American Journal of Epidemiology

Vol. 187, No. 9
DOI: 10.1093/aje/kwy081
Advance Access publication:
April 7, 2018

Original Contribution

Contribution of Smoking to Tuberculosis Incidence and Mortality in High-Tuberculosis-Burden Countries

Genet A. Amere, Pratibha Nayak, Argita D. Salindri, K. M. V. Narayan, and Matthew J. Magee*

* Correspondence to Dr. Matthew J. Magee, Division of Epidemiology and Biostatistics, Georgia State University, School of Public Health, 140 Decatur Street Suite 456 Atlanta, GA 30303 (e-mail: Mjmagee@gsu.edu).

Initially submitted June 13, 2017; accepted for publication March 29, 2018.

Globally, 10 million incident cases of tuberculosis (TB) are reported annually, and 95% of TB cases and 80% of tobacco users reside in low- and middle-income countries. Smoking approximately doubles the risk of TB disease and TB mortality. We estimated the proportion of annual incident TB cases and TB mortality attributable to tobacco smoking in 32 high-TB-burden countries. We obtained country-specific estimates of TB incidence, TB mortality, and smoking prevalence from the World Health Organization Global TB Report (2017), tobacco surveillance reports (2015), and the Tobacco Atlas. Risk ratios for the effect of smoking on TB incidence and TB mortality were obtained from published meta-analyses. An estimated 17.6% (95% confidence interval (CI): 8.4, 21.4) of TB cases and 15.2% (95% CI: 1.8, 31.9) of TB mortality were attributable to smoking. Among high-TB-burden countries, Russia had the highest proportion of smoking-attributable TB disease (31.6%, 95% CI: 15.9, 37.6) and deaths (28.1%, 95% CI: 3.8, 51.4). Men had a greater proportion of TB cases attributable to smoking (30.3%, 95% CI: 14.7, 36.6) than did women (4.3, 95% CI: 1.7, 5.7). Our findings highlight the need for tobacco control in high-TB-burden countries to combat TB incidence and TB mortality.

population attributable fraction; tobacco; tuberculosis

Abbreviations: CI, confidence interval; LMIC, low- and middle-income countries; LTBI, latent tuberculosis infection; PAP, population attributable proportion; TB, tuberculosis; WHO, World Health Organization.

Tuberculosis (TB) remains a leading cause of morbidity and mortality worldwide. In 2016, 10.4 million people developed active TB, and 1.3 million died from the disease, accounting for more deaths than any other infectious disease (1, 2). The vast majority of TB disease (87%) occurs in 30 high-burden countries, and 95% of TB cases and deaths occur in low- and middle-income countries (LMIC) (1, 2). The convergence of TB with noncommunicable diseases and tobacco use in LMIC threatens the End TB Strategy and Sustainable Development goals and highlights the need to modify established epidemiologic approaches to TB control (3, 4).

Compared with nonsmokers, those who smoke tobacco have twice the risk of TB disease, and patients with TB who smoke have twice the risk of death during TB treatment (5–9). Currently, there are more than 1 billion tobacco users, nearly 80% of whom live in LMIC (10, 11). Separately, active TB and tobacco-related diseases constitute a substantial portion of morbidity and mortality in LMIC, where limited health resources are available to manage these costly diseases (12). However, an improved understanding of the contribution of smoking to TB disease and TB mortality is needed to better characterize the joint impact of smoking and TB on health burdens in LMIC.

Although tobacco use is declining in many high-income countries, it is increasing in LMIC (13) where tobacco control policies are not well established (13–15). The extent to which changes in smoking prevalence may affect current efforts to reduce global TB incidence is largely unknown.

According to previous reports, an estimated 20% of adult TB cases are attributable to smoking, compared with 16% for human immunodeficiency virus and 15% for diabetes (16, 17). However, previous studies have not estimated the proportion of country-specific TB deaths attributable to smoking in high-TB-burden countries. Furthermore, previous estimates of the proportion of TB cases attributable to smoking were not age- and sex-adjusted and did not include sensitivity analyses to assess bias from smoking-prevalence measurement error.

In this study, we provide reliable estimates of the proportion of latent TB infection (LTBI) and TB disease incidence due to tobacco smoking in 32 countries with a high burden of TB. We have also estimated the proportion of TB deaths due to tobacco use.

METHODS

Data and study population

Data from adult male and female individuals aged 15 years or older who lived in 32 high-TB-burden countries were included in the analyses. Thirty high-TB-burden countries were defined by the 2016 World Health Organization (WHO) Global TB Report as the top 20 countries with the highest absolute number of TB cases and the top 10 countries with the highest incidence rates of TB, with at least 10,000 new cases per year (1, 18). We added Uganda and Afghanistan, which were not among the 2016 WHO high-TB-burden countries but were included in 2015 (2, 19).

We used 6 population-based cross-sectional data sources for our analyses (Table 1). We obtained TB case notification and TB mortality data from the 2017 WHO Global TB Report (1). Tobacco use data was acquired from the: 1) Global Adult Tobacco Survey (20), 2) WHO Global Report on Trends in Prevalence of Tobacco Smoking 2015 (21), 3) Tobacco Free Initiative country profiles (22), and 4) Tobacco Atlas (23). We obtained population size data from the US Census Bureau (24).

The WHO Global TB Report has provided epidemiologic TB surveillance at global and country levels annually since 1997 (2). The Global Adult Tobacco Survey is a household survey, developed in 2007 by the Global Tobacco Surveillance System, which collects nationally representative tobacco-use data among persons aged 15 years or older. The Global Adult Tobacco Survey includes 25 LMIC where tobacco burdens are high (22). The WHO Global Report on Trends in Prevalence of Tobacco Smoking 2015 includes estimated age-specific current tobacco smoking prevalence based on Bayesian hierarchical meta-regression modeling and projected tobacco smoking prevalence trends in WHO regions (21). The Tobacco Free Initiative provides country-specific tobacco surveillance data (22).

Tuberculosis incidence and mortality. To estimate country-specific TB incidence rates, we obtained TB notification data from the 2017 WHO Global TB Report for the 32 highest TB-burden countries (1). In the absence of directly measured, country-level TB incidence rates, TB case notification rates provide proxy estimates for TB incidence that include notified and undiagnosed TB cases (19). A TB notification indicates that TB has been diagnosed in a patient and reported within the national surveillance system to WHO (25). The TB notification rate comprises the number of new and relapsed TB cases notified in a given year per 100,000 population (25). In 2017, 201 countries reported TB incidence data to WHO (1). We used TB notification rates for our estimates of TB incidence, because it includes sex- and age-specific data. In 2016, notifications of newly diagnosed TB cases represented 61% of estimated incident cases worldwide (1).

To determine country-specific rates of TB mortality, we used the reported number of TB deaths where treatment outcome was indicated as TB deaths. A TB death was defined as all-cause mortality during TB treatment (19). We extracted 2015 TB mortality data from the 2017 WHO Global TB Report for all countries except for Angola, for which only 2014 data was available (1).

