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Global lung health: the colliding epidemics of tuberculosis, tobacco smoking, HIV and COPD

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Abstract

Tuberculosis (TB), smoking, HIV and chronic obstructive pulmonary disease (COPD) are burgeoning epidemics in developing countries. The link between TB and HIV is well established. Less well recognised is the strong relationship between tobacco smoking and the development and natural history of TB. These associations are of considerable relevance to public health and disease outcomes in individuals with TB. Moreover, tobacco smoking, a modifiable risk factor, is associated with poorer outcomes in HIV-associated opportunistic infections, of which TB is the commonest in developing countries. It is now also becoming clear that TB, like tobacco smoke, besides its known consequences of bronchiectasis and other pulmonary morbidity, is also a significant risk factor for the development of COPD. Thus, there is a deleterious and synergistic interaction between TB, HIV, tobacco smoking and COPD in a large proportion of the world's population. Further work, specifically mechanistic and epidemiological studies, is required to clarify the role of tobacco smoke on the progression of TB and HIV infection, and to assess the impact of smoking cessation interventions. These interactions deserve urgent attention and have major implications for coordinated public health planning and policy recommendations in the developing world.

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STATEMENT OF INTEREST

None declared.

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Keywords

Chronic obstructive pulmonary disease; HIV; smoking; tuberculosis

An association between tobacco smoke and tuberculosis (TB) has been debated for nearly 100 yrs [1]. There is now considerable evidence confirming the presence, strength and consistency of this association and the different levels at which it operates. Indoor air pollution is a second risk factor for TB and, although often linked with passive smoke inhalation, emerges as an independent risk factor in epidemiological studies [2–4]. By contrast, the interaction between TB and HIV infection became evident soon after the HIV epidemic commenced, and new associations continue to be recognised, including treatment-related complications and drug interactions [5]. More recently, research has focused on the role of tobacco smoke in patients at risk of infection or infected with HIV [4, 6]. In this perspective we further highlight the potential associations linking tobacco smoke, air pollution, TB and HIV with the development of chronic obstructive pulmonary disease (COPD) and chronic pulmonary disability (fig. 1).

Recent predictions based upon current exposures to risk factors and disease trends suggest that COPD will become the third commonest cause of death globally by the year 2030, eclipsing deaths from HIV and TB [7]. This dramatic prediction is based on the fact that the epidemic will centre on the large populations of developing countries in Africa, Asia, the Indian subcontinent and China, where there is not only an increasing uptake of tobacco smoking through the targeted marketing strategies of tobacco companies, but also in many countries a high and rising prevalence of cofactors such as air pollution and respiratory infections, important in the pathogenesis of COPD [8, 9]. Evidence for this demographic shift towards an ageing population and the developing world is already evident in the results of prevalence surveys of COPD [10]. Unlike the smoking “epidemic” in the developed world, which occurred at a time when exposure to TB and environmental pollution was decreasing, the modern COPD epidemic is, in addition, being fuelled by industrialisation and the rampant spread of TB and HIV [10–13]. The extent to which these factors interact in both additive and synergistic ways to produce chronic lung disease, and especially chronic diseases of the airways, is only now being realised.

This perspective article aims to highlight these potential interactions and their public health implications. We present each interaction separately, and review the possible biological mechanisms involved. Finally, we discuss their potential combined impact and propose strategies for addressing these colliding epidemics.

METHODOLOGY AND SEARCH STRATEGY

We searched PubMed for peer-reviewed literature published over the last three decades with a focus on studies that reported data on the associations between smoking, TB, COPD and HIV. No language restrictions were imposed, although only English language studies were eventually included. In addition, we identified three systematic reviews [2–4] on the association between tobacco and TB, one systematic review on the association between tobacco and HIV [14] and several narrative reviews [15–19] on the association between

tobacco and all the conditions of interest. The reference lists of these reviews were also used to supplement the search. In addition, we identified a comprehensive report entitled “A WHO/The Union monograph on TB and tobacco control: joining efforts to control two related global epidemics” [20]; this was used as an additional resource to complement our searches. Key words included TB, HIV, COPD and tobacco smoking.

