ERJ Express. Published on October 14, 2010 as doi: 10.1183/09031936.00084310

Tuberculosis and non-communicable diseases: neglected links, missed opportunities

Authorship list: Jacob Creswell[1], Mario Raviglione[1], Salah Ottmani[1], G.B. Migliori[2], Mukund Uplekar[1], Leopold Blanc[1], Giovanni Sotgiu[3], Knut Lonnroth[1]

1. Stop TB Department, World Health Organization, Geneva, Switzerland.

2. WHO Collaborating Centre for TB and Lung Disease, Fondazione S. Maugeri, Care and Research Institute, Tradate, Italy

3. Hygiene and Preventive Medicine Institute, University of Sassari, Sassari, Italy

Disclaimer: JC, MR, SO, MU, LB and KL are staff members of the World Health Organization. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of the World Health Organization. The research was funded by the World Health Organization.

Word count: 8,142

ABSTRACT (169 words)

Globally, incidence of tuberculosis is declining very slowly, and the non-communicable disease burden for many countries is steadily increasing. Several non-communicable diseases, such as diabetes, alcohol use disorders, and smoking-related conditions are responsible for a significant proportion of tuberculosis cases globally and in the European region represent a larger attributable fraction for tuberculosis disease then HIV. Concrete steps are needed to address non-communicable diseases and their risk factors. We reviewed published studies involving tuberculosis and non-communicable diseases and present a review and discussion of how they are linked, the implications for case detection and management and how prevention efforts may be strengthened by integration of services. These non-communicable diseases put patients at increased risk for developing tuberculosis and at risk for poor treatment outcomes. However, they also present an opportunity to provide better care through increased case detection activities, improved clinical management and better access to care for both tuberculosis and non-communicable diseases. Hastening the global decline in tuberculosis incidence may be assisted by strengthening these types of activities.

Tuberculosis and non-communicable diseases: neglected links, missed opportunities

INTRODUCTION

While infectious disease have dominated the disease burden in the developing world for much of the last century, the incidence of many non-communicable diseases (NCD) such as cardio-vascular diseases, diabetes, those related to smoking and alcohol abuse, chronic obstructive pulmonary disease (COPD), and mental illness is growing in low- and middle-income countries, as well as in certain populations in high-income countries. This epidemiological shift adds to the existing infectious disease load, creating a double burden of communicable and non-communicable diseases in these populations. [1-12] NCD have often been depicted as diseases of development and it is a common notion that they mainly affect the non-poor. However, most NCDs[1], like most infectious diseases, are more common in the lower socioeconomic groups. This is certainly true in high income countries, but to a growing extent also in middle- and low-income countries. [13] Therefore, the double burden of communicable diseases and NCD is most pronounced among the poor, and this is further underscored by the casual links between them. There is a growing body of evidence describing the links between tuberculosis and an number of non-communicable diseases, and their risk factors, such as diabetes, smoking and alcohol- related conditions, COPD, mental illness, and malnutrition. [14-17]

[1] The term NCD in this paper is used to refer to a group of non-communicable diseases (e.g. diabetes, alcohol dependency, COPD, malnutrition, mental illness, silicosis) and their related risk factors (e.g. smoking, poor diet, heavy drinking).

Tuberculosis (TB) has long been a disease of the poor. Crowded living conditions and compromised immune system due to causes such as under-nutrition have contributed to a disease that caused one in every seven deaths in late 19th century Europe, and which continues to cause immense human suffering across the world today. Although many lives have been saved by widely available and inexpensive tuberculosis treatment over the past decades, due to the expansion of DOTS as a global management strategy,[18] TB continues to be a leading cause of burden and death among infectious diseases worldwide. [19] Furthermore, the growing problem of multi- and extensively- drug resistant TB (M/XDR-TB) has been well documented, especially in the European region, and poses a great challenge to treatment and care.[20-22] Globally, TB incidence is declining, but at a slow pace.[23] Additional efforts are needed to speed up the decline. Improved diagnosis and treatment of all forms of TB will be required, backed by poverty alleviation and general socioeconomic development, for long-term TB control and elimination. However, there is also a need to address a set of major TB risk factors and co-morbidities. [18]

HIV-infection has driven the TB epidemic in sub-Saharan Africa, and the links between TB and HIV have been well documented. [24] There has been an intense focus on improved TB/HIV collaboration in recent years, with an aim to: improve early TB diagnosis and treatment among people with HIV-infection, and vice versa, in order to improve clinical outcomes for both diseases; use of isoniazid as TB preventive therapy as well as co-trimoxazole preventive treatment for opportunistic infections in people with HIV-infection; and contribution by national TB programmes to HIV prevention, and thus

indirectly TB prevention.[25] Lessons and models of TB/HIV collaboration [26] may be applied to non-communicable co-morbidities. The dual epidemics of TB and HIV have led to the use of the phrase "two diseases, one patient." With an increasing prevalence and focus on NCD, clinicians treating TB need to acknowledge that they may deal with multiple diseases in a single patient.

Several NCDs, such as diabetes, alcohol use disorders, and smoking-related conditions are responsible for a significant proportion of TB cases.[18] These risk factors are particularly important attributable factors in the European region where their prevalence are much higher than, for example, the prevalence of HIV and under-nutrition.[27-29] With the ongoing epidemiological transition the disease and risk factor patterns in low- and middle income countries may resemble those of Europe in coming decades. COPD is the fourth leading cause of death globally now, and is expected to be the 3rd by 2030.[30] Diabetes prevalence is expected to more than double by 2030, and 7 of the 10 expected high-burden countries for diabetes in 2030 are high-burden TB countries today.[31] Alcohol consumption seems to be increasing in most developing countries following a general rule that as people have better access and purchasing power, consumption increases, while those with low socioeconomic status have the highest risk of harmful use. [32-34]

The rise of NCDs is important for TB control for a variety of reasons. First, many NCDs are risk factors for TB, especially for progression from infection to disease due to negative impact on host defense mechanisms against *M. tuberculosis*.[17, 35-39] Second, NCDs may complicate treatment and management of TB, due to clinical challenges (e.g.

among people with diabetes) as well as behavioral challenges (e.g. among people with alcohol use disorders).[40-41] Third, TB can trigger or aggravate NCDs. For instance, TB, like other infections, can worsen glucose control and trigger diabetes mellitus, [40] and a history of TB, although not a classical risk factor for COPD, is one of the leading causes of lung sequelae and bronchiectasis and has been linked to is an independent risk factor for COPD in a recent review.[42] In addition TB, and especially MDR-TB, may aggravate the social and financial stress contributing to substance abuse and mental illness. [43]

However, the link between TB and NCDs also creates opportunities for improved diagnosis and management of both. Presence of a NCD may indicate the need to actively screen for TB, especially in high burden countries, which can help improve early TB case detection.[44] Similarly, diagnosis of TB should alert clinicians to actively screen for common non-communicable comorbidities, which may otherwise go undiagnosed, especially in low- and middle-income countries where services for NCDs are vastly underdeveloped. Finally, preventive therapy of TB may be warranted in individuals with some of these comorbidities.

While there have been a number of reviews of relationships between certain NCDs and TB[16,17,29,45-46] a discussion of the implications that the expected growth in NCD prevalence on TB will have and what can be done to address the situation is needed.
In this paper we discuss the overall knowledge base concerning TB and the related NCDs and then examine the implications for both increased case detection and improved

clinical management of TB and NCDs. Finally, we suggest how prevention efforts might be strengthened and the implications of the growing NCD burden for TB control programmes and how to work with NCD programmes to improve service and care.

METHODS

We searched PubMed, the Cochrane library and the email send-list "TB-Related News and Journal Items Weekly Update" (prepared by the Centers for Disease Control and Prevention, Atlanta, USA), and relied on previously identified key publications. The available literature was searched from inception until May 2010 inclusive. We purposively selected the publications that were judged most relevant for the review, with a preference for high-quality systematic reviews. We favoured publications in the past five years, but did not exclude highly regarded older publications. The search was conducted using multiple combinations of the following key words: tuberculosis, alcohol, silicosis, COPD, smoking, diabetes, malnutrition, nutrition, mental health, prevalence, and incidence.

LINKS BETWEEN NONCOMMUNICABLE DISEASES AND TB

Diabetes Mellitus

A systematic review of 13 observational studies reported a relative risk of TB in patients with diabetes mellitus of 3.1 in cohort studies and odds ratios that ranged from 1.16-7.83 in case control studies.[14] These results were similar to those reported in a previous

systematic review [47], and further supported by a recent narrative review emphasizing the link between TB and diabetes mellitus. [48] The potential public health importance of this link has been underscored by an epidemiological model suggesting that diabetes mellitus might account for nearly 15% of pulmonary tuberculosis in India.[49] An analysis of the population attributable fractions of different risk factors for TB in different WHO regions suggests that diabetes is the second most important factor in the central Europe region and among established market economies (table 1). Other conditions, such as chronic renal disease, are long term consequences of diabetes and linked to TB although it is unclear how much risk can be attributed directly to the conditions. Furthermore, given that the prevalence of diabetes is expected to increase rapidly in the coming decades, it could become an even more important factor in all regions. An expert meeting on TB and diabetes in 2009 considered the findings in these reviews as well as findings in a new, and presently unpublished, extended systematic review. The meeting concluded that a causal relationship between diabetes mellitus and TB is likely, but further research is needed to verify earlier results and to better document the strength of the association and the possible causal mechanisms. The meeting also concluded that some studies have showed increased TB risk with poorer glucose control; and that there is a lack of evidence for increased risk of TB infection among people with diabetes. There is some evidence that diabetes mellitus leads to delayed culture conversion; [50,51] and that the risk of death during TB treatment is increased [52,53] as was the risk of relapse[54,55]. The evidence base on the link between diabetes mellitus and acquired drug-resistance is mixed and inconclusive. Finally, it has been argued that prolonging the standard TB treatment regimen for people with diabetes mellitus may

improve outcomes, but presently little data exist to support the claim.[40] There are no quality data on the effectiveness and feasibility of early case detection and chemoprophylaxis of TB among the diabetics.