Relative risk for TB disease and TB mortality associated with smoking. We obtained relative risk estimates for the associations between smoking and LTBI, between smoking

Table 1. Epidemiologic Data Sources for Population Attributable Risk Calculations for the Contribution of Smoking to Tuberculosis Incidence and Mortality in High-Tuberculosis-Burden Countries, 2009–2016

Data[a]	Data Sources[b]	Countries	Variables	Measurement
Smoking prevalence	Global Adult Tobacco Survey	Bangladesh, Brazil, China, India, Indonesia, Nigeria, Pakistan, Philippines, Russia, Thailand, Vietnam	Current tobacco smoking	Self-reported
	WHO Global Report on Trends in Prevalence of Tobacco Smoking 2015	Cambodia, Congo, Ethiopia, Kenya, Lesotho, Liberia, Mozambique, Myanmar, Namibia, Sierra Leone, South Africa, Tanzania, Uganda, Zambia, Zimbabwe	Current tobacco smoking	Self-reported
	WHO Tobacco Free Initiative	North Korea, Papua New Guinea	Current tobacco smoking	Self-reported
	Tobacco Atlas	Afghanistan, Angola, CAR, DRC	Daily tobacco smoking	Self-reported
TB incidence and TB mortality	WHO 2017 TB Report			N/A
Population	United States Census Bureau			N/A

Abbreviations: CAR, Central African Republic; DRC, Democratic Republic of Congo ; N/A, not applicable; TB, tuberculosis; WHO, World Health Organization.

[a] We obtained TB case notification and TB mortality data from the 2017 WHO Global TB Report (1). Tobacco use data was acquired from: 1) Global Adult Tobacco Survey (20), 2) WHO Global Report on Trends in Prevalence of Tobacco Smoking 2015 (21), 3) Tobacco Free Initiative country profiles (22), and 4) the Tobacco Atlas (23). We obtained age- and sex-specific population data from the US Census Bureau (24).

[b] Data sources were chosen in order of priority from the first row to the fourth.

and TB incidence, and between smoking and TB mortality from studies reported by Bates et al. (6), Slama et al. (5), and Lin et al. (26), all in 2007. The relative risk of TB disease in smokers versus nonsmokers was reported to be 2.3 (95% confidence interval (CI): 2.0, 2.8) (6), 2.3 (95% CI: 1.8, 3.0) (5), and 2.0 (95% CI: 1.6, 2.6) (26). The reported relative risk for TB mortality, comparing smokers with nonsmokers, was reported as 2.1 (95% CI: 1.4, 3.4) (6), 2.2 (95% CI: 1.3, 3.7) (5), and 2.0 (95% CI: 1.1, 3.5) (26). For LTBI, we used a relative risk of 1.7 (95% CI: 1.5, 2.0) from Bates et al. (6). We used a relative risk of 2.3 (95% CI: 1.5, 2.8) for smoking-TB disease as reported in 2 systematic reviews (5, 6). For TB mortality, we used a relative risk of 2.0 (95% CI: 1.1, 3.7), comparing smokers with nonsmokers (26).

Smoking prevalence. Smoking prevalence data were obtained from 4 previously described sources for 32 countries (Table 1). Age- and sex-specific smoking prevalence data were extracted from the Global Adult Tobacco Survey for 11 countries (age-bands (years) reported as 15–24, 25–44, 45–64, ≥65) (22), which was our primary data source, and from the WHO Global Report on Trends in Prevalence of Tobacco Smoking 2015 for 15 countries (age-band (years) reported as 15–24, 25–39, 40–54, 55–69, and ≥70) (21). When country data were unavailable in the primary source, we used the next available data source (Table 1). For countries without age-stratified data, we used Tobacco Free Initiative country profiles and the Tobacco Atlas to estimate smoking prevalence (22, 23).

The smoking prevalence data used for this study was based on the definition of current tobacco use, except for Afghanistan, Angola, and the Central African Republic. For Afghanistan, Angola, and the Central African Republic, we used daily tobacco use. Current tobacco use included daily smoking and occasional smoking of any type of smoked tobacco (27, 28). Smoked tobacco included manufactured cigarettes, bidi, hookah (water pipes), hand-rolled cigarettes, pipes of tobacco, cigars, cheroots, cigarillos, dhaba (bamboo water pipes), and any other tobacco products (27).

Population data. The 2016 age- and sex-specific population data for the 32 highest TB-burden countries were extracted from the US Census Bureau (24). The US Census Bureau estimates the population size of countries by collecting demographic data from censuses, surveys, vital registration, and administrative records (24).

Statistical calculations

We estimated the proportions of LTBI, TB disease, and TB death due to smoking using standard population attributable proportion (PAP) formulas (29). We first calculated unadjusted estimates of PAP for LTBI, TB disease incidence, and TB mortality for the 32 countries (29). PAP calculations were made using age- and sex-specific smoking prevalence data. For each PAP calculation (LTBI, active TB incidence, and TB mortality) we used estimated country-specific smoking prevalence and respective relative risks comparing smokers with nonsmokers.

We used 95% confidence intervals of the relative risks from published estimates (5, 6, 26) to calculate the upper and lower PAP estimates for each country. We estimated excess numbers of active TB cases attributable to smoking for each country in each age and sex stratum by multiplying age- and sex-specific PAPs by the corresponding country-specific reported TB cases from WHO. Numbers of TB deaths attributable to smoking were estimated by multiplying the PAP for each country by the number of reported TB deaths from corresponding countries. Formulas for PAP calculations were:

$$\text{Latent TB Infection} = \text{Prevalence of smoking (RR} - 1)/ (1 + \text{Prevalence of smoking (RR} - 1))$$

$$\text{Where RR} = \text{Relative risk of LTBI } (1.7,\ 95\%\ \text{CI: } 1.5,\ 2.0)$$

$$\text{TB Incidence} = \text{Prevalence of smoking (RR} - 1)/ (1 + \text{Prevalence of smoking (RR} - 1))$$

$$\text{Where RR} = \text{Relative risk of TB disease } (2.3,\ 95\%\ \text{CI: } 1.5,\ 2.8)$$

$$\text{TB Mortality} = \text{Prevalence of smoking (RR} - 1)/ (1 + \text{Prevalence of smoking (RR} - 1))$$

$$\text{Where RR} = \text{Relative risk of TB mortality } (2.0,\ 95\%\ \text{CI: } 1.1,\ 3.7)$$

In secondary descriptive ecological analyses, we compared the 5-year change in smoking prevalence with the 5-year change in estimated TB incidence for the 26 countries where smoking prevalence data were available in the same data sets described above (21). We plotted the country-level changes in smoking prevalence and change in TB incidence rate for 2010 and 2015 using a scatter plot. To estimate the relationship between 5-year change in TB incidence and smoking prevalence from 2010 to 2015, we calculated the Pearson correlation coefficient and *P* value.