SIZE OF THE TB, HIV SMOKING AND COPD EPIDEMICS

One-third of the world’s population, or 2 billion people, is thought to be latently infected with *Mycobacterium tuberculosis*. The latest estimates from the World Health Organization are that in 2007 there were 9.3 million new TB cases, including 0.5 million cases of multidrug-resistant (MDR)-TB and 1.8 million TB deaths [21]. By the end of that year, 33 million people (range 30–36 million) were living with HIV, 2.7 (range 2.2–3.2) million people had become infected in that year and 2.1 million died of AIDS [22]. AIDS remains the leading cause of death in Africa. To date only one-third of the estimated 9.7 million people needing antiretroviral therapy under current treatment recommendations have received therapy [23]. Around 0.45 million patients co-infected with HIV died of TB in 2007 [21], and TB is the leading cause of death among people living with HIV, even in those receiving antiretroviral therapy. The emergence of drug-resistant TB in countries with a high HIV prevalence poses an additional public health threat, not only to people with HIV but also to the broader community.

In 2006, approximately 5.763 trillion cigarettes were manufactured, an average of 2.4 per day for all 6,528,051,823 inhabitants of the world [2]. Current estimates of tobacco smoking rates are 49% for males and 8% for females in low- and middle-income countries, and 37% for males and 21% for females in high-income countries [2]. Tobacco is the single most preventable cause of death in the world today. It kills more than 5 million people per year, with more than 80% of those deaths occurring in the developing world [24].

The Global Burden of Disease and Risk Factors project confirmed that, in 2004, COPD was the fourth leading cause of death worldwide, accounting for 5.1% of total deaths [7]. A further estimate is that, in high-income countries, 73% of COPD mortality is related to smoking, while in low- to middle-income countries only 40% is related to smoking and a further 35% to indoor smoke from biomass fuels [25]. Furthermore, it is suggested that 36% of mortality from lower respiratory disease as a whole is related to indoor smoke exposure; by contrast, urban air pollution is responsible for only 1% of COPD cases in high-income countries and 2% in low- and middle-income countries [25].

Although the effect is quite consistent across meta-analyses, the estimated relative risk (RR) is modest. The real impact of any risk factor is determined by the magnitude of the association (*i.e.* RR), and the prevalence of the exposure in the population. Thus, even if the true effect is modest, the population-attributable risk (PAR) is likely to be substantial because of the widespread nature of tobacco exposure. Multiple risk factors are often involved for common diseases, and the PARs of the individual factors are usually estimated in a multiplicative model that assumes mutual independence of the factors. From this model,

the overall impact (combined attributable risk) of n independent factors may be given by the following formula:

$$\text{Combined PAR}=\prod_{i=1}^{n}(1-\text{PARi})$$

where PARi is the PAR of the i^{th} individual risk factors.

This formula has been applied to the estimation of the combined effect of smoking and solid fuels (biomass fuels plus coal) in China, where the national adult smoking prevalence was 49.6% for males and 3% for females in 2003 and more than 70% of Chinese households use solid fuels, such as wood, crop residues and coal, for heating and cooking [26]. In that study, 82% of COPD deaths and 75% of lung cancer deaths were attributable to the combined effects of smoking and solid-fuel use. In reality, many risk factors tend to be clustered in vulnerable populations, and the assumption of independence used in the above formula may not hold entirely. The excess number of cases among population groups with over-concentration of risk factors generally outweighs the reduction among less affected population groups, thus the actual impact could even be larger.

