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Tuberculosis comorbidity with communicable and non-communicable diseases: integrating health services and control efforts

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Recent data for the global burden of disease reflect major demographic and lifestyle changes, leading to a rise in non-communicable diseases. Most countries with high levels of tuberculosis face a large comorbidity burden from both non-communicable and communicable diseases. Traditional disease-specific approaches typically fail to recognise common features and potential synergies in integration of care, management, and control of non-communicable and communicable diseases. In resource-limited countries, the need to tackle a broader range of overlapping comorbid diseases is growing. Tuberculosis and HIV/AIDS persist as global emergencies. The lethal interaction between tuberculosis and HIV coinfection in adults, children, and pregnant women in sub-Saharan Africa exemplifies the need for well integrated approaches to disease management and control. Furthermore, links between diabetes mellitus, smoking, alcoholism, chronic lung diseases, cancer, immunosuppressive treatment, malnutrition, and tuberculosis are well recognised. Here, we focus on interactions, synergies, and challenges of integration of tuberculosis care with management strategies for non-communicable and communicable diseases without eroding the functionality of existing national programmes for tuberculosis. The need for sustained and increased funding for these initiatives is greater than ever and requires increased political and funder commitment.

Introduction

In recent decades, the prevalence of non-communicable diseases has risen, an increase attributable to historic and projected demographic shifts of the world's population, together with urbanisation and accompanying lifestyle changes.[1] Countries of low and middle income now have a large burden of non-communicable disease, which overlaps with the unfinished agenda of communicable diseases; the risk factors of poverty, unhealthy lifestyles, tobacco use, and alcohol misuse are common to both categories of disease.[2–6] People living with chronic communicable diseases such as tuberculosis and HIV/AIDS are most likely to develop comorbidity with non-communicable diseases. Moreover, coexisting communicable and non-communicable diseases augment the risk or effect of the other. Health-care systems in resource-limited settings are poorly equipped to deal with this double burden of disease,[7] and disease-specific health-care approaches do not represent the most efficient response.[8,9] Therefore, traditional approaches to global health need to be reassessed, with greater emphasis on multidisciplinary collaboration and integrated strategies.

In the 2010 Global Burden of Disease study,[2–4] the number of deaths per year (1980–2010) from 235 causes were estimated for 187 countries. In 2010, 52·8 million deaths were recorded worldwide, of which 24·9% were attributable to communicable diseases related to maternal, neonatal, and nutritional causes, a fall from 34·1% of 46·5 million deaths in 1990.[3] These data show a continued shift from communicable to non-communicable diseases and from premature deaths to years lived with disability. However, disease projections that reflect ever decreasing rates of communicable diseases fail to appreciate their highly dynamic and unpredictable nature. Globalisation, increased population density, and environmental disruption present a fertile ground for emergence of new communicable diseases.[10] Movement of people and growing drug resistance are important factors hampering global tuberculosis control efforts.[11–15]

In sub-Saharan Africa, communicable diseases and maternal, neonatal, and nutritional disorders remain the dominant causes of disease burden.[3,4] Deaths from HIV/AIDS increased from 0·30 million in 1990 to 1·5 million in 2010, and malaria mortality rose by an estimated 19·9% since 1990, to 1·17 million deaths in 2010. WHO estimates show that, in 2011, 8·7 million new cases of tuberculosis were recorded and 1·4 million people died from the disease, including 350 000 deaths associated with HIV coinfection.[16] Sub-Saharan Africa, India, and China have the highest number of tuberculosis cases,[16] and multidrug-resistant tuberculosis has become widespread in eastern Europe.[17]

Here, we focus on the close relationship between tuberculosis and non-communicable disease, and tuberculosis and other communicable diseases, in terms of comorbidity, causation, and health care. We also investigate commonalities, synergies, and challenges for integration of tuberculosis care and control efforts and make proposals for change.

Factors affecting comorbidity

Identification of the best strategies for prevention and management of overlapping disease burdens supports progress towards attainment of the Millennium Developmental Goals (MDGs). For example, after correction for health system variables, lower burdens of non-communicable diseases and HIV infection were associated with much greater progress towards MDG goals for child mortality and tuberculosis than were gains in gross domestic product.[18] Although social determinants of health are the main factors that drive the current tuberculosis pandemic,[19,20] other risk factors for *Mycobacterium tuberculosis* infection and progression to active tuberculosis disease are well known (panel 1). Figure 1 shows the geographical variation in burden of tuberculosis and associated comorbidities.

HIV-associated tuberculosis

Tuberculosis and HIV/AIDS are both chronic diseases and continue as global emergencies. Tuberculosis is a leading cause of death in people coinfected with HIV.[16] The lethal bidirectional interaction between these two diseases in sub-Saharan Africa exemplifies the need for well integrated approaches to disease identification, management, and control. HIV infection increases the risk of tuberculosis by 20–40-fold, and tuberculosis accounts for 25% of HIV-related deaths worldwide—the single biggest cause.[16] The HIV epidemic fuelled the threefold to fivefold rise in tuberculosis notification rates between 1990 and 2005 in sub-Saharan Africa, which bears 80% of the global burden of HIV-associated tuberculosis. Thus, health systems are generally weakest where the disease burden is greatest. In the mid-1990s, early application of WHO's global DOTS (directly observed treatment, short-course) strategy, without explicit tuberculosis–HIV collaborative activities, proved inadequate to stem the tuberculosis epidemic in settings with a high prevalence of HIV.[21]

WHO published a comprehensive three-pronged strategy for collaborative tuberculosis–HIV activities in 2004, which was updated in 2012.[21,22] First, mechanisms for delivery of integrated tuberculosis and HIV services need to be established and strengthened at all levels of the health service. Second, the burden of tuberculosis in people living with HIV needs to be reduced by implementation of early combination antiretroviral therapy together with isoniazid preventive therapy, intensified case-finding, and improved infection control. Third, the burden of HIV in patients with suspected or diagnosed tuberculosis needs to be reduced through provider-initiated HIV testing and counselling, HIV prevention services for those who test negative, and optimised case management for those who test positive.