Sensitivity analysis

We used Monte Carlo simulation to measure the amount of systematic error due to uncertainty in the smoking prevalence and relative risk estimates (30). We simulated smoking prevalence for each country using a normal distribution with mean equal to the reported point estimates for each country according to the Global Adult Tobacco Survey and the WHO Global Report on Trends in Prevalence of Tobacco Smoking 2015 and standard deviation derived from the 95% confidence intervals. We reproduced the natural logarithms of the relative risks for TB disease and TB mortality using the normal distribution with corresponding mean of the relative risk and standard deviation derived from the 95% confidence interval around the relative risk (for TB disease, relative risk = 2.3, 95% confidence interval (CI): 1.5, 2.8; for TB mortality, relative risk = 2.0, 95% CI: 1.1, 3.7). The relationships between smoking prevalence and the relative risks were assumed to be independent. The estimated PAPs for TB disease and TB mortality were based on 1,000 Monte Carlo simulations.

RESULTS

In 2016, an estimated 3.4 billion people over the age of 15 years lived in 32 high-TB-burden countries; in those countries, the estimated number of TB cases and TB deaths that year were 8.3 million and 1.1 million, respectively,. The crude smoking prevalence in the 32 countries was 21.5% (95% CI: 20.2, 23.0), representing 722 million smokers (Web Figure 1A and 1B, available at https://academic.oup.com/aje). Smoking prevalence was higher among men (38.8%) than among women (3.9%).

In adults aged 15 years or older, LTBI attributable to smoking was 13.2% (95% CI: 8.8, 17.7). The proportion of LTBI attributable to smoking ranged from 2.8% (95% CI: 1.8, 3.9) in Nigeria to 22.2% (95% CI: 15.2, 28.9) in Russia (Web Table 1).

The crude proportion of TB disease incidence attributable to tobacco smoking was 19.6% (95% CI: 8.7, 24.5), and the age-adjusted PAP was 17.6% (95% CI: 8.4, 21.4), accounting for an estimated 1.3 million excess cases each year (Table 2). The country-specific proportion of TB disease attributable to tobacco smoking ranged from 4.7% (95% CI: 1.9, 6.3) in Nigeria to 31.6% (95% CI: 15.9, 37.6) in Russia (Table 2, Web Figure 1C). Smoking-attributable TB disease was higher among men (30.3%) than among women (4.3%) (Table 3). Among men, the proportion of TB disease attributable to smoking ranged from 8.7% in Nigeria to 46.6% in Indonesia. Among women, the proportion ranged from 0.0% in North Korea to 22.0% in Russia (Table 3).

Overall, 15.2% (95% CI: 1.8, 31.9) of TB deaths in adults aged 15 years or older were attributable to tobacco smoking. The proportion of TB deaths attributed to smoking ranged from 3.8% (95% CI: 0.4, 9.5) in Nigeria to 28.1% (95% CI: 3.8, 51.4) in Russia. Russia (28.1%), Indonesia (25.8%), and Sierra Leone (24.2%) were the top 3 countries in terms of proportion of smoking-attributable TB deaths (Table 4). Although the proportions of TB cases (14.3%, 95% CI: 6.5, 17.8) and TB deaths (12.3%, 95% CI: 1.4, 27.4) attributable to tobacco smoking in India were low (ranked 19 and 22, respectively), the absolute number of TB cases and TB deaths were highest.

In Monte Carlo simulation to estimate smoking prevalence misclassification and relative risk misspecification, the proportions of TB disease and TB death attributable to smoking were 17.7% (95% CI: 9.4, 27.0) and 17.9% (95% CI: 1.5, 35.7), respectively (Table 5).

The scatterplot examining ecological trends in country-specific smoking prevalence and PAP for TB disease incidence did not suggest a relationship between 5-year change in smoking prevalence and 5-year change in TB incidence for 26 countries (Web Figure 2). The correlation between 5-year change in smoking prevalence with change in TB incidence was $r = 0.05$ ($P = 0.81$).

DISCUSSION

Overall, we estimated that tobacco smoking accounted for more than 1 of every 6 cases of incident TB disease in the 32 high-TB-burden countries. Similarly, we estimated that tobacco smoking accounted for more than 1 of every 7 TB deaths in these same countries. We estimated that the proportion of TB disease attributable to smoking was more than 6 times higher in men than in women, due to high smoking prevalence among men. Our PAP calculations demonstrate an enormously negative impact of smoking on TB disease and TB death. These findings highlight an urgent need to improve existing efforts to integrate tobacco control initiatives within TB control programs and vice versa.

Previous studies from individual countries have estimated the proportion of TB incidence attributable to smoking and reported findings consistent with our results. For example, 17% of TB cases in Taiwan (31) and 14% of TB cases in India (32) were attributable to smoking. Our results aligned with those from a study from Hong Kong that reported that 33% of TB cases were attributable to smoking among men and 9% to smoking among women (8). In most countries, smoking prevalence among TB patients is higher than in the general population. For example, in 2008, 43% of men with active TB disease in Ethiopia were smokers while the population prevalence estimate of smoking among Ethiopian men was 8.1% (33). In South Africa during 2011, 56% of all TB patients were current smokers, and the population smoking prevalence was 19.4% (34). Our PAP estimate was lower than that reported in a 2010 study by Lönnroth et al. (16), who estimated that 21% of incident TB was attributable to smoking among 22 high-TB-burden countries. Our study's inclusion of 10 more countries than Lönnroth et al. and adjustment for age may partially explain our lower estimate of the proportion of smoking-attributable TB disease. Moreover, Lönnroth et al. used 2008 smoking prevalence data, and the global prevalence of smoking decreased between 2008 and 2014, when our smoking prevalence estimates were made. For example, from 2008 to 2014, smoking prevalence dropped substantially in Russia (−10%, from 49% to 39%) and China (−7%, from 35% to 28%) (16).

Although only an ecological-level hypothesis, it is plausible that global reductions in smoking during the past decade contributed to reduced TB incidence. Reductions in smoking prevalence in Russia and China correlated with reductions in TB incidence during the past 10 years. Annual TB incidence rates (per 100,000) decreased from 107 to 84 in Russia and from 97 to 68 in China between 2008 and 2014 (18, 19, 35). Confounding by factors specific to country-level TB dynamics and individual patient-level characteristics could not be accounted for in this ecological analysis and may account for the lack of a strong correlation between 5-year change in smoking prevalence and change in TB disease.

