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The New Paradigm of Immunity to Tuberculosis

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The New Paradigm of Immunity to Tuberculosis

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Epidemiology of Tuberculosis Immunology

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Abstract Immunological impairment plays a major role in the epidemiology of TB. Globally, the most common causes of immunological impairment are malnutrition, diabetes, HIV/AIDS, aging, and smoking. With the notable exception of HIV, each factor leads to relatively mild immunological impairment in individuals. However, as these conditions affect a significant proportion of the population, they contribute substantially to the incidence of TB at a global scale. Understanding immunological impairment is central to understanding the global TB pandemic, and vital to the development of effective disease control strategies.

Keywords Prevalence · Association · Impact · *Mycobacterium tuberculosis* · Malnutrition · Vitamin deficiency · Diabetes · HIV · Aging · Immunosenescence · Smoking · Alcohol use · Chronic kidney disease · Chronic obstructive pulmonary disease · Rheumatoid arthritis

1 Introduction

1.1 Global Trends in Tuberculosis Epidemiology

Tuberculosis (TB) is an airborne bacterial infection that causes disease in 9.4 million people a year worldwide, most of whom live in low- and middle-income

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countries [1]. The disease causes 1.7 million deaths each year, of which 20 % are estimated to occur in people living with HIV (PLHIV) [1]. The global prevalence of disease has begun to fall slowly since peaking in 2003 [2, 3], however TB control programs are yet to make a measurable impact upon the burden of disease in most regions of the world [4].

The epidemiology of TB is driven by the natural history of the disease and the susceptibility of the at-risk population. About one-third of the world's population has been infected with TB and has latent tuberculosis infection (LTBI) [3, 5].

1.2 The Role of Immunological Factors in Global Tuberculosis Epidemiology

Most exposed individuals are able to mount a sufficient immune response to contain or eliminate the bacteria, and therefore do not develop disease [5].

About 10 % of individuals with latent infection will progress to active TB during their lifetimes [5–7]. The greatest risk of progression is within the initial 2–5 years after infection, however disease reactivation may occur at any time. Individual susceptibility to progressing from latent infection to active disease varies considerably, and is strongly affected by immunological factors [7–10].

A recent study of TB rates in 134 countries identified a number of biological risk factors that were associated with higher rates of TB [4]. These risk factors included undernourishment, HIV infection, diabetes, and tobacco smoking—all of which are known to increase immune susceptibility. This study demonstrated that the impacts of immunological impairment are evident at both an individual and a population level.

Similarly, indicators of improving general health of the whole population have been associated with declining TB incidence. A recent study of national data from 165 countries, from 1990 to 2005, found that increasing life expectancy and improving vaccination rates were associated with declining TB incidence [11]. This suggests that improved immunological function, likely to be associated with improved general health, has an impact upon TB at a population level.

The epidemiological impact of conditions that impair immunity depends both upon the prevalence of the condition and the severity of immunological impairment that it causes. For example, the immunological impairment due to HIV infection confers a risk of developing TB of over 20 times than that of the general population [12, 13]. Consequently, HIV has had an important impact upon the TB epidemic, with an estimated 12 % (95 % CI 8–15 %) of TB-related deaths attributable to HIV infection [14]. In contrast, the relative risks of TB conferred by diabetes [9] and smoking [15] are less than five times that of healthy control subjects. However, although these conditions may not confer as high a risk of disease, they are much more common, and therefore also have an important impact upon TB epidemiology.

Together, immunological risk factors are major drivers of the ongoing global TB pandemic. Malnutrition affects around 1 billion people [16], diabetes affects

200 million people, alcohol abuse is highly prevalent in many populations, and there are 1.45 billion smokers worldwide [17]. The impact, or contribution that these risk factors make to overall incidence of TB in a population, termed the population attributable fraction (PAF), increases as the prevalence of these risk factors increases in the population.

This chapter will examine the relationship between TB and key risk factors that increase immunological susceptibility. It will examine the evidence that common causes of immunological impairment such as malnutrition, diabetes, aging, smoking, alcohol, chronic disease, and HIV increase the risk of TB. The complex interaction between TB and host immune function must be better understood if the TB pandemic is to be tackled effectively.

1.3 Sources of Evidence for the Impact of Immunologic Disease Upon Tuberculosis

The evidence for an association between immunologic disease and TB ranges from small clinical case series to large studies of entire populations. Even if a given risk factor is biologically plausible, and has been shown to be associated with TB, it is often quite difficult to prove a causal relationship definitively. In particular, it is notoriously difficult to adjust for confounding factors that coincide with the risk factors being studied. In contrast to laboratory studies, epidemiological studies occur in a complex environment where many variables are impossible or difficult to control or measure. For example, low socioeconomic status is often co-located with other environmental risk factors such as crowded housing, poor nutrition, limited access to health care, and increased tobacco and alcohol use.

Evidence for the impact of immunological factors upon TB can be derived from a variety of study designs [18]. The randomized-controlled trial design provides the best level of evidence for an association and best controls for confounding factors. However, it is not possible to randomly allocate exposures that will cause immunological impairment.

Observational studies are more feasible, ethically and morally acceptable, and are commonly used to test for associations in epidemiological studies. However, evidence derived from observational studies is limited, as the exposures in these studies are not experimentally assigned. Consequently, observational studies provide weaker evidence of a true association because they cannot avoid the influence of confounding factors upon the study outcome. It can be very challenging to dissect the contribution of each of the biological factors from the background social determinants of disease [19]. Cohort studies have the advantage of ensuring that a risk factor (such as alcohol consumption or diabetes) is measured prior to the time that the outcome occurs, which somewhat overcomes recall and selection bias.

Case-control studies have a number of limitations. In particular, these studies face difficulty in selecting a control group that is comparable with the group with

disease. This can lead to selection bias or confounding. Cross-sectional studies (also called *prevalence studies*) are unable to show a temporal association between the risk factor and outcome, or properly control for confounders.

Given the weaknesses inherent in the designs of most published studies, it is important to draw evidence about a particular risk factor from a variety of studies in a range of settings, before concluding that there is actually a causal relationship. Each study must be assessed for its intrinsic methodological weaknesses and interpreted with caution. Consequently, systematic reviews and meta-analyses [9, 20–26] can provide a very useful indication of overall trends. However, even these studies must be interpreted with caution as their conclusions are prone to publication bias, and may not necessarily apply to all settings.

1.4 Key Epidemiological Terms

This chapter applies a number of key terms that are important in interpretation of the epidemiological evidence.

Prevalence refers to the number of individuals in a population with disease at a specific point in time.

