaee M, Rashedi J, Arabi S, Poor BM, Kafil HS, Pourostadi M, Kazemi A, Asgharzadeh M. Stopping of the downtrend of Tuberculosis in Iran, a systematic review of associated risk factors. Infect Disord Drug Targets 2018. https://doi.org/10.2174/1871526519666181228162837

[10] Nasiri MJ, Dabiri H, Darban-Sarokhalil D, Rezadehbashi M, Zamani S. Prevalence of drug-resistant tuberculosis in Iran: systematic review and meta-analysis. Am J Infect Control 2014;42:1212-8.

[11] Javad Nasiri M, Chirani AS, Amin M, Halabian R, Imani Fooladi AA. Isoniazid-resistant tuberculosis in Iran: a systematic review. Tuberculosis (Edinb) 2016;98:104-9.

[12] Jimma W, Ghazisaeedi M, Shahmoradi L, Abdurahman AA, Kalhori SRN, Nasehi M, Yazdi S, Safdari R. Prevalence of and risk factors for multidrug-resistant tuberculosis in Iran and its neighboring countries: systematic review and meta-analysis. Rev Soc Bras Med Trop 2017;50:287-295. https://doi.org/10.1590/0037-8682-0002-2017

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Correspondence: Nicola Luigi Bragazzi, Department of Mathematics and Statistics, Laboratory for Industrial and Applied Mathematics (LIAM), York University, Toronto, Canada - E-mail: bragazzi@yorku.ca

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Tuberculosis: an ancient disease that remains a medical, social, economical and ethical issue

M. MARTINI[1,2,3], N. RICCARDI[3,4], A. GIACOMELLI[5,6], V. GAZZANIGA[7,8], G. BESOZZI[3,9]
[1] Department of Health Sciences, University of Genoa, Italy; [2] UNESCO Chair "Anthropology of Health - Biosphere and Healing System", University of Genoa, Italy; [3] StopTB Italia Onlus, Milan, Italy; [4] Department of Infectious - Tropical Diseases and Microbiology, IRCCS Sacro Cuore Don Calabria Hospital, Negrar, Verona, Italy; [5] III Infectious Disease Unit, ASST-FBF-Sacco, Milan, Italy; [6] Department of Biomedical and Clinical Sciences, L. Sacco, University of Milan, Italy; [7] Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Rome, Italy; [8] President of Italian Society of Human Sciences in Medicine (SISUMed), Rome Italy; [9] Villa Marelli Insitute, Niguarda Ca' Granda Hospital, Milan, Italy

Keywords

Tuberculosis • Disease of poverty • History • Ethics

At the end of the eighteenth century, following the middle-class and industrial revolution, important urbanization phenomena arose – dragging with them social and sanitary issues [1].

In this evolving historical scenario, tuberculosis spread quickly by taking advantage from rapid urbanization leading to metropolitan overcrowding combined with poor quality of hygienic conditions. Thus, tuberculosis became the first cause of death in Europe.

At the end of the eighteenth century one citizen out of four was dying of tuberculosis in London and comparable percentages were recorded in big cities of Northern America.

The causes of the disease were not yet clarified: the so called "*scientific visions*" supported the theory of a congenital disease, already argued by Hippocrates, opposed to the idea of an infectious and transmissible illness, already speculated by Aristotle [2-4].

Over the centuries, several attempts to demonstrate that "*phthisis*" was spread through unknown microorganisms can be found.

Girolamo Fracastoro (1476-1553) was the first to blame an invisible microorganism as a causative agent of tuberculosis. Nevertheless, he did not understand that the transmission could occur by air. His theory was resumed by Benjamin Marten in 1720. He speculated that tuberculosis was due to "*animacula*", microscopic living beings able to survive in a new body, as a previous theorized by Anton van Leuwenhoek (1632-1723).

In this age the first theories about tuberculosis arose from a careful observation of clinical and anatomic phenomena.

Moreover, a change in the diagnostic approach to the disease was happening. In fact, by the end of the eighteenth century tuberculosis was still diagnosed by thoracic chest percussion introduced by J. Leopold Auenbrugger (1722-1809).

The advent of auscultation, thanks to the invention of the stethoscope in 1818 by Renéè Laennec, significantly improved the diagnostic path of tuberculosis. Unfortunately, the same Laennec – died at the age of 45 due to tuberculosis, presumably as a consequence of close contact with contagious patients [5].

Approximately fifty years later, in 1865, Jean Antoine Villemin finally proved the infectiousness of the disease by combing the clinical observations with laboratory experimentation on guinea pigs [6, 7].

The path traced by Villemin was completed on the 24th of March 1882, when Robert Koch revealed the discovery of "*the bacillus responsible of the disease*" [8].

All debates were suddenly over: tuberculosis is an infectious and contagious disease.

In addition, Koch's discovery further improved the diagnosis of tuberculosis through the microscopic identification of the bacillus. The discovery was not well received by all the scientific environment: Rudolf Ludwig Karl Virchow (1821-1902), who is considered the father of social and hygiene medicine, was still claiming the multifactorial genesis of the illness.

In fact, he realized that the infection with the bacillus was not enough to get sick, but multiple causes contributed to the development of an active disease.

Moreover, he understood that the presence of what we call today the "clinical and social determinants" (immunological status, poverty, malnutrition, lack of hygiene, individual behaviors) were strictly related to the development of tuberculosis. In other words, he realized the systemic complexity of the disease. A few years later, in 1895, Wilhem Roentgen, with the X-ray discover, finally managed to see the damages generated by the disease [9].

Nowadays, chest X-ray and bacteriological examination of the expectorate are still the diagnostic tools that we use to support and confirm the clinical suspicion of tuberculosis. Those confirm the pivotal role of the discovery made by Koch and Roentgen in the fight against tuberculosis.

The new awareness of contagiousness, arisen from Koch's discovery, implied the need for patient's isolation. As a consequence, sanatoriums were then born [10].

The recognition of the social determinants that foster the disease obliged to provide assistance and preventive in-