Young children from HIV-affected households are at high risk of tuberculosis exposure.[23] Tuberculosis remains a major unrecognised cause of death in young children—both HIV-infected and HIV-uninfected—in endemic areas.[24,25] Young children are also at risk of HIV infection through the infected mother.[26] Active screening of household contacts to rule out tuberculosis and provide preventive treatment to vulnerable individuals, particularly young children, could be linked to active HIV case-finding by simple point-of-care testing.[26] Close links with maternal and child health programmes are essential to ensure universal tuberculosis and HIV screening of pregnant mothers, implementation of effective strategies to prevent mother-to-child HIV trans-mission, and early initiation of combined antiretroviral therapy in all HIV-infected infants.[27]

Adverse drug reactions complicate concurrent treatment of HIV/AIDS and tuberculosis.[27] Although efavirenz-based combined antiretroviral regimens can be used with standard tuberculosis drugs, use of protease inhibitors with rifampicin is problematic because rifampicin significantly reduces concentrations in serum of protease inhibitors; use of dose-adjusted lopinavir and ritonavir with rifampicin, or substitution of rifampicin with rifabutin, is needed.[28] Study findings show that early initiation of combined antiretroviral therapy in people with low CD4+ T-cell counts reduces mortality and

> **Key messages**
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> - Comorbidity of tuberculosis with non-communicable diseases (eg, diabetes mellitus, malnutrition, smoking-related and alcohol-related diseases) and other communicable diseases (eg, HIV/AIDS) is prevalent in regions of the world that are highly endemic for tuberculosis; integrated and efficient responses are required to tackle these comorbidities in resource-poor countries
> - Wider integration of tuberculosis control activities presents opportunities to investigate commonalities and potential synergies in management and control of communicable and non-communicable diseases, which have been overlooked by traditional vertical approaches, without sacrificing recent gains in health care or eroding the functionality of existing programmes
> - Early initiation of antiretroviral therapy should be a priority for HIV-infected individuals with newly diagnosed tuberculosis; bidirectional screening for diabetes mellitus and tuberculosis is needed
> - Levels of unsuspected comorbidity are high; patients with concurrent communicable or non-communicable diseases, or pregnant women attending antenatal clinics who have concurrent active or subclinical tuberculosis, are frequently overlooked
> - Efficient integration of tuberculosis services should be encouraged while maintaining some vertical elements to secure essential functions, such as drug supply, monitoring, assessment, and national surveillance, to a point at which the national tuberculosis programme could be restricted to a small central team doing general oversight

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AIDS-defining disorders.[29–31] Thus, WHO recommends such regimens should be started as soon as possible and within the first 8 weeks of tuberculosis treatment initiation.[32] This recommendation requires a patient-centred approach tailored to national and local health infrastructure, such that patients with HIV-associated tuberculosis can receive treatment for both diseases at the same health facility, either in different clinics or in the same clinic but always in a coordinated and integrated manner. Furthermore, in a systematic review[33] of studies looking at the effect of combined antiretroviral therapy on the incidence of tuberculosis in adults with HIV infection, combined regimens were associated strongly with a reduction in the incidence of tuberculosis across all CD4+ T-cell strata, and early initiation of combined antiretroviral therapy was proposed as a key component of national strategies to control HIV-associated tuberculosis.

Panel 1: Risk factors associated with *Mycobacterium tuberculosis* infection and progression to active tuberculosis disease

Social determinants of tuberculosis
- Poverty
- Stress
- Poor housing
- Poor ventilation (domestic and workplace)
- Crowded living conditions (eg, prisons, refugee camps, homeless shelters, mass gatherings, shanty compounds)
- Malnutrition
- Alcohol or substance misuse
- Air pollution (eg, biomass fuels, cigarette smoke)
- Extremes of age: very old and very young people
- Pregnancy and childbirth
- Travel to a country highly endemic for tuberculosis

Risk factors for development of active tuberculosis
- HIV
- Diabetes mellitus
- Poor nutrition
- Chronic lung disease
  - Chronic obstructive pulmonary disease
  - Silicosis
- Active smoking
- Alcohol
- Substance (drug) misuse
- Immunosuppressive treatment
- Contact with a person with active pulmonary tuberculosis
- Genetic factors
- Congenital immunodeficiencies (eg, chronic granulomatous disease, common variable immunodeficiency)

Clinically observed associations with tuberculosis
Patients with communicable diseases
- HIV/AIDS
- Sexually transmitted infections
- Viral hepatitis
- Bacterial, viral, fungal pneumonias
- Empyema
- Helminth infestations

