



## REVIEW

# Tuberculosis, social determinants and co-morbidities (including HIV)



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**Abstract** The risk of exposure, progression to active tuberculosis (TB) and then to cure is a process affected by several risk factors. Along with well known risk factors such as human immunodeficiency virus (HIV), use of immunosuppressive drugs and being of young age, emerging risk factors such socio-economic and behavioral aspects play a significant role in increasing the susceptibility to infection, and unsuccessful treatment outcomes. This paper summarizes the effects of these socio-economic determinants and co-morbidities (including HIV) on TB infection and disease.

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## Introduction

Tuberculosis (TB) control and elimination rely on an early detection of active TB cases, prompt anti-TB treatment, identification of persons in risk of exposure and infection and prevention of secondary TB cases.<sup>1</sup> All this depends on good diagnosis methods and effective treatment regimens for TB, but it is not enough.<sup>2</sup> Socio-economic determinants of health include the social, political, and economic conditions in which people are born, develop, live, work, and age.<sup>3</sup> Apart from medical care, there is increasing evidence of the role of these factors in health<sup>4,5</sup> and TB epidemiology.<sup>6–8</sup>

The epidemiology of tuberculosis reflects how these social determinants are distributed, with a clear influence in all stages of TB pathogenesis: risk of exposure, susceptibility to progression of disease, time to diagnosis and treatment, compliance and successful treatment.<sup>6</sup>

Risk of exposure to *Mycobacterium tuberculosis* (MTB) is dependent on social and risk behaviors. Living or working in a high incident setting, overcrowding and poor ventilation increase the risk of exposure.<sup>9</sup> Factors that delay diagnosis similarly increase the length of exposure to an infectious TB patient.

Malnutrition increases the susceptibility to disease,<sup>10,11</sup> income constraints can limit the use of health care services.<sup>12</sup> TB stigma, recognized as a social determinant of health and health inequalities, associated with lack of social support can potentially lead to non-compliance and poor treatment outcome.<sup>13</sup>

In recent years, the role of risk factors and social determinants of TB have been more intensively studied and the role of some highly prevalent determinants such as human immunodeficiency virus (HIV), smoking, diabetes mellitus (DM), alcohol use and under-nutrition have been highlighted.<sup>14</sup> Others include overcrowding, housing conditions or economic deprivation. It has been shown that the areas with the highest TB incidence are also those with high incidence of HIV infection, incarceration, overcrowding, unemployment and immigrants.<sup>15,16</sup>

The World Health Organization (WHO) has identified the need for a holistic approach to TB, including the underlying social-economic determinants of TB in order to achieve elimination.<sup>17</sup> This proposal is in line with the sustainable development goals that put social inclusion together with economic development and environmental sustainability as common aims to be achieved for all countries by 2030.<sup>13</sup>

The objective of this paper is to offer an overview of the different effects of socio-economic determinants on TB, aiming to provide a better understanding of the complex factors involved in the occurrence of the disease.

## Methods

We searched PubMed and Scopus for studies written in English, French, Spanish or Portuguese that evaluated the socioeconomic determinants on TB. Broad search terms included the following: tuberculosis, risk factors, and socioeconomic determinants. Additional manuscripts were selected from the references of the initially chosen articles. The WHO, the International Union Against Tuberculosis and Lung Diseases (The Union), Centers for Disease Control

(CDC), and European Centre for Disease Prevention and Control (ECDC) websites were visited searching for publications or reports regarding social determinants and TB.

## Risk factors for TB infection, disease and treatment default

Socioeconomic status can influence all stages of TB pathogenesis. Risk of exposure is related to the underlying disease burden and the environment in which people live.<sup>18</sup> People living or working in high burden places are at higher risk of exposure. The characteristics of the environment, airflow and number of people sharing the space will influence the risk of exposure.<sup>8</sup>

Once the MTB infection has occurred, increased susceptibility to disease can be related to co-morbidities such as infection with human infection virus (HIV), diabetes, silicosis or rheumatoid arthritis and other chronic illnesses or immunosuppressive therapies but also to malnutrition, alcohol or tobacco abuse. An analysis that included the 22 High TB Burden Countries estimated the population attributable fraction of malnutrition (27%), smoking (23%), HIV (19%), diabetes (6%) and alcohol abuse (13%).<sup>19</sup> The importance of the risk factor depends on prevalence – HIV is a more important risk factor in high prevalent countries of Sub-Saharan Africa (PAF > 50%).<sup>19</sup>