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terventions for the sick and families. Consequently, dispensary networks and hospitals for preventive care were established.
In the history of vaccine and vaccination we remember that in 1895 Edoardo Maragliano could announce to the scientific community, at the Second Congress of the French Society of Internal Medicine, the existence of a tubercular antitoxin in infected animals (dogs, asses, and hors- es), and the consequent use of animal serum as therapeutic agent, by immunizing various animals with two different liquid cultures of M. tuberculosis, one of which obtained from a heated to 100° C, filtered and concentrated culture, the other from a filtered and evaporated culture by vacuum at 30° C [11, 12].
After demonstrating the prophylactic and the protective effect in guinea pigs, serum was administrated to patients: in 1896, Maragliano published data about 412 patients affected by tuberculosis and treated with serum, reporting a complete recovery in 16%, significant improvement in 40%, no change in 37% and death in 11%. Maragliano also claimed that better results of serum therapy were obtained in patients with circumscribed lesions with good nutritional conditions than patients with diffuse illness [12-14].
In 1896, Maragliano proposed a vaccination practice against *Mycobacterium tuberculosis*: after the administration of dead strains in a cohort of children by subcutaneous grafting, an increase in the antibody titer was found in sera of these children. Nevertheless his discovery was ignored by the scientific community, above all because of the large use in the western world of Calmette and Guerin (BCG)'s vaccine, made of live strains, from 1928 [12, 15].
We can therefore say that many efforts have been made to fight and win the challenge against this dangerous disease and now more than ever a clear and decisive joint commitment is needed.
The strong social and economic impact that the disease still carries today entails forced governments to sensitize inhabitants and raise public awareness about prevention and treatment.
The great campaign against tuberculosis came to light. The same industrial revolution that played a huge part in spreading the disease through urbanization facilitated, at the same time, a slow economic and social growth that resulted in better living and sanitation.
Tuberculosis related mortality reverted its trend and began to decrease in the early twentieth century. The discovery of effective treatments after the II World War allowed the cure of the sick and, at the same time, prevented the transmission.
Progressively, the health and social emergency of the "white plague" seemed to be over.
The institutions adapted quickly and sanatoriums were closed such as dispensaries which were redirected to other functions. Control programs were then targeted according to the new epidemiological situation. Today, for people living in high income countries, tuberculosis is an ancient disease, a memory of the past, a memory of time of poverty. Sadly, the current perception of the disease is incorrect. Nothing has changed all over the planet: those "socio-economical determinants", intuited by Wirchow, still exist today.
Starvation, wars, poverty affect million of people, and tuberculosis remains a global health emergency with one and a half million death and nine million new patients every year, even if new diagnostic tools and effective therapies are available [16]. Since the early eighties the detrimental intersection between tuberculosis and HIV infection posed new diagnostic, therapeutic and management challenges. The two diseases since the HIV advent appeared clearly to be connected by the same underlying "socio-economical determinants".
Every effort to end these diseases should be collaborative as advocated by the WHO to break the barriers related to the TB/HIV double stigma [17].
Vaccines are important in the prevention and control of tuberculosis, but the only now available preventive vaccine against TB, bacilli Calmette-Guérin (BCG), is not effective for prevention of pulmonary TB. For this reason, it is very important to develop new vaccines for TB prevention and control in adults [18].
Around 14 TB vaccine candidates are in this moment in clinical evaluation, they can be classified into two groups including preventive pre- and post-exposure vaccines: subunit vaccines, and whole-cell vaccines [19].
Once again, the problem of tuberculosis is not only a medical challenge, but a social, economical and ethical issue that needs to be ended [20].

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Authors' contributions

GB and MM conceived the study, GB, MM, NR drafted the manuscript, GB, AG and VG revised the manuscript. GB, MM, AG performed a search of the literature. All authors critically revised the manuscript. All authors have read and approved the latest version of the manuscript.

References

[1] Martini M, Besozzi G, Barberis I. The never-ending story of the fight against tuberculosis: from Koch's bacillus to global control programs. J Prev Med Hyg 2018; 28;59:E241-E247. https://doi.org/10.15167/2421-4248/jpmh2018.59.3.1051

[2] Hippocrates, Epidemics I, 1,3. Li. 2, 633, 3.

[3] Grmek MD, Les représentations figurées de la consumption et du corps émacié dand l'antiquité. Med Sec 1995, pp. 249-272.

[4] Daniel TM1, Iversen PA2. Hippocrates and tuberculosis. Int J Tuberc Lung Dis 2015;19:373-4; Aristot. HA VIII 21-23, Passi TBC). https://doi.org/10.5588/ijtld.14.0736

[5] Ariel Roguin. Rene Theophile Hyacinthe Laënnec (1781–1826): The Man Behind the Stethoscope. Clin Med Res 2006;4:230-5. https://doi.org/10.3121/cmr.4.3.230

[6] Villemin JA. Gazette hebdomadaire de médecine et de chirurgie. Paris: V. Masson et fils; 1866. De la phtisie et des maladies qui la simulent dans la série zoologique.

[7] Villemin JA. Cause et nature de la tuberculose. Paris: Bulletin de l'Académie de Médecine 1865.

[8] Cambau M, Drancourt M, Steps towards the discovery of Mycobacterium tuberculosis by Robert Koch, 1882, Clin Microbiol Infect 2014;20:196-201. https://doi.org/10.1111/1469-0691.12555

[9] Tubiana M. Wilhelm Conrad Röntgen and the discovery of X-rays. Bull Acad Nati Med 1996;180:97-108

[10] Martini M, Gazzaniga V, Behzadifar M, Bragazzi NL, Barberis I. The history of tuberculosis: the social role of sanatoria for the treatment of tuberculosis in Italy between the end of the 19th century and the middle of the 20th. J Prev Med Hyg. 2018;15;59:E323-E327. https://doi.org/10.15167/2421-4248/jpmh2018.59.4.1103

[11] Maragliano E. La terapia specifica della tubercolosi e la sua vaccinazione. Con- ferenza tenuta in Philadelphia nel "The Henry Phipps Institute" il 28 marzo 1904. Gazzetta degli Ospedali e delle Cliniche, n. 145. Milan: Vallardi 1904.

[12] Martini M, Paluan. F. Edoardo Maragliano (1849-1940): the unfortunate fate of a real pioneer in the fight against tuberculosis. Tuberculosis (Edinb) 2017;106:123. https://doi.org/10.1016/j.tube.2017.07.007

[13] Glatman-Freedman A, Casadevall A. Serum therapy for tuberculosis revisited: reappraisal of the role of antibody-mediated immunity against Mycobacterium tuberculosis. Clin Microbiol Rev 1998;11:514e32. https://doi.org/10.1128/CMR.11.3.514

[14] Martini M, Barberis I, Bragazzi NL, Paluan F. The fight against tuberculosis in the mid-nineteenth century: the pivotal contribution of Edoardo Maragliano (1849-1940). Adv Exp Med Biol 2018;1057:95-100. https://doi.org/10.1007/5584_2017_125

[15] Towey F. Léon Charles Albert Calmette and Jean-Marie Camille Guérin. Lancet Resp Med 2015;3:186e7. https://doi.org/10.1016/S2213-2600(15)00065-X

[16] Riccardi N, Alagna R, Motta I, Ferrarese M, Castellotti P, Nicolini LA, Diaw MM, Ndiaye M, Cirillo D, Codecasa L, Besozzi G. Towards ending TB: civil community engagement in a rural area of Senegal: results, challenges and future proposal. Infect Dis (Lond) 2019;51:392-4. https://doi.org/10.1080/23744235.2019.1572920

[17] Daftary A, Frick M, Venkatesan N, Pai M. Fighting TB stigma: we need to apply lessons learnt from HIV activism. BMJ Glob Health 2017;2:e000515. https://doi.org/10.1136/bmjgh-2017-000515

[18] Gong W, Liang Y, Wu X. The current status, challenges, and future developments of new tuberculosis vaccines. Hum Vaccin Immunother 2018;14:1697716. https://doi.org/10.1080/21645515.2018.1458806