The situation is more complex for an infectious disease like TB, because infected patients also act as sources for sustaining infection in the population, and risk factors like smoking and solid-fuel use may affect multiple steps, from infection to disease and death. In the above-mentioned study, a deterministic compartmental susceptible–latent–infectious–recovered model was applied for estimation of disease trend. In that model, complete cessation of smoking and solid-fuel use by 2033 would reduce the projected annual TB incidence in 2033 by 14–52% if 80% directly observed treatment, short course (DOTS) coverage is sustained, 27–62% if 50% DOTS coverage is sustained or 33–71% if 20% DOTS coverage is sustained [26]. With the potential clustering and mutual interaction of smoking, solid-fuel use, HIV and TB in underprivileged populations/population groups, even figures of such magnitude could have been underestimated.

ASSOCIATION BETWEEN TOBACCO SMOKING AND TB

Although the association between tobacco smoke and TB has been debated for over a century [1], only recently has clear epidemiological evidence emerged. Evidence of the impact of tobacco smoking on TB infection has been confounded by its almost universal association with poverty, overcrowding and alcohol usage. In the past few years, three independent systematic reviews and meta-analyses have synthesised a large body of evidence on tobacco and TB [2–4]. These reviews summarise evidence of the association between active smoking and three TB outcomes: TB infection (detected using tuberculin skin testing), active TB disease and mortality due to TB. Table 1 provides an overview of the outcome-specific pooled RR estimates from three independent meta-analyses.

These analyses indicate that smokers are almost twice as likely to be infected with TB and to progress to active disease (RR of ~1.5 for latent TB infection (LTBI) and RR of ~2.0 for TB disease). Smokers are also twice as likely to die from TB (RR of ~2.0 for TB mortality), but

data are difficult to interpret because of heterogeneity in the results across studies. Evidence is strong for TB disease, but less strong for TB infection and TB mortality. These associations also pass the test of biological plausibility.

The association between tobacco and TB is now clear enough to demand attention both from practising clinicians as well as policy-makers. For example, if the RR for TB disease is conservatively assumed to be only 1.5, with 30% of the population exposed to tobacco smoke, the PAR will be about 13%. In other words, 13% of the TB cases in the world each year may be attributable to tobacco exposure [19]. Tobacco cessation must become an integral part of all TB control programmes. Recognising this, the International Union Against Tuberculosis and Lung Disease, supported by the Bloomberg Initiative to Reduce Tobacco, has put together several resources for tobacco cessation in TB patients [2]. The extent to which such interventions will have an impact on TB control remains unclear. Benefits of quitting to the individual are numerous, but in addition, the societal and global impact have been highlighted by a recent publication from China which projects that a complete cessation of tobacco and solid-fuel use would reduce the TB incidence by 14–52% by 2033 [26].

Immunological mechanisms that underpin the mechanistic link between smoking and TB are unclear, although several have been proposed [6, 27]. A large body of scientific evidence in non-cigarette-smoke-associated animal and human models suggests that macrophages, CD4+ and CD8+ T-cells [28–30], apoptosis of infected cells [31, 32], autophagy [33, 34], anti-mycobacterial peptides [35, 36], interferon (IFN)-γ, interleukin (IL)-12 and tumour necrosis factor (TNF)-α are important in host immunity against *M. tuberculosis* [37]. In models not using TB organisms or antigens, cigarette smoke selectively downregulates the production of IL-12 and TNF-α [38]. Nicotine, through an interaction with α7 nicotinic acetylcholine receptors, enhances the replication of intracellular organisms such as *Legionella* and turns off production of TNF-α by macrophages while leaving the secretion of IL-10 intact [39].

Cigarette smoke also prevents pathogen-specific expansion and activation of CD4+ T-cells [40] and reduces IFN-γ-producing adenoid-specific CD4+ and CD8+ T-cell numbers [41]. Other potential mechanisms whereby smoking may attenuate host defence mechanisms include oxidative stress at the site of infection and impairment or mechanical disruption of cilial function in the tracheobronchial tree [17].