Alcohol

A systematic review of observational studies on the link between alcohol consumption and risk of TB concluded that people who consume more than 40 grams of alcohol a day on average (heavy drinkers) and/or have an alcohol use disorders have three times the risk of developing TB, while low to medium alcohol consumption does not seem to increase the risk of disease.[29] A subsequent narrative review of epidemiological studies, clinical research and animal studies concluded that this association seems to be causal. [41] While the relative importance of adverse effects on the immune system of alcohol vs. increased risk of transmission due to the pattern of social interactions among heavy drinkers is not clear, both factors are likely important. Heavy drinkers may be more exposed to more *M. tuberculosis* at bars, prisons, shelters or other congregate settings. Alcohol use-related health disorders are associated with several clinical conditions that may impair the immune system. In addition, alcohol has a direct toxic effect on the immune system. Animal studies suggest that chronic and acute alcohol consumption impairs cell mediated immunity and macrophage functions (which are essential for the host response to *M. tuberculosis* infection).[36,56] Furthermore, heavy alcohol use may be a secondary cause of micro- and macronutrient deficiency which can also impair immunity.[57] Excessive alcohol use is also associated with poor TB treatment adherence, and a number of studies have found higher relapse rate among

heavy drinkers and those with alcohol use-related health disorders.[41] Though it would be plausible that this would also increase the risk of MDR-TB, there is presently no strong evidence base supporting this hypothesis. Alcohol abuse is a leading TB risk factor in Eastern Europe and Latin America (table 1). There is very little published data on the effectiveness, cost-effectiveness and feasibility of TB screening and preventive chemotherapy among people with alcohol use disorders.

Smoking and COPD

Mathematical modeling has shown the potential importance of smoking and have suggested that a large part of the tuberculosis burden in many regions of the world can be attributed to smoking (table 1). Two recent systematic reviews on smoking and TB concluded that smokers have 2-3 times elevated risk of TB, and that there is a dose-response relationship for both quantity of cigarettes and duration of smoking, after adjustment for alcohol intake and socioeconomic status.[16,58] There is also evidence linking passive smoking to higher TB risk, especially in children.[16] The biological explanation of the casual relationship between smoking and tuberculosis infection and disease has been increasingly well documented. The tracheobronchial mucosal surface is a first level of host defense that prevents *M. tuberculosis* from reaching the alveoli. Tobacco and other environmental pollutants may impair this defense mechanism. [59] Smoke also impairs the function of pulmonary alveolar macrophages. [38] Nicotine is hypothesized to act directly on nicotinic acetylcholine receptors on macrophages to decrease intracellular tumor necrosis factor-a production and thus impair intracellular killing of *M. tuberculosis*. [60] It is still unclear if COPD is a risk factor for TB,

independently from smoking.[61] However, TB history seems to be an independent risk factor for COPD. [6,62-65] COPD is therefore a marker for both smoking and previous TB (which also is a risk factor for future tuberculosis disease), and thus a predictor of risk.

Smoking also effects chance of cure from TB. Severity of TB at the time of diagnosis as well as risk of relapse has been linked to smoking. In addition, a few studies have found that smokers have a higher risk of death from TB and other poor treatment outcomes than non smokers. [16] A number of studies from the UK and the US also found an independent association between COPD comorbidity and death in TB patients while others found no effect. Problems controlling for the effects of smoking may be partially to blame for the lack of clear evidence. [45]

Malnutrition

Malnutrition is a cause of tuberculosis disease and wasting is a consequence of TB, which explains why a large proportion of TB patients are undernourished at the time of diagnosis. The ecological evidence linking declines in TB to better nutrition has long been clear. [66-68] It has been difficult to verify this link through analytical epidemiology, mainly because the temporal relationship is difficult to establish with cross sectional data obtained at the time of TB diagnosis. However, a recent systematic review of prospective cohort studies found a consistent log-linear inverse relationship between baseline body-mass index (BMI), and subsequent TB incidence.[69] There was a reduction of incidence of almost 14% for each unit of BMI increase which was consistent

between BMI 18.5 kg/m^2 and 30 kg/m^2. It is interesting to note that obesity may be protective against TB with one large cohort study showing significantly lower risk of TB among overweight and obese patients compared to those with normal weights. [70] There is more evidence needed to confirm the findings. More recent data has also provided detailed evidence of the mechanisms involved. A narrative review of studies in humans and animals demonstrated the negative impact of various macro- and micro-nutritional deficiencies on TB immunity. Although the exact biological pathways are not fully understood, it is clear that poor nutrition, and specifically protein deficiency, impedes the ability of the cell-mediated immune system to fight *M. tuberculosis* as it does for other infections. [17] Malnutrition is an important contributing factor to TB on population level, especially in poor countries (table 1). Low BMI at the time of diagnosis has also been linked to risk of treatment failure, death during TB treatment, and relapse. [71-73]

Silicosis

The association between silicosis and pulmonary TB has been well documented. Silicosis is caused by the inhalation of crystalline silica particles almost always due to occupational environments including mining, sandblasting, quarrying, ceramic working and iron smelting. [74] Studies in South Africa showed relative risks of developing pulmonary TB between 2.8 and 4.7 depending on the grade of silicosis. [75,76] A large case-control study in the US found a mortality odds ratio for pulmonary tuberculosis of 39.5 among silicotics [77] but most of the work around silicosis and TB has focused on occupational risk groups like miners and has not looked at silicosis as a risk factor for

poor TB outcomes. There is evidence of an increased case-fatality rate, [78] but silicosis and silica dust exposure are not deemed risk factors for relapse or reinfection. [79]

Other NCD

Although there have been few studies to document any casual relationships between mental illness and TB, they can in theory negatively impact the cell-mediated immune system which may put the *M. tuberculosis*-infected patient at increased risk for developing TB. The role of mental disorders, both in contracting *M. tuberculosis* infection though physical location (homeless shelters, hospitals or other congregate settings) and TB through the plausible biological pathway discussed by Prince in a discussion of mental disorders and links with other disease, is not well described but conceivable.[80] A systematic review of the literature on this topic could help better describe the relationships. However, there are strong links between economic and social burdens of TB, especially in its more severe forms, leading to alcohol abuse, malnutrition and depression. [43, 81-83]

Cardiovascular diseases have links with TB, but they have not been documented as direct risk factors for TB, but rather TB sequelae have been know to be a risk factor for cardio pulmonary failure. [84] Other chronic conditions such as autoimmune and systematic disorders, chronic renal failure, liver failure, certain malignancies, and a wide range of immunosuppressant treatments are also associated with TB. [14, 85-89] It is essential to keep TB in mind during clinical management of these conditions, especially in high TB

burden settings, even though they are less important from a public health viewpoint due to relatively low prevalence.

IMPLICATIONS FOR CASE DETECTION STRATEGIES

Programmatic TB case detection activities, under the Stop TB Strategy, have mainly focused on "passive case finding" approaches, i.e. waiting for patients with symptoms to present to health services and then screening those with chronic cough for TB (usually defined as cough for a duration of more than 2-3 weeks). [90-91] While the expansion of DOTS has led to impressive gains in the proportion of the estimated incident cases detected, from 10% in the early 1990's to 61% in 2008, the rates of increase have flattened over the past five years and the former 70% case detection rate target, set by WHO for 2005, has yet to be achieved. [23] Additionally, it is unlikely that reaching the 70% target will be sufficient to generate the decline in TB incidence expected when the targets were set. The global target has now been made more ambitious, with an ultimate goal to achieve as close as possible to universal case detection. [18] Early case detection, which includes the removal of infectious cases out of the prevalent pool as soon as possible, is essential to cut transmission effectively. It is also important to alleviate suffering and improve the chance of cure for the individual patient. To meet these goals, more intensified and prioritized case detection strategies will be needed, and active screening among risk groups is one potential approach.

The adoption of targeted screening for latent infection and its treatment in certain groups have been done in certain settings primarily in Europe and the US as well as other

countries where TB prevalence is quite low and there is a move towards elimination. While this article focuses on detection and management of active TB, screening and treatment of *M. tuberculosis* latent infection maybe useful in certain groups. Isoniazid preventive therapy (IPT) has been promoted for HIV infected people after screening for TB due to the high risk of developing TB if HIV-infected [25]. Patients with identified NCD will also benefit from IPT, but the number of treatments to avoid an incident TB case would theoretically be greater due to the different relative risks. Currently, there is little documentation about the benefits of IPT in patients with NCD but it may be beneficial for programmes currently providing IPT to screen NCD patients for latent TB infection.

TB is more common among people with the NCDs discussed here than among the general population. Therefore more active screening for TB among them would, in principle, help increasing TB case detection. However, it is not clear what screening strategy may be most effective, feasible and affordable. There are a number of potential strategies that clinicians and public health managers may use to ensure early diagnosis among people with NCDs, but four main considerations should be made before pursuing them: 1) what will the yield be?, 2) is it practical to reach the risk group?, 3) is it cost effective?, and 4) is it affordable?

The decision of which groups to actively screen may be very different depending on local TB epidemiology, health system context and clinical setting. Moreover, for individual patient management the considerations for clinical decision-making may look very

different from the decision tree for public health interventions. Nevertheless, it seems reasonable that in all medium to high TB burden settings, heightened awareness among clinicians about these NCDs as risk markers for TB is important to ensure early diagnosis and optimal individual care. Table 2 summarizes some of the observations for the different NCDs discussed in this paper.