[19] Méndez-Samperio P. Development of tuberculosis vaccines in clinical trials: Current status. Scand J Immunol 2018;88:e12710. https://doi.org/10.1111/sji.12710

[20] Canetti D, Riccardi N, Martini M, Villa S, Di Biagio A, Codecasa L, Castagna A, Barberis I, Gazzaniga V, Besozzi G. HIV and tuberculosis: The paradox of dual illnesses and the challenges of their fighting in the history. Tuberculosis 2020;122:101921. https://doi.org/10.1016/j.tube.2020.101921

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Correspondence: Niccolò Riccardi, Department of Infectious - Tropical Diseases and Microbiology, IRCCS Sacro Cuore Don Calabria Hospital, Negrar (VR), Italy - E-mail niccolo.riccardi@yahoo.it

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Tuberculosis in Siena: evolution of the disease and its treatment, from the Unification of Italy to the 1930s

D. ORSINI
University of Siena, University Museum System of Siena (SIMUS), Siena, Italy

Keywords

History of tuberculosis • Public health • Tuberculosis • Prophylaxis activities • Carlo Livi • Achille Sclavo

Summary

Between the end of the nineteenth century and the first half of the twentieth century, the city of Siena experienced elevated tuberculosis-related morbidity and mortality, to the point that on January 1, 1929 the newspaper La Nazione wrote that "Siena ranks second in the official Tuberculosis (TB) incidence rate". The author presents statistical data relating to a time span ranging from 1898 to 1935, interpreting them in light of social and sanitary conditions found in the city. The result is an exhaustive picture of the most important actions implemented at city level to prevent tuberculosis and to assist and treat the sick, such as: the creation of seaside hospices conceived by Carlo Livi for children suffering from scrofula, as well as centers committed to the prevention of childhood poverty and malnutrition; the realization of activities in the green areas of the ramparts of the Fortress, upon recommendation by the great hygienist Achille Sclavo; the establishment of a Preventorium on the premises of the Monastery of Santa Maria Maddalena to accommodate children from families that included pulmonary tuberculosis patients, and countless activities carried out by the Anti-TB Dispensary. Of particular interest is the identification of the main cause of high TB incidence in the unhealthy houses located in some areas of Siena's district, which, in 1930 engendered a lively debate hinging upon the notion of building restoration.

Introduction

On March 30, 1856, at the age of 26, Matilde, daughter of the Italian poet and novelist Alessandro Manzoni, died in Siena "of the slow disease".

The words the poet wrote for the epigraph of his young daughter convey the cruelty of a disease – tuberculosis (TB) – which continued to decimate young lives year after year. And that "slow disease", recalled and emphasized in Romantic literature, was the primary cause of death in the European continent, affecting first and foremost people who lived under low socio-economic and hygienic standards.

Siena was no exception. Indeed, its "Urban center ranked high among other Italian cities that experienced high rates of TB-related deaths, surpassing the most important populous and industrial centers for the intensity of the epidemic event" [1]. "Bearing in mind the trend of annual quotients during the 1898-1920 period, it seems evident that TB-related mortality in the Municipality of Siena has the character of a persistent endemic phenomenon" [1].

In the second half of the nineteenth century, such data had surprised Carlo Livi, at the time Director of Siena's San Niccolò Asylum, where scrofulous children received treatment, to the point that he wondered: "Who, amongst you, can tell me why in Siena, a hilly and windy city, with fine, pure and healthy air, that terrible disease called scrofula is rampant, with its sad patient headcount?" [2].

The causes must certainly be sought in the bad environmental conditions of the city's oldest districts. It should be remembered that immediately after the unification of Italy, a new urbanization impetus led to a significant increase in the number of residents of Siena. In most cases, it was poor families that moved to the city, hoping to find work and, due to their limited financial means settled in unhealthy dwellings located in the city's poorest districts. In a few years, this situation engendered overcrowding of some urban areas and the rapid spreading of diseases fueled by the poor sanitary conditions within the city walls. In fact, Siena lacked a modern aqueduct and sewer system. Only in 1914, following long and costly works for the construction of a new aqueduct, did water from the Monte Amiata springs could reach Siena. The construction of the sewerage network began after World War I, but conditions remained challenging until the beginning of the 1930s.

It was in this context that the "leprosy of modern times", tuberculosis, proliferated in a variety of forms.

Three different contemporary studies have left us significant statistics, which provide us with an account of a particularly difficult and serious situation. In the first period under consideration, stretching from the end of the nineteenth century to 1913, tuberculosis mortality in Siena ranged from a maximum of 32.2 deaths per ten thousand inhabitants to a minimum of 22.3, which was recorded precisely in 1913. "In the series of proportional values, the tendency to a kind of epidemic rhythm is manifestly evident: increase is generally followed by decreases, after which a new increase is experienced" [3].

It must be taken into account that the average TB mortality rate in the Kingdom of Italy in 1898 stood at 17.46 deaths per ten thousand inhabitants, and remained unchanged in the following years. These figures concerning Siena were consistent with those of much bigger cities like Bologna (33.6), Genoa (33.2), Rome (30.4), Milan and Naples (29.3) [4].
The National figures decreased in 1912 at 14.9 deaths per ten thousand inhabitants thanks to the diffusion of the radiological diagnostics, the collapse therapy according to Forlanini and to the creation of the first sanatoria. In the same years in Siena – as just mentioned – the figures stood at 22.3 deaths per ten thousand inhabitants.
In the following period, 1914-1920, which is the subject of the second study, tuberculosis mortality in the city of Siena rose significantly during the War years (1915: 24.70 deaths per ten thousand inhabitants; 1916 31.20; 1917: 40.40; 1918: 40), to decrease in 1919 to 29.65 for every ten thousand inhabitants and to 21.62 in 1920.
The raising of the number of infected and death people due to tuberculosis during the last years of World War (1917-1918) – which reached in the city centre of Siena 54 deaths per ten thousand inhabitants – is attributable to the suffering and deprivation caused by the War and were worsened by houses unhealthiness which helps the spread of morbidity.
Regarding the rapid decline in mortality in the two years following the end of World War I, Filippo Neri, Health Officer of the Municipality of Siena and assistant of Achille Sclavo, at the Institute of Hygiene of the University of Siena, wrote: "This decrease certainly cannot depend on the return to normal living conditions, because hardship in this two-year period remained as severe as it had been during the War. An explanation of the rapid decrease of tuberculosis mortality can be surmised only if we keep in mind the 1918-19 flu pandemic. [...] If we admit - as it can be easily assumed - that a large number of deaths from influenza had occurred in tuberculosis patients, whose compromised immune system was easily overtaken by the influenza virus, we have a better understanding of what triggered the rapid decrease in tuberculosis mortality between 1919 and 1920" [5].
In the last period under consideration, from 1921 to 1935, tuberculosis mortality in Siena stabilized in the 1920s, standing at about 22.2 deaths per ten thousand inhabitants, then it progressively declined from 1928, in response to a series of significant preventive actions implemented by the State and the municipal administration: in 1932, the rate was 9.5 and in 1935, 10.4.
However, if we consider the mortality rate due to tuberculosis per one thousand inhabitants, the figures concerning the Municipality of Siena during the decade 1924-1934 were still higher than those concerning the whole Kingdom of Italy (in 1924, 1.80 in Siena, 1.56 in the Kingdom; in 1930, 1.35 in Siena, 1.12 in the Kingdom; in 1934, 1.18 in Siena and 0.69 in the rest of Italy).
The data presented above give us a very accurate idea of the gravity of the situation in Siena due to tuberculosis morbidity and mortality.