Smoking-attributable TB mortality has been previously estimated for individual countries. For example, 25%, 32%, and 35% of TB deaths in men were attributable to smoking in South Korea, India, and Bangladesh, respectively (36–38). In a 2004 study from South Africa, investigators estimated that smoking-attributable TB mortality was 20% in both sexes (39), modestly higher than our estimated 16%, a difference likely due to higher smoking prevalence estimates used in that study. A study from China, published by Jiang et al. in 2009 (40), reported that 22.5% of TB deaths in men and 6.6% in women were attributable to smoking. Although we were unable to stratify our estimate of smoking-attributable TB deaths by sex or age, our estimate of 21.9% of TB deaths due to smoking in China was similar to the 2009 estimate among Chinese males.

The biological mechanisms by which tobacco smoking increases susceptibility to pulmonary TB are likely related to alteration in cellular and humoral immune responses (41, 42) in smokers. For example, smokers have altered mucociliary clearance function (43), suppressed alveolar macrophage function (41, 44), increased iron content in the alveolar macrophages (which promotes *Mycobacterium tuberculosis* growth) (45, 46), and depressed phagocyte activity of monocytes (41, 47). In the context of known biologic mechanisms and numerous observational studies that have reported negative impacts of smoking on TB outcomes (48, 49), our PAP study results suggest that existing efforts in LMIC to integrate smoking cessation in patients

Table 2. Estimated Proportion of Tuberculosis Disease Attributable to Tobacco Smoking Among Adults in 32 High-Tuberculosis-Burden Countries, 2009–2016

Country	Smoking Prevalence[a]	Crude[b]		Age-Adjusted[c]		No. of Excess TB Cases[d]
		PAP, %	95% CI	PAP, %	95% CI	
Afghanistan	13.0[e]	14.4	6.1, 18.5			
Angola	9.2[e]	10.7	4.4, 13.9			
Bangladesh	23.0	23.0	10.3, 28.7	18.6	9.2, 22.3	59,130
Brazil	17.2	18.3	7.9, 23.1	18.1	7.9, 22.8	14,037
Cambodia	21.2	21.6	9.6, 27.1	18.7	9.0, 22.7	8,422
CAR	8.6[e]	10.0	4.1, 13.0			
China	28.1	26.8	12.3, 33.0	22.4	11.4, 26.6	176,649
Congo	13.9	15.3	6.5, 19.6	13.4	6.1, 16.7	3,195
DRC	6.4	7.7	3.1, 10.1			
Ethiopia	4.3	5.3	2.1, 7.0	4.8	2.0, 6.3	7,932
India	14.0	15.4	6.5, 19.7	14.3	6.5, 17.8	363,861
Indonesia	34.8	31.2	14.8, 37.9	24.9	13.2, 29.1	238,368
Kenya	13.5	14.9	6.3, 19.1	13.3	6.0, 16.6	15,758
Lesotho	22.6	22.7	10.2, 28.3	18.7	9.3, 22.3	2,554
Liberia	12.1	13.6	5.7, 17.5	12.6	5.5, 15.8	1,681
Mozambique	18.9	19.7	8.6, 24.9	16.6	7.6, 20.6	24,605
Myanmar	20.0	20.6	9.1, 26.0	20.8	9.7, 25.5	35,727
Namibia	21.6	21.9	9.8, 27.4	20.3	9.3, 25.2	2,622
Nigeria	3.9	4.8	1.9, 6.4	4.7	1.9, 6.3	34,819
North Korea	20.1	20.7	9.1, 26.0			
Pakistan	12.4	13.9	5.8, 17.8	12.1	5.5, 15.0	55,900
PNG	26.3	25.5	11.6, 31.5			
Philippines	28.3	26.9	12.4, 33.1	24.1	11.7, 29.1	120,731
Russia	39.1	33.7	16.4, 40.6	31.6	15.9, 37.6	26,678
Sierra Leone	31.9	29.3	13.8, 35.8	26.1	12.7, 31.7	5,367
South Africa	19.4	20.1	8.84, 25.4	19.5	8.9, 24.2	72,580
Tanzania	16.3	17.5	7.5, 22.2	10.9	4.8, 13.6	17,471
Thailand	24.0	23.8	10.7, 29.6	23.9	11.5, 29.7	26,345
Uganda	10.1	11.6	4.8, 15.0	10.2	4.4, 13.0	8,078
Vietnam	23.8	23.6	10.6, 29.4	19.7	9.9, 23.5	21,678
Zambia	14.6	16.0	6.8, 20.4	14.0	6.3, 17.5	9,563
Zimbabwe	14.6	16.0	6.8, 20.4	13.9	6.4, 17.2	4,486
Weighted average	21.5	19.6	8.7, 24.5	17.6	8.4, 21.4	1,358,237

Abbreviations: CAR, Central African Republic; CI, confidence interval; DRC, Democratic Republic of Congo; PAP, population attributable proportion; PNG, Papua New Guinea; TB, tuberculosis.

[a] Current tobacco smoking prevalence.

[b] TB disease incidence based on relative risk of 2.3 (95% CI: 1.5, 2.8) (crude).

[c] TB disease incidence based on relative risk of 2.3 2.3 (95% CI: 1.5, 2.8) (age-adjusted); blank if no age-specific data.

[d] Excess cases based on age-adjusted PAP except for countries with no age-specific data.

[e] Daily smoking prevalence (percentage of population).

with TB are insufficient. To date, randomized controlled trials of smoking-cessation interventions for patients with TB have not been reported, highlighting the lack of progress in evaluating and promoting tailored cessation programs for patients with TB (50).

Although tobacco control policies are available worldwide, policy implementation related to TB and smoking in LMIC is inadequate (51). Of the 32 countries in our study, only 28% had evidence-based integrated tobacco guidelines, and only 25% had cessation programs within primary health care (52). Existing

Table 3. Estimated Number and Proportion of Tuberculosis Disease Attributable to Tobacco Smoking According to Sex Among Adults in 32 High-Tuberculosis-Burden Countries, 2009–2016