Health care costs associated with TB are both from direct user fees charged at the healthcare centres and from indirect costs of the visit. The money spent on transportation, co-payments for medication, and loss of work due to a medical appointment are all indirect costs associated with the use of health care services.<sup>20</sup> These economic barriers may cause a delay in contact to the health system where diagnosis is made,<sup>12</sup> and high costs often constitute a catastrophic economic burden for TB affected household.<sup>21</sup>

Successful treatment of TB involves taking anti-tuberculosis drugs for at least six months. Low income, alcohol abuse, HIV co-infection have been identified as predictive factors for default.<sup>19</sup>

## Link between socioeconomic status and TB

Socioeconomic deprivation can be described as lacking social and economic basic necessities.<sup>22</sup> This is a complex concept that includes a combination of factors, such as lack of education, low income, overcrowding, and unemployment, among others. The structural determinants and the conditions in which people live are responsible for an important part of health inequities<sup>22</sup> and the increased risk of TB.

Several studies have found an association between per capita gross domestic product and TB incidence. Inclusion of more proximal determinants in multivariate models indicate that the impact of poverty on TB represent the effect of multiple determinants and pathways.<sup>23</sup> Socioeconomic deprivation gives rise to poor living conditions, overcrowding, and undernutrition which increases the risk of exposure to a TB case, increases vulnerability to disease and risk of bad treatment outcome.<sup>23–25</sup>

The association between TB and homelessness has long been recognized and studies have reported a higher risk of TB and lower treatment success rate in this group of patients.<sup>26–28</sup> However, predictors of unsuccessful treatment among these patients were age, intravenous drug use and HIV co-infection.<sup>27</sup>

Overcrowding has been also associated with higher risk of exposure to TB. Housing conditions can affect the risk of exposure through poor ventilation or the quality of the indoor air.<sup>29</sup> Significant associations have been identified with overcrowding and TB notification.<sup>18</sup>

An additional risk factor for tuberculosis is poor nutritional status. There is a clear dose–response relationship between degree of undernutrition and risk of TB incidence.<sup>11</sup> Undernutrition is also a consequence of TB and undernutrition at time of diagnosis is associated with higher risk of death, although there is insufficient data to judge if food or supplements as an adjuvant to anti-TB medicines can improve TB treatment outcomes.<sup>30</sup>

People facing socioeconomic deprivation have a higher risk of contact with people with TB, higher likelihood of living and working in crowded and badly ventilated places, higher risk of malnutrition, less healthy behaviors (smoking, alcohol abuse) and face barriers to accessing health care.<sup>8</sup>

Migration has been pointed as a risk factor for TB, particularly among migrants originating from high burden countries. But other conditions may have an impact on the higher risk. Deprived conditions, overcrowding, malnutrition, poor access to health care have been described in mobile communities.<sup>31</sup>

Injecting drug users have a higher risk for TB due to socioeconomic and risky behaviors, such as deprivation, homelessness, imprisonment, HIV infection and malnutrition. They also face barriers to health care due to ill perception of disease.<sup>31,32</sup>

## Tobacco and alcohol

There is increasing evidence of tobacco effect on TB. Recent studies indicate that active and passive tobacco smoking are risk factors for latent tuberculosis infection, progression to active disease and lower rates of treatment success and higher TB-related death. Additionally, smoking has been associated with more frequent cavitation and bilateral radiological findings, higher bacillary load, delay of smear and culture conversion, higher risk of reactivation.<sup>29,33</sup> Other studies identified a dose–response relation between number of cigarettes smoked, years of smoking and tuberculosis.<sup>34,35</sup> Smoking cessation has been associated with higher cure rates (highest among non-smokers) when compared with smokers.<sup>36</sup> It has been recommended that smoking cessation programs should be part of TB control plans.<sup>36–38</sup>

The causal relation between heavy alcohol use and TB has long been described, but only recently has it been possible to estimate the alcohol attributable disease burden. According to new estimates, 17% of TB cases and 15% of deaths due to TB could have been prevented if there had not been heavy alcohol consumption.<sup>39</sup>

Many studies have looked at the effect of alcohol abuse on TB with a consistent association of alcohol abuse and more contagious and severe manifestations of the disease.