Urban renewal as a first step in the fight against tuberculosis

The improvement recorded at the beginning of the 1930s is certainly due to new treatment options delivered at dispensaries, but, above all, to find a solution to the causes that for decades had been deemed to be responsible for a high mortality rate in the center of Siena: population density and unhealthy dwellings. "Mortality is higher where agglomeration is greater. The streets that were especially affected were narrow, thus not exposed to the beneficial influence of sun rays, covered in buildings that did not meet even the most basic sanitary conditions, and were generally overcrowded [...]. Homes, overcrowding and, therefore, the risk of direct contagion accounted for the impressive mortality in a given area rather than another" [6]. This problem has already been reported at the beginning of the century; indeed, in November 1908, a report on social housing found the conditions of working-class districts to be the primary cause of the tuberculosis outbreak [7, 8].
Hence, in 1928, becoming the "need for urban rehabilitation increasingly clear and forceful, without which it is useless to expect efforts against TB to be long-lasting" [1], the project to demolish the Salicotto district, one of the most affected by the disease, began. In this area, in the heart of Siena, as late as the first half of the twentieth century, poor families often cohabited with scrofulous patients in dwellings located below street level, consisting of one or, at most, two dark rooms that received air from the stairs. This condition stood in stark contrast with Achille Sclavo's recommendations in his Decalogue of Hygiene: "Love sunlight, which gives you everything together with health to your body. Love fresh air and store plenty of it in your home, keeping windows open as long as you can" [9].
The demolition of the houses in the areas which most needed radical sanitary assistance and the building of new houses meeting the modern hygiene criteria, well-furnished and sunny houses, surely represented a key moment for the improvement of population sanitary conditions and particularly in reducing the risk of tuberculosis transmission.
Building rehabilitation in Siena was certainly a fundamental but not sufficient approach – also because it was limited to a small area – for the improvement of the sanitary conditions of the population and, in particular, the reduction of TB risks. The often cited study by Aristide Londini provides significant pre- and post-restoration data relating to the Salicotto district: until 1930 Via Salicotto experienced an average annual TB mortality incidence rate of 33.2, which fell to 16 in 1935, for every ten thousand inhabitants [6].
However, the persisting high incidence eventually pushed the city government and the local politicians to identify as a fundamental objective the "fight against the serious disease that afflicts this land in an impressive way [...] and that kills a large part of our youth" [10].

Sickly youth

If TB-related mortality in Siena in the first decades of the twentieth century was greater than rates attributable to any other disease, what still surprises for its social implications is the fact that most of those who died of tuberculosis were included in the 16-20 year age group.
In the 1898-1913 period, this age group was the most affected by the TB outbreak, with 120.5 deaths per 1000 due to tuberculosis of all ages. The 21-25 and 26-30 year ranges came immediately thereafter, with 125 deaths for each group.
In the period between 1914 and 1920, data are quite similar: the 16-20 year age group recorded 136.04 deaths out of 1000 TB deaths of all ages; with 130.7 deaths for the 21-25 year range group and the 101.43 for the 26-30 year range group.
Finally, in the 1921-1935 period, the age group that recorded most deaths was the 26-30 year range group, with 118.64 deaths, followed by the 21-25 year range group, with 117.87 deaths, every 1000 TB deaths of all ages.
In most cases, women were most affected by the disease.
These data dramatically convey the devastating social, economic, and health-related consequences of TB, which was decimating young people precisely at the historical juncture in which they should have given an important contribution to the country's workforce. Furthermore, the extremely high number of women who succumbed to tuberculosis before the age of thirty had a significant impact on reproduction and, by extension, on population growth. In addition, we must factor the challenges that families and society at large had to face during an illness, which was often a long stretch of time.

The slow start of TB prophylaxis activities

If at the beginning of the twentieth century TB patients were mostly cared for by voluntary associations, whose goal was to alleviate pain for the sick, the resurgence of the disease during the Great War led to the implementation of prevention and care activities on a national scale.
At the end of 1916, after fierce discussions in the Parliament, the army was provided with hospital departments for diagnosing the tuberculosis. In 1917, about 20,000 soldiers were recovered in these departments. Incurable soldiers were immediately discharged, those who could be treated were recovered in special sanatoria for at least 4 months, before being subject to a further examination.
The call to arms of millions of men increased the chances of contagion in the 18-45 year age group, and, at the same time, the massive recruitment of women, children and the elderly to work in factories in order to fill places left empty by men now engaged at the war front, extended contagion to the entire civilian population.
In 1918, 73,000 people died of tuberculosis in Italy. At the end of World War I, the Government decided that those who had contracted tuberculosis while in the army had to be treated at State expenses and received a grant.
With the massive spread of tuberculosis, also new ways for its containing were explored.
As a result, the Anti-TB Association of Siena was born in the city in 1919. It inherited the legacy of the Standing Committee against Tuberculosis which had been active in Siena since 1898, though its efforts had hardly been paid off. The Association, led by Professor Vittorio Remedi, and with Achille Sclavo as its Vice President, "focused on sad and unhealthy homes, where TB was incubated; joined families in their home environments to identify TB patients, trying to instruct and assist them as much as possible in their own dwellings, all the while seeking to diminish the risk of contagion with the available means" [11].
The following year, as inadequate as its spaces may have been, the Dispensary was operational, becoming the fulcrum of efforts against TB and providing Siena with a center specialized in fighting and containing the disease and its spread.
In 1923, the Law 2889 effectively suppressed provincial committees, establishing anti-TB consortia in their place. In Siena, the Consortium between the Provincial Administration and the Municipalities of the Siena province met for the first time on June 1, 1924. Within a few months, it approved a series of important measures aimed at fighting TB, chief among them, the establishment of 5 dispensaries in the major centers and the hospitalization of tuberculosis patients with partial reimbursement of expenses to the Municipalities. "Professor Achille Sclavo, then Director of the Chair of Hygiene at the University of Siena, joined the Consortium in 1925: thus, propaganda work began in earnest, greatly contributing to TB awareness and the implementation of additional targeted countervailing measures" [11]. Conferences were aimed at all citizens, information brochures were circulated, and an Anti-TB Day was held on July 2, 1925. From a social welfare point of view proper, medical care was provided by the Dispensary.
Finally, in 1928 Siena began witnessing the construction of its Sanatorium [12], which was inaugurated on November 3, 1935, followed by the opening of the new Dispensary, which featured a test laboratory, a radiology room "equipped with a Tetravalvo Rangoni device that could meet the needs of modern radiological diagnostics" and its relative darkroom, a room for TB vaccination, a large terrace for natural heliotherapy and an artificial heliotherapy room "outfitted with five quartz lamps" [11].