An *association* occurs when an environmental exposure or host characteristic is statistically correlated with a disease or health outcome. Not all associations are causal. Even if there is an association between an exposure and an outcome, it may not be possible to conclude that one event caused the other. In fact, there may be a third independent factor common to both exposure and outcome that explains the association, or the direction of causation may be the reverse (i.e. what is assumed to be the outcome, is actually the exposure).

Risk is the probability that an event (such as a disease) will occur following a particular exposure. In this chapter, a *risk factor* is an exposure that is statistically related to a particular disease outcome [27].

An *impact* is an outcome that is caused by exposure to a risk factor, such as "*the impact* of HIV on tuberculosis disease or mortality".

In the subsequent sections, we have included a wide variety of epidemiological evidence that examines the association between TB and key risk factors related to immunological impairment. Where evidence is available, we have examined the impact of these risk factors on TB infection, development of disease and mortality.

1.5 Immunological Impairment and the Natural History of Tuberculosis

An individual whose immune function is impaired will only develop TB in the presence of the *Mycobacterium tuberculosis* bacillus. Therefore, a person's risk of

developing active disease is not only influenced by the degree of immune impairment of the person but also depends upon exposure to TB and the biology of the bacterium.

After exposure to airborne droplets containing *M. tuberculosis*, an individual may become infected. He or she may either rapidly progress to TB disease after a short incubation period (so-called 'primary progressive disease'), may develop 'latent tuberculosis infection' (LTBI) or may eradicate the organism. In individuals with longstanding LTBI, lasting 6 months or more, TB may undergo subsequent reactivation and progress to active disease [28]. Hence, there is a dynamic interplay between the determinants of immunological impairment and the stage of the infection in each individual.

A condition impairing immunity in an individual may increase the risk of initial infection and primary progression after recent exposure, or it may increase the risk of subsequent reactivation of LTBI, or both. The condition may also affect the risk of mortality compared to an individual with normal immunity.

In this chapter, we explore the evidence for associations between common causes of immunological impairment and TB.

1.6 Methods of this Review

A literature review was undertaken to identify risk factors associated with TB. We first identified the main factors known to be associated with immunological susceptibility to TB at a population level in multiple countries, based on recent reviews of epidemiologic risk factors for TB [19]. We also conducted a search using PubMed for reviews of immunity and TB. We performed a series of searches on PubMed, combining "tuberculosis" with keywords for the identified risk factors including nutritional status, diabetes, smoking, chronic disease, alcohol, aging, and immunosuppressive medications. Based on these searches, we obtained recent systematic reviews for each topic [27, 29–36] and the full text of other relevant primary studies. We also identified information about the epidemiology of each risk factor from reports by the World Health Organization (WHO) and the United Nations.

2 Specific Immunologic Factors Associated with Tuberculosis

2.1 Malnutrition

2.1.1 The Global Burden of Malnutrition

Malnutrition, or the lack of nutritional elements necessary for human health, is common in populations with a high TB prevalence [19]. According to United

Nations data, an estimated 925 million people were undernourished in 2010, comprising almost 16 % of the population of low- and middle-income countries [16]. There have been dramatic improvements in food supply and per capita food availability over recent decades in many regions of the world [37]. However, these gains have not been uniform. Substantial improvements in nutrition have been made in India and China, while improvements have been much less in regions such as sub-Saharan Africa. Children are at a particularly high risk of the effects of malnutrition, not only due to protein and energy insufficiency but also as a result of limited access to essential micronutrients.

Micronutrient deficiency, also called "hidden hunger", is extremely common in resource-limited settings. Globally, it is estimated that iron deficiency anemia affects more than 1.2 billion people, Vitamin A deficiency affects between 100 and 140 million children and that almost 1 billion people are at risk of iodine deficiency [37]. These nutritional deficiencies are often closely linked to poverty, inadequate access to food, poor sanitation, and water supply—each of which have an impact upon the health of these populations.

2.1.2 The Mechanism for Malnutrition and Susceptibility to Tuberculosis

Nutrition, immunity, and infection are known to interact in complex and dynamic ways. Infection is both a cause and a perpetuating factor in protein energy malnutrition within a population, by reducing productivity, increasing socioeconomic and political stability, and impairing productive capacity of the society (Fig. 1) [38].

An association between malnutrition and TB is certainly biologically plausible. In experimental mice models of TB, protein calorie malnutrition has been shown to impair biological mechanisms in TB control including production of TNF, iNOS, and interferon-gamma. This deficiency could be reversed by restoring protein nutrition [39, 40]. Other experimental evidence also supports the association [40]. However, epidemiological studies are required to assess the relevance of these models to the human setting.

2.1.3 Malnutrition and the Risk of Tuberculosis

Tuberculosis and malnutrition have long been understood as being closely linked [41], as both are the consequence of poverty, economic instability, and food insecurity. However, until recently it has been surprisingly difficult to prove an association among malnutrition, immunological impairment, and TB at a population level [40].

We found little evidence of an association between malnutrition and susceptibility to latent infection. However, a range of epidemiologic studies have shown an association between malnutrition and active disease [38, 40, 42–45]. The main

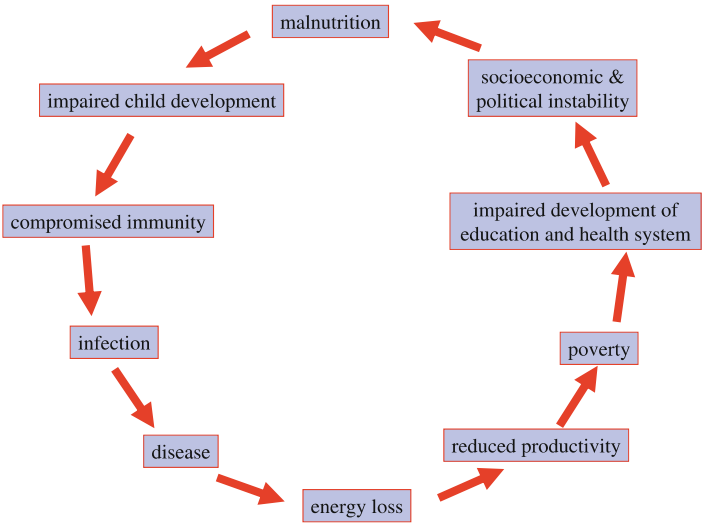

Figure 1. Protein Energy Malnutrition Increases Prevalence of Infection, Leading to Energy Loss for the Individual
On the community level, this burden reduces productivity, including food production, and perpetuates the relentless spiral of further malnutrition, infection, disease, poverty, and socioeconomic and political instability.