Country	Men				Women			
	No. of TB Cases[a]	PAP, %	95% CI[b]	No. of Excess TB Cases[c]	No. of TB Cases[a]	PAP, %	95% CI[b]	No. of Excess TB Cases[c]
Afghanistan	9,004	22.9	10.3, 28.6	2,066	14,519	3.5	1.4, 4.7	510
Angola	14,001	17.8	7.7, 22.6	2,497	9,317	2.0	0.8, 2.7	190
Bangladesh	125,646	36.8	18.3, 43.9	46,179	87,336	1.9	0.7, 2.6	1,670
Brazil	50,383	21.9	9.7, 27.4	11,046	22,537	14.6	6.1, 18.6	3,280
Cambodia	15,089	34.5	16.9, 41.5	5,213	13,171	4.5	1.8, 5.9	589
CAR	5,275	17.1	7.4, 21.8	904	3,574	1.9	0.7, 2.6	68
China	535,618	40.7	20.9, 48.1	218,252	238,185	3.0	1.2, 4.0	7,207
Congo	5,294	25.5	11.6, 31.5	1,349	4,037	2.2	0.8, 2.9	87
DRC	64,101	15.6	6.6, 19.9	9,989	48,684	1.5	0.6, 2.1	748
Ethiopia	61,198	9.5	3.9, 12.4	5,830	48,956	0.6	0.2, 0.9	316
India	1,107,520	24.0	10.8, 29.8	265,875	551,470	3.6	1.4, 4.8	20,035
Indonesia	192,516	46.6	25.1, 54.0	89,621	133,490	3.4	1.3, 4.5	4,527
Kenya	44,799	24.6	11.2, 30.5	11,022	24,865	2.7	1.0, 3.5	661
Lesotho	4,194	37.5	18.8, 44.7	1,574	2,536	0.6	0.2, 0.9	16
Liberia	4,293	23.3	10.5, 29.1	1,001	2,015	3.5	1.4, 4.7	71
Mozambique	33,255	30.0	14.2, 36.6	9,983	29,301	7.3	3.0, 9.6	2,153
Myanmar	67,911	32.9	15.9, 39.8	22,376	37,977	9.6	3.9, 12.5	3,658
Namibia	4,710	30.2	14.3, 36.8	1,423	3,306	12.5	5.2, 16.1	414
Nigeria	57,163	8.7	3.5, 11.3	4,955	34,872	0.5	0.2, 0.7	180
North Korea	61,102	36.3	18.0, 43.4	22,201	35,648	0.0	0.0	0
Pakistan	160,044	22.4	10.0, 28.0	35,844	154,588	2.7	1.0, 3.5	4,108
PNG	2,247	32.7	15.7, 39.5	734	2,095	15.7	6.7, 20.6	332
Philippines	188,226	38.3	19.3, 45.5	72,044	96,016	10.5	4.3, 13.6	10,057
Russia	62,462	43.9	23.1, 51.3	27,422	26,672	22.0	9.8, 27.5	5,869
Sierra Leone	7,195	39.3	20.0, 46.6	2,831	4,477	15.8	6.7, 20.1	706
South Africa	128,842	29.4	13.8, 35.9	37,852	87,642	9.2	3.8, 12.0	8,069
Tanzania	36,162	27.3	12.6, 33.6	9,876	21,973	4.7	1.9, 6.2	1,034
Thailand	46,870	37.7	18.9, 44.9	17,682	22,324	3.3	1.3, 4.4	730
Uganda	26,573	18.6	8.1, 23.5	4,948	12,927	3.4	1.3, 4.5	438
Vietnam	76,979	38.1	19.2, 45.3	29,349	23,275	1.8	0.7, 2.4	416
Zambia	23,197	24.7	11.2, 30.6	5,724	12,960	4.9	2.0, 6.5	641
Zimbabwe	15,436	26.7	12.3, 32.9	4,119	10,349	2.5	1.0, 3.4	262
Weighted average[d]	3,237,305	30.3	14.7, 36.6	981,781	1,821,094	4.3	1.7, 5.7	79,042

Abbreviations: CAR, Central African Republic; CI, confidence interval; DRC, Democratic Republic of Congo; PAP, population attributable proportion; PNG, Papua New Guinea; TB, tuberculosis.

[a] Number of TB cases reported in 2016 among men and women in each country.

[b] Confidence interval calculated based on relative risk of 2.3 (95% CI: 1.5, 2.8).

[c] Number of excess TB cases based on reported number of TB cases.

[d] The weighted average calculated based on the number of TB cases.

efforts to integrate TB and smoking control can be augmented by practical cessation programs supported by existing data and should be rigorously evaluated (53–55). First, because smoking among TB index patients increases the risk of TB infection among their contacts (56), cessation programs for patients with active TB that emphasize the harmful impact of tobacco use on household contacts may improve smoking-cessation adherence. Second, studies suggest that health-care providers who provide TB care often do not believe that smoking has an impact on TB treatment, do not perceive smoking cessation to be a part of TB care, and rarely have formal training in supporting smoking cessation efforts (57, 58). Effective coordination of tobacco cessation

Table 4. Estimated Proportion and Number of TB Deaths Attributable to Tobacco Smoking Among Adults in 32 High-Tuberculosis-Burden Countries, 2009–2016

Country	Crude TB Mortality[a]		No. of Deaths Attributable to Smoking[b]	No. of TB Deaths[c]	Estimated No. of TB Cases[d]	Estimated No. of TB Deaths[d]
	PAP, %	95% CI				
Afghanistan	11.5	1.3, 26.0	62	542	57,000	11,000
Angola	8.4	0.9, 19.9	119	1,417	95,000	18,000
Bangladesh	18.7	2.25, 38.3	1,460	7,806	324,000	66,000
Brazil	14.7	1.7, 31.7	891	6,069	77,000	5,400
Cambodia	17.5	2.1, 36.4	83	475	47,000	3,200
CAR	7.9	0.9, 18.8	17	212	15,900	2,700
China	21.9	2.7, 43.1	1,950	8,890	795,000	50,000
Congo	12.2	1.4, 27.3	16	129	23,100	3,100
DRC	6.0	0.6, 14.7	265	4,413	223,000	53,000
Ethiopia	4.12	0.4, 10.4	153	3,712	158,000	26,000
India	12.3	1.4, 27.4	7,061	57,494	2,557,000	423,000
Indonesia	25.8	3.4, 48.4	2,042	7,908	960,000	110,000
Kenya	11.9	1.3, 26.7	552	4,639	147,000	29,000
Lesotho	18.4	2.2, 38.0	201	1,093	13,600	1,100
Liberia	10.8	1.2, 24.6	31	283	12,600	2,800
Mozambique	15.9	1.9, 33.8	538	3,384	137,000	22,000
Myanmar	16.7	2.0, 35.1	1,087	6,523	169,000	25,000
Namibia	17.8	2.1, 36.8	129	728	13,000	750
Nigeria	3.8	0.4, 9.5	188	5,016	351,000	115,000
North Korea	16.7	2.0, 35.2	469	2,802	116,000	11,000
Pakistan	11.0	1.2, 25.1	488	4,425	467,000	44,000
PNG	20.8	2.6, 41.5	28	134	31,000	3,600
Philippines	22.1	2.8, 43.3	1,470	6,665	502,000	22,000
Russia	28.1	3.8, 51.4	2,259	8,035	84,000	12,000
Sierra Leone	24.2	3.1, 46.3	52	216	19,900	3,400
South Africa	16.3	1.9, 34.4	3,111	19,148	380,000	23,000
Tanzania	14.0	1.6, 30.6	495	3,531	151,000	28,000
Thailand	19.4	2.3, 39.3	918	4,743	110,000	8,600
Uganda	9.2	1.0, 21.4	281	3,058	75,000	11,000
Vietnam	19.2	2.3, 39.1	450	2,340	111,000	13,000
Zambia	12.7	1.4, 28.3	270	2,116	54,000	4,800
Zimbabwe	12.7	1.4, 28.3	328	2,571	31,000	1,200
Weighted average[e]	15.2	1.8, 31.9	27,462	180,517	8,307,100	1,152,650

Abbreviations: CAR, Central African Republic; CI, confidence interval; DRC, Democratic Republic of Congo; PAP, population attributable proportion; PNG, Papua New Guinea; TB, tuberculosis.