Alcohol consumption above 40 g of ethanol per day or a diagnosis of an alcohol disorder resulted in a nearly three-fold increased risk for TB.<sup>40</sup> Excessive alcohol consumption has also been associated with a higher risk of smear-positivity, cavitory disease, longer time to smear conversion, increased risk of drug toxicity, poor adherence and death due to TB.<sup>40–42</sup>

Alcoholism has also been linked to other socioeconomic determinants such as low socioeconomic status, homelessness and malnutrition, all of them independent risk factors for TB and treatment failure.

## HIV

On top of the socioeconomic factors, other TB risk factors have also already been widely described. Among them, infection with HIV stands out.

It is known that HIV-infected patients have a higher risk for TB development compared to persons without HIV. The incidence is higher in patients with lower CD4+ T cell count and detectable viral load but other risk factors might play a role, such as diabetes, alcohol, malnutrition, homelessness, IV-drugs use, hepatitis C, tobacco smoke.<sup>43–46</sup>

In patients with overlapping health issues, having effective strategies to deliver HIV, TB and drug dependency care in combination are crucial. Portugal's experience shows that integration is possible and depends on four key factors: collaborative networks and shared protocols; involvement of outreach teams; provision of uninterrupted opioid substitution therapy; and flexibility over treatment location.<sup>47</sup>

Over recent years there has been a move toward early initiation of antiretroviral therapy (ARV) during treatment for tuberculosis, given that the results of several trials have shown that this strategy significantly reduces mortality and morbidity due to HIV and TB.<sup>48</sup> However, when we look at latent TB the scenario is a bit different. For several years WHO has strongly recommended screening for latent TB and scaling up preventive isoniazid treatment in all HIV patients, regardless of TB incidence in the country. However, it is not known what the implementation of this recommendation is overall. Data from ECDC show that in 2014, 142,197 newly diagnosed HIV infections were reported in the WHO European Region, but only 21,000 (14.7%) were provided with TB preventive therapy.<sup>49</sup> Several factors might explain the low coverage of screening among HIV patients. Evenblij et al. in Netherlands shed some light on this problem, using quantitative and qualitative methods to understand the disconnection between clinical practice and evidence-based recommendations concerning screening and treatment of TB latent infection.<sup>25</sup>

## Comment

Socioeconomic determinants have an effect on degree of exposure, risk behaviors and access to health care. TB additionally has a negative effect on the productivity and socioeconomic status of the individual.

The identification of the risk factors and determinants of tuberculosis is particularly important as an increasing number of low and middle-income countries enter a phase of epidemiological transition where non-communicable

diseases and conditions replace infectious diseases as main causes of ill health and deaths. The existing relationship between non-communicable conditions and TB demands holistic strategies and interventions. Actions directed at the reduction of smoking, poverty, undernutrition, and better living conditions can have an important impact on TB control. Screening and management of common comorbidities and risk behaviors that increase risk of poor TB outcomes is important in order to optimize clinical care. Conversely, screening for TB in high-risk groups should be considered.<sup>50</sup>

Social interventions are often needed to enable TB patients to access care and adhere to treatment.<sup>51</sup> Most of these interventions will require interdisciplinary collaboration as well as intervention from outside the health sector. Although there is limited evidence on the best interventions, it is proposed that actions aimed to increase social protection; livelihoods strength or urban renovations may have an impact on TB epidemiology.<sup>6</sup>

At the present time, in HIV population, defining who, when and how frequently latent TB should be screened are the questions that remain to be answered. Should we define subsets of patients to be screened according to CD4+ count, viral load, country of origin? Should we repeat annual screening even in countries with intermediate or low level TB incidence? Which is the most cost effective strategy to adopt in each setting? These questions must be answered by new studies that evaluate in an integrated way the best care practices with the social factors that impact TB occurrence and the search for care by the patient with TB.

## Conflicts of interest

The authors have no conflicts of interest to declare.

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