TB AND HIV

The effect of the HIV epidemic on TB has been well documented, with incident rates of TB, particularly in Africa, rising rapidly as a result of HIV [21]. The risk of active TB doubles in the first year of HIV co-infection [42], and the risk of developing active disease in those who have LTBI is ~10% per yr [43]. HIV–TB co-infected individuals have reduced survival [44] and are at higher risk for subsequent opportunistic infections [45, 46]. In overcrowded and poor living conditions, the combined effect of the two epidemics is magnified as evidenced by >2,000 per 100,000 population prevalence rates in certain South African communities

[47]. Added complications in co-infected individuals include drug-resistant TB and immune reconstitution inflammatory syndrome [48].

Strategies to combat the epidemics include: improvement of socioeconomic conditions and political stability; development and access to improved drugs, diagnostic tools and vaccines; improved access to treatment, addressing gender and operational research questions; and combining the efforts of TB control and HIV treatment programmes. Broad access to antiretroviral therapy and TB control measures will help to control the epidemic [5, 47, 49, 50]. It is noteworthy that in many parts of Africa poverty has worsened in the last decade, and the global economic downturn is likely to make the millennium development goals more difficult to attain.

ASSOCIATIONS BETWEEN TOBACCO SMOKE AND HIV

HIV is driving the TB epidemic as previously mentioned. If tobacco smoking increases the impact of TB in HIV-negative individuals, its effect in HIV-positive individuals may be significantly greater. Preliminary data from a small study in sub-Saharan Africa supports the association of tobacco smoke and TB in HIV-infected individuals [51]. Larger studies will be required to compare the magnitude of the effect between HIV-infected and uninfected populations.

Although both tobacco smoking and HIV infection may be associated through their common links with poverty and high-risk behaviour, tobacco smoking appears to be an independent and important risk factor for contracting HIV [52–55]. Other studies have demonstrated higher viral loads [56] and rate of progression of HIV infection to AIDS in smokers [57, 58], but this association has not been observed in all studies [59–62]. A possible reason for the conflicting results might be the many confounding factors, such as nutritional status, alcohol and poverty, which may have masked the association.

Other health consequences of tobacco smoking in HIV-infected individuals include the risk of TB, pneumonia and malignancy. MIGUEZ-BURBANO *et al.* [63] showed a doubling of the risk of developing TB in HIV-positive people who smoke. Several studies have demonstrated an increased risk (1.5–2.6 times higher) of community-acquired bacterial pneumonia in those who smoke [64–68]. It is not clear whether this applies to *Pneumocystis jiroveci* pneumonia (PCP): some studies showed a two- to three-fold increased risk of developing PCP in smokers [67], but others did not [60, 65, 66]. HIV-infected people are at increased risk of Kaposi’s sarcoma and lymphoma, as well as primary lung cancer. With increased life expectancy achieved with antiretroviral therapy, the risk of lung cancer from smoking is likely to increase further [69].

The use of combination antiretroviral therapy has dramatically reduced the incidence of opportunistic infections in HIV-infected subjects [70–72]. However, LE MOING *et al.* [70] found that, although the risk for bacterial pneumonia is reduced by antiretroviral therapy, the magnitude of this reduction was significantly less in smokers. Evidence from the community-based studies in high-burden countries suggests that merely raising a single

individual's CD4 count may not be sufficient to reduce the burden of disease if overcrowding, alcohol and tobacco smoking are not adequately addressed.

In smokers, HIV infection appears to cause a form of accelerated emphysema in young HIV-positive individuals. This is discussed below.

TB, HIV, SMOKING AND BIOMASS FUELS AS RISK FACTORS FOR COPD

Causality between tobacco smoke and COPD is well established and it remains the primary risk factor for COPD [73]. As well as the documented dose-dependent risk of COPD from tobacco smoke [74], the importance of the "total burden of inhaled particles", including occupational, household and environmental exposures, is increasingly being recognised [75–78]. An estimated 50% of all households worldwide (~3 billion people) use solid fuels for cooking and heating [79]. Indoor biomass fuel burning, in addition to air pollution, has been well documented in case–control studies to be a significant risk factor for COPD (odds ratios (ORs) ranging from 1.35 to 6.61 [8, 9, 13, 80]). Moreover, projections from these studies highlight the global risk, in particular to females in developing countries, of obstructive airway disease from biomass fuel exposure.