Patients with non-communicable diseases
- Diabetes mellitus
- Chronic lung diseases (eg, emphysema, chronic bronchitis, silicosis)
- Chronic kidney disease or end-stage renal failure
- Autoimmune hepatitis
- Gut malabsorption syndromes
- Gastric bypass or gastrectomy
- Crohn's disease
- Ulcerative colitis
- Organ transplants
- Malignant disease (eg, oral, oesophageal, nasopharyngeal, lung)
- Reticuloendothelial disorders (eg, leukaemia, Hodgkin's lymphoma, multiple myeloma)
- Rheumatoid arthritis
- Autoimmune diseases
- Psoriasis
- Alopecia areata
- Sarcoidosis
- Solid organ transplants

Micronutrient and vitamin deficiencies
- Zinc deficiency
- Vitamin D deficiency
- Vitamin A deficiency

Pharmacological treatments that could reactivate latent tuberculosis infection
- Immunosuppressants
  - Steroids (eg, prednisone, prednisolone, methylprednisolone)
- Antimetabolites (eg, methotrexate, azathioprine, leflunomide)
- T-cell inhibitors (eg, ciclosporin, tacrolimus)
- Alkylating agents (eg, cyclophosphamide, chlorambucil)
- Biological agents
  - Tumour necrosis factor or interleukin 2 blockers (eg, etanercept, infliximab, adalimumab)
  - Humanised chimaeric monoclonal antibodies (eg, basiliximab, daclizumab, muromonab-CD3, tacrolimus)
- Non-steroidal anti-inflammatory drugs (eg, ibuprofen, diclofenac)

Occupation or high-risk work environment
- Miners
- Health-care workers
- Laboratory personnel
- Residential care staff
- Prison staff
- Refugee camp workers
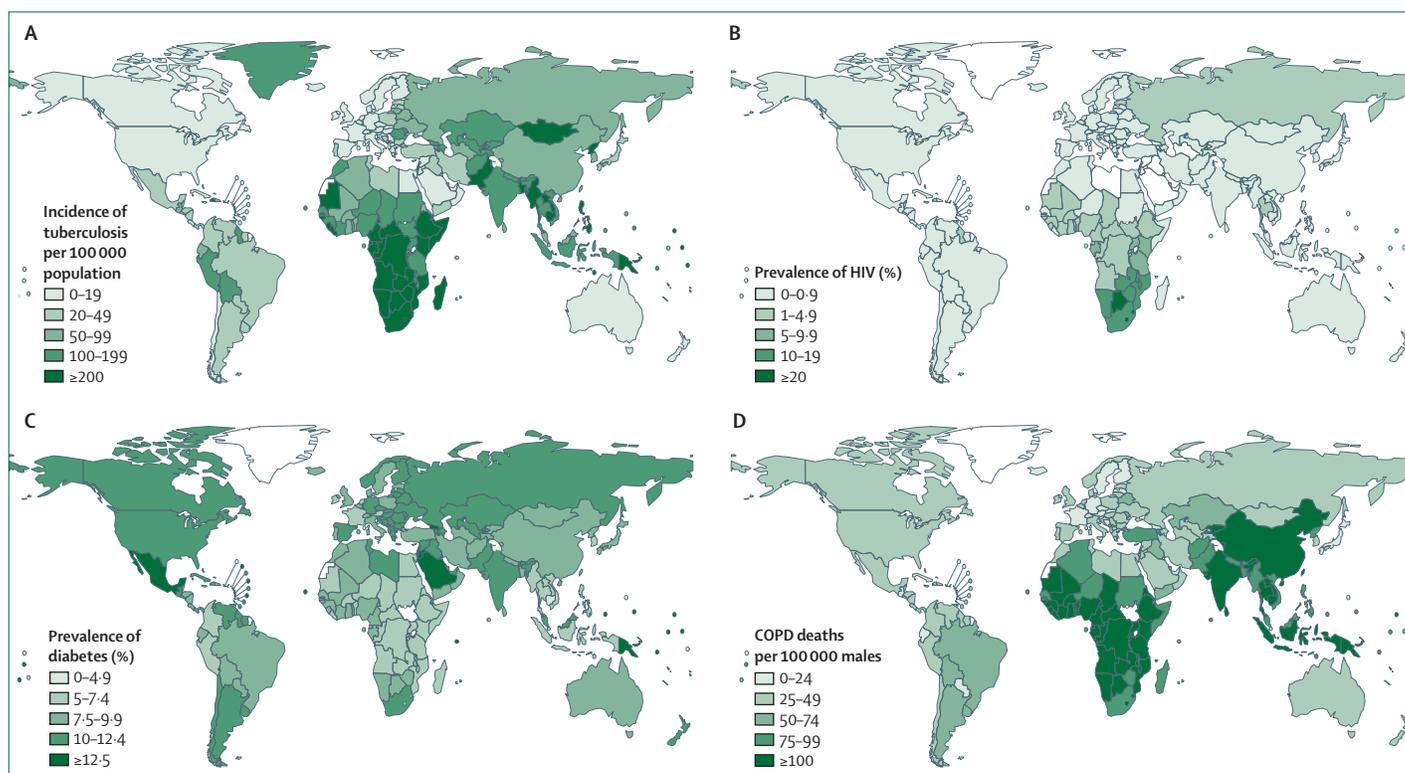
Figure 1: **Worldwide incidence of tuberculosis, prevalence of HIV and diabetes in adults, and deaths from COPD in boys and men**
(A) Estimated incidence of tuberculosis per 100 000 population in 2011. Data sourced from reference 16. (B) Prevalence of HIV in people age 15–49 years in 2011. (C) Prevalence of adults age 25 years or older with blood glucose greater than 7 mmol/L in 2008. (D) COPD mortality per 100 000 boys and men in 2008. Data for B–D sourced from WHO's Global Health Observatory (accessed Nov 20, 2012). COPD=chronic obstructive pulmonary disease.

