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

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Keywords

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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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Conflict of interest statement

The authors declare no conflict of interest.

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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