Prevention in children

But actually, the greatest attention in TB prophylaxis was given to children [13]. Among the actions announced by the Consortium in 1924, child prevention played a fundamental role, to be implemented through "the immediate organization of the Grancher approach, which entailed the removal of children from households with TB patients, and their placement elsewhere.

The Consortium also oversaw the construction of a Preventorium designed to accommodate the children temporarily removed from their homes, the creation of a preventive and healing seaside camp and of day camps held in the countryside" [11].
These actions were not easy to implement, so much that in 1929 Giorgio Alberto Chiurco, politician and Director of the Institute of Surgical Pathology of the University of Siena, wrote: "these poor children are held by coughing old men, made to sleep together with TB patients, sit in front of the fireplace alongside sick individuals who, without any medical guidance, are allowed to sow bacilli left and right, infecting infants" [10].
Indeed, as reported by contemporary scientific documents, families of 9-10 people lived in 2-3 dark and damp rooms, with 3-4 children per bed in contact with sick parents and relatives, often at the terminal stage of the disease.
On that same year, the *Podestà* [14] of Siena, Fabio Bargagli Petrucci – buttressed by the positive opinion of Achille Sclavo – oversaw the construction, not without difficulty, of a TB Preventorium on the premises of the monastery of Santa Maria Maddalena. Divided across 3 floors, the facility included male and female dormitories in ventilated and sunny rooms, a kitchen and a refectory and, as suggested by the Health Officer, could host as many as 60 children up to the age of 9 (males) and 12 years (females), who were housed until the danger of infection at their homes was deemed to have disappeared completely.
The facility also included a nursery for infants and a special section for sick children.
Removal from an environment that led to contagion, better nutrition, outdoor living in the sun and pure air were fundamental remedies at a time when no drugs were available to treat TB.
But preventive actions aimed at children actually began much earlier, in the mid-nineteenth century, due to the particular interest of Carlo Livi, who, in 1864 founded the Popular Association for Siena's Scrofulous Children. At the urging of Giuseppe Barellai [15], his colleague and great friend, Livi was active in the construction of seaside hospices in Viareggio and Porto Santo Stefano, in the 1860s and 1870s, aware that "every year, the sea, beneficial [...], opens its great arms to welcome infirm, meager and hunched children and youngsters partially blinded by scrofula, and sends them back to their homes healthy, vegetative, robust and cheerful" [2].
Livi's ideas and work were carried out by his colleagues and students, including Paolo Funaioli and Flaminio Tassi, who, through medical and statistical reports, gave us an account of the results on children who "stayed on the beach, which, if not unique, is at minimum the most powerful of the remedies to be leveraged against the terrible disease" [16].
Over the years, other preventive actions were also implemented: starting in 1919, a summer camp was held on the ramparts of the Fortress, welcoming about 100 children, from 3 to 12 years of age, who were placed under the care of health personnel also during the year; an outpatient heliotherapy center - with 14 beds - was carved out of the garden of the Santa Maria della Scala Hospital, which operated according to guidelines established by Dr. Auguste Rollier. Therefore, for decades, before antibiotics became available, the sea, "a great drug for scrofulous children" [17], and sun exposure played a fundamental role in the prevention and treatment of tuberculosis. It should be emphasized that no scientific reasons were known at the time about the beneficial exposure to sea and sun.

Conclusion

Between the second half of the nineteenth century and the first three decades of the twentieth century, tuberculosis, mainly in its pulmonary form and, secondarily, in other forms, was the most pernicious disease in Siena due to its high rate of morbidity and mortality.
Without drugs available to treat TB, whose causes were known, it became necessary to combine efforts to neutralize any situation that could promote TB onset and contagion. The result was an important project that brought together Province, Municipality, University, Hospital, Associations and citizens to prevent and treat, not only medically speaking, but also in a manner that had clear social implications.

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Authors' contributions

The Author conceived the study, drafted and revised and approved the manuscript.

References

[1] Neri F. La tubercolosi nel Comune di Siena. Nota II (periodo 1914-1920). Atti Accad Sci Siena 1921; IX(XIII):159-83.

[2] Livi C. La scrofola e gli ospizii marini: lettura fatta nella Gran Sala della R. Università di Siena/per Carlo Livi. Milano: Treves 1873.

[3] Neri F. La tubercolosi nel Comune di Siena durante il periodo 1898-1913. Firenze: Tipografia Fattori e Puggelli già Claudiana 1915.

[4] Bizzozzero G. Contro la tubercolosi. Milano: Fratelli Treves Editori 1899.

[5] Martini M, Gazzaniga V, Bragazzi NL, Barberis I. The Span-

ish influenza pandemic: a lesson from history 100 years after 1918. J Prev Med Hyg 2019;60:E64-E67. https://doi.org/10.15167/2421-4248/jpmh2019.60.1.1205

[6] Londini A. La tubercolosi nel comune di Siena (periodo 1921-1935). Atti Accad Sci Siena 1921;XI(V):293-323.

[7] Cinughi de' Pazzi A. Case popolari in Siena. Siena: Stab. Carlo Nava 1908.

[8] For national studies focusing on the relationship between the spread of the TB outbreak and the most degraded and overcrowded urban areas, see Badaloni G., La mortalità per tubercolosi polmonare in Bologna. Boll Sc Med 1905;V:119-33.

[9] Orsini D. Il decalogo dell'Igiene di Achille Sclavo. Un messaggio educativo per le scuole italiane, in I labirinti della Medicina, Atti del 50° Congresso della Società Italiana di Storia della Medicina. Palermo: Edizacco-Pittographie 2015, pp. 59-63.

[10] Chiurco G.A. Pernio del programma fascista senese dell'anno VII: combattere la tubercolosi. Il Popolo Senese 1928;86:3-6.

[11] Corsini F. Attività antitubercolare dal 1919 al 1940. Siena: Stabilimento Grafico Combattenti 1942.

[12] Martini M, Gazzaniga V, Behzadifar M, Bragazzi NL, Barberis I. The history of tuberculosis: the social role of sanatoria for the treatment of tuberculosis in Italy between the end of the 19th century and the middle of the 20th. J Prev Med Hyg 2018;59:E323-E327. https://doi.org/10.15167/2421-4248/jpmh2018.59.4.1103

[13] Orsini D. The struggle against infant scrofula in Siena between the nineteenth and twentieth centuries [published online ahead of print, 2020 Jan 24]. Adv Exp Med Biol 2020. https://doi.org/10.1007/5584_2019_468

[14] During the fascist era, municipality democratic bodies were abolished and all the functions previously performed by the Mayor and the town council were transferred to the Podestà who was appointed by the government. The noble Fabio Bargagli Petrucci, historian and politician, was elected Mayor of Siena in 1923 and from 1926 to 1936 held the office of Podestà.