[a] TB death attributable to smoking calculated based on relative risk of 2.0 (95% CI: 1.1, 3.7).

[b] Excess TB death based on reported TB deaths.

[c] Number of reported TB deaths in 2015.

[d] Estimated number of TB cases (2016) and deaths (2015).

[e] The weighted average calculated based on the number of TB deaths.

within TB control programs will require training for health-care workers to understand the negative impacts of smoking on TB outcomes and how to support patients in their cessation attempts.

Our study had limitations. First, this study relied on data reported by WHO for estimates of TB cases and TB mortality. Although an estimated 61% of TB cases were reported to WHO in 2016, only 50% of TB cases were reported among the 32 high-burden countries (1). WHO uses reported TB cases and reported TB deaths to estimate TB incidence and TB mortality; however, the gap between reported and estimated TB cases and TB deaths is vast, especially in LMIC. For example, in 2016 there was a 4.1-million-count difference between reported TB cases (6.3 million)

Table 5. Sensitivity Analysis for Proportion of TB Disease and Deaths, Among Adults in 32 High-Tuberculosis-Burden Countries, Attributable to Tobacco Smoking Based on Monte Carlo Analysis, 2009–2016

Country	Smoking Prevalence		TB Disease		TB Mortality	
	Point Estimate, %[a]	95% CI[a]	PAP, %	95% CI	PAP, %	95% CI
Afghanistan[b]	13.0	10.0, 15.9	11.5	5.6, 18.7	11.9	1.0, 25.9
Angola[b]	9.2	6.2, 12.2	8.4	3.5, 14.4	8.7	0.5, 20.4
Bangladesh	23.0	21.9, 24.2	18.6	10.0, 28.3	18.9	1.6, 37.2
Brazil	17.2	16.7, 17.7	14.7	7.7, 22.4	15.0	1.2, 30.8
Cambodia	21.2	16.2, 27.3	17.5	9.2, 27.2	17.9	1.8, 36.2
CAR[b]	8.6	5.6, 11.5	7.9	3.5, 13.7	8.2	0.6, 19.7
China	28.1	26.7, 29.7	21.8	11.9, 32.7	21.9	2.0, 42.4
Congo	13.9	9.9, 18.3	12.1	5.5, 19.8	12.5	1.0, 27.5
DRC[b]	6.4	3.5, 9.3	6.1	2.4, 11.3	6.3	0.4, 15.2
Ethiopia	4.3	3.0, 5.6	4.2	1.8, 7.3	4.4	0.3, 10.5
India	14.0	13.4, 14.6	12.3	6.4, 19.4	12.7	1.0, 27.2
Indonesia	34.8	33.2, 36.4	25.7	14.2, 37.3	25.8	3.1, 48.5
Kenya	13.5	9.9, 17.3	11.9	5.8, 19.6	12.3	1.0, 26.2
Lesotho	22.6	16.6, 29.4	18.3	9.2, 28.5	18.6	1.5, 38.0
Liberia	12.1	6.5, 20.8	10.7	3.6, 20.4	11.0	0.7, 26.2
Mozambique	18.9	12.2, 27.7	15.8	7.2, 26.6	16.0	1.5, 33.5
Myanmar	20.0	16.1, 29.6	16.6	8.1, 26.7	16.9	1.6, 35.5
Namibia	21.6	15.5, 28.8	17.6	8.8, 28.6	17.9	1.4, 36.9
Nigeria	3.9	3.3, 4.5	3.8	1.8, 6.5	4.0	0.3, 9.4
North Korea[b]	20.1	17.2, 23.0	16.7	8.8, 26.0	17.0	1.4, 34.3
Pakistan	12.4	11.2, 13.3	11.1	5.7, 17.6	11.5	0.8, 24.4
PNG[b]	26.3	23.4, 29.2	20.7	11.1, 32.8	20.9	1.9, 41.4
Philippines	28.3	27.0, 29.5	21.9	11.9, 32.8	22.1	2.0, 42.3
Russia	39.1	37.8, 40.5	27.9	15.9, 40.4	27.6	2.7, 50.1
Sierra Leone	31.9	22.0, 42.3	23.9	11.9, 37.0	23.9	2.6, 47.0
South Africa	19.4	15.5, 24.1	16.2	8.2, 25.7	16.5	1.5, 34.8
Tanzania	16.3	11.7, 21.3	13.9	6.5, 22.3	14.2	1.2, 30.9
Thailand	24.0	22.8, 25.1	19.3	10.2, 29.0	19.5	1.7, 38.3
Uganda	10.1	7.3, 13.6	9.3	4.3, 15.4	9.6	0.7, 21.4
Vietnam	23.8	22.7, 24.9	19.2	10.2, 29.4	19.4	1.7, 38.4
Zambia	14.6	10.0, 19.5	12.8	6.1, 21.5	13.2	0.9, 28.5
Zimbabwe	14.6	10.8, 18.5	12.6	6.1, 20.4	13.0	0.9, 28.9
Weighted average	21.5	20.2, 23.0	17.7	9.4, 27.0	17.9	1.5, 35.7

Abbreviations: CAR, Central African Republic; CI, confidence interval; DRC, Democratic Republic of Congo; PAP, population attributable proportion; PNG, Papua New Guinea; TB, tuberculosis.

[a] Point estimate and 95% confidence interval for smoking prevalence from World Health Organization reports (20, 21).

[b] 95% confidence intervals were calculated based on the average standard error from the 26 countries.

and estimated TB cases (10.4 million). Nonetheless, we believe our estimated TB cases and estimated TB deaths reflect the actual TB burdens due to smoking and that limitations of WHO TB reporting rates did not affect our PAP estimates. Second, TB cases and deaths due to secondhand smoke were not included in our analyses, which may underestimate our estimates of the proportion of smoking-attributable TB disease and death. Third, smoking prevalence measurement and data collection methods varied from country to country, and we did not account for the intensity or duration of smoking. Although most countries used WHO guidelines to collect smoking prevalence data, tobacco use could be underreported, especially for products other than cigarettes, commonly used in developing countries. Fourth, we assumed the relative risk estimates applied for TB disease and TB death were causal (59) and homogeneous across analyses, although the relative effect of smoking on TB disease risk and TB mortality likely varies according to sex, age, and country. Nonetheless, our sensitivity analyses accounted for various relative risk values and did not result in meaningfully different PAP estimates for either TB disease or TB mortality. Despite these limitations, we used current and reliable nationally representative data sources and sensitivity analyses, which improved the validity and generalizability of our estimates.