Millions of HIV-infected people are at risk of communicable lung diseases. In view of the effectiveness of modern combined antiretroviral therapy regimens, HIV infection has become a chronic illness. Non-communicable diseases affecting the lung (such as chronic obstructive pulmonary disease [COPD]) and metabolic disorders (such as diabetes mellitus) are on the rise. Increasingly, the health-care needs of people on combined antiretroviral drugs resemble those of individuals with chronic non-communicable disorders. Since vertical programmes are difficult to sustain when health systems are under-resourced and strained, calls have been made to focus care at the primary level for people with chronic diseases.[34]

Tuberculosis and non-communicable diseases
Non-communicable diseases were not included explicitly during formulation of the MDGs. This oversight was partly corrected when the UN published a declaration on the prevention and control of non-communicable diseases,[1] which was supported by all 193 member states. Despite intercountry heterogeneity resulting from variable demographic and socioeconomic transition, most non-communicable and communicable diseases are associated with a strong social gradient, mostly affecting poor and marginalised populations.

Historically, efforts to control communicable and non-communicable diseases had little in common and tended to emphasise differences rather than similarities.[8] However, despite being transmissible, management and control of chronic infectious diseases such as tuberculosis has more in common with non-communicable diseases than with acute communicable diseases (table). Synergies that could be investigated in public health efforts include joint health promotion strategies and reciprocal screening and coordinated management programmes (panel 2). Non-communicable diseases interact adversely with tuberculosis by increasing both individual vulnerability to disease and the likelihood that the epidemic will be sustained within a population.[35] Individual vulnerability is affected by the number and severity of comorbid disorders, whereas the total burden of comorbidity determines vulnerability at the population level.

Diabetes mellitus and tuberculosis
The link between diabetes mellitus and tuberculosis has long been recognised, but the looming threat of these convergent global epidemics has only recently been appreciated.[35–39] Study findings consistently show a twofold to threefold higher risk of developing tuberculosis in patients with diabetes mellitus

	Communicable diseases		Non-communicable diseases (eg, diabetes, COPD, coronary artery disease, cancer, chronic renal failure)
	Acute (eg, influenza, meningococcal meningitis, bacterial pneumonia, malaria)	Chronic (eg, tuberculosis, HIV, leprosy, syphilis, leishmaniasis, schistosomiasis)	
Transmission	Possible	Possible	Not possible
Infection control	Important	Important	No issues
Prevention	Necessary	Necessary	Necessary
Point-of-care testing	Limited	Available for HIV	Common
Cure	Mostly curable or transient	Mostly curable	Rarely curable
Management	Short-term treatment	Long-term management	Long-term management
Problems with treatment adherence	Limited	Major	Major
Change to lifestyle	None required	Required	Required
Case management	Mostly triage at primary health-care level, management of severe cases at referral centres	Most cases managed at primary health-care level	Most cases managed at primary health-care level

COPD=chronic obstructive pulmonary disease.

Table: **Differences and similarities between communicable and non-communicable diseases**

Panel 2: Potential synergies and advantages of integrated health care

Best care for patients
- Consolidates continuity of care
- Avoids multiple clinic attendances

Optimum use of available resources
- Combined and coordinated human resource development and training activities
- Cross-utilisation of health-care workers and multiskilling
- Reciprocal screening programmes
- Combined infrastructure development
- Integrated recording and reporting systems

Combined prevention strategies
- Poverty alleviation
- Creation of an environment that sustains health and wellbeing
- Health messaging and communication
- Community and user education and engagement

compared with people without diabetes. However, the prevalence of diabetes mellitus among patients with tuberculosis varies according to the setting,[40,41] possibly attributable to differences in background prevalence of diabetes mellitus between populations and alternative clinical and laboratory methods of screening and diagnosing diabetes mellitus. In India, an estimated 2·2 million cases of tuberculosis are recorded per year and about 60 million people have diabetes mellitus; 14·8% of the tuberculosis burden has been attributed to diabetes mellitus.[39] In a study from the Indian state of Tamil Nadu, nearly 50% of patients with tuberculosis had either diabetes mellitus (25·3%) or prediabetes (24·5%).[39] In a Chinese survey of 8886 registered tuberculosis cases, 1090 (12·4%) patients had diabetes mellitus and 575 (7·8%) had impaired fasting glucose.[40,41] Prevalence of diabetes mellitus was significantly higher in patients with tuberculosis in urban areas (14·0%) versus rural populations (10·6%), and it was higher among people with tuberculosis than in the general population in both urban and rural areas. Africa also has rising rates of diabetes mellitus, particularly in urban populations.[42,43] In Zambia, unsuspected tuberculosis among adult inpatients was significantly associated with diabetes mellitus (odds ratio 6·6, 95% CI 1·7–25·3).[44] In Hispanic populations in the USA, diabetes mellitus has long been recognised as a factor contributing to high prevalence of tuberculosis.[45] People with diabetes also show impaired sputum conversion and cure rates on tuberculosis treatment, with increased risk of death and relapse.[46–48]