[15] Diana E. L'opera di Giuseppe Barellai nel contesto europeo dell'igiene e dell'architettura sanitaria: gli ospizi marini. Firenze: Polistampa 2014.

[16] Funaioli P. I poveri bambini scrofolosi di Siena inviati all'ospizio marino di Viareggio nell'estate 1872. Siena: Stab. Tip. Di A. Mucci 1874.

[17] Tassi F. Relazione sanitaria sui bambini poveri scrofolosi di Siena inviati all'ospizio marino di Porto Santo Stefano nell'estate del 1877. Siena: Stab. Tip. Di A. Mucci 1878.

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Correspondence: Davide Orsini, University Museum System of Siena (SIMUS), History of Medicine, University of Siena, via P.A. Mattioli 4/B, 53100 Siena, Italy - Tel. +39 0577 235470 - E-mail: davide.orsini@unisi.it

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Social determinants, ethical issues and future challenge of tuberculosis in a pluralistic society: the example of Israel

N.L. BRAGAZZI[1], M. MARTINI[2], N. MAHROUM[3,4]
[1] Department of Mathematics and Statistics, York University, Toronto, Canada; [2] Department of Health Sciences, University of Genoa, Italy; [3] The Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Israel; [4] Sackler Faculty of Medicine, Tel-Aviv University, Israel

Keywords

Health policy • Ethical issues • Tuberculosis • Israel • Multi-cultural • Immigrant society • Globalization

Summary

Tuberculosis is a very serious respiratory infectious disease, caused by the bacillus Mycobacterium tuberculosis, which generates a relevant societal and clinical burden. It has always represented a permanent concern and a public health challenge over the course of human history, because of its severe epidemiological, and economic-financial implications. The present review aims at over-viewing the impact of tuberculosis on the Israeli healthcare system, its temporal trend and evolution, stratified according to ethnicities and minorities, the need of establishing new facilities and implementing screening techniques, public health strategies and diagnostic tests, following massive immigration waves from countries characterized by a high incidence rate of tuberculosis during the fifties-sixties until the nineties, and the policies implemented by the Israeli government in the control, management and treatment of tuberculosis, as well as the role played by Israeli prominent scientists in discovering new druggable targets and finding bioactive compounds and bio-molecules in the fight against tuberculosis. Israel represents a unique, living laboratory in which features of developed and developing countries mix together. This country as a case-study of immigrant, pluralistic society underlines the importance of adopting a culturally-sensitive community intervention approach. The understanding of the subtle interplay between race/ethnic host and pathogen factors, including the role of gene variations and polymorphisms can pave the way for a personalized treatment and management of tuberculosis patients, contributing to the development of new tools for targeted tuberculosis therapeutics, immunodiagnostics and vaccination products.

Introduction

Tuberculosis (TB) is a very serious respiratory infectious disease, caused by the bacillus *Mycobacterium tuberculosis* (*M. tuberculosis*), which generates a relevant societal and clinical burden. It has always represented a permanent concern and a public health challenge over the course of human history, because of its severe epidemiological, and economic-financial implications [1]. More in detail, according to the latest available "Global Tuberculosis Report" published in 2019 by the World Health Organization (WHO) [2], TB is one of the top ten causes of death worldwide and the leading cause of mortality across all infections, followed by the human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS). Specifically, in 2018, 10 million people have become ill, 484,000 have developed multidrug resistant TB and 1 million and half have died. The present review aims at over-viewing the impact of TB on the Israeli healthcare system, its temporal trend and evolution, stratified according to ethnicities and minorities, the need of establishing new facilities and implementing screening techniques, public health strategies and diagnostic tests [3-5], following massive immigration waves from countries characterized by a high incidence rate of TB during the fifties-sixties [6, 7] until the nineties [8-10], and the policies implemented by the Israeli government in the control, management and treatment of TB [8], as well as the role played by Israeli prominent scientists in discovering new druggable targets and finding bioactive compounds and bio-molecules in the fight against TB [11].

Israel as pluralistic society

Globalization has profound, complex effects on human health [12]. Living "in an ever more connected global village linked through international travel, politics, economics, culture and human-human and human-animal interactions" [13] may result in a widespread diffusion of communicable disorders, including monkey pox, "severe acute respiratory syndrome" (SARS), avian influenza and TB outbreaks.
Israel represents a complex, multicultural and pluralistic society characterized by the co-existence of sometimes clashing and opposite tendencies, lifestyles and habits. More in detail, Israel comprises two major ethno-national groups, Israeli Jews and Israeli Arabs, with about 79% and 21 of the population being Jewish and Arabs, respectively.

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The two groups profoundly differ in terms of religious, social and cultural values as well as ideologies and constructs: for example, whereas Israeli Arabs hold highly traditional collectivist values and a cohesive culture, Western codes and values profoundly influence Israeli Jews. Furthermore, the two groups reside in two geographically different areas and settings, using separate social and cultural networks, like schools, educational organizations and religious institutions, as well as mass media, social networks and other channels [14].
Additionally, these differences and discrepancies between the two groups reflect in various levels of health literacy and in the usage of healthcare services and provisions: Israeli Arabs tend to underutilize healthcare facilities and medical support when compared with Israeli Jews. Different factors may explain this, including the lack of proper information and knowledge concerning the delivery of healthcare services and provisions, perceived barriers, like language and stigma, as well as a preference for alternative, non-conventional treatments (including religious/traditional management of the disease) and informal social support. For instance, Arab-Israeli patients tend to seek medical advice and consult physicians with a two-fold delay with respect to Jews, due to lower educational level and distrust in the Western remedies and treatments.
Health literacy can be, as such, considered as a proxy of use of healthcare provisions and empirical studies have shown how low literacy, especially among vulnerable segments of the population and minorities, translates into underutilized preventive services, low immunization practice and vaccination coverage [15, 16].
These differences reflect also, as we will see in the next paragraphs, in different incidence/prevalence rates of TB.