Yield of Screening Activities among Patients with NCD

Figure 1 presents a theoretical model that can be used to help guide programmatic decisions about which groups to target for intensified case finding. The yield of such strategies will depend on the sensitivity of the screening approach, the relative risk for TB associated with each risk factor, the prevalence of the risk factor, the TB prevalence, and the case detection gap in a specific risk group in a given setting. The variability even within a single risk factor is demonstrated by the findings that the number of diabetes patients needed to screen to detect one TB case ranged from 4 in Korea to 100 in Hungary while the number of those needed to be followed-up to identify a TB case within one year ranged from 152 in Tanzania to 1,000 in Ethiopia.[40] Different approaches may thus be considered depending, for example, on TB and NCD prevalence, TB case detection gap, and health care resources in a given setting.

Most COPD patients meet the TB suspect definition. However, chronic coughers more often then not pass through health facilities without being screened for TB, especially in low-TB prevalance settings.[92-94] All COPD patients could receive periodic screening to rule out TB and clinicians can probably increase the diagnosis of both diseases by

actively screening TB patients for COPD and vice versa, as advocated within WHO's Practical Approach to Lung Health for which there are comprehensive guidelines.[95] COPD is common in some populations (between 4-10% of adults in various countries where it has been rigorously measured) [96], and the potential yield may therefore be large if people with COPD in high TB burden settings are screened systematically. Prevalence of COPD is much lower than the prevalence of smokers which was about 30% overall and 38% in European males as of 2002. Furthermore at least 11 Eastern European countries have prevalence rates of more than 50%. [97] Screening all smokers for TB would potentially give an even higher yield, but feasibility and cost-effectiveness would be much lower since smokers in general would be harder to reach than people diagnosed with COPD (see discussion about feasibility below).

The estimated prevalence of heavy drinking is more than 15% among adults in Europe [98], and the prevalence of alcoholism among TB patients is around 50% in some countries. [29] Heavy drinking and alcohol use disorder might account for nearly 35% of pulmonary tuberculosis in central European countries (table 1). This therefore represents a significant risk group in some countries, and screening for TB among alcoholics may potentially yield significant numbers. However, as for smoking, COPD and diabetes, we do not have good evidence showing the feasibility and cost-effectiveness of systematic screening in these groups.

Practicality of Screening

Diabetes Mellitus: Some of the populations are quite difficult to reach and screen through both public health approaches and at a clinical level due to lack of specific services for them (smokers and the malnourished) while others are much more easily identified as a group (known diabetics, people with diagnosed COPD, silicotics, mentally ill people). Diabetes patients should be regularly seen at health care facilities where they could be screened for TB upon diagnosis and periodically while diabetes is being managed. Although diabetes mellitus with poorly controlled blood sugar levels has been identified as a risk factor for TB, the best screening methods have not been identified. Additionally, the optimal time to screen for diabetes needs to be specified as the inflammatory process associated with TB may results in a temporary hyperglycemia which can produce false positive results for diabetes and the definitions should be standardized.

Alcohol abuse and tobacco use: In clinical settings, a heightened awareness for TB symptoms could be employed with active screening for TB symptoms among patients with known or suspected alcohol abuse and or smoking. Although smokers as a general population are difficult to reach, they probably seek care more often than non-smokers,[99] and opportunities to engage and screen smokers for TB symptoms should not be missed. A high index of suspicion for TB among patients who smoke, and among those who present with other risk factors for TB (contacts, COPD, alcohol use etc) can increase case detection.

Malnutrition: When undernourished people are identified in health services, this should alert clinicians to actively probe for TB symptoms, especially in medium-to-high TB

prevalence settings. However, comprehensive screening of this group on population level is challenging. Population based case finding measures targeting the undernourished are probably better off focusing on proxies such as urban slum dwelling and homeless shelters. In US settings, a few studies have found low yield in homeless shelters due to low participation rates, rather than low prevalence. [100-101] In Brazil more success has been achieved in screening at risk groups in these populations. Two studies in Sao Paulo showed that large populations in shelters and prisons could be screened in short periods of time with fairly good yield. [102-103]

Silicosis: Even though the relationship between TB and silicosis is well documented, a study in Spain found that presence of silicosis was an independent risk factor for health system delay in diagnosing and treating patients with TB. [104] This may be due to the fact that the diagnosis of tuberculosis among silicotics can be very difficult, especially in lower grades, when the clinical manifestations can be benign and the radiological alterations can be indistinguishable from those resulting from the preexisting silicosis. [105] Patients with known occupational exposure to silica can be continuously monitored for both TB and silicosis.

Clinicians seeing patients with certain the NCD described here as well as other less prevalent ones which require administration of immunosuppressant therapies should be closely monitored, especially in high TB burden settings, as many of these conditions put patients at increased risk of developing TB. [57]

Costs and cost-effectiveness of intensified case finding

Although data on the costs of TB control show both that it is an effective intervention in terms of disability adjusted life years saved [106] and that investments in TB will actually create a return on investment, [107] there have been few studies looking at the cost effectiveness of intensified screening initiatives. Part of the reason is that passive detection was promoted as the most cost-effective and efficient approach for developing countries. [108] While national programmes are certainly still restricted in terms of resources, there are more funding opportunities for new ways to reach cases that have not been captured under the basic approaches used in the past. At the same time, there is a growing realization that it may cost more to detect the harder to reach cases, as well as to diagnose TB early. A review of historical active case finding approaches among high risk groups found that while there was good evidence that several interventions were feasible and generated additional detection of TB cases, there has been little analysis of how this affected transmission and TB incidence. Additionally, few rigorous cost-effectiveness analyses have been done. [109] While increased screening of people at higher risk of TB will certainly be more expensive than the current passive approach, it is not unrealistic to believe that intensified detection activities among certain risk groups may have good yields as well as possibly increasing early case detection. However, more research is required to demonstrate epidemiological impact, cost-effectiveness and affordability.

CLINICAL MANAGEMENT STRATEGIES

While there has been a focus on HIV associated TB, national TB programmes have paid little attention to proper management of non-communicable TB co-morbidities. This may

be due to many reasons, including not diagnosing the comorbidity, weak existing services for NCDs, poor coordination between disease programmes, lack of desire within TB programmes to take on other conditions, and lack of awareness about the necessary steps to take. There are a number of strategies that can be employed to help ensure better diagnosis, case management and outcomes for patients with co-morbidities. Just as patients with risk factors for TB should be screened for active disease, TB patients should be screened for NCD co-morbidities as and when indicated. During TB treatment, optimized TB management, with strict supervision when required should be employed. Likewise, careful NCD management is vital to overall good health outcomes. Finally, risk groups may require monitoring after cure, to check regularly for TB relapse. Table 2 summarizes some of the observations for the different NCDs discussed here.

Optimal TB Treatment and Support

All TB patients should have close TB treatment supervision combined with appropriate patient support mechanisms, as outlined in the Stop TB Strategy and the International Standards of TB Care.[23,110] This becomes especially important for some patients with NCD that are at higher risk for poor treatment outcomes, such as people with alcohol use disorder, smokers and undernourished patients. For example, alcohol use is a strong risk factor for treatment interruption.[41] Some studies have found an association between drug resistance and alcohol dependence but it is unclear if it is because of adherence issues or as a risk factor due to other social interactions. [111-112] Studies of the pharmacokinetics of isoniazid in the treatment of TB patients with alcohol dependence have shown significant decreases in absorption of the drug and its accelerated metabolism

after oral administration to heavy drinkers. [113] A review of studies on the pharmacokinetic relationship between diabetes and tuberculosis medications showed that apart from glipizide, diabetes medications had reduced pharmacokinetic parameters in subjects administered rifampicin. [40] There is a knowledge gap on the interactions between diabetes medications and other TB drugs. Additionally, there is some evidence that rifampicin levels may be reduced among diabetes patients due to malabsorption. [114] This may have important implications, resulting in poor DM control in patients who are administered TB treatment regimens that include rifampicin as well as implications for TB treatment with regimens containing rifampicin among diabetics. TB drug hepatotoxicity might also increase with diabetes mellitus and alcohol use disorder.[115-116] Peripheral neuropathy is associated with both isoniazid use and certain NCD including diabetes; especially if glucose levels are poorly controlled, alcohol use disorder, malnourishment; specifically vitamin deficiencies, and certain autoimmune disorders. Close monitoring of patients with these NCD on TB treatment IPT is warranted. Finally, patients beginning treatment with poor nutritional status are at risk for poor outcomes. [17] Optimal TB treatment is therefore required for these patients, especially since standard TB treatment has been shown to be a great mediator for return to normal nutritional status. [73]

It is thus clear that the standard TB treatment and management approach recommended by WHO should be optimized in these particularly vulnerable groups. Understanding the possible interactions and complications of TB treatment due to factors such as diabetes, alcohol use disorder, undernutrition and smoking should improve clinical care and focus

attention to the specific TB treatment needs of those patients. Critically, the strict application of directly observed treatment, enhanced clinical monitoring, and optimal patient support structures need to be considered for these patients.

It is much less evident that TB treatment regimens need to be changed in people with certain NCDs. It is common clinical practice in some settings to extend the TB treatment duration in people with diabetes. In 13 studies reviewed in the expert meeting on TB and diabetes mellitus, the results suggested that diabetes has a minor effect on TB treatment success. [14] However, this is somewhat contradicted by some findings that diabetes may be associated with delay in sputum culture conversion at 2-3 months of TB treatment, may increase death during TB treatment and relapse, and may have a relationship with MDR-TB although the findings are not strong and more evidence is needed. [40] No trial on the effectiveness of extended treatment duration has been published. Nonetheless, US Centers for Disease Control and Prevention is developing guidelines for pacific islanders which consider extending TB treatment to 9 months,[117] while emphasizing that this is based on clinical experience only, and pointing out that additional research is required to determine if prolonged treatment actually improves treatment outcomes and/or reduced risk of relapse or acquired drug resistance.