To address the double burden of tuberculosis and diabetes mellitus and the absence of international guidelines, WHO and the International Union Against Tuberculosis and Lung Disease developed a collaborative framework for care and control of these diseases,[49] which sets outs out principles for bidirectional screening and coordinated management of the two diseases. The framework is based on data from systematic reviews on the diagnosis and management of diabetes and tuberculosis. Similarly, the International Diabetes Federation recognises the link between communicable and non-communicable diseases and supports the reorientation and integration of the health workforce and services to simultaneously address this double burden of disease.[50] An important limitation of dual screening for tuberculosis in patients with diabetes mellitus, and vice versa, is cost-effectiveness. WHO recommends screening for tuberculosis only if the estimated prevalence of the disease in the population is more than 100 cases per 100 000 population, which implies screening around 100 people to detect one case of tuberculosis. However, good examples of integration of diabetes mellitus and tuberculosis screening come from China.[40,41]

Risk of metabolic disease is increased in HIV-infected patients on lifelong combined antiretroviral therapy. In one study,[51] the incidence of diabetes rose with cumulative exposure to combined antiretroviral therapy, and stavudine and zidovudine were significantly associated with diabetes risk. In a prospective study,[52] use of a protease inhibitor was associated with a threefold increased risk of incident diabetes mellitus. This finding is a particular concern in sub-Saharan Africa, where first-line antiretroviral therapy typically uses lower cost drugs that often have more metabolic complications.[42] Even with increased availability of cheaper, less toxic, generic fixed-drug

combinations, zidovudine remains an important component of first-line combined antiretroviral treatment, and lopinavir and ritonavir are vital components of second-line regimens worldwide. HIV-infected patients in resource-limited settings are at high risk of developing metabolic abnormalities, with suboptimum assessment for and management of potential long-term complications.

Malnutrition

Countries in epidemiological transition are affected adversely by both overnutrition and undernutrition. An individual who is either moderately to severely underweight or micronutrient-deficient is at increased vulnerability to develop tuberculosis,[53–56] although evidence for the detrimental effect of milder nutrient deficiencies is less robust. A reanalysis was done of US National Health and Nutrition Examination Survey data gathered in 1971–75 and matched to tuberculosis outcomes in 1982–92.[57] Disease rates of 24·7 per 100 000 person-years (95% CI 13·0–36·3) were recorded in normal-weight individuals. After controlling for demographic, socioeconomic, and medical characteristics, adjusted hazard ratios in people who were underweight, overweight, and obese were 12·4 (95% CI 5·8–27·0), 0·3 (0·1–0·6), and 0·20 (0·1–0·6), respectively.[57] The fact that malnutrition is very common in many parts of the world accounts for its large contribution to the attributable risk for tuberculosis. The effects of malnutrition, notably in utero and in early life, also take a major toll in the form of obesity, diabetes mellitus, hypertension, and heart disease in later life,[57] thus serving to reinforce the double burden of disease in poorer countries and among disadvantaged subpopulations of wealthier nations.

Rates of malnutrition, anaemia, and micronutrient deficiencies are amplified by chronic worm infestation, although the contribution is poorly quantified.[58] Worm infestation might also increase vulnerability to tuberculosis via immune-mediated mechanisms, but the exact pathways await better characterisation.[59] Excessive exposure to mycotoxins (aflatoxins and fumonisins) is a particular risk factor in underdeveloped rural areas, where food is not stored in temperature-controlled and humidity-controlled environments. Fungal contamination of stored food could result in immunosuppression or various systemic adverse effects[60] that could increase tuberculosis vulnerability.

Tobacco, alcohol, and drug dependency and tuberculosis

Cigarette smoking, including passive smoking, has been associated consistently with an increased risk of M tuberculosis infection, subsequent disease development, and poor treatment outcomes.[61,62] The mechanisms have not been elucidated fully, but airway immunity is affected negatively by cigarette smoke inhalation, and we are only

starting to appreciate the importance of local immune responses within the lung in the pathogenesis of tuberculosis.[63,64] In China, findings of a multiple risk factor modelling study assessing the effects of smoking and solid-fuel use on COPD, lung cancer, and tuberculosis showed that complete gradual cessation of smoking and solid-fuel use by 2033 could avoid 26 million deaths from COPD and 6·3 million deaths from lung cancer and would reduce the projected incidence of tuberculosis in 2033 by 14–52% if 80% DOTS coverage were sustained.[65] WHO and the International Union Against Tuberculosis and Lung Disease have developed a framework for coordinated action on tuberculosis and tobacco control.[66]

Misuse of alcohol and other addictive substances also augments the likelihood of developing tuberculosis, although separation of its independent effect from associated malnutrition, other comorbidities, and increased tuberculosis exposure is difficult within the social context.[67,68] Alcohol misuse is associated with poor treatment adherence and a significantly amplified risk of relapse and death during and after tuberculosis treatment.[67,68] Diagnosis and treatment of harmful drinking and alcohol misuse disorders should be part of basic clinical care for people with tuberculosis, particularly in settings with high alcohol consumption. More research is needed to assess the effect of such interventions on tuberculosis outcomes.[69] In a review of autopsies done on people who died with tuberculosis in London, UK, 35 of 46 cases had comorbidities, mainly hepatitis C virus and HIV infections, cancer, cardiovascular disease, and COPD.[70] Hepatitis C infection is especially prevalent in injecting drug users. Control measures for tobacco, alcohol, and drug misuse are an obvious priority for improved public health.