Tuberculosis and ethnicity

Both host and pathogen factors play a key role in determining innate immune responses to *M. tuberculosis*, even though their roles are yet to be fully established from a cellular and molecular standpoints. Furthermore, there is a dearth of data concerning the interplay of ethnicity, pathogen strain and immune response.
Nahid and colleagues [17] have assessed host macrophage immune responses of 3 different ethnicities (namely, Filipino, Chinese and non-Hispanic White subjects) to 3 genetically and geographically diverse *M. tuberculosis* lineages. Authors found that Filipino macrophages released less amounts of interleukin type 1 (IL-1), IL-6, and higher concentrations of IL-8, when compared to macrophages from the other two ethnicities, whereas the levels of IL-10, IL-12p70, tumor necrosis factor alpha (TNF-α) and granulocyte-macrophage colony-stimulating factor (GM-CSF) did not significantly vary according to race/ethnic factors. Ethnicity affected the response to the Toll-like receptor 2 agonist lipoteichoic acid (TLR2/LTA) and TLR4 agonist lipopolysaccharide (TLR4/LPS).
This research, together with a consistent body of studies, has led Aravindan [18] to formulate the hypothesis that TB represents a "genetically primed and determined infectious disease", with polymorphisms of a number of genes – including the natural resistance-associated macrophage protein type 1 (NRAMP-1/SLC11A1), the vitamin D receptor (VDR), the low molecular weight polypeptide/transporter with antigen processing, the chemokine monocyte chemoattractant protein type 1 (CCL-2/MCP-1), the immunity-related GTPase family M protein type 1 (IRGM-1), IL-1, several interleukins, such as IL-8, IL-10, IL-12, TLR, nucleotide-binding oligomerization domain-containing protein type 2 (NOD-2), human leukocyte antigen (HLA), mannose-binding lectin (MBL), major histocompatibility complex (MHC), TNF, the purinoceptor P2X7, epiregulin, the SP110 nuclear antigen, and interferon gamma (IFN-γ) – finely tune and modulate immune response and progression from infection to disease.

Tuberculosis in Israel

Specifically concerning Israel, according to the 2019 "Global Tuberculosis Report", the incidence rates of TB and multidrug resistant TB are 4.0 [95%CI 3.4-4.6] and 0.36 [95%CI 0.20-0.58] cases *per* 100,000 people, respectively [2].
However, in the fifties-sixties the incidence rate was much higher, reaching 200 cases *per* 100,000 population, due to a massive arrival of refugees from a post-war Europe and North-African countries [8].
Regarding the seventies-eighties, Dolberg and coauthors [19] and Greene and coworkers [20] performed a 10-year survey at the Soroka Medical Center (Be'er Sheva, Negev), from 1978 to 1987, identifying 279 TB cases (67% pulmonary and 33% extra-pulmonary; 48% affecting Ethiopian Jews, 28% and 24% involving Bedouin Arabs and Jews of other origins, respectively). In terms of socio-demographic characteristics, the Bedouin and Ethiopian patients were younger, had fewer co-morbidities, with mainly pulmonary TB, but were less adherent to pharmacological treatment. Furthermore, the Ethiopian patients have been hospitalized longer than other ethnic groups. Authors concluded that clinical presentations of TB could vary according to ethnicity, reflecting the diversity of the population, combining characteristics of both a developing and a developed country.
Concerning the nineties, according to the epidemiological observational, retrospective study performed between 1999 and 2011 by Bishara and colleagues [21], the incidence of TB in native ethnic minorities could remain high also in developed, high-income countries. More in detail, authors found 831 cases of TB among Israeli-born individuals: 530 (64%) and 301 cases (36%) affecting Israeli Jews and Israeli Arabs, respectively, with an average annual TB rate of 1.1 and 1.6 cases *per* 100,000 population, respectively, which was lower than the national average (7.0 cases *per* 100,000 population).

Thanks to the adoption of effective public health policies and strategies, TB rates began to decline both in Israel Arabs and Israel Jews, until they converged to 1 case *per* 100,000 people, even though ethnicity reflected in subtle differences in terms of clinical presentation and symptoms. For instance, Israel Arabs tended to be older, were more likely to have pulmonary TB and to report a lower treatment success rate when compared to Israel Jews. However, increasing older age and HIV co-infection status were independent predictors of treatment success rate, differently from ethnicity.
Summarizing, differences related to race/ethnic factors, initially particularly striking among some minorities, have begun to decrease over the time until convergence. For instance, treatment success rate has become rather high and satisfactory in various ethnic groups, and has not been associated with race/ethnic factors.
This has been possible thanks to profound changes in TB-related policies. In the nineties, Daniel Weiler-Ravell, expert in pulmonary and internal medicine, and Daniel Chemtob, a clinical epidemiologist, have obtained the chairs of the "National Advisory Committee on Tuberculosis" within the Israeli Ministry of Health (MOH) [4,8]. To cope with an increasing TB incidence rate, due to massive immigration from countries such as Ethiopia and geographic regions of the former Soviet Union, Israeli government has decided to centralize TB centers offering *ad hoc* services for immigrants, and to adopt the "Directly Observed Therapy, Short course" (DOTS) approach recommended by the WHO. In 1993, the "Advisory Committee on Tuberculosis" was settled, in 1994 a National Coordinator was designated, followed by cost-driven, population-based strategies for improving management and plans to increase adherence to treatment in 1995. Always in 1995, major epidemiological studies have documented the reality, providing the stakeholders, policy- and decision-makers with numbers to substantiate their decisions. In 1996 the scandal of the "Blood Affair", in which Ethiopians' donated blood had been secretly discarded for more than a decade since 1984, resulted in the establishment of a National "Tuberculosis and AIDS unit" and in new laws and regulations being enforced. Together with juridical provisions, in 1997 economic-financial and budgetary plans enabled the creation of new infrastructures and facilities specifically devoted to the fight against TB. This was followed by the release of national clinical and organizational guidelines, informing, in an evidence-based fashion, healthcare workers of the most effective and appropriate management options for TB patients.
Interestingly, these efforts have paralleled the issue of the "National Health Insurance Law", which has dramatically transformed the country and led to the establishment of four healthcare maintenance organizations (HMOs) or health providers, making insurance universal and not anymore on voluntarily basis [4, 8].

Future challenges

Israeli scientists have pioneered discoveries that could profoundly impact on the management and treatment of TB patients. A group of researchers at the Weizmann Institute of Science and Technology, including Shelly Hen-Avivi, Roi Avraham and Noa Bossel Ben Moshe [22], have made efforts to dissect the complex interactions between different host immune cell types underlying the outcome of the immune response to *M tuberculosis* infection, exploiting the latest advancements in the field of single cell RNA-sequencing (scRNA-seq). Authors have developed and implemented dynamic deconvolution algorithms using bulk scRNA-seq measurements of infected human peripheral blood cells.
The use of artificial intelligence and new machine learning-based techniques appears promising in advancing the treatment of TB and predicting its insurgence and progression by means of predictive biomarkers [23].
Other major challenges that need to be addressed are:
a) the need of new facilities and tools to implement and expand the access of Arabic population and other minorities to TB centers;
b) the emergence of drug/multidrug-resistant TB strains related to migration and/or climate change [24].

Conclusion

Israel represents a unique, living laboratory in which features of developed and developing countries mix together. This country as a case-study of immigrant, pluralistic society underlines the importance of adopting a culturally-sensitive community intervention approach [25, 26].
The understanding of the subtle interplay between race/ethnic host and pathogen factors, including the role of gene variations and polymorphisms can pave the way for a personalized treatment and management of TB patients, contributing to the development of new tools for targeted TB therapeutics, immunodiagnostics and vaccination products [27].

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Authors' contributions

NLB and NM conceived the study, NLB and MM drafted the manuscript; NLB, MM and NM revised the man-

uscript. NLB an NM performed a search of the literature. All authors critically revised the manuscript. All authors have read and approved the latest version of the manuscript.