Infections, particularly in childhood, have been regarded as risk factors for COPD [81]. Post-tuberculous "obstructive airways disease" was described in the medical literature in the 1950s and 1960s by several authors [82–85]. MARTIN and HALLET [84] reported that "It is increasingly evident that a diffuse obstructive pulmonary syndrome is often associated with tuberculosis". They further make reference to the documentation of emphysema and TB by Laennec in the 1800s [83]. Although this association continues to be widely recognised by clinicians in developing countries [86–88], it has been poorly studied [88, 89]. A nationwide survey in South Africa, a high-prevalence country for TB, has demonstrated that a history of previous TB is a strong predictor of chronic bronchitis (OR 4.9, 95% CI 2.6–9.2 in males; OR 6.6, 95% CI 3.7–11.9 in females) [11]. In addition, several clinical studies have confirmed airflow limitation as a consequence of tuberculous disease [78, 86, 88, 90]. International comparisons of COPD prevalence using the Burden of Obstructive Lung Disease methodology [10, 75] and a similar study from Latin America [91] have identified previous TB as a risk factor for COPD. Absence of detailed clinical information in these surveys prevents conclusions about pathophysiology and whether such cases fall within the definitions of clinical COPD or represent one or several other forms of structural lung disease.

In addition to the burden of tobacco smoking, air pollution (indoor and environmental) and poverty, HIV is prevalent in many developing countries, particularly in sub-Saharan Africa. HIV infection alone is increasingly being recognised as a cause of premature emphysema [92–96]. Two recent reviews by CROTHERS [12] and PETRACHE *et al.* [96] have highlighted current knowledge on this association. It would appear that emphysema occurs earlier, with fewer pack-yrs of smoking, and may be associated with colonisation by *P. jiroveci*. In addition to the complex pathological pathways identified in HIV-negative smokers, excess cytotoxic T-lymphocyte activity, endothelial dysfunction and increased apoptosis have been suggested as possible pathological mechanisms. The natural history of

COPD in HIV is unclear. It is also not known if the use of anti-inflammatory or bronchodilator therapy is of any value or if antiretroviral therapy will halt the development, or progression, of the disease. Long-term follow-up and therapeutic intervention trials are needed.

PUBLIC HEALTH AND PULMONARY IMPLICATIONS

Patients in developing countries, especially those with a high prevalence of infectious disease, frequently present with complex lung disease resulting from the varying insults of tobacco smoke and other harmful environmental exposures, TB, HIV and COPD. The impact of current and projected exposures to these conditions will result in a heavy burden of lung diseases in resource-poor countries in coming decades. There is little prospect for improvement unless there is a concerted and coordinated effort by all involved parties, such as health authorities, practitioners, researchers and society in general. Public health measures are required to improve air quality and reduce passive exposure to tobacco smoke, reduce overcrowding, improve housing and reduce reliance on biomass fuels in homes.

Also required are access to antiretroviral therapy, measures to reduce transmission of HIV, and the development of effective vaccines for TB and other respiratory pathogens, hopefully also for HIV infection. New effective drugs and diagnostic tools are urgently required. There should in addition be greater integration of TB, HIV and respiratory services and the provision of smoking cessation programmes.

Knowledge of causal links and interactions between HIV, TB and COPD would assist with identification of novel targets for intervention and add significant scientific weight to the messages of health advocates and lobby groups campaigning for the welfare of patients.

Although the combined effects of all the epidemics may only be recognised in developing countries, the developed world is not immune to the risk. Eastern Europe has a high incidence of MDR-TB and smoking. In North America, although TB may be infrequently seen, HIV and tobacco smoking frequently coexist. The emergence of multi- and extensively drug-resistant TB pose a global threat, since spillover through migration and travel is inevitable.