Screening and managing NCDs in TB patients

Screening for NCDs allows the TB clinician to provide better general care for TB patients, so that TB outcomes as well as general health outcomes can be optimized. For

all of these co-morbidities providers should be coordinating closely with other specialties and other disease programmes to ensure the best diagnostic approach and best care for the patient. There is as least one example of HIV/AIDS programs linking with chronic disease clinics to provide integrated care and TB programs could do the same.[118] Linking patients with other departments for management of co-morbidities has been shown to improve TB/HIV collaboration [44, 119] and depending on the circumstances, having TB programmes work more closely with NCD units or programmes will be helpful. Based on the experience from TB/HIV collaboration, asking a substance abuse clinic or diabetes clinic to systematically screen patients for TB should be more easily accepted if the TB programme can contribute to alcohol use disorder and diabetes case finding and management.

The DOTS approach offers some opportunities for optimal management also of NCDs. Potentially, clinicians can use the DOTS approach for standardization and treatment support also for NCD. A recent proposed framework to improve primary care in NCDs also explores to the potential benefits that can be realized by adapting delivery systems to help identify, manage and prevent NCDs at the primary care level. [120] By employing a well developed and tested strategy to help control NCDs, health care systems may be able to provide better care to patients with both chronic and acute conditions and help alleviate the double burden of infectious and chronic disease. A good example of this possibility is for diabetes. Regular interaction with the health service and/or outreach health workers/volunteers for TB treatment, especially in the intensive treatment phase, provides excellent opportunities to provide health education and behavior change messages for

improved diabetes management. [121-122] Since poor glucose control is associated with higher risk of TB, it is plausible that it is also associated with poorer treatment outcomes and risk of relapse, though the direct evidence for this is lacking. Nevertheless, optimizing diabetes management during TB treatment should be a high priority for improving the general health status of the patient, especially since TB can aggravate diabetes and worsen glucose control. Similar arguments can be made for alcohol abuse and smoking.

Interventions in clinical settings have shown to have a positive impact in different settings for the reducing heavy drinking [123-125] and effective treatments for severe alcohol dependence have been described. [126] Appropriate measures should be routinely offered to those screened positively for heavy alcohol use and alcohol use disorder - especially in settings where a high proportion of TB patients are alcohol-dependant. As alcohol use disorders can cause the deterioration of living conditions both social and financial in nature, as well as impact TB treatment outcomes, addressing the condition may be the key for successful treatment. [127-128]

Interventions for smoking are widespread with varying degrees of success. [129] Simple smoking cessation programs in clinical settings can be effective and quite cost efficient although simple trainings to clinicians will likely not be sufficient for larger impact. [130-131] One study in Sudan has demonstrated it was feasible to implement a large scale smoking cessation program within TB services despite the workload of local staff and produce positive results for TB treatment success as well as smoking cessation [132]

Enrolment in smoking cessation programmes, can help and will certainly benefit the overall health of the patient. Information and education should be used to curb the activity as much as possible.

Although nutritional support during TB treatment is often recommended, there is little evidence on the effectiveness of such support for TB specific outcomes. A Cochrane review found limited evidence for the use of dietary supplements as a means for improving TB treatment outcomes, but recommended further research since the evidence base was found to be very thin. [133] While awaiting more data it is important to recognize that there is clear evidence that nutritional support is important for nutritional rehabilitation and general quality of life. [134] In addition, food support can act as an enabler for TB diagnosis and treatment completion. [135] However, though many countries have had large scale programmes to provide nutritional support to TB patients, there have been very few rigorous evaluations to determine the best type of nutritional support, the best way to deliver it, whether it should be directly for patient or for the family, and in what setting. [136]

There is no specific treatment for silicosis that is efficient and based on clinical trials. Managing TB patients with silicosis demands early diagnosis of both disease [46]. There is very limited evidence that tetrandrine may improve pulmonary function and delay in disease progression. [137] As most TB providers are not skilled in managing mental illness, co-morbidity with such disorders can be quite challenging. Depression, for example, has an important effect on adherence to treatment for many health conditions

but there are few studies that have investigated these associations. [80] This underscores the importance of close collaboration with other specialities and programmes.

PREVENTING TB BY ADDRESSING NON-COMMUNICABLE DISEASES

Addressing the NCD that are risk factors for TB can strengthen efforts to prevent TB in a number of ways. First, improving diagnosis of NCD among TB patients and better coordination with NCD services for patient management could diminish the risk of future TB recurrence (relapse, or re-infection). However, addressing NCDs in people with TB only would affect just a small fraction of all people with these conditions. The preventive impact would be greater if TB programmes and TB specialists would facilitate better diagnosis, care and prevention of these conditions throughout the health system, and beyond. TB control programs in many countries have been decentralized and integrated into primary health centers. They see patients at a much more peripheral level then some more specialized services which provide NCD management. By contributing to screening efforts for NCDs, TB programme affiliated staff can contribute to better collaboration, early NCD diagnosis, as well as overall health systems strengthening through the spread of primary care services to a larger population which is a major goal for WHO. [138]

Second, and more significantly, population level interventions aimed at reducing prevalence of NCDs would potentially have a dramatic impact on TB incidence and prevalence. The population attributable fractions of these risk factors are significant, and in many European countries the population attributable fractions of NCD are much higher than for HIV (table 1). The differences among regions as to which risk factors to

prioritize can vary significantly although only in one region is HIV the leading risk factor. Malnutrition likely contributes heavily to the TB burden in many regions and is the strongest factor in three of the WHO regions listed in table 1. Many of the NCD discussed here are modifiable through behavior change and through policy and regulatory interventions. For example, there is ample evidence that taxes and policy changes including marketing restrictions, and limiting availability of alcohol and tobacco can reduce consumption.[16, 139-140] These policy changes may not only have positive effects the incidence of TB, but on health in general and the costs of medical care. [141]

Third, although out of reach for many national TB control programmes and NCD control programmes, larger efforts to address the social determinants common to both TB and NCD will have a positive impact on both as well as a larger impact on the overall population health. [32] The improvement in nutritional status on a population level along with better living conditions and other social advances has been suggested as partial cause of the enormous TB incidence decline in Europe in the 20th century. Promoting better food security and support for the general population, and certainly for those in most need, can have a large impact on TB control. Eastern European and former Soviet Union countries experienced a rapid increase in TB incidence in the 1990s [142-143] that can be traced to the erosion of health and social support systems, as well as a rise in conditions like alcohol use disorders. If left unchecked, increasing prevalence of NCD can have an impact on TB and vice versa.

IMPLICATIONS FOR TB CONTROL PROGRAMMES

National TB control programmes and NCD programmes are already over burdened and understaffed, especially in resource poor countries. Adding NCD diagnosis and management to the TB agenda, and vice versa, may be perceived as overwhelming by many programmes. However, better coordination and some pooling of resources may create mutual benefits. More active screening for both TB and NCD will help management of the patient and treatment outcomes through comprehensive identification of treatment and support needs. Better coordination with specialists and other care providers will improve overall patient health.

Reaching out to other disease programmes and providers is something that national TB control programmes have traditionally not done well, but the experiences of MDR-TB and TB/HIV management provide two good examples of how working with other programmes can strengthen the programme. These lessons may be used for collaboration between NCD and TB programmes.

The intense focus on MDR-TB and TB/HIV over the last 10 to 15 years and how best to support such patients can provide some good examples of how basic TB control programmes can strengthen themselves by working outside the programme. MDR-TB represents a failure to effectively treat TB patients in and outside of TB programmes. The steps that have been taken to rectify these failures for MDR-TB have been impressive and necessary. For instance, patient support groups are seen as an important factor for successful treatment outcomes as the mental health issues surrounding MDR-TB have

gotten good attention.[43] Some MDR-TB programmes have developed strong links with substance dependency interventions while recognizing that there is a limited arsenal of TB drugs to combat the disease and substance abuse can hinder adherence and drug absorption.[144] The guidelines for treating co-morbidities for MDR-TB patients are more developed than for drug susceptible TB patients, due to the importance of drug interactions in various co-morbidities and the effect on treatment outcomes these possess. [145-146] Although standardized treatment for pan-sensitive TB has been very successful, there are still questions about how to best manage certain patients such as those with diabetes, alcohol and drug dependency and mental illness. Using the models of some MDR-TB programmes to better engage other programmes is an opportunity for TB control programmes to impact the health of patients across disease areas and contribute to health systems strengthening and better overall care.

In TB/HIV care, WHO has launched a number of initiatives that recognize the importance of the two disease programmes working together to address the dual epidemics. In 2004, the WHO Stop TB Department and HIV/AIDS Department released basic suggestions for how to better integrate TB and HIV care and treatment. It has helped scale up of HIV testing among TB patients, which has increased more than 7 times since 2002 and reported TB testing among HIV positive patients has been even more dramatic. [147] The other measures in the 12 point package for better cooperation include HIV prevention and TB infection control which aim to reduce the continued spread of the diseases. The generic elements of improved collaboration may be applicable

for collaboration with other public health programmes as well, including those dealing with NCDs.

While the relationship between NCD and TB is complex and requires more careful attention and research, it certainly presents an opportunity for strengthening both areas in health service delivery as well as for achieving the larger goal of general health systems strengthening. With progress towards global case detection of TB stalled, [18] there is growing recognition that more intensive case detection efforts are needed and that quality of treatment and overall case management need be further improved. The status quo in the case detection trend, the limitations of the "passive case finding" approach, and the slow decline in TB burden globally calls for intensified action, including more attention to TB risk groups in general, and TB related NCDs in particular [44, 148-149]. However, the feasibility, costs- and cost effectiveness of required interventions have not been well documented, and more research is needed before judging which risk groups to target, and how. What is clear is that clinicians need to be especially alert to identify conventional TB screening indications in people with risk conditions.