Fig. 1 The cycle of malnutrition, infection, disease, and poverty associated with tuberculosis in low-income settings [38]

limiting factor in most studies is the difficulty adjusting for independent factors related to poverty that may confound the association, such as crowded housing, smoking, or limited access to health care. This area of research is particularly challenging because the causal link may operate in either direction—it may actually be the TB itself that causes reduced body mass, muscle bulk, and biochemical parameters. We can obtain some fairly weak evidence from a number of ecological, cross-sectional, and case-control studies.

Ecological studies provide an insight to the association between nutritional deficiency and TB. An historical report from Denmark during the First World War described TB rates reducing dramatically once food supplies were restored to the population, in comparison to surrounding countries where shortages persisted [40]. During both the First and Second World Wars, there were increases in TB incidence in many European countries [46, 47]. Populations that maintained reasonable nutritional status tended to avoid the increase, while in the Netherlands a rise in TB coincided with periods of severe famine during the later years of the war [47]. Although such observations are suggestive of a correlation between malnutrition and TB at a population level, there are other potential confounders such as health system disarray that may also explain the phenomenon.

A study from Trondheim Naval School in Norway found that improvements to housing did not change TB incidence, but subsequent reductions in TB incidence

occurred with the supplementation in the diet of margarine, cod liver oil, whole wheat bread, fresh fruits and vegetables, and milk [48]. McKeown's analysis of TB mortality in England from 1770 to 1900 elaborated on the alternate hypotheses for explanation of reducing rates, and concluded that diet was highly likely to be responsible [48].

The beneficial impact of social interventions, including improved nutrition, was evident in the English village of Papworth during the period 1918–1943. Tuberculosis patients and their families were brought into the village and received adequate wages, improved nutrition and housing. Child contacts of TB patients born within the village, and receiving adequate nutrition, had a significantly lower risk of TB than contacts born outside this environment. The study provides an interesting example of how social and nutritional improvements correlate with reductions in TB [49].

Several published case series patients show an increase in TB risk associated with the nutritional deficiency associated with intestinal bypass [50, 51]. A number of cross-sectional studies have also shown that low body mass index (BMI) is associated with TB [43, 52]. A recent systematic review of six studies found an inverse log-linear relationship between TB incidence and BMI. The study showed a reduction of TB incidence of 13.8 % for each unit increase in BMI [52].

There are surprisingly few cohort studies available. This study design is relevant to establishing the direction of causation, by assessing the nutritional status of patients before they develop disease. One cohort study of 823,000 US navy recruits showed that TB occurred three times more commonly in young men who were 10 % or more below their ideal body weight, compared to those who were 10 % above it [53]. However, despite the large sample size, low socioeconomic status, and smoking may have been independently associated with susceptibility to TB in this cohort.

Objective measures of underweight have also been associated with TB. One study in Tanzania found that low levels of low subcutaneous fat and low hand grip strength were associated with TB [43]. Other studies have found that low BMI and mid arm circumference [54] were associated with TB in patients compared to a control group.

2.1.4 Vitamin Deficiency and Tuberculosis

In addition to low weight and energy malnutrition, reduced micronutrients (particularly vitamins A, C, E, zinc and selenium) have been associated with impaired immune response. Micronutrients are nutrients that are essential in the diet in small quantities, to enable a range of normal physiological functions. They include minerals, vitamins, and other organic compounds. A number of studies have studied the association between micronutrient deficiency and TB, but often it is difficult to determine whether such deficiencies are the cause or effect of TB [24, 55–57].

(a) Vitamin D and TB

Vitamin D has a range of important physiological functions, including a role in infectious immunity [58]. Vitamin D levels in individuals commonly fluctuate

annually, and are particularly low during the winter months in North American and European countries due to reduced sun exposure. This observation, and finding of an association between low vitamin D levels and TB [24], has led to the hypothesis that Vitamin D deficiency contributes to TB susceptibility. Vitamin D deficiency has been offered as a possible explanation for reactivation of TB among migrants from sunshine-rich tropical countries to Northern Europe and North America [24]. However, although peaks of TB coincide with low Vitamin D levels, this finding is not seen consistently [59].

A meta-analysis of seven studies evaluating the relationship between Vitamin D and TB showed a significantly lower levels of the vitamin in TB patients compared to controls (with an effect size of 0.68 (95 % CI 0.43–0.93). However, the included studies did not measure nutritional status prior to disease onset and so the direction of causation is not certain [24].

Hence, while both environmental [59] and genetic [60] factors influence the way that Vitamin D affects immunity, the association between Vitamin D and TB still remains unclear [58].

(b) Vitamin C and TB

Vitamin C, or ascorbic acid, has a number of essential metabolic functions including in cell-mediated immunity [61]. A large cohort study showed a correlation between low levels of Vitamin C and TB, however this became non-significant when adjusted for nondietary factors [55]. A number of other studies have also established associations between Vitamin C and TB [62].

(c) Vitamin A and TB

Vitamin A is an essential dietary vitamin that is important for vision and epithelial cell function and has a number of important roles in the immune system [61]. A small case-control study in India found lower Vitamin A levels in TB patients than in healthy controls. However, retinol binding may independently be lowered by acute illness [63, 64].

Other studies from Africa have found low Vitamin A levels in patients with TB and HIV co-infection [65, 66]. There is also evidence that HIV infection may also contribute to low Vitamin A levels. In one South African study, 90 % of TB patients had low levels of the vitamin [67], and another study found that a 64 % of HIV-positive blood donors also had low Vitamin A levels. Consequently, there is not yet clear evidence for a relationship between Vitamin A and TB susceptibility.

(d) Evidence for vitamin supplementation in TB

A 2008 Cochrane study examined the role of vitamin and micronutrient supplementation in TB [68]. The authors identified no evidence that supplements affected sputum conversion or cure rates, however there was a benefit for high energy supplements, multivitamins, and Vitamin A plus zinc in achieving significant weight gain compared to placebo. Additional recent trials have failed to demonstrate benefit [69], and other trials are currently underway to address the role of supplements in enhancing immune function in TB patients.

In a recent randomized controlled trial [56], TB treatment outcomes were unchanged by Vitamin D supplementation. Unfortunately, this study was underpowered and both arms had excellent outcomes. Furthermore, it does not address the relationship between Vitamin D deficiency and reactivation of latent TB infection.

Hence, while there are some evidences of an association between TB and micronutrient deficiency, further research is required to investigate whether there is a causal relationship between deficiency of specific micronutrients and TB susceptibility.

2.1.5 Malnutrition and Tuberculosis Mortality

Malnutrition is also associated with increased mortality due to TB. The link between TB mortality and nutritional factors was addressed in a recent systematic review [26], which showed evidence that TB outcomes were worse for underweight and malnourished patients.