Chronic lung disease and tuberculosis

Chronic lung disease reflects the cumulative effect of multiple lung insults, including inhalation of cigarette and solid-fuel smoke, silica, and other air pollutants, and allergens, together with recurrent chest infections.[71] Modelling the effects of cigarette smoking and solid-fuel exposure in China,[65] and the well-known comorbidity between pulmonary silicosis and tuberculosis,[72–74] shows how chronic lung disease increases vulnerability to tuberculosis, and the cycle is mutually reinforcing.[75] Tuberculosis, COPD, and smoking have major implications for global lung health.[73] Chronic lung disease[74] accounts for some of the substantial differences in life expectancy noted within Europe, emphasising the importance of integrated lung health initiatives such as the practical approach to lung health (PAL)[75] and the European respiratory roadmap.[76]

Concomitant tuberculosis in immunocompromised people

Tuberculosis is seen increasingly in patients with medical conditions and those who are receiving treatment that compromises the immune system.[77–81] WHO estimates

that nearly 2 billion people globally have latent *M tuberculosis* infection,[79] and these individuals are at risk of developing active tuberculosis disease when the body's immune system is perturbed. Apart from immuno-suppression due to HIV, any immunocompromised state increases susceptibility to either development of active tuberculosis after infection or reactivation of latent infection. These include physiological (very young and elderly people), pathological (malignant disease), therapeutic (immunosuppressive treatment), and chronic disease states (panel 1). Targeted biological agents that block tumour necrosis factor α have trans-formed treatment of chronic inflammatory, rheumato-logical, and autoimmune diseases. However, reactivation of latent *M tuberculosis* infection in patients using these drugs is leading increasingly to comorbidity of active tuberculosis and non-communicable diseases.[78] Although this occurrence is not a major public health issue, it has important implications for management of individual patients in countries with low endemicity for tuberculosis and a large migrant population from highly endemic regions harbouring latent infection.[81]

Cancer and tuberculosis associations

A growing number of bacterial and parasitic infections are associated with development of cancer.[82] Three main interactions have been noted between tuberculosis and cancer. First, tuberculosis increases lung cancer risk.[83] Second, cancers can promote reactivation of latent *M tuberculosis* infection.[84] Third, immunosuppression attributable to cancer treatment can reactivate latent tuberculosis infection.[85] In a comparison of 4480 Taiwanese adults with newly diagnosed tuberculosis and more than 700 000 patients without tuberculosis,[84] after adjustment for COPD and smoking-related cancers, lung cancer incidence was 11 times higher in people with tuberculosis. Significant risk factors were oral, nasopharyngeal, oesophageal, lung, and haematological cancers (eg, non-Hodgkin lymphoma and leukaemia).

Subclinical and undiagnosed tuberculosis

One of the challenges at busy referral centres with a high turnover of patients, in countries highly endemic for tuberculosis, is that the immediate focus of the admitting doctor is to deal with the acute medical or obstetric condition that necessitated admission. Many patients with communicable or non-communicable diseases who could have concurrent active overt or subclinical tuberculosis are overlooked. High levels of unsuspected tuberculosis comorbidity with other non-communicable and communicable diseases have been reported among general internal medicine inpatients. In a study from Zambia,[44] all patients who could produce a sputum sample were tested for tuberculosis, irrespective of their reason for admission. The presence of unsuspected active pulmonary tuberculosis indicated a large number of undiagnosed cases in the community. Tuberculosis

screening services are needed at all points of care for non-communicable and communicable diseases.

Maternal and child health and tuberculosis

Several maternal illnesses and lifestyle factors during pregnancy (eg, smoking, malnutrition, substance mis-use) can affect the health of an unborn child and contribute to poor intrauterine growth and low birth-weight, subsequently increasing the risk of non-communicable disease in adulthood. Babies born to malnourished or anaemic mothers are at increased risk of perinatal death and are likely to have higher rates of metabolic disease in adulthood. The in-utero and nutritional environment is important because it establishes susceptibility to metabolic diseases in later life. Intrauterine growth restriction followed by accelerated postnatal growth is associated with obesity, type 2 diabetes, and other features of the metabolic syndrome.[86]

Pregnant women and young children are more susceptible to development of active tuberculosis than other groups.[87] At all levels of health care in sub-Saharan Africa, diagnosis of tuberculosis in women is easily overlooked. Furthermore, the low sensitivity of sputum smear microscopy and the time and infrastructure constraints of mycobacterial culture mean that not all tuberculosis cases are identified. In sub-Saharan Africa, tuberculosis causes 15–34% of non-obstetric maternal deaths.[88–90] Maternal and childhood tuberculosis are linked epidemiologically.[91–93] In HIV-infected women, maternal tuberculosis was linked independently to increased risk of mother-to-child-transmission of HIV. Risk of culture-confirmed tuberculosis is more than 20-fold higher in HIV-infected versus HIV-uninfected infants[94] living in tuberculosis-endemic areas.