This review provides some arguments for systematic and active screening in special clinical groups that can be easily identified and reached. This may include people with diabetes, silicosis, alcohol use disorder, undernourished people and/or people with COPD, depending on the health system set-up and capacity, as well as on the local epidemiological situation. If urban slums or other defined vulnerable groups can be used as a proxy for malnourishment, poor health in general, and high exposure to other risk

factors such as poor access to care, crowding, other infections etc. they also may present good opportunities to increase TB case detection, as indicated by a recent study. [150] In certain non-health care setting, such as home-less shelters, prisons, and social institution, active case finding among alcoholics may prove useful.

While standardized TB treatment regimens have been able to effectively treat upwards of 85% of TB cases globally, non successful treatment outcomes are high (33%) in the European region, many times related to drug resistance, and weak health systems and access problems. [18, 23] Additionally many of the NCDs discussed in this paper put patients at higher risk of poor outcomes and are highly prevalent in the European region. Optimized TB treatment, management and patient support is the first essential measure in people with co-morbidities associated with poor treatment outcomes. Improved management of the co-morbidities themselves is the next logical step, which should improve both TB outcomes and general health.

These clinical interventions should be combined with public health policy measures aimed to prevent NCDs and TB. The NCD discussed in this article can be addressed through combinations of behavior change interventions, policy, regulation, taxation, environmental action, and structural interventions to address underlying social determinants. Such interventions largely lay outside the purview of health service providers, but are essential elements of the broader public health agenda. Though they may not be well suited to take the lead, TB programmes and clinicians working in TB care should play important roles in the process, at least as advocates. There are

increasingly more models showing how TB programmes can reach outside of what have traditionally been disease specific systems, and in the future, with increasing focus on primary health care and health systems strengthening, collaborative efforts will be necessary as evidenced by recently developed frameworks for TB/HIV and TB and smoking. [129,138]

RESEARCH PRIORITIES

Although the NCD-TB link has received quite some attention in recent years, there are many questions that need to be addressed. Better data are needed to guide policy decisions on priority actions to intensify case detection, including better estimates of precision, potential yield, impact on early case detection, cost-effectiveness, and feasibility of different screening and diagnostic approaches in different target groups. Better evidence to answer questions such as the profile of patients which should receive screening for TB, which risk factors, at what intervals, and using what screening and diagnostic tools is lacking and should be the subject of future research. More research will need to be conducted on the impact that smoking cessation has on treatment outcome in smokers, and what the impact is of glycemic control on the outcomes of diabetic patients with tuberculosis. Systematic reviews in areas such as mental health and TB should be undertaken to better document the knowledge base and gaps. A systematic review of the many studies looking at TB treatment indicators such as culture conversion, death and relapse is also needed to help guide policy and management. More investigations are needed to evaluate also programmatic and managerial aspects of improved collaboration between TB and NCD interventions and programmes. Ultimately,

in order to plan appropriate action, each country need also to map out the main TB risk factors, the distribution, availability and quality of health services for concerned NCDs, and opportunities for improved coordination.

CONCLUSIONS

The growing burden of NCD has important implications for TB epidemiology, TB case management and TB treatment outcomes. Several NCD put people at increased risk for *M. tuberculosis* infection and weaken immune responses which increases risk for TB. Some of them can make detection more difficult, affect TB drug effectiveness, worsen the general conditions of the patient, worsen treatment adherence, and increase the risk of treatment failure, TB recurrence and death. At the same time, these diseases and conditions are preventable and treatable. TB programmes and clinicians treating TB must work more closely with those in general health services providing prevention and care for NCDs, within the context of primary care and the general health system. Ultimately, the many opportunities for improved collaboration, which will strengthen control efforts in both communicable and non-communicable disease control, will need to be exploited to provide the best care and have a greater impact on both TB and NCD control.

Disclaimer: JC, MR, SO, MU, LB and KL are staff members of the World Health Organization. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of the World Health Organization. The research was funded by the World Health Organization.

REFERENCES

[1] Gaziano TA. Cardiovascular disease in the developing world and its cost-effective management. *Circulation* 2005; 112(23): 3547-53.

[2] Miranda JJ, Kinra S, Casas JP, Davey Smith G, Ebrahim S. Non-communicable diseases in low- and middle-income countries: context, determinants and health policy. *Trop Med Int Health* 2008; 13(10): 1225-34.

[3] Mayosi BM, Flisher AJ, Lalloo UG, Sitas F, Tollman SM, Bradshaw D. The burden of non-communicable diseases in South Africa. *Lancet* 2009; 374(9693): 934-47.

[4] Abegunde DO, Mathers CD, Adam T, Ortegon M, Strong K. The burden and costs of chronic diseases in low-income and middle-income countries. *Lancet* 2007; 370(9603): 1929-38.

[5] Ramaraj R, Alpert JS. Indian poverty and cardiovascular disease. *Am J Cardiol* 2008; 102(1): 102-6.

[6] van Zyl Smit RN, Pai M, Yew WW, Leung CC, Zumla A, Bateman ED, Dheda K. Global lung health: the colliding epidemics of tuberculosis, tobacco smoking, HIV and COPD. *Eur Respir J* 2010; 35(1): 27-33.

[7] Slama K. Global perspective on tobacco control. Part I. The global state of the tobacco epidemic. *Int J Tuberc Lung Dis* 2008; 12(1): 3-7.

[8] Laniado-Laborín R. Smoking and chronic obstructive pulmonary disease (COPD). Parallel epidemics of the 21 century *Int J Environ Res Public Health*. 2009; 6(1): 209-24.

[9] Hossain P, Kawar B, El Nahas M. Obesity and diabetes in the developing world--a growing challenge. *N Engl J Med* 2007; 356(3): 213-5.

[10] Rahman A, Prince M. Mental health in the tropics. *Ann Trop Med Parasitol* 2009; 103(2): 95-110.

[11] Patel V. Mental health in low- and middle-income countries. *Br Med Bull* 2007; 81-82: 81-96.

[12] Patel V, Araya R, Chatterjee S, Chisholm D, Cohen A, De Silva M, Hosman C, McGuire H, Rojas G, van Ommeren M. Treatment and prevention of mental disorders in low-income and middle-income countries. *Lancet* 2007; 370(9591): 991-1005.

[13] World Health Organization. Closing the gap in a generation: health equity through action on the social determinants of health. Final Report of the Commission on Social Determinants of Health. Geneva: World Health Organization; 2008.

[14] Jeon CY, Murray MB. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. *PLoS Medicine* 2008; 5: e152

[15] Lönnroth K, Williams BG, Stadlin S, Jaramillo E, Dye C. Alcohol use as a risk factor for tuberculosis – a systematic review. *BMC Public Health* 2008; 8: 289 doi:10.1186/1471-2458/8/289

[16] Lin HH, Ezzati M, Murray M. Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis. *PLoS Medicine* 2007; 4: e142.

[17] Cegielski P, McMurray DN. The relationship between malnutrition and tuberculosis: evidence from studies in humans and experimental animals. *Int J Tuberc Lung Dis* 2004; 8: 286-98

[18] Lönnroth K, Castro K, Chakaza JM Chauhan SL, Floyd K, Glaziou P, Raviglione MC. Tuberculosis control and elimination 2010–50: cure, care, and social development. Lancet 2010: Published Online May19; DOI:10.1016/S0140-6736(10)60483-7.

[19] World Health Organization. *Global Health Risks: Mortality and burden of disease attributable to selected major risks.* Geneva, World Health Organization, 2009.

[20] Sotgiu G, Ferrara G, Matteelli A, Richardson MD, Centis R, Ruesch-Gerdes S, Toungoussova O, Zellweger JP, Spanevello A, Cirillo D, Lange C, Migliori GB. Epidemiology and clinical management of XDR-TB: a systematic review by TBNET. *Eur Respir J*. 2009; 33(4): 871-81.

[21] Migliori GB, Besozzi G, Girardi E, Kliiman K, Lange C, Toungoussova OS, Ferrara G, Cirillo DM, Gori A, Matteelli A, Spanevello A, Codecasa LR, Raviglione MC; SMIRA/TBNET Study Group. Clinical and operational value of the extensively drug-resistant tuberculosis definition. *Eur Respir J*. 2007; 30(4): 623-6.

[22] Migliori GB, Loddenkemper R, Blasi F, Raviglione MC. 125 years after Robert Koch's discovery of the tubercle bacillus: the new XDR-TB threat. Is "science" enough to tackle the epidemic? *Eur Respir J.* 2007; 29(3): 423-7.

[23] World Health Organization. Global tuberculosis control: a short update to the 2009 report. Geneva: World Health Organization; 2009.

[24] Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC, Dye C. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med* 2003; 163: 1009-1021.

[25] World Health Organization. Interim Policy on Collaborative TB/HIV Activities. Geneva: World Health Organization; 2004.

[26] Friedland G, Harries A, Coetzee D. Implementation issues in tuberculosis/HIV program collaboration and integration: 3 case studies. *J Infect Dis* 2007 Aug 15;196 Suppl 1:S114-23.

[27] Coker R, McKee M, Atun R, Dimitrova B, Dodonova E, Kuznetsov S, Drobniewski F. Risk factors for pulmonary tuberculosis in Russia: case-control study. *BMJ* 2006; 332: 85–87.

[28] Tocque K, Bellis MA, Beeching NJ, Syed Q, Remmington T, Davies PD. A case-control study of lifestyle risk factors associated with tuberculosis in Liverpool, North-West England. *Eur Respir J* 2001; 18: 959–964.

[29] Lönnroth K, Williams BG, Stadlin S, Jaramillo E, Dye C. Alcohol use as a risk factor for tuberculosis - a systematic review. *BMC Public Health* 2008; 8: 289.

[30] World Health Organization. World health statistics 2008. Geneva: World Health Organization; 2008.

[31] Wild S, Roglic G, Green A, Sicree R, King H. Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; 27: 1047–1053.