A retrospective cohort study from the United States showed the odds of death to be 3.2 (95 % CI 2.1–4.9) times higher in malnourished patients [44]. Another study from Australia also found that patients with malnutrition had 3.2 times the odds of death (95 % CI 1.0–9.9) [70].

Another study in Malawi demonstrated that severe malnutrition was associated with death during the initial 4 weeks of treatment, and that risk of mortality was greater at lower body mass indices (a BMI of less than 16 had an odds ratio of 2.2 (95 % CI 1.3–3.8) [71]. Other studies in the United States [44] and Latvia [42] have also found an association.

A number of epidemiologic studies have shown a correlation between biochemical parameters, such as serum albumin and TB mortality [26]. However, as discussed previously, the temporal association is unclear. It is conceivable that such measures of malnutrition actually reflect the consequences of delayed diagnosis. Therefore, more advanced malnutrition may merely reflect prolonged disease and hence predict an understandably higher mortality rate.

2.1.6 The Impact of Malnutrition Upon Tuberculosis at a Population Level

According to a United States Surgeon General report “malnutrition may account for a greater population attributable risk of TB than HIV infection, and certainly a much more correctable one” [72].

Since a very large number of people worldwide suffer from some degree of malnutrition, modest reductions in malnutrition at a population level may translate to a substantial impact on TB incidence. However, there remains little direct evidence showing a benefit from nutritional supplementation upon TB incidence within a whole population. Ecological observations, such those described above from Europe during the Second World War, suggest that improving nutrition at a

population level may reduce TB incidence fairly rapidly [47]. Quasi-experimental studies such as the Papworth experiment also suggest a role for a comprehensive social and nutritional support to reduce the progression to disease [49].

The Millennium Villages program that is currently underway in Africa represents a modern equivalent that applies comprehensive social, nutritional, and health care interventions to improve health in whole communities [73]. Such strategies offer an excellent opportunity to evaluate the relationship between nutrition and TB in settings where marked socioeconomic improvements are achieved.

2.2 Diabetes and Tuberculosis

2.2.1 The Global Burden of Diabetes

Diabetes is an increasingly common condition globally, with a recent review of data from 199 countries showing a prevalence of 9.8 % among adults aged 25 years or over [74]. There were 171 million prevalent cases worldwide in 2000, and this number is projected to rise to 366 million by 2030 [75]. In high-income countries, diabetes prevalence has increased substantially over recent decades, and now 23.1 % of Americans aged over 60 years have diabetes. In Europe, noncommunicable diseases (particularly diabetes and alcohol) are now thought to be more significant causes of immunological impairment in TB patients than HIV [76].

Diabetes is also becoming more common in low- and middle-income countries, as these countries face the so-called "double-burden" of both communicable and noncommunicable disease [77].

2.2.2 Diabetes and Risk of Tuberculosis

Two recent systematic reviews of TB and diabetes have shown consistent evidence of an association [9, 78]. One such review included 13 studies, of which three were cohort studies and 10 were case control studies. The pooled relative risk of TB in the cohort studies was 3.1 (95 % CI 2.3–4.3) across these studies. This effect was also seen in the included case-control studies [9].

The second systematic review identified nine studies that compared the prevalence of TB in diabetics to that in nondiabetics, and found all studies showed an increased prevalence among diabetics. This study did not attempt to provide a summary statistic due to heterogeneity in study designs and research methods [78]. The included studies that quantified the prevalence of TB were from South Korea (OR 3.5 (95 % CI 3.0–4.0)), India (OR 2.4 (95 % CI 1.2–5.1)), Russia (OR 2.7 (95 % CI 1.1–6.5)), the United Kingdom (3.8 (95 % CI 2.3–6.1)), two studies from Indonesia (OR 4.2 (95 % CI 1.2–11.7) and OR 4.7 (95 % CI 2.7–8.1)), Mexico (6.8 (95 % CI 5.7–8.2)) and two studies from the United States of America (OR 2.95 (95 % CI 2.6–3.3) and 1.82 (95 % CI 1.6–2.1)).

A Pakistani cohort study found TB prevalence in diabetic patients was 10 times higher than in nondiabetic patients [79]. In Tanzania, a case-control study found diabetes was four times as frequent and impaired glucose tolerance was twice as frequent in diabetics than in controls [80]. A South Korean longitudinal study among 800,000 civil servants found 5.2 (95 % CI 3.8–7.0) times more microbiologically confirmed cases in diabetics [81], and 3.5 (95 % CI 3.0–4.0) times more among all diabetics. However, in this study people with no diabetic history were not tested for diabetes.

A large prospective cohort from Canada, comprising over 500,000 people, found the diabetic population had a relative risk of 1.2 (95 % CI 1.1–1.4) compared to nondiabetics [82].

It is important to recognize that the prevalence of latent TB infection in a population will influence the absolute risk of a diabetic patient developing TB. In countries with a low prevalence of TB, such as Canada, diabetic patients are very unlikely to be exposed to infectious organism. Hence, although they may be more susceptible, in the absence of infection this susceptibility will usually not result in TB.

By contrast, in countries with a high prevalence of latent TB infection, patients with diabetics are more likely to be infected. Consequently, patients with diabetes have a much greater likelihood of progressing to TB than those in low-prevalence settings. This observation explains why studies conducted in countries with low incidence of TB require much larger sample sizes to detect an effect due to diabetes, and the overall effect size appears small.

2.2.3 Does the Adequacy of Diabetic Control Affect Tuberculosis Susceptibility?

A small number of studies show that poorly controlled diabetes is more likely to be associated with TB.

In a Hong Kong study of 42,116 diabetics aged 65 or above with a glycosylated hemoglobin (HbA1c) of seven or more (poorer diabetes control) had 3.1 (95 % CI 1.6–5.9) times the odds of developing culture confirmed pulmonary (but not extrapulmonary) TB compared to the group of diabetics with better control [83].

A prospective cohort study of diabetes in Tanzania found that 8.8 % of patients with type 1 diabetes developed pulmonary TB, compared to 2.2 % of patients with type 2 diabetes that did not require insulin [84]. In this study, nutritional status may have been a confounding factor as patients with type 2 diabetes had a higher mean BMI than type 1 diabetics, and may have been protected against TB due to better nourishment.

The relationship between BMI and diabetes is complex. In some settings such as India, the gains made by improvements in nutrition may be offset by rising levels of diabetes [85].

2.2.4 Diabetes and Treatment Outcomes of Tuberculosis

Evidence from two cohort studies, one from India [86] and one from the United States found that the time to sputum conversion was not significantly different in diabetic patients with active TB [87].