Smoking plays a harmful role in the global TB pandemic, contributing greatly to increased risk of TB disease and TB death in high-TB-burden countries. The considerable impact of smoking on TB epidemics highlights the importance of promoting smoking cessation for people at risk of TB, especially in LMIC where the prevalence of smoking and the risk of TB are highest. Despite improvements in global tobacco control policy, most countries do not have coordinated mechanisms between TB and tobacco-control programs, and tobacco-cessation support for patients with TB is limited. Our findings suggest that increased availability and implementation of smoking-cessation interventions targeted for TB patients will reduce global TB mortality and support the goals of the End TB Strategy. Continued and expanded political commitment and strong coordination among various stakeholders, both globally and nationally, are required to effectively and aggressively enforce tobacco control and ensure that it includes policy that benefits patients with TB.

ACKNOWLEDGMENTS

Author affiliations: Division of Epidemiology and Biostatistics, School of Public Health, Georgia State University, Atlanta, Georgia (Genet A. Amere, Argita D. Salindri, Matthew J. Magee); Georgia State University's Tobacco Center of Regulatory Science, School of Public Health, Georgia State University, Atlanta, Georgia (Pratibha Nayak); and Emory Global Diabetes Research Center, Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, Georgia (K. M. V. Narayan).

Research reported in this publication was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (award R03AI133172).

We thank Dr. Ruiyan Luo, Georgia State University, for her support in performing Monte Carlo simulations. We also thank Michelle Ping-Lee D'Amico for her assistance in reviewing the manuscript.

Data from these analyses were presented at the 2017 Annual Meeting of the American Public Health Association, November 4–8, 2017, Atlanta, Georgia.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflict of interest: none declared.

REFERENCES

1. World Health Organization. Global Tuberculosis Report 2017. Geneva, Switzerland: World Health Organization; 2017. http://apps.who.int/iris/bitstream/handle/10665/259366/9789241565516-eng.pdf;jsessionid=8F31CA8593E4A4AE5180663B4797F6E8?sequence=1. Accessed January 15, 2018
2. World Health Organization. Tuberculosis. http://www.who.int/mediacentre/factsheets/fs104/en/. Updated October 2016. Accessed December 2, 2016.
3. Uplekar M, Weil D, Lonnroth K, et al. WHO's new end TB strategy. *Lancet*. 2015;385(9979):1799–1801.
4. Lönnroth K, Raviglione M. The WHO's new end TB strategy in the post-2015 era of the Sustainable Development Goals. *Trans R Soc Trop Med Hyg*. 2016;110(3):148–150.
5. Slama K, Chiang CY, Enarson DA, et al. Tobacco and tuberculosis: a qualitative systematic review and meta-analysis. *Int J Tuberc Lung Dis*. 2007;11(10):1049–1061.
6. Bates MN, Khalakdina A, Pai M, et al. Risk of tuberculosis from exposure to tobacco smoke: a systematic review and meta-analysis. *Arch Intern Med*. 2007;167(4):335–342.
7. Alcaide J, Altet MN, Plans P, et al. Cigarette smoking as a risk factor for tuberculosis in young adults: a case-control study. *Tuber Lung Dis*. 1996;77(2):112–116.
8. Leung CC, Li T, Lam TH, et al. Smoking and tuberculosis among the elderly in Hong Kong. *Am J Respir Crit Care Med*. 2004;170(9):1027–1033.
9. Gajalakshmi V, Peto R, Kanaka TS, et al. Smoking and mortality from tuberculosis and other diseases in India: retrospective study of 43,000 adult male deaths and 35,000 controls. *Lancet*. 2003;362(9383):507–515.
10. World Health Organization. Tobacco. http://www.who.int/mediacentre/factsheets/fs339/en/. Updated June 2016. Accessed October 9, 2016.
11. World Health Organization. MPOWER: A Policy Package To Reverse The Tobacco Epidemic. Geneva, Switzerland: World Health Organization; 2008. http://www.who.int/tobacco/mpower/mpower_english.pdf. Accessed February 27, 2017.
12. World Health Organization. Tuberculosis & tobacco. Geneva, Switzerland: World Health Organization; 2009. http://www.who.int/tobacco/resources/publications/factsheet_tb_tobacco_sep09.pdf. Accessed January 20, 2017.
13. Méndez D, Alshanqeety O, Warner KE. The potential impact of smoking control policies on future global smoking trends. *Tob Control*. 2013;22(1):46–51.
14. Anderson CL, Becher H, Winkler V. Tobacco control progress in low and middle income countries in comparison to high income countries. *Int J Environ Res Public Health*. 2016;13(10):E1039.
15. Husain MJ, English LM, Ramanandraibe N. An overview of tobacco control and prevention policy status in Africa. *Prev Med*. 2016;91S:S16–S22.
16. Lönnroth K, Castro KG, Chakaya JM, et al. Tuberculosis control and elimination 2010–50: cure, care, and social development. *Lancet*. 2010;375(9728):1814–1829.
17. Lönnroth K, Roglic G, Harries AD. Improving tuberculosis prevention and care through addressing the global diabetes epidemic: from evidence to policy and practice. *Lancet Diabetes Endocrinol*. 2014;2(9):730–739.
18. World Health Organization. *Unite to End TB: On the Road to Ending TB*. Geneva, Switzerland: World Health Organization; 2016. http://apps.who.int/iris/bitstream/10665/204662/1/WHO_HTM_TB_2016.06_eng.pdf. Accessed March 3, 2017.
19. World Health Organization. *Global Tuberculosis Report 2015*. Geneva, Switzerland: World Health Organization; 2015. http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf. Accessed December 1, 2016
20. World Health Organization. Global Adult Tobacco Survey (GATS). http://www.who.int/tobacco/surveillance/survey/gats/en/. Accessed August 9, 2016.
21. World Health Organization. *WHO Global Report on Trends in Prevalence of Tobacco Smoking 2015*. Geneva, Switzerland:

World Health Organization; 2015. http://apps.who.int/iris/bitstream/10665/156262/1/9789241564922_eng.pdf. Accessed December 10, 2016
22. World Health Organization. Tobacco Free Initiative: tobacco control country profiles. http://www.who.int/tobacco/surveillance/policy/country_profile/en/. Accessed December 12, 2016.
23. The Tobacco Atlas. Countries. https://tobaccoatlas.org/countries/. Accessed December 2, 2016.
24. United States Census Bureau. International Programs. Population by five-year age groups, individual country data only (2016). https://www.census.gov/data-tools/demo/idb/informationGateway.php. Updated August 2017. Accessed January 10, 2018.
25. World Health Organization. *Definitions and Reporting Framework for Tuberculosis–2013 Revision*. Geneva, Switzerland: World Health Organization; 2013. http://www.who.int/tb/publications/definitions/en/. Updated December 2014. Accessed December 7, 2017.
26. Lin HH, Ezzati M, Murray M. Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis. *PLoS Med*. 2007;4(1):e20.
27. Bilano V, Gilmour S, Moffiet T, et al. Global trends and projections for tobacco use, 1990–2025: an analysis of smoking indicators from the WHO Comprehensive Information Systems for Tobacco Control. *Lancet*. 2015;385(9972):966–976.
28. Prignot JJ, Sasco AJ, Poulet E, et al. Alternative forms of tobacco use. *Int J Tuberc Lung Dis*. 2008;12(7):718–727.
29. Walter SD. The estimation and interpretation of attributable risk in health research. *Biometrics*. 1976;32(4):829–849.
30. Agresti A. *An Introduction to Categorical Data Analysis*. 2nd ed. Hoboken, NJ: John Wiley & Sons, Inc.; 2007. https://mregresion.files.wordpress.com/2012/08/agresti-introduction-to-categorical-data.pdf.
31. Lin HH, Ezzati M, Chang HY, et al. Association between tobacco smoking and active tuberculosis in Taiwan: prospective cohort study. *Am J Respir Crit Care Med*. 2009;180(5):475–480.
32. Kolappan C, Gopi PG, Subramani R, et al. Selected biological and behavioural risk factors associated with pulmonary tuberculosis. *Int J Tuberc Lung Dis*. 2007;11(9):999–1003.
33. Ramin B, Kam D, Feleke B, et al. Smoking, HIV and non-fatal tuberculosis in an urban African population. *Int J Tuberc Lung Dis*. 2008;12(6):695–697.
34. Brunet L, Pai M, Davids V, et al. High prevalence of smoking among patients with suspected tuberculosis in South Africa. *Eur Respir J*. 2011;38(1):139–146.
35. World Health Organization. *Global Tuberculosis Control: WHO Report 2011*. Geneva, Switzerland: World Health Organization; 2011. http://apps.who.int/iris/bitstream/10665/44728/1/9789241564380_eng.pdf. Accessed March 3, 2017.
36. Jee SH, Golub JE, Jo J, et al. Smoking and risk of tuberculosis incidence, mortality, and recurrence in South Korean men and women. *Am J Epidemiol*. 2009;170(12):1478–1485.
37. Pednekar MS, Gupta PC. Prospective study of smoking and tuberculosis in India. *Prev Med*. 2007;44(6):496–498.
38. Alam DS, Jha P, Ramasundarahettige C, et al. Smoking-attributable mortality in Bangladesh: proportional mortality study. *Bull World Health Organ*. 2013;91(10):757–764.
39. Sitas F, Urban M, Bradshaw D, et al. Tobacco attributable deaths in South Africa. *Tob Control*. 2004;13(4):396–399.
40. Jiang J, Liu B, Nasca PC, et al. Smoking and risk of death due to pulmonary tuberculosis: a case-control comparison in 103 population centers in China. *Int J Tuberc Lung Dis*. 2009;13(12):1530–1535.
41. Sopori M. Effects of cigarette smoke on the immune system. *Nat Rev Immunol*. 2002;2(5):372–377.
42. Shang S, Ordway D, Henao-Tamayo M, et al. Cigarette smoke increases susceptibility to tuberculosis–evidence from in vivo and in vitro models. *J Infect Dis*. 2011;203(9):1240–1248.
43. Houtmeyers E, Gosselink R, Gayan-Ramirez G, et al. Regulation of mucociliary clearance in health and disease. *Eur Respir J*. 1999;13(5):1177–1188.
44. O'Leary SM, Coleman MM, Chew WM, et al. Cigarette smoking impairs human pulmonary immunity to *Mycobacterium tuberculosis*. *Am J Respir Crit Care Med*. 2014;190(12):1430–1436.
45. Boelaert JR, Gomes MS, Gordeuk VR. Smoking, iron, and tuberculosis. *Lancet*. 2003;362(9391):1243–1244.
46. Lounis N, Truffot-Pernot C, Grosset J, et al. Iron and *Mycobacterium tuberculosis* infection. *J Clin Virol*. 2001;20(3):123–126.
47. Aryanpur M, Mortaz E, Masjedi MR, et al. Reduced phagocytic capacity of blood monocyte/macrophages in tuberculosis patients is further reduced by smoking. *Iran J Allergy Asthma Immunol*. 2016;15(3):174–182.
48. Gegia M, Magee MJ, Kempker RR, et al. Tobacco smoking and tuberculosis treatment outcomes: a prospective cohort study in Georgia. *Bull World Health Organ*. 2015;93(6):390–399.
49. Mahishale V, Patil B, Lolly M, et al. Prevalence of smoking and its impact on treatment outcomes in newly diagnosed pulmonary tuberculosis patients: a hospital-based prospective study. *Chonnam Med J*. 2015;51(2):86–90.
50. Jeyashree K, Kathirvel S, Shewade HD, et al. Smoking cessation interventions for pulmonary tuberculosis treatment outcomes. *Cochrane Database Syst Rev*. 2016;(1):CD011125.
51. World Health Organization. *South-East Asia Regional Response Plan for Integration of TB and Tobacco – 2017–2021*. New Delhi, India: World Health Organization; 2017. http://apps.who.int/iris/bitstream/10665/258976/1/9789290225836-eng.pdf. Accessed October 20, 2017.
52. World Health Organization. WHO Framework Convention on Tobacco Control Implementation Database: parties. http://apps.who.int/fctc/implementation/database/parties. Accessed October 18, 2017.
53. Bam TS, Aditama TY, Chiang CY, et al. Smoking cessation and smokefree environments for tuberculosis patients in Indonesia-a cohort study. *BMC Public Health*. 2015;15:604.
54. El Sony A, Slama K, Salieh M, et al. Feasibility of brief tobacco cessation advice for tuberculosis patients: a study from Sudan. *Int J Tuberc Lung Dis*. 2007;11(2):150–155.
55. Kaur J, Sachdeva KS, Modi B, et al. Promoting tobacco cessation by integrating 'brief advice' in tuberculosis control programme. *WHO South East Asia J Public Health*. 2013;2(1):28–33.
56. Godoy P, Caylà JA, Carmona G, et al. Smoking in tuberculosis patients increases the risk of infection in their contacts. *Int J Tuberc Lung Dis*. 2013;17(6):771–776.
57. Magee MJ, Darchia L, Kipiani M, et al. Smoking behavior and beliefs about the impact of smoking on anti-tuberculosis treatment among health care workers. *Int J Tuberc Lung Dis*. 2017;21(9):1049–1055.
58. Lin Y, Wang LX, Qiu LX, et al. A smoking cessation intervention among tuberculosis patients in rural China. *Public Health Action*. 2015;5(3):183–187.
59. Bishwakarma R, Kinney WH, Honda JR, et al. Epidemiologic link between tuberculosis and cigarette/biomass smoke exposure: limitations despite the vast literature. *Respirology*. 2015;20(4):556–568.