[32] Blas E., Sivasankara A.K. (Eds). Priority Public Health Conditions: From Learning to Action on Social Determinants of Health. Geneva: World Health Organization, 2010.

[33] Szabo G: Alcohol and susceptibility to tuberculosis. Alcohol. *Health Res World 1997*, 21:39-41.

[34] WHO Expert Committee on Problems Related to Alcohol Consumption: Second Report. In WHO Technical Report Series 944 Geneva: World Health Organization; 2007.

[35] Mellencamp M. Symposium: Effects of Ethanol Consumption on Susceptibility to Pulmonary and Gastrointestinal Infections. *Alcoholism: Clinical and Experimental Research* 1996; 20: 192-195.

[36] Szabo G: Alcohol's Contribution to Compromised Immunity. *Alcohol, Health & Research World 1997*; 21(1): 30-41.

[37] Houtmeyers E, Gosselink R, Gayan-Ramirez G, Decramer M. Regulation of mucociliary clearance in health and disease. *Eur Respir J* 1999; 13: 1177–1188.

[38] Sopori M. Effects of cigarette smoke on the immune system. *Nat Rev Immunol* 202; 2: 372–377.

[39] Wang H, Yu M, Ochani M, Amella CA, Tanovic M, Susarla S, Li JH, Wang H, Yang H, Ulloa L, Al-Abed Y, Czura CJ, Tracey KJ. Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. *Nature* 2003; 421: 384–388.

[40] World Health Organization, International Union Against Tuberculosis and Lung Disease, World Diabetes Foundation. Report from the Expert Meeting on Tuberculosis and Diabetes Mellitus. 2009

[41] Rehm J, Samokhvalov AV, Neuman MG, Room R, Parry C, Lönnroth K, Patra J, Poznyak V, Popova S. The association between alcohol use, alcohol use disorders and tuberculosis (TB). A systematic review. *BMC Public Health 2009*; 9: 450. doi:10.1186/1471-2458-9-450.

[42] Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. *Lancet* 2009; 374: 733-43.

[43] Sweetland A, Acha J, Guerra D. Enhancing adherence: the role of group psychotherapy in the treatment of MDR-TB in urban Peru. *In*: Cohen A, Kleinman A, Saraceno B, eds. World mental health casebook: social and mental health programmes in low-income countries. New York, USA: Kluwer Academic Press, 2002: 57–85.

[44] Lönnroth K, Raviglione M. Global Epidemiology of Tuberculosis: Prospects for Control. *Semin Respir Crit Care Med* 2008; 29: 481-491.

[45] Chakrabarti B, Calverley P, Davies P. Tuberculosis and its incidence, special nature, and relationship with chronic obstructive pulmonary disease. *International Journal of COPD* 2007:2(3) 263–272.

[46] Barboza CE, Winter DH, Seiscento M, Santos UP, Filho MT. Tuberculosis and silicosis: epidemiology, diagnosis and chemoprophylaxis. *J Bras Pneumol* 2008; 34(11): 961-968.

[47] Stevenson CR, Critchley JA, Forouhi NG, Roglic G, Williams BG, Dye C, Unwin NC. Diabetes and the risk of tuberculosis: a neglected threat to public health. *Chronic Ill* 2007; 3: 228 – 245.

[48] Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. *Lancet Infect Dis* 2009; 9: 737 – 746.

[49] Stevenson CR, Forouhi NG, Roglic G, Williams BG, Lauer JA, Dye C, Unwin N. Diabetes and tuberculosis: the impact of the diabetes epidemic on tuberculosis incidence. *BMC Public Health* 2007; 7: 234.

[50] Guler M, Unsal E, Dursun B, Aydln O, Capan N: Factors influencing sputum smear and culture conversion time among patients with new case pulmonary tuberculosis. *Int J Clin Pract*. 2007;61:231-5.

[51] Wada M: [The effectiveness of pyrazinamide-containing six-month short course chemotherapy]. *Kekkaku*. 2000;75:665-73.

[52] Wang CS, Yang CJ, Chen HC, Chuang SH, Chong IW, Hwang JJ, Huang MS: Impact of type 2 diabetes on manifestations and treatment outcome of pulmonary tuberculosis. *Epidemiol Infect*. 2009;137:203-10.

[53] Dooley KE, Tang T, Golub JE, Dorman SE, Cronin W: Impact of diabetes mellitus on treatment outcomes of patients with active tuberculosis. *Am J Trop Med Hyg*. 2009;80:634-9.

[54] Maalej S, Belhaoui N, Bourguiba M, Mahouachi R, Chtourou A, Taktak S, Fennira H, Slim L, Kheder AB, Drira I: [Pulmonary tuberculosis and diabetes. A retrospective study of 60 patients in Tunisia]. *Presse Med*. 2009;38:20-4.

[55] Mboussa J, Monabeka H, Kombo M, Yokolo D, Yoka-Mbio A, Yala F: [Course of pulmonary tuberculosis in diabetics]. Rev Pneumol Clin. 2003;59:39-44.

[56] Mellencamp M. Symposium: Effects of Ethanol Consumption on Susceptibility to Pulmonary and Gastrointestinal Infections. *Alcoholism: Clinical and Experimental Research* 1996, 20:192-195.

[57] Rieder H. Epidemiologic basis of tuberculosis control. Paris: International Union Against Tuberculosis and Lung Disease; 1999.

[58] Slama K, Chiang CY, Enarson DA, Hassmiller K, Fanning A, Gupta P, Ray C. Tobacco and tuberculosis: a qualitative systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2007; 11(10): 1049–106.

[59] Houtmeyers E, Gosselink R, Gayan-Ramirez G, Decramer M. Regulation of mucociliary clearance in health and disease. *Eur Respir J* 1999; 13: 1177–1188.

[60] Wang H, Yu M, Ochani M, Amella CA, Tanovic M, Susarla S, Li JH, Wang H, Yang H, Ulloa L, Al-Abed Y, Czura CJ, Tracey KJ. Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. *Nature* 2003; 421: 384–388.

[61] Inghammar M, Ekbom A, Engstro¨m G, Ljungberg B, Romanus V, Löfdahl CG, Egesten A. COPD and the Risk of Tuberculosis - A Population-Based Cohort Study. *PLoS ONE* 2010; 5(4): e10138. doi:10.1371/journal.pone.0010138

[62] Lam KB, Jiang CQ, Jordan RE, Miller MR, Zhang WS, Cheng KK, Lam TH, Adab P. Prior TB, smoking, and airflow obstruction: a cross-sectional analysis of the Guangzhou Biobank Cohort Study. *Chest* 2010 Mar;137(3):593-600.

[63] Willcox PA, Ferguson AD. Chronic obstructive airways disease following treated pulmonary tuberculosis. *Respir Med* 1989; 83: 195–198.

[64] Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med* 2001; 163: 1256–1276.

[65] Snider GL, Doctor L, Demas TA, Shaw AR. Obstructive airway disease in patients with treated pulmonary tuberculosis. *Am Rev Respir Dis* 1971;103:625–640.

[66] Leyton G B. Effects of slow starvation. *Lancet* 1946; 2: 253–255.

[67] McKeown T, Brown R G. Medical evidence related to English population changes in the eighteenth century. *Population Studies* 1955; ix: 119–141.

[68] McKeown T, Record R G. Reasons for the decline of mortality in England and Wales during the nineteenth century. *Population Studies* 1962; xvi: 94–122.

[69] Lönnroth K, Williams BG, Cegielski P, Dye C. A consistent log-linear relationship between tuberculosis incidence and body-mass index. *Int J Epidemiology* 2010; 39(1):149-155.

[70] Leung CC, Lam TH, Chan WM, Wing WY, Ho KS, Leung G, Law WS, Tam CM, Chan CK, Chang KC. Lower risk of tuberculosis in obesity. *Arch Intern Med* 2007; 167: 1297-304.

[71] Leimane V, Riekstina V, Holtz TH, Zarovska E, Skripconoka V, Thorpe LE, Laserson KF, Wells CD. Clinical outcome of individualised treatment of multidrug-resistant tuberculosis in Latvia: a retrospective cohort study. *Lancet*. 2005;365(9456):318-26.

[72] Kim DK, Kim HJ, Kwon SY, Yoon HI, Lee CT, Kim YW, Chung HS, Han SK, Shim YS, Lee JH. Nutritional deficit as a negative prognostic factor in patients with miliary tuberculosis. *Eur Respir J* 2008; 32(4): 1031-6.

[73] Khan A, Sterling TR, Reves R, Vernon A, Horsburgh CR. Lack of weight gain and relapse risk in a large tuberculosis treatment trial. *Am J Respir Crit Care Med* 2006; 174(3): 344-348.

[74] Rees D, Murray J. Silica, silicosis and tuberculosis. *Int J Tuberc Lung Dis* 2007; 11(5): 474-84.

[75] Hnizdo E, Murray J. Risk of pulmonary tuberculosis relative to silicosis and exposure to silica dust in South African gold miners. *Occup Environ Med* 1998; 55(7): 496-502.

[76] teWaternaude JM, Ehrlich RI, Churchyard GJ, Pemba L, Dekker K, Vermeis M, White NW, Thompson ML, Myers JE. Tuberculosis and silica exposure in South African gold miners. *Occup Environ Med* 2006; 63(3): 187-92.

[77] Calvert GM, Rice FL, Boiano JM. Sheehy JW, Sanderson WT. Occupational silica exposure and risk of various diseases: an analysis using death certificates from 27 states of the United States. *Occup Environ Med* 2003; 60: 122–129.

[78] Churchyard GJ, Kleinschmidt I, Corbett EL, Murray J, Smit J, De Cock KM. Factors associated with an increased case-fatality rate in HIV-infected and non-infected South African gold miners with pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2000; 4: 705–712.