Most studies examining mortality among TB patients found significantly increased mortality in diabetics. One study from the United States found all-cause mortality was 4.7 (95 % CI 1.9–12.5) times greater in diabetics when adjusted for age [88]. A second retrospective cohort study from Baltimore found the odds of death were 6.5 (95 % CI 1.1–38.0) times higher in patients with diabetes (1.1–38.0), when adjusted for HIV, age, weight, and foreign birth [87]. Another small cohort study found that diabetes was associated with a mortality of 3.8 (95 % CI 1.4–10.3) [89] times that of nondiabetics. In contrast, a retrospective cohort study from St Louis found no association with mortality [44].

Consequently, it appears likely that diabetes, particularly if it is poorly controlled, does increase the mortality of patients with TB.

There is conflicting evidence about the impact that diabetes has upon treatment failure rates, as distinct from overall mortality. The aforementioned study from Baltimore found no significant difference between treatment failure in patients with and without diabetes [87].

A case-control study from Egypt did find diabetes to be a risk factor for treatment failure among those who were compliant with treatment (OR 10.08, 95 % CI 2.5–41.3), although the sample was small and drug resistance patterns were not reported [90].

A study from Saudi Arabia found no difference in treatment outcomes, but found that diabetics had lower rates of multi-drug-resistant (MDR) disease and higher initial sputum load of acid-fast bacilli and higher 3-month conversion rates than nondiabetics [91]. Interestingly, in this study the mean time for sputum conversion was longer in diabetics, even though they had lower rates of MDR disease. By contrast, another from the United States actually found higher rates of MDR in among diabetic patients with TB [92] (adjusted OR 5.3, 95 % CI 1.9–14.6)). It is difficult to be certain about the reason for this finding, particularly since the odds actually increased when failure rates were adjusted for participation in observed therapy (OR 8.6 (95 % CI 3.1–23.6)), meaning that primary resistance was unlikely to have caused the MDR TB. One possible explanation is that diabetic patients were more likely to utilize hospital services, and that increased nosocomial transmission may drive the higher prevalence in these patients, particularly given the high rates of MDR in New York City at the time.

The evidence for the impact of diabetes upon the clinical presentation of TB is mixed. Radiological studies give varying evidence about the lobar distribution of TB among diabetics. Some studies have showed more lower lobe involvement in TB with diabetes [83], one study found more cavitatory disease [93], while another found the pattern of disease diagnosed radiologically among diabetics to be similar

to that of nondiabetics [94]. The difference in radiologic signs between diabetics and nondiabetics is probably overstated [36]. Two studies identified in a recent systematic review found that the risk of diabetes was highest risk in the young, and declined with older age [78]. These findings may be specific to the populations in which they were studied, and further research is warranted to further explore the clinical presentation of TB among diabetics.

2.2.5 The Impact of Diabetes Upon Tuberculosis at a Population Level

Not only is there is strong evidence for an association between TB and diabetes in individuals, but there are also clear public health implications behind increasing rates of diabetes worldwide [78]. Particularly in populous countries such as India, with a large proportion of both the world's TB and diabetes, the interplay between the two is likely to continue to undermine efforts at TB control [95].

2.3 HIV and Tuberculosis

2.3.1 The Global Burden of HIV

There were 33.3 million PLHIV and 2.6 million new cases in 2009 [96]. Despite the rapid rise in HIV incidence in the 1980s and 1990s, the number of new cases peaked globally in 1999. Incidence has been falling due to a variety of factors including preventive efforts, behavioral change, and better access to treatment [96]. Despite improvements in most countries, there were still seven countries where incidence increased by more than 25 % from 2001 to 2009 [96]. HIV prevalence varies considerably between and within countries, ranging from 0.1 % of adults aged 15–49 years in East Asia to 5.0 % in sub-Saharan Africa [96]. The latter region is home to 68 % of the total number of people living with the virus, where HIV infects more women than men.

Globally, the majority of people who acquire human immunodeficiency virus (HIV) do so through unprotected heterosexual intercourse. Consequently, in settings with a 'generalized' epidemic (HIV prevalence is 1 % or more of the general population), women and men are often affected to a similar degree [97]. In 'concentrated' epidemics, the prevalence is less that 1 % in the general population but over 5 % in specific at-risk populations [97] such as injecting drug users. Consequently, the results of HIV-related immunological impairment predominantly affect those groups.

If untreated, affected individuals are at high risk of acquiring opportunistic infections and AIDS-related illnesses and suffering increased mortality. Approximately, 1.8 million people died due to HIV/AIDS in 2009. As with the global

trend in the disease, HIV-related mortality has also begun to decline, particularly among children [96].

2.3.2 The Mechanism for HIV Infection and Susceptibility to Tuberculosis

People living with HIV (PLHIV) are highly susceptible to TB. This may be either due to the rapid progression of new TB infection or re-infection, or due to the reactivation of pre-existing latent TB [98]. Not only does HIV affect TB, by causing profound immunological impairment, but TB disease may also accelerate the progress of HIV [99]. Conversely, treating TB improves HIV control [23]. Therefore, the epidemiologic impacts of both pathogens are closely related.

2.3.3 HIV and Progression to Tuberculosis Disease

There is very strong evidence for an association between HIV and TB, which has been evident since the beginning of the HIV epidemic in the early 1980s [100].

The risk of TB among PLHIV is significantly higher than the general population, although the magnitude of the risk varies depending upon the background population prevalence of both HIV and TB. A WHO report of directly measured data from 64 countries found that HIV-positive people are over 20 times more likely than HIV-negative people to develop TB in settings with a generalized HIV epidemic. In countries with a low prevalence of HIV, the risk was 26–37 times that of HIV-negative individuals [101].

Another analysis found that in countries with a generalized HIV epidemic, the relative incidence of TB among PLHIV was 20.6 (95 % CI 15.4–27.5) compared to uninfected individuals. In settings with an HIV prevalence of less than 5 %, risk of TB was 36.7 (95 % CI 11.6–116) times that of the HIV uninfected population [12].

As for all HIV-related opportunistic infections, the prevalence of TB increases at lower CD4 T cell counts [31].

The high degree of susceptibility was highlighted in a cluster outbreak study from the United States, where 37 % of PLHIV developed active TB compared to no cases among the uninfected group [98]. A recent meta-analysis of molecular epidemiologic studies showed HIV to be significantly associated with clustering of disease (adjusted OR 0.13 (95 % CI −0.19 to 0.44)) [20]. However, molecular epidemiology studies are likely to be biased toward detecting an association between TB and HIV, because clustering is based upon recent transmission. The inclusion of a case in a cluster usually requires a diagnosis within 2 years of the initial index case. Consequently, as there is more rapid progression to disease in HIV-infected patients, it is likely that they will be over-represented. An additional source of possible bias is that outbreak investigations often begin within health care institutions, where HIV is more likely to occur. The alternative explanations for the markedly higher rates of disease in clusters, that HIV-infected patients are

more likely to be infected or that they are more likely to transmit disease, are both unlikely. More likely, HIV is independently related to the identification of the sorts of patients included in an outbreak investigation.