In paediatric autopsy studies,[24,95] tuberculosis was a major cause of death, although comorbidity with other lung infections was common. Tuberculosis can be easily overlooked in women, particularly those who are HIV-infected, who access routine maternal and child health services, because non-specific tuberculosis symptoms such as fatigue or night sweats are common in pregnancy, childbirth, and postnatally.[87] Antenatal and postnatal clinics should screen mothers and children for relevant communicable and non-communicable diseases.

Other associations between tuberculosis and disease

Links between cytomegalovirus, *Chlamydia pneumonia*, *M tuberculosis*, and non-communicable diseases such as coronary artery atherosclerosis and diabetes have been studied and debated intensively.[96,97] Although tuberculosis has been linked to coronary artery atherosclerosis and acute myocardial infarction,[98] a causative link has yet to be established. Blood-borne and sexually transmitted infections, including viral hepatitis, are relevant to tuberculosis risk, since affected patients could also have

HIV or latent *M tuberculosis* infection. Integrated models of care for tuberculosis, HIV, and sexually transmitted infections have particular relevance in settings in which overlapping disease burdens affect the same sexually active population.[99] Guidelines for prevention and control of tuberculosis, HIV infection, viral hepatitis, and sexually transmitted infections, and for people using illicit drugs, are available.[99–101]

Despite a striking decline in recent years, malaria remains a major cause of chronic anaemia in tropical areas, particularly affecting young children and pregnant women. Diabetes mellitus in adulthood has also been associated with an increased risk of malaria.[102] Induction of the hepatic cytochrome P450 enzyme system by rifampicin results in a halving of the concentrations in serum of artemisinin and its derivatives, complicating the concurrent management of tuberculosis and acute malaria.[103]

Leprosy can present as multisystem illness at any non-communicable disease clinic.[104] It remains a major challenge in isolated pockets within the Asia-Pacific, Africa, and South America regions. Although control efforts are combined in many countries, programme integration is rarely optimised. Active house-to-house case-finding efforts to identify minimally symptomatic leprosy patients in some Pacific island nations presents an opportunity for expanded interventions, including childhood immunisation efforts and screening for tuberculosis, diabetes mellitus, and hypertension.

Data from the 1918 influenza epidemic show a clear association between increased risk for tuberculosis-related disease and death during this period.[105] Influenza and other acute respiratory infections are likely to augment vulnerability to tuberculosis[106] and could partly account for some of the seasonal variability noted in temperate regions. Findings of a randomised controlled trial to assess the effect of pneumococcal vaccination showed decreased rates of culture-confirmed and clinically diagnosed tuberculosis in vaccinated children, indicating the intriguing possibility that pneumococcal coinfection might increase children's vulnerability to develop active tuberculosis.[107]

Community vulnerability

More than 90% of immune-competent individuals who acquire *M tuberculosis* infection never progress to active tuberculosis,[23] indicating a high level of herd immunity (figure 2). Control efforts focus mainly on early identification, isolation, and treatment of active disease as a means of interrupting the transmission cycle. Although this work makes an important contribution to reduce transmission within communities, it has been inadequate to eliminate the continuing epidemic.[108,109]

Tuberculosis provides a barometer of poverty and deprivation, since its incidence is driven by socioeconomic factors, poor access to and delivery of health services, inconsistent treatment practices, HIV, and migration from countries that are highly endemic for tuberculosis.
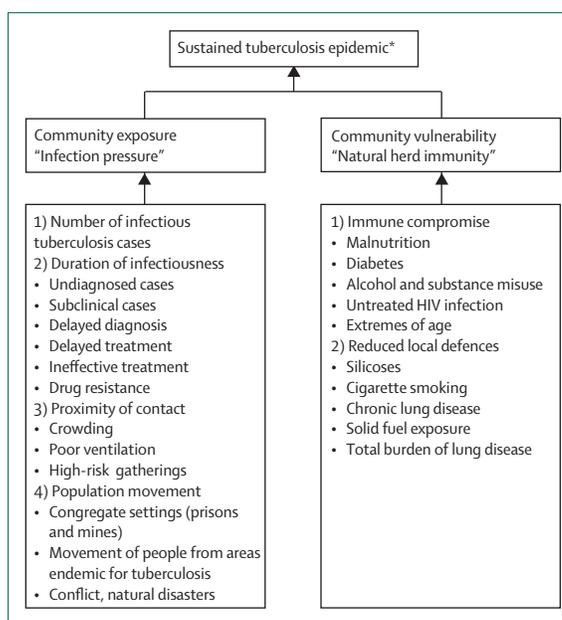
Figure 2: Determinants of community exposure and vulnerability that sustain the tuberculosis epidemic
*Optimum control interventions for tuberculosis should achieve reductions in community exposure and vulnerability.