References

[1] Barberis I, Bragazzi NL, Galluzzo L, Martini M. The history of tuberculosis: from the first historical records to the isolation of Koch's bacillus. J Prev Med Hyg 2017;58:E9-E12.

[2] Global Tuberculosis Report 2019. Geneva: World Health Organization; 2019. Available at https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf?ua=1

[3] Dara M, Gushulak BD, Posey DL, Zellweger JP, Migliori GB. The history and evolution of immigration medical screening for tuberculosis. Expert Rev Anti Infect Ther 2013;11:137-46. https://doi.org/10.1586/eri.12.168

[4] Chemtob D, Leventhal A, Berlowitz Y, Weiler-Ravell D. The new National Tuberculosis Control Programme in Israel, a country of high immigration. Int J Tuberc Lung Dis 2003;7:828-36.

[5] Wartski SA. Epidemiology and control of tuberculosis in Israel. Public Health Rev 1995;23:297-341.

[6] Wolowelsky A. The problem of tuberculosis in Israel. Harefuah 1950;38:24-6.

[7] Wayl P, Rakower J. Tuberculosis among Yemenite Jews in Israel. Harefuah 1949;36:133-7.

[8] Weiler-Ravell D, Leventhal A, Berlowitz Y, Rishpon S, Chemtob D. Circumstances leading to the formulation and implementation of a new TB control program in Israel: a case study in public health and policy. J Public Health Policy 2004;25:23-37. https://doi.org/10.1057/palgrave.jphp.3190002

[9] Wortham JM. TB Anywhere is TB everywhere. Isr J Health Policy Res 2018;20:40; https://doi.org/10.1186/s13584-018-0233-0

[10] Mor Z, Nuss N, Savion M, Nissan I, Lidji M, Maneshcu S, Kaidar-Shwartz H, Amitai Z, Rorman E, Sheffer R. Tuberculosis outbreak in a nursing home involving undocumented migrants and Israeli citizens. Isr J Health Policy Res 2018;15;7:36. https://doi.org/10.1186/s13584-018-0219-y

[11] Kana BD, Karakousis PC, Parish T, Dick T. Future target-based drug discovery for tuberculosis? Tuberculosis (Edinb) 2014;94:551-6. https://doi.org/10.1016/j.tube.2014.10.003

[12] Pang T, Guindon GE. Globalization and risks to health. EMBO Rep 2004;5 Spec No:S11-6. https://doi.org/10.1038/sj.embor.7400226

[13] Garavelli PL, Peduzzi P. Globalization and infectious diseases. Recenti Prog Med 2006;97:528-32.

[14] Adawi M, Amital H, Mahamid M, Amital D, Bisharat B, Mahroum N, Sharif K, Guy A, Adawi A, Mahagna H, Abu Much A, Watad S, Bragazzi NL, Watad A. Searching the Internet for psychiatric disorders among Arab and Jewish Israelis: insights from a comprehensive infodemiological survey. Peer J 2018;14;6:e4507. https://doi.org/10.7717/peerj.4507

[15] Castro-Sánchez E, Chang PWS, Vila-Candel R, Escobedo AA, Holmes AH. Health literacy and infectious diseases: why does it matter? Int J Infect Dis 2016;43:103-10. https://doi.org/10.1016/j.ijid.2015.12.019

[16] Muniyandi M, Rao VG, Bhat J, Yadav R, Sharma RK, Bhondeley MK. Health literacy on tuberculosis amongst vulnerable segment of population: special reference to Saharia tribe in central India. Indian J Med Res 2015;141:640-7. https://doi.org/10.4103/0971-5916.159566

[17] Nahid P, Jarlsberg LG, Kato-Maeda M, Segal MR, Osmond DH, Gagneux S, Dobos K, Gold M, Hopewell PC, Lewinsohn DM. Interplay of strain and race/ethnicity in the innate immune response to M. tuberculosis. PLoS One 2018; 22;13:e0195392. https://doi.org/10.1371%2Fjournal.pone.0195392

[18] Aravindan PP. Host genetics and tuberculosis: theory of genetic polymorphism and tuberculosis. Lung India 2019;36:244-52. https://doi.org/10.4103/lungindia.lungindia_146_15

[19] Dolberg OT, Alkan M, Schlaeffer F. Tuberculosis in Israel: a 10-year survey of an immigrant society. Isr J Med Sci 1991;27:386-9.

[20] Greene VW, Dolberg OT, Alkan ML, Schlaeffer FC. Tuberculosis cases in the Negev 1978-1987: ethnicity, sex, and age. Public Health Rev 1992-1993;20:53-60.

[21] Bishara H, Goldblatt D, Rorman E, Mor Z. Tuberculosis in native Israeli Arabs and Jews: trends and treatment outcomes, 1999-2011. Epidemiol Infect 2015;143:3203-10. https://doi.org/10.1017/S0950268815000382

[22] Bossel Ben-Moshe N, Hen-Avivi S, Levitin N, Yehezkel D, Oosting M, Joosten LAB, Netea MG, Avraham R. Predicting bacterial infection outcomes using single cell RNA-sequencing analysis of human immune cells. Nat Commun 2019;10:3266. https://doi.org/10.1038/s41467-019-11257-y

[23] Dande P, Samant P. Acquaintance to artificial neural networks and use of artificial intelligence as a diagnostic tool for tuberculosis: a review. Tuberculosis (Edinb) 2018;108:1-9.

[24] Sergi C, Serra N, Colomba C, Ayanlade A, Di Carlo P. Tuberculosis evolution and climate change: how much work is ahead? Acta Trop 2019;190:157-8. https://doi.org/10.1016/j.actatropica.2018.11.016

[25] Shariff NM, Shah SA, Kamaludin F. Impact of ethnic disparities on the treatment outcomes of HIV-negative drug-resistant tuberculosis patients in Kuala Lumpur, Malaysia: a call for a culturally-sensitive community intervention approach. J Glob Antimicrob Resist 2019;19:274-9. https://doi.org/10.1016/j.jgar.2019.05.009

[26] Riccardi N, Alagna R, Motta I, Ferrarese M, Castellotti P, Nicolini LA, Diaw MM, Ndiaye M, Cirillo D, Codecasa L, Besozzi G. Towards ending TB: civil community engagement in a rural area of Senegal: results, challenges and future proposal. Infect Dis (Lond) 2019;51:392-4. https://doi.org/10.1080/23744235.2019.1572920

[27] Marais BJ, Buddle BM, de Klerk-Lorist LM, Nguipdop-Djomo P, Quinn F, Greenblatt C. BCG vaccination for bovine tuberculosis; conclusions from the Jerusalem One Health workshop. Transbound Emerg Dis 2019;66:1037-43. https://doi.org/10.1111/tbed.13089

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Correspondence: Mariano Martini, Department of Health Sciences, via Pastore, 16132 Genoa, Italy - Tel. +39.010353.85.02 - E-mail mr.martini@unige.it

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