The risk of acquiring TB increases after the patient undergoes HIV seroconversion and doubles within the first year of HIV infection [102]. In advanced AIDS, the risk of progression from latent infection to active disease increases significantly compared with that of a person who is HIV negative [100] HIV is also a predisposing factor for developing MDR-TB [103].

2.3.4 HIV and Susceptibility to LTBI

While HIV is clearly associated with progression from LTBI to active disease, there is little data to determine whether HIV infection initially increases susceptibility to latent TB infection. A meta-analysis of 168 studies of contact investigation found the prevalence of LTBI in HIV-infected individuals was similar to the prevalence of LTBI in all contacts. However, there was considerable heterogeneity in the outcomes of included studies, in part due to variations in study design and different epidemiological settings in which the studies were conducted [104].

2.3.5 Mortality of HIV/Tuberculosis Co-infection

HIV infection also appears to increase the risk of mortality due to TB. Of the estimated 1.8 million deaths each year among PLHIV worldwide, 0.4 million deaths (22 %) occurred among incident TB cases with HIV [1].

All-cause mortality in a cohort of 239 TB patients treated in Zambia found the mortality among HIV-positive patients to be five times that of an HIV-negative patient over 24 months following diagnosis with TB [105]. A total of 42 out of the 47 patients in this study who died were HIV positive [105].

Autopsy studies from a West African city found that TB was present in 54 % of people dying with AIDS [106].

2.3.6 The Impact of HIV Upon Tuberculosis at a Population Level

HIV can have a significant effect upon the incidence of TB at a population level. One study of population-wide data from 134 countries showed that the annual increase in TB incidence in Latin American and the Caribbean countries positively correlates with HIV rates in those countries [4]. The impact of HIV was a major driving force behind the sharp increases in TB incidence in sub-Saharan Africa in the 1980s and 1990s [33]. Indeed, global TB incidence would have fallen substantially between 1990 and 2000 if there had been no concomitant HIV epidemic. [14, 33].

Although the global incidence of HIV has peaked [96] sustained access to effective therapy and health care capacity remain major barriers to global HIV

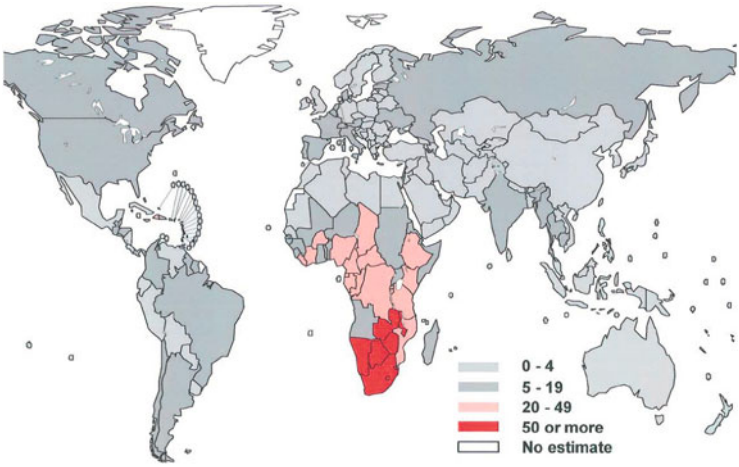

Figure 2. Estimated HIV infection prevalence (%) among new adult patients with tuberculosis (15–49 years of age). Reprinted from the World Health Organization [7]. The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city, or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines denote approximate borders on which there may not yet be full agreement.

Fig. 2 Estimated HIV infection prevalence among new adult patients with tuberculosis [33]

control. Consequently, the impact of immunological impairment due to HIV will remain a major factor in global TB epidemiology this century (Fig. 2).

2.4 Aging and Tuberculosis

2.4.1 Global Trends in Aging

The world population is aging at a scale unprecedented in human history, with the older population (aged 60 or over) increasing at 1.9 % per annum compared to 1.2 % growth of the overall population. The median age of the world's population is currently 26 years, but by 2050 the median age will increase to 36 years [107, 108]. By then, people aged 60 and above will comprise 21 % of the world's population, and exceed the number of people aged younger than 15 years [107]. These trends will have profound implications for the patterns of disease in these populations.

2.4.2 The Impact of Age Upon Immune Function

Immune function varies dynamically with age. At both extremes, TB susceptibility is increased, and these changes are accompanied by differences in presentation of the disease [109].

Early pre-antibiotic studies show the risk of children developing TB was greatest in children up to 4 years of age, and it then slowly declined up to 10 years of age [8]. Following primary infection, the mortality of childhood TB is highest in infancy, subsequently declining to 1 % between 1 and 4 years of age, before rising to 2 % from 15 to 25 years of age. This reflects the changing immunological function over the early life span [8], as well as socioeconomic and nutritional factors.

Age-related decline in immune function is known as immunosenescence. The predominant changes in immune function with aging are progressive decline in cell-mediated immunity, including both defects in T and B cells as well as innate immune function [110]. These findings have also been shown in mice, where T cells undergo age-associated functional changes [111]. In addition to direct immunological effects of aging, malnutrition also contributes significantly to the increase in infectious diseases in the elderly. The impacts of age-related chronic diseases also have an impact on immunological susceptibility to TB [112], and are addressed in detail in other sections of this chapter.

2.4.3 The Impact of Aging Upon the Epidemiology of Tuberculosis

Population aging clearly has differing impacts upon TB epidemiology depending upon the demographic factors and existing burden of disease affecting each country.

In high-income countries, there has been a steady decrease in TB over at least the past 50 years [113]. However, the elderly population has experienced a relatively slower rate of decline in incidence. This is largely because the elderly populations, having been exposed to *M. tuberculosis* in their youth, experience reactivation of the disease in later life [114].

In the United States, the incidence of TB increases steadily with age albeit from a relatively low absolute rate. The same trend has been seen in Japan, which has decreased its TB notification rate from 303 per 100,000 population in 1962 to 22 per 100,000 by 2005 [115].

In low- and middle-income countries, the age distribution of TB differs dramatically from high-income settings. In African countries, the age-specific case-notification rate is in the age group 25–44, while in the USA it is highest in the population above 65 years of age [115].