CONCLUSION

Historically, TB and HIV have been the focus of infectious disease specialists, smoking and COPD the focus of pulmonologists, and biomass fuel exposure the interest of public health researchers. It is now clear that in day-to-day clinical practice a more complex picture is emerging as the epidemics of HIV, tobacco smoking and biomass fuel exposure, TB and COPD interact on a global scale. These interactions deserve urgent attention and have major implications for co-ordinated public health planning and policy recommendations in the developing world.

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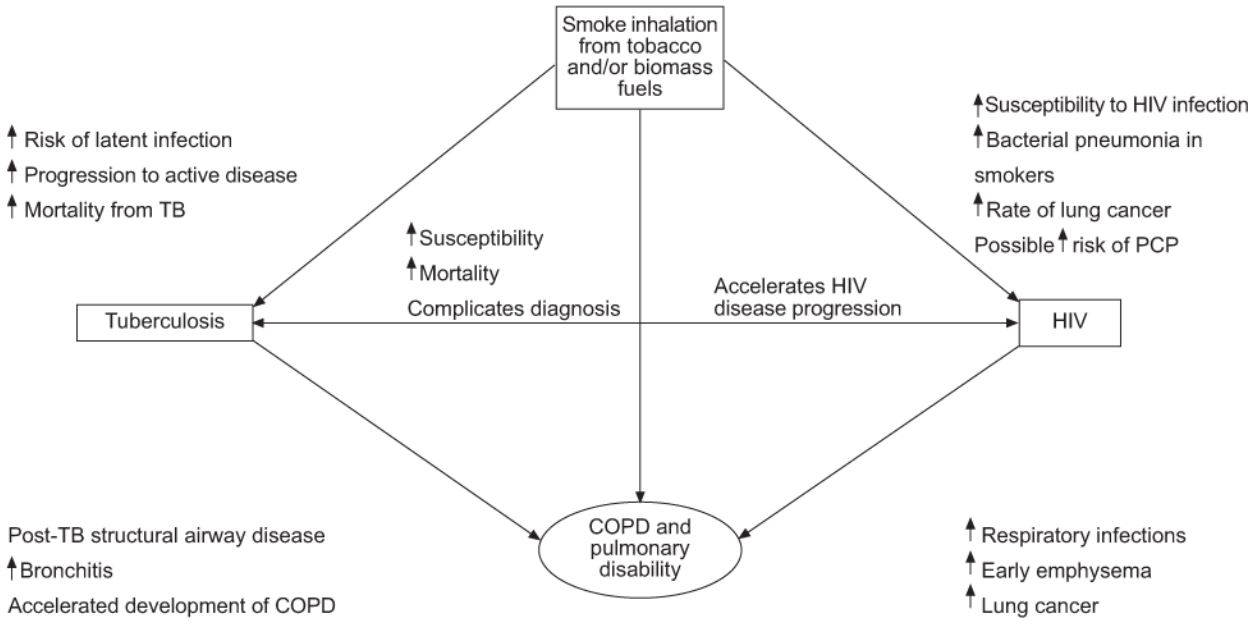

FIGURE 1.

Potential interactions between tobacco smoking, HIV, tuberculosis (TB) and chronic obstructive pulmonary disease (COPD) with resultant pulmonary disability. PCP: *Pneumocystis jiroveci* pneumonia.

TABLE 1

Associations between smoking and the relative risk of latent tuberculosis (TB) infection, progression to active disease and mortality from active TB disease

Meta-analysis	Pooled relative risk (95% CI)		
	TB infection	TB disease	TB mortality
Studies n	~6	~15	~5
SLAMA [2]	~1.8 (1.5–2.1)	~2.3 (1.8–3.0)	~2.2 (1.3–3.7)
LIN [3]	1.7–2.2 (1.5–2.8)	~2.0 (1.6–2.6)	~2.0 (1.1–3.5)
BATES [4]	~1.7 (1.5–2.0)	~2.3 (2.0–2.8)	~2.1 (1.4–3.4)