In the WHO European region, researchers investigated the prospective association of a nation's wealth, level of egalitarianism, migration rate, health-related lifestyle, and social capital with tuberculosis incidence and prevalence over a 10-year period (2000–09).[110] Nearly 50% of tuberculosis variation was accounted for by a nation's wealth and level of egalitarianism. National income levels per person and income inequality are important predictors for tuberculosis incidence and prevalence in the WHO European region.[111]

How can vulnerability be reduced at the population level? Development of an effective vaccine is proving especially challenging in view of the fine immune balance that is needed to contain *M tuberculosis* infection.[63,64] A complementary strategy would be to reduce factors that increase vulnerability at the community level, such as malnutrition, cigarette smoking, indoor air pollution, diabetes mellitus, HIV-related immune compromise, and alcohol misuse (figure 2).[112,113]

Tuberculosis and social determinants of health

Calls for unconventional approaches to control tuberculosis are not new.[114] Biomedical approaches to curing tuberculosis, which fail to account for social circumstances that predispose people to disease, will have limited effect. More recently, a shift has taken place in the policy discourse towards a social determinants model of health,[111–115] which recognises that health inequalities arise directly from the unequal distribution of resources at a global, national, and local level[115] and are shaped by the social structures and economic

environments in which people are "born, grow, live, work, and age".[116] This observation is especially apparent with respect to differences in life expectancy, as high as 29 years between countries across the world (eg, Botswana and Japan)[117] and 17 years between the richest and poorest parts of London, UK.[118] These differences cannot be attributed to biology alone. Susceptibility to disease and the ability to access health care and sustain a course of treatment is also related to inequalities of wealth, power, and status, and yet many public health interventions aim to address individual lifestyle factors rather than the underlying causes of health inequalities.

Accessible health care is an important aspect of tuberculosis case-finding, yet the inverse care law[119] suggests the availability of good health care is inversely related to the needs of the population served. If people in greatest need are less likely to access appropriate health care, this factor will have important implications for the organisation and delivery of tuberculosis services for socially and economically marginalised populations. At an operational level, responsive outreach services delivered at scale and integrated into existing health systems, with the ability to address the health and social care needs of specific populations in distinct contexts, are likely to entail mixed economies of care,[108] which might raise concerns about fragmentation of services.

Although integrated delivery of care for communicable and non-communicable diseases has several advantages, evidence is scanty for its effectiveness[120] and how best to achieve it.[121] Vertical service delivery models target very specific health outcomes, frequently diverting resources away from comprehensive primary care services that are already constrained. Adopting a so-called diagonal approach to scaling up primary women-centred health care—since many diseases affecting women are interrelated—has been suggested.[122] Service configurations based on MDGs 4, 5, and 6 (actions on maternal and child mortality, HIV, malaria, and tuberculosis) could incorporate services for non-communicable diseases (heart disease, obesity, smoking, diabetes,

cancer), which are the leading causes of death in women aged 15–44 years. However, services organised around maternal health could disadvantage older people and women of non-child-bearing age and those with specific non-communicable diseases.

Models of service provision, which offer outreach and social support through networks of formal health, social care, and third-sector organisations coordinated by outreach and link working staff, have proved popular when clinical caseloads comprise patients with complex health and social care needs, including homelessness and substance and alcohol misuse in high-income settings.[123] Evidence supports use of mobile radiography in combination with models of care that aim to ameliorate the social risk factors associated with non-adherence to treatment.[124] Such models can be provided as a centralised service, working across areas or integrated into individual tuberculosis clinics. A more contextualised approach to risk management and targeting of resources might be needed. Study findings on the adverse health outcomes of crisis populations[125] suggest a need to attend to the type of risk environments[126] that contribute to excess risk of tuberculosis, such as overcrowding in urban environments, poor nutrition, previous health status before displacement, and dispersed populations, all of which make identification, monitoring, and treatment of tuberculosis and other associated communicable and non-communicable diseases difficult. A lack of specificity can serve to homogenise risk based on group identity (eg, asylum seekers) and to stigmatise those very groups.

Action across the social gradient, which is proportionate to the level of disadvantage, is needed for both preventative and curative services.[112] In relation to non-communicable diseases, perspective is needed that links the effect of early lifestyle experiences on later adult life and highlights the cumulative effects of disadvantage throughout life. Thus, structural interventions are needed outside formal health-care sectors,[127] such as programmes for urban regeneration, job creation, and social protection initiatives. In this current climate of austerity, finding ways to fund such initiatives in countries of low income and with a high disease burden is difficult, particularly when substantial political commitment and redistribution of resources is needed. Although health services remain largely focused on curative services, further investment in effective prevention measures remains important because these will be more cost effective in the long run.

Conclusions

In the current poor global economic climate, we must avoid destructive competition between communicable and non-communicable diseases for the limited funds available for health services. Integrated solutions should seek to unlock potential commonalities and synergies and optimise scarce resources. Efficient integration of tuberculosis services with those for non-communicable

and other communicable diseases should be a priority (panel 3) while maintaining some vertical elements to secure essential functions, such as drug supply, monitoring and assessment, and national surveillance, to a point at which a small central team could oversee the national tuberculosis programme. Appropriate balance should be realised, based on the best solution in a particular situation, and should not be an issue of integration or not, or horizontal versus vertical. Focus on local ownership is especially important, as is increasing equitable domestic investment in universal health coverage and sustainable health services. Rates of tuberculosis are a useful indication of socioeconomic inequality and deprivation. Meeting the social and medical care needs of vulnerable communities needs a cohesive response from many groups, including the private sector.[128]

Prevention and management of chronic communicable and non-communicable diseases is a litmus test for health-systems strengthening.[120] Integrated strategies should be designed to build capacity and encourage local ownership to develop contextualised solutions to key health challenges (panel 3). The need for continued and increased funding is greater than ever before. Countries of low and middle income need to augment international political and financial commitment to tackle these global health issues with increased mobilisation of domestic resources.

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