The clinical presentation of TB appears to be similar across different age groups. A meta-analysis of 12 studies assessed the effects of aging on pulmonary TB and found that there were no significant differences between patients aged over 60 years and patients who were younger, with respect to most clinical, radiological, and biochemical parameters [35]. The analysis showed slightly higher rates of sputum smear positivity, and reduced lung cavitation as well as lower albumin levels. In some studies, extrapulmonary disease has been reported to be more common among the elderly [30]. Elderly patients are also more likely to suffer cardiovascular disorders, diabetes, chronic obstructive pulmonary disease (COPD), and malignancy, each of which may confer susceptibility to TB [115].

The effects of aging on the epidemiology of TB are therefore complex. As the overall rate of TB in a population is decreasing, the rate of decline is likely to be slower in the elderly.

2.4.4 The Impact of Aging Upon Tuberculosis Infection, Reactivation and Mortality

The prevalence of LTBI increases as a person ages, due to the increased lifetime risk of exposure to *M. tuberculosis*. In high-incidence countries, the prevalence of latent infection steadily rises throughout the life of most individuals, so that by the age of 30, the majority of people will have been infected [113]. Although some go on to develop disease immediately, a proportion will retain the infection for years. *M. tuberculosis* may then reactivate as the person ages [109].

Hence, the risk of disease in the elderly is both related to the cumulative lifetime risk as well as the risk of transmission in the past decades [115]. Unless there are high rates of ongoing transmission, the disease is much more likely to represent reactivation than progression following recent infection.

2.4.5 Malnutrition in the Elderly

While immunological impairment in the elderly may be attributed to immunosenescence, malnutrition is in fact an important contributor to the increase in infectious diseases [116], 5–10 % of community dwelling individuals and up to 60 % of hospitalized elderly suffer from protein, energy, and micronutrient deficiency.

2.4.6 The Impact of Aging on Global Tuberculosis Incidence

Aging is affecting the global TB pandemic in different ways depending upon demographic factors within each country. In high-income countries, the elderly comprise an increasing proportion of all TB patients. This population is also often more likely to be infected with TB due to past exposure. Consequently, in Japan the prevalence of latent TB infection among those over 70 years is as high as 70 %, but among those aged 20 years it is only 1 %. The elderly are therefore both at risk due to the immune impairment of aging as well as their higher likelihood of past exposure [115].

In contrast, the role that aging has in TB is much less in countries with younger populations. In Africa, the highest incidence is in 15–24 years old and elderly people comprise a relatively small proportion of all cases [115]. However, as populations of countries such as India and China age, the contribution of immune impairment among the elderly to the population incidence of disease will also steadily increase.

2.5 Smoking, Indoor Air Pollution, and Tuberculosis

2.5.1 The Global Burden of Smoking and Indoor Air Pollution

Worldwide there are an estimated 1.45 billion smokers, with rates of smoking among males five times higher than among females [17]. Per capita cigarette consumption is continuing to increase in low- and middle-income nations, while it has steadily declined in high-income countries. Today, the vast majority of smokers live in low- and middle-income countries. China, where 52.9 % of men and 2.4 % of women smoke [117], is now home to 301 million current smokers. This has significant implications for the health of the whole population.

In most low- and middle-income countries, the majority of the population uses heavily polluting combustion heaters to heat and cook, burning wood, dung, and crop residues [118]. These materials are typically incompletely combusted, and associated with considerable indoor air pollution. Children and women are particularly exposed to high levels of indoor air pollution, and biofuel use is particularly associated with poverty [118]. Although its use is declining in many countries, the slow progress in economic development in many countries makes it likely that biofuel use will remain an important contributor to morbidity among the poor.

2.5.2 The Impacts of Smoke Exposure Upon Immune Function

Chronic exposure to both tobacco smoke and other indoor air pollutants may directly impair immune function—by impairing normal clearance of secretions [119], and therefore impair the initial clearance of bacteria. Smoke exposure may also impair alveolar macrophage function [120]. Cigarette smoke contains more than 4,500 compounds, many of which are immunosuppressive, including nicotine. Therefore, it is biologically plausible that smoking impairs the host immune response to TB [120]. For example, components of tobacco such as nicotine may decrease TNF production by macrophages. Consequently, it is conceivable that smoking will impact upon the susceptibility of individuals and populations to TB.

2.5.3 Smoking and Susceptibility to LTBI

Tobacco smoking has been clearly recognized to increase the risk of latent TB infection in smokers [22]. A meta-analysis in 2007 identified 38 papers relating to the effects upon TB susceptibility by tobacco. Data from six included studies showed that the odds of having a tuberculin skin test (TST) result of 5 mm or more was 2.1 (95 % CI 1.5–2.8) times higher in smokers, and the odds of having a TST of 10 mm or more was 1.8 (95 % CI 1.5–2.2) [22]. When adjusted for alcohol, the odds ratio was still 1.8 (95 % CI 1.4–2.2). Interestingly, the significant difference in infection rates was found only among cross-sectional studies but not case-control studies.

Another study in nursing homes showed that subjects were more likely to have latent TB infection if they were than smokers than if they were nonsmokers (OR 1.6) [121]. The study found that Heaf test positivity directly related to pack years of smoking. Similarly, migrant workers in California showed increased prevalence in former smokers than nonsmokers (OR 3.1 (95 % CI 1.2–8.9)) [122].

2.5.4 Associations Between Smoking and Tuberculosis

There is considerable evidence that smoking is associated with TB disease. An early study compared smoking habits in 1,200 TB patients to 979 controls from non-TB inpatient and outpatient settings. They concluded there is a "direct association between smoking habits and respiratory tuberculosis" [123].

A meta-analysis of 23 studies addressing the effect of smoking upon TB from 12 countries showed a significantly higher risk of active TB among smokers compared to nonsmokers for both pulmonary TB and all TB [22]. This meta-analysis was limited by the considerable heterogeneity associated with inter-study variation.

A separate review of seven studies showed an association between TB and smoking. Four of these studies showed a dose–response effect, where higher tobacco consumption was associated with a higher risk of active disease [124].

A cross-sectional study from Shanghai that compared heavy smokers to non-smokers found the odds of smokers developing TB were 2.2 (95 % CI 1.3–2.6) times higher than nonsmokers, after adjustment for possible confounders including age, sex, and contact with TB patients. This study found no association for patients reporting mild or moderate levels of smoking [125].

The amount smoked also appears to influence the risk of TB. A study from the United States found that smoking conferred a TB risk of 30–50 % higher than the risk for nonsmokers [126]. The largest risk was for those smoking more than 30 years. Another study showed that in a cross-sectional study of 76,589 volunteers that there was a gradient of increase in TB rate for increasing amount smoked in both men and women [127].

Smoking has also been shown to increase the risk of relapse after successful treatment for TB [128].