[79] Murray J, Sonnenberg P, Shearer S, Godfrey-Faussett P. Drug resistant pulmonary tuberculosis in a cohort of southern African gold miners with a high prevalence of HIV infection. *S Afr Med J* 2000; 90: 381–386.

[80] Prince M, Patel V, Saxena S, Maj M, Maselko J, Phillips MR, Rahman A. No health without mental health. *Lancet* 2007; 370: 859–877

[81] Aghanwa HS, Erhabor GE. Demographic/socioeconomic factors in mental disorders associated with tuberculosis in southwest Nigeria. *J Psychosom Res* 1998; 45: 353–60.

[82] Carta MG, Coppo P, Carpiniello B, Mounkuoro PP. Mental disorders and health care seeking in Bandiagara: a community survey in the Dogon Plateau. *Soc Psychiatry Psychiatr Epidemiol* 1997; 32: 222–29.

[83] Schuckit MA. Comorbidity between substance use disorders and psychiatric conditions. *Addiction* 2006, 101: S76-88.

[84] Levinsky L. Tuberculosis and Cardiopulmonary Failure. *Dis Chest* 1961; 40: 564-571.

[85] Ehlers S. Tumor necrosis factor and its blockade in granulomatous infections: differential modes of action of infliximab and etanercept? *Clin Infect Dis* 2005; 41 Suppl 3: S199-203.

[86] Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, Siegel JN, Braun MM. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 2001; 345(15): 1098-1104.

[87] Gomez-Reino JJ, Carmona L, Angel Descalzo M. Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. *Arthritis and rheumatism* 2007; 57(5): 756-761.

[88] Al Shohaib S. Tuberculosis in chronic renal failure in Jeddah. *J Infect* 2000; 40(2): 150-3.

[89] Abdelrahman M, Sinha AK, Karkar A. Tuberculosis in end-stage renal disease patients on hemodialysis. *Hemodial Int* 2006; 10(4): 360-4.

[90] World Health Organization. Global Tuberculosis Control: surveillance, planning, financing. Geneva: World Health Organization; 2007.

[91] Raviglione MC, Uplekar MW. WHO's new Stop TB Strategy. *Lancet* 2006; 367: 952–955.

[92] Me'emary F, Ottmani SE, Pio A, Baghdadi S, Assafin G, Koraym M, Saleh M, Bashour H, Seita A, Blanc L. Results of the feasibility test of the Practical Approach to Lung Health in the Syrian Arab Republic. *East Mediterr Health J* 2009;15(3): 504-15.

[93] Camacho M, Nogales M, Manjon R, Del Granado M, Pio A, Ottmani S. Results of PAL feasibility test in primary health care facilities in four regions of Bolivia. *Int J Tuberc Lung Dis* 2007; 11(11): 1246-52.

[94] Brimkulov N, Ottmani SE, Pio A, Chubakov T, Sultanova A, Davletalieva N, Kalieva A, Rittman J, Erhola M, Cholurova R, Blanc L. Feasibility test results of the Practical Approach to Lung Health in Bishkek, Kyrgyzstan. *Int J Tuberc Lung Dis* 2009;13(4):533-9.

[95] World Health Organization. Practical Approach to Lung Health - Manual on initiating PAL implementation. Geneva: World Health Organization; 2008.

[96] Halbert RJ, Isonaka S, George D, Iqbal A. Interpreting COPD Prevalence Estimates: What Is the True Burden of Disease? *Chest* 2003; 123; 1684-1692.

[97] Shafey O, Dolwick S, Guindon GE, editors. Tobacco Control Country Profiles 2003. 2nd ed. Atlanta: American Cancer Society; 2003. 32 p.

[98] World Health Organization. WHO Global Status Report on Alcohol 2004. Geneva: World Health Organization, 2004.

[99] Alberg AJ. Cigarette smoking: health effects and control strategies. *Drugs Today*. 2008; 44(12): 895-904.

[100] Kimerling M E, Shakes C F, Carlisle R, Lok K H, Benjamin W H, Dunlap N E. Spot sputum screening: evaluation of an intervention in two homeless shelters. *Int J Tuberc Lung Dis* 1999; 3: 613–619.

[101] Barry MA, Wall C, Shirley L, Bernardo J, Schwingl P, Brigandi E, Lamb GA. Tuberculosis screening in Boston's homeless shelters. *Public Health Rep* 1986; 101: 487–494.

[102] Goldgrub N, Santos LAR, Galesi VMN. Active case finding campaign in homeless shelters in Sao Paulo City, Brazil. *Int J Tuberc Lung Dis* 2002; 6 (Suppl 1): S153.

[103] Galesi VMN, Almeida MMMB, Santos LAR. Tuberculosis case-finding campaign, Sao Paulo, Brazil. *Int J Tuberc Lung Dis* 2001; 5: S91–S92.

[104] Dıez M, Bleda MJ, Alcaide J. Determinants of health system delay among confirmed tuberculosis cases in Spain. *Eur J Public Health*, 2005; 15(4): 343–349.

[105] Snider DE. The relationship between tuberculosis and silicosis. *Am Rev Respir Dis* 1978; 118(3): 455-60.

[106] Dye C, K Floyd. "Tuberculosis." In Disease Control Priorities in Developing Countries. 2nd ed. Jamison DT, Breman JG, Measham AR, Alleyne G, Claeson M, Evans DB, Jha P, Mills A, Musgrove P editors. New York: Oxford University Press; 2006. 289–309.

[107] Laxminarayan R, Klein E, Dye C, Floyd K, Darley S, Adeyi O. Economic Benefit of Tuberculosis Control. World Bank Policy Research Working Paper No. 4295. 2007.

[108] Baily GVJ, Savic D, Gothi G D, Naidu V B, Nair S S. Potential yield of pulmonary tuberculosis cases by direct microscopy of sputum in a district of South India. *Bull World Health Org* 1967; 37: 875–892.

[109] Golub JE, Mohan CI, Comstock GW, Chaisson RE. Active case finding of tuberculosis: historical perspective and future prospects. *Int J Tuberc Lung Dis* 2005; 9(11): 1183–1203.

[110] Tuberculosis Coalition for Technical Assistance. International Standards for Tuberculosis Care (ISTC), second edition. The Hague: Tuberculosis Coalition for Technical Assistance; 2009.

[111] Franke MF, Appleton SC, Bayona J, Arteaga F, Palacios E, Llaro K, Shin SS, Becerra MC, Murray MB, Mitnick CD: Risk factors and mortality associated with default from multidrug - resistant tuberculosis treatment. *Clin Infect Dis* 2008; 46:1844-5.

[112] Gelmanova IY, Keshavjee S, Golubchikova VT, Berezina VI, Strelis AK, Yanova GV, Atwood S, Murray M: Barriers to successful tuberculosis treatment in Tomsk, Russian Federation: non-adherence, default and the acquisition of multidrug resistance. *Bull World Health Organ* 2007; 85:703-11.

[113] Koriakin VA, Sokolova GB, Grinchar NA, Iurchenko LN. Pharmacokinetics of isoniazid in patients with pulmonary tuberculosis and alcoholism. (Article in Russian). *Probl Tuberk* 1986; 12:43-6.

[114] Nijland HM, Ruslami R, Stalenhoef JE, Nelwan EJ, Alisjahbana B, Nelwan RH, van der Ven AJ, Danusantoso H, Aarnoutse RE, van Crevel R. Exposure to rifampicin is strongly reduced in patients with tuberculosis and type 2 diabetes. Clin Infect Dis 2006; 43: 848-54.

[115] Thompson NP, Caplin ME, Hamilton MI, et al. Antituberculosis medication and the liver: dangers and recommendations in management. *Eur Respir J* 1995; 8: 1384–1388.

[116] Pande JN, Singh SP, Khilnani GC, Khilnani S, Tandon RK. Risk factors for hepatotoxicity from antituberculosis drugs: a case-control study. *Thorax* 1996 ;51:132-136.

[117] United States Asian and Pacific Islanders Standards for the Management of Tuberculosis and Diabetes Mellitus. *Draft*

[118] Janssens B, Van Damme W, Raleigh B, Gupta J, Khem S, Soy Ty K, Vun MC, Ford N, Zachariah R. Offering integrated care for HIV/AIDS, diabetes and hypertension within chronic disease clinics in Cambodia. *Bull World Health Organ* 2007;85:880–885.

[119] Laserson KF, Wells CD. Reaching the targets for tuberculosis control: the impact of HIV. *Bull World Health Organ* 2007; 85(5): 377-81.

[120] Maher D, Harries AD, Zachariah R, Enarson D. A global framework for action to improve the primary care response to chronic non-communicable diseases: a solution to a neglected problem. *BMC Public Health* 2009, 9:355.37.

[121] Diabetes and Tuberculosis symposium. 40th Union World Conference on Lung Health Cancun, Mexico 2009.

[122] Brostrom R. Integrating Diabetes and TB Programs. National Web-based seminar. Dec 10, 2009.

[123] Wilk AI, Jensen NM, Havighurst TC. Meta-analysis of randomized control trials addressing brief interventions in heavy alcohol drinkers. *J Gen Intern Med* 1997; 12: 274–83.

[124] Poikolainen K. Effectiveness of brief interventions to reduce alcohol intake in primary health care populations: a metaanalysis. *Prev Med* 1999; 28: 503–09.

[125] Room R, Babor T, Rehm J: Alcohol and public health: a review. *Lancet* 2005, 365:519-30.

[126] Berglund M, Thelander S, Jonsson E: *Treating alcohol and drug abuse. An evidenced based review*. Weinheim, Germany: Wiley-Vch Verlag GmbH & Co. KGaA; 2003.

[127] Nolen-Hoeksema S. Gender differences in risk factors and consequences for alcohol use and problems. *Clin Psychol Rev*. 2004;24(8):981-1010.