2.5.5 Smoking and Tuberculosis Mortality

There is mixed evidence about the association between smoking and TB mortality. Five studies have looked at TB mortality related to smoking. There was substantial heterogeneity in the findings form different settings, however among patients with pulmonary TB mortality among smokers was twice that of nonsmokers [22]. Other studies have found no association between TB deaths and smoking [26].

2.5.6 Indoor Air Pollution and Tuberculosis

There is currently mixed evidence about the impact of indoor air pollution on the risk of developing TB. One systematic review of the available literature identified six studies, of which only two adjusted for cigarette smoking [34]. Many of these studies did not adequately quantify the exposure. The results from three studies reached statistical significance, showing odds of TB to be increased by 2.5 (95 % CI 1.1–6.0), 2.6 (95 % CI 2.0–3.4), and 2.2 (95 % CI 1.1–4.2) times, respectively. Another more recent case-control study in China found no significant association [129]. A challenge in these studies is quantifying the true long-term exposure to biofuels.

Consequently, there is still insufficient evidence to confirm the biologically plausible association between indoor air pollution and TB. Further studies are required to elucidate the issue, and to quantify the necessary threshold of exposure.

2.5.7 Passive Smoking and Tuberculosis

Passive smoking has also been shown to be a risk factor for TB. An unmatched case-control study from Spain compared 93 child contacts of TB patients who developed disease to 95 contacts who did not develop disease [130]. The study showed passive smoking is a risk factor for TB (OR 5.4 (2.4–11.9, $p < 0.01$)), particularly in children aged less than 10 years. It also found a dose response association between risk of acquiring active TB and amount smoked in the household. This study adjusted for socioeconomic status of the parents and age of the children, and still showed an association. The relationship was only significant for >20 cigarettes per day consumed in the household.

2.5.8 The Impact of Smoking and Indoor Air Pollution Upon TB at a Population Level

At a population level, exposure to cigarette smoke and other airborne pollutants have an important effect upon prevalence of TB [131]. Modeling in one study suggested that complete cessation of smoking would reduce the projected incidence of TB in China by between 14 and 52 % [132]. At a population level, cigarette smoking is likely to be a key reason why men are more likely to develop TB than women. In the south of Vietnam, where males are more than four times more likely to develop TB than women [133], current smoking rates are 67.8 % in men, and only 1.1 % in women [134]. It is very likely that this striking difference in smoking rates explains some of the difference in TB prevalence. Clearly smoking cessation is an important health care priority for many reasons, including its impact upon TB.

2.6 Alcohol and Tuberculosis

2.6.1 The Global Burden of Alcohol Use

Alcohol is one of the most commonly abused substances worldwide. The annual per capita consumption in 2005 was 6.13 liters of pure alcohol per person aged 15 years and older, of which 28.6 % was homemade [135]. According to a recent WHO report on global alcohol status, there is significant variation in consumption of alcohol, with the highest levels found in high-income countries, medium levels of consumption found in southern Africa, North and South America and lower consumption found in North Africa, southern Asia, and the Eastern Mediterranean [135]. More than 45 % of alcohol is consumed in the form of spirits and 36 % is consumed as beer. Global estimates suggest that consumption is stable in most regions, but there has been an increase in Africa and South-East Asia.

2.6.2 The Impact of Alcohol on Immune Function

Alcohol is a common cause of immunological impairment in both developed and developing countries. In addition to an association with smoking, alcohol abuse is often associated with malnutrition. All of these factors confer a strong biological explanation for immunological susceptibility to TB. The mechanisms by which alcohol impairs immune function have been well described [136].

2.6.3 The Impact of Alcohol on Tuberculosis Risk

There is now a substantial body of literature that shows a strong association between alcohol and TB, independent of smoking. A recent meta-analysis on the risk of TB with alcohol use disorders found a pooled relative risk of 2.9 (95 % CI 1.9–4.6) [25]. The meta-analysis combined the effect of three cohort studies and eight case-control studies including patients that consumed 40 g of alcohol or more daily. Another meta-analysis of molecular epidemiology studies showed alcohol abuse was associated with increased clustering of TB cases, suggesting increased risk of transmission in this setting [20].

There is evidence that heavy alcohol use will increase susceptibility to active disease TB and reactivation of latent infection as well as other respiratory infections [25]. A number of studies also show an association between alcohol use, earlier TB relapse and more destructive forms of TB [25]. Heavy drinkers also have higher rates of MDR-TB and treatment default than nondrinkers [25].

Alcohol use may also be associated with higher rates of mortality in TB, although there have been mixed findings. A systematic review found evidence of an association between TB-related death and alcohol in Russia and Brazil, however no association was found in another Indian study [26]. Another study from the

United States found that the people with heavy alcohol consumption had twice the rate of TB even after adjusting for smoking (OR 2.0, 95 % CI 1.1–3.7) [126].

2.6.4 The Population Impact of Immunological Impairment Due to Alcohol on Tuberculosis

Alcohol is likely to have a marked impact on TB epidemiology globally, despite the inherent difficulty in quantifying alcohol consumption in individuals or at a population level. One systematic review estimated that 10 % of TB globally could be attributed to alcohol [25]. As alcohol consumption varies considerably between populations, also does its impact upon TB.

Heavy alcohol consumption is likely to be one of the reasons that explain why males are more likely to develop TB than females [137]. However, it is difficult to disentangle the confounding factors that may cause increased risk of TB, particularly smoking, malnutrition, and poverty.

2.7 Chronic Disease and Tuberculosis

2.7.1 The Epidemiology of Chronic Disease

Chronic diseases, such as heart disease, diabetes, COPD, and cancer, are now the leading causes of mortality worldwide [138]. In addition to being the major cause of illness in high-income countries, chronic illness is responsible for an increasing proportion of morbidity in low- and middle-income settings [139]. Many of these diseases are related to lifestyle changes that have accompanied increases in per capita income, including smoking, lack of physical exercise, changes in diet, and use of alcohol. There is a vast literature on the epidemiology of different chronic diseases, including a recent global report by the WHO [138].

2.7.2 The Impact of Chronic Illness Upon Tuberculosis Epidemiology

As societies in low- and middle-income countries become wealthier, they tend to undergo an epidemiologic transition from primarily infectious disease to higher rates of chronic disease [77]. Paradoxically, even if TB rates are falling as overall health standards rise, those individuals with chronic illness may become more susceptible.

The relationship between chronic disease and TB is well documented. Higher rates of TB have been shown in patients with chronic kidney disease, COPD, and other chronic diseases in comparison to the unaffected population [36].

Chronic kidney disease is becoming increasingly common in many societies, and a number of studies have identified it as a risk factor for TB. For example, one