[128] Batty GD, Lewars H, Emslie C. Internationally recognized guidelines for 'sensible' alcohol consumption: is exceeding them actually detrimental to health and social circumstances? Evidence from a population-based cohort study. *J Public Health 2009*; 31(3): 360-36.

[129] International Union Against Tuberculosis and Lung Disease, World Health Organization. A WHO/The Union monograph on TB and tobacco control – Joining efforts to control two related global epidemics. Geneva: World Health Organization; 2007.

[130] Solberg L I, Maciosek M V, Edwards N M, Khanchandani H S, Goodman M J. Repeated tobacco-use screening and intervention in clinical practice. Health impact and cost effectiveness. *Am J Prev Med* 2006; 31: 62–71.

[131] Lancaster T, Stead L. Physician advice for smoking cessation. Cochrane Database Syst Rev 2004; 4: CD000165.

[132] El Sony A, Slama K, Salieh M, Elhaj H, Adam K, Hassan A, Enarson DA. Feasibility of brief tobacco cessation advice for tuberculosis patients: a study from Sudan. *Int J Tuberc Lung Dis* 2007 Feb;11(2):150-5.

[133] Abba K, Sudarsanam TD, Grobler L, Volmink J. Nutritional supplements for people being treated for active tuberculosis. *Cochrane Database of Systematic Reviews* 2008; Issue 4. Art No.:CD006086. doi: 10.1002/14651858.CD006086.pub2

[134] Jamieson C, Norton B, Day T, Lakeman M, Powell-Tuck J. The quantitative effect of nutrition support on quality of life in outpatients. *Clinical Nutrition* 1997; 16(1): 25-28.

[135] Lettow MV, Kumwenda JJ, Harries AD, Whalen CC, Taha TE, Kumwenda N, Kang'ombe C, Semba RD. Malnutrition and the severity of lung disease in adults with pulmonary tuberculosis in Malawi. *Int J Tuberc Lung Dis*. 2004;8:211-217.

[136] Papathakis P, Piwoz E. Nutrition and Tuberculosis: A review of the literature and considerations for TB control programs. USAID: Africa's Health in 2010 project. 2008 Available at http://www.aidsportal.org/repos/Nutrition%20and%20TB_Final.pdf

[137] Xie QM, Tang HF, Chen JQ, Bian RL. Pharmacological actions of tetrandrine in inflammatory pulmonary diseases. *Acta Pharmacol Sin*. 2002; 23(12): 1107-13.

[138] World Health Organization. The Stop TB Strategy – building on and enhancing DOTS to meet the TB-related Millennium Development Goals. Geneva: World Health Organization; 2006.

[139] Rehm J, Greenfield TK: Public alcohol policy: current directions and new opportunities. *Clin Pharmacol Ther* 2008; 83:640-3. 108.

[140] Babor T, Caetano R, Casswell S, Edwards G, Giesbrecht N, Graham K, Grube J, Gruenewald P, Hill L, Holder H, Homel R, Österberg E, Rehm J, Room R, Rossow I: Alcohol: No ordinary commodity. Research and public policy. Oxford and London: Oxford University Press; 2003.

[141] van den Berg M, van Baal PH, Tariq L, Schuit AJ, Ardine de Wit G, Hoogenveen DT. The cost-effectiveness of increasing alcohol taxes: a modeling study. *BMC Med*. 2008;6:36.

[142] Shilova MV, Dye C. The resurgence of tuberculosis in Russia. *Philosophical Transactions of the Royal Society of London, Series B, Biological Sciences* 2001; 356: 1069–1075.

[143] Arinaminpathy N, Dye C. Health in financial crises: economic recession and tuberculosis in Central and Eastern Europe. *J. R. Soc. Interface* 2010. doi:10.1098/rsif.2010.0072 (In Press).

[144] Oeltmann JE, Kammerer JS, Pevzner ES, Moonan PK. Tuberculosis and substance abuse in the United States, 1997-2006. *Arch Intern Med 2009*; 169(2): 189-97.

[145] World Health Organization. WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis. Geneva: World Health Organization; 2008.

[146] Francis J. Curry National Tuberculosis Center and California Department of Public Health. Drug-Resistant Tuberculosis: A Survival Guide for Clinicians. 2nd ed. San Francisco: Francis J. Curry National Tuberculosis Center; 2008.

[147] World Health Organization. Global tuberculosis control 2009. Geneva: World Health Organization; 2009.

[148] Elzinga G, Raviglione MC, Maher D. Scale up: meeting targets in global tuberculosis control. *Lancet* 2004 Mar 6;363(9411):814-9.

[149] Dye C, Watt CJ, Bleed DM, Williams BG. What is the limit to case detection under the DOTS strategy for tuberculosis control? *Tuberculosis*. 2003; 83(1-3): 35-43.

[150] Corbett L. Impact of periodic case finding for symptomatic smear-positive disease on community control of prevalent infectious tuberculosis. A community randomized trial of two delivery strategies in Harare, Zimbabwe. 40th Union World Conference on Lung Health, Cancún, Mexico, 2009.

Table 1. Relative Risk, Prevalence and Population Attributable Fraction of HIV and selected NCD[a,b] as Risk Factors for TB Among Adults, in 8 WHO Regions and Established Market Economies

	HIV			Malnourishment			Smoking			Diabetes			Alcohol		
Region[c]	RR	HIV %	PAR (%)	RR	Malnourishment %	PAR (%)	RR	Smoking %	PAR (%)	RR	DM%	PAR (%)	RR	Heavy Drinkers %	PAR (%)
ARFO High HIV	**26.7**	7.05	**64.4**	**3.2**	29.11	39.0	**2.0**	10.10	9.2	**3.1**	3.12	6.2	**2.9**	15.67	22.9
AFRO Low HIV		1.28	24.7		21.65	**32.3**		12.16	10.8		4.14	8.0		8.22	13.5
CEURO		0.03	8.3		2.91	6.0		34.82	**25.8**		8.19	14.7		8.97	14.6
EEURO		0.67	14.8		6.74	12.9		40.51	28.8		8.24	14.8		28.03	**34.7**
EME		0.27	6.4		1.00	2.2		25.88	**20.6**		8.01	14.4		8.62	14.1
EMRO		0.09	2.4		13.17	**22.5**		19.07	16.0		7.87	14.2		0.19	0.4
LAC		0.52	11.8		8.62	15.9		21.17	17.5		7.00	12.8		12.50	**19.2**
SEARO		0.34	7.99		20.63	**31.2**		21.93	18.0		6.55	12.1		1.12	2.1
WPRO		0.11	2.69		9.59	17.4		30.99	**23.7**		4.72	9.0		4.17	7.3

a) Diabetes is the main risk factor for chronic renal disease and data on chronic renal disease without diabetes are not available

b) Data on mental illnesses are not available for this table.

c The acronyms in the table refer to WHO regional designations and for the following areas

AFRO - African Region

CEURO - Central European Region

EEURO - Eastern European Region

EME - Established Market Economies

EMRO - Eastern Mediterranean Region

LAC - Latin American and Caribbean Region

SEARO - South East Asian Region

WPRO Western Pacific Region

Table 2. Summary of Case Detection and Management Strategies as well as Research Priorities for Different Non Communicable Diseases

NCD	Case Detection Strategies	Case Management Implications	NCD Reduction	Research Priorities
Diabetes Mellitus	• Diabetes patients are regularly seen at health care facilities where they can be screened for TB upon diagnosis and periodically while the diabetes is being managed.	• TB drug hepatotoxicity might increase • Diabetes is somewhat associated with delay in sputum culture conversion at 2-3 months • May increase death during TB treatment • May increase risk of MDR-TB	• Better control and management of diabetes • Exercises and diet	• The best screening methods have not been identified. • The optimal time to screen for diabetes needs to be specified and the definitions should be standardized. • Impact of interventions on TB outcomes
Smoking and COPD	• Hard to systematically screen smokers but may seek care more often and it can heighten awareness for TB screening • COPD patients may be periodically screened as they meet TB definition and COPD is a independent risk factor	• Linked to severity of TB at the time of diagnosis, risk of relapse and higher risk of death from TB than non smokers • Unclear if COPD is a risk factor for TB, independently from smoking. However, TB seems to be an independent risk factor for COPD	• National policies including taxes • Smoking cessation interventions	• The best screening methods have not been identified. • Impact of interventions on TB outcomes • Effectiveness of tobacco cessation among TB patients
Alcohol use >40gr/day	• Hard to systematically screen but may seek care more often and it can heighten awareness for TB screening	• Added importance of DOT • TB drug hepatotoxicity might increase with diabetes mellitus and alcohol use disorder. • Significant decreases in absorption of isoniazid and its accelerated metabolism after oral administration to heavy drinkers • Effective treatment strategies for alcohol reduction exist	• National policies including taxes • Alcohol reduction programmes	• The links between alcohol use and TB outcomes, and y acquired drug resistance • The best screening methods have not been identified. • Impact of interventions on TB outcomes • Effectiveness of brief interventions on alcohol use disorders
Malnutrition	• Hard to systematically screen. May be useful to concentrate on proxies like poverty and screen slum areas with poor service access	• Patients beginning treatment with poor nutritional status are at risk for poor outcomes • Nutritional support is often recommended but there is not much evidence to substantiate the practice	• National policies addressing food security, distribution, etc	• Further research for the use of dietary supplements and nutritional support as a means for improving TB treatment outcomes • How to best use and deliver nutritional support to enhance adherence
Mental Illness	• Mentally ill people are seen regularly at health care facilities and can be screened for TB and offered chemotherapy	• Added importance of DOT • Drug interactions must be considered • Social support	• Social support mechanisms • Stigma reduction	• Better establish links between mental illness and TB disease • Feasibility of screening and early case detection • Feasibility of IPT

Figure 1. Decision Framework for Targeting NCD Risk Groups for TB Case Detection, Management and Prevention