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Population Attributable Fraction of Smoking for Tuberculosis (TB) Disease Incidence and TB Mortality in High-Burden TB Countries

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ABSTRACT

POPULATION ATTRIBUTABLE FRACTION OF SMOKING FOR TUBERCULOSIS (TB) DISEASE INCIDENCE AND TB MORTALITY IN HIGH-BURDEN TB COUNTRIES
by

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Background: Globally, there are 10 million new cases of tuberculosis (TB) disease annually and 95% of cases occur in low- and middle-income countries (LMIC). More than 1 billion people use tobacco, and 80% of tobacco users reside in LMIC. Smoking approximately doubles the risk of TB disease and is associated with excess mortality during TB treatment. We aimed to estimate the proportion of annual incident TB cases and TB mortality attributable to tobacco smoking in high burden TB countries.

Methods: To estimate population attributable fractions (PAF), we obtained country specific estimates of TB incidence and TB mortality rates from the WHO 2015 Global TB Report. Country specific smoking prevalence was estimated from WHO 2015 tobacco surveillance reports and the Tobacco Atlas. Risk ratios for the effect of smoking on TB incidence and TB mortality were obtained from previously published meta-analyses. Country specific PAF of smoking for TB disease were age and sex adjusted.

Results: In high burden countries during 2014, an estimated 4.5 million adults developed TB disease and 163,000 people died from TB. An estimated 740 million adult smokers lived in those high burden countries in 2014. We estimated that tobacco smoking was attributable for 17.7% (95% confidence interval [CI] 8.6-21.9%) of TB cases and 15.0% (95% CI 1.9-31.6%) of TB mortality. Of the high burden countries, Russia had the highest proportion of smoking attributable TB disease (31.8%, 95% CI 16.0-37.8%) and death (28.1%, 95% CI 3.8-51.3%). India had the greatest absolute number of TB cases (233,000) and TB deaths (7,400) attributable to smoking. Men (30.5%, 95% CI 14.9%-36.9%) had a greater proportion of TB cases attributable to smoking than women (4.7%, 95% CI 1.9%-6.2%).

Conclusion: In high-burden TB countries, nearly one-sixth of all TB cases and TB deaths were attributable to smoking. Our findings highlight the need for tobacco control in high TB burden regions and specifically among patients with TB. Reaching key populations and integrating smoking cessation efforts into TB programs will be essential to achieve global TB control goals.

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BY

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APPROVAL PAGE

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Author's Statement Page

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CHAPTER I

INTRODUCTION

1.1 Background

Tuberculosis (TB) is a bacterial infection caused by Mycobacterium tuberculosis (MTB), which is transmitted via droplet nuclei. According to World Health Organization (WHO), 10.4 million people developed TB disease and 1.8 million died from it in 2015. The majority of TB disease (87%) occurs in 30 high burden countries and 95% of cases occur in low- and middle-income countries (LMIC) (WHO, 2015a, 2016a).

A third of the world population is infected with MTB but are asymptomatic and non-infectious. A small proportion of those infected will develop TB disease; the lifetime risk of developing TB disease is estimated at 10%. However, the risk of developing TB disease increases in immunocompromised people such as patients with HIV/AIDS, malnutrition, diabetes, and among individuals who use tobacco (WHO, 2015).

Tobacco smoking is the most preventable cause of premature death and disease worldwide (CDC, March 15, 2016). The risk of diseases such as lung cancer, chronic obstructive pulmonary disease, and cardiovascular disease increase with smoking. Globally, more than 1 billion people use tobacco, which kills more than 5 million people annually

and this figure is expected to exceed 8 million by 2030 on current trends, with more than 80% of deaths occurring in LMIC (WHO, 2016a).

The prevalence of smoking is 4.4 times higher in men than in women globally. However, there is regional variation in tobacco consumption in both males and females. For instance, in Americas Region (1.6 times) and European Region (2 times) higher in men, whereas South-East Asia Region (9.3 times) and Western Pacific Regions (11.4 times) higher among men than women. Furthermore, countries with large population have sex-linked disparity in tobacco consumption. For example, the male smoking prevalence rates are 22 times higher and 23 times higher than women in China and India, respectively (WHO, 2010).

To achieve the 2030/35 newly adopted Sustainable Development Goals (SDG) which includes ending TB epidemic (WHO, 2015e), it is important to address all risk factors including smoking. Although smoking prevalence is decreasing in most developed countries, many countries with the highest TB burden have very high smoking rates. For instance, smoking prevalence among U.S. adults declined from 20.9% to 16.8% between 2005 and 2014 (Jamal et al., 2015). However, in Indonesia (67.0%), Russia (60.2%), and China (52.9%) the majority of the adult male population smokes (WHO, October 2015).

Although the number of legislated tobacco control polices increased globally from 2007 to 2014, including in LMIC, implementation of tobacco

control policies is still at low levels in most LMIC (Anderson, Becher, & Winkler, 2016; Bump & Reich, 2013). In addition, many tobacco corporations have shifted the focus of advertisement and distribution from high-income countries to LMIC where the burden of TB is highest (Mendez, Alshanqeety, & Warner, 2013). The limited policy implementation and the shift in tobacco marketing strategies would impact the burden of TB in LMIC.

Tobacco use greatly increases the risk of TB infection, TB disease, and TB death. Systematic reviews performed by Bates et al. and Slama et al. in 2007 indicated that smokers are almost twice more likely to be infected with TB than non-smokers (Bates et al., 2007; Slama et al., 2007). Smokers are also estimated to have twice the risk of developing TB disease and die from TB (Bates et al., 2007; Lin, Ezzati, & Murray, 2007; Slama et al., 2007). In addition, tobacco smoking increases the risk of recurrent TB after treatment completion (Mahishale, Patil, Lolly, Eti, & Khan, 2015; Yen et al., 2014). Yen YF et al reported that after successful treatment completion, the risk of TB recurrence among subjects who smoked >10 cigarettes a day was two times more than among subjects who never/former smokers. Overall, more than 20% of adult TB cases and 16% of all TB cases in the world are attributable to smoking (Lonnroth et al., 2010). The objective of this study is to determine the proportion of TB disease and TB mortality attributable to smoking in the 32 high burden TB

countries by estimating age and sex specific population attributable fraction using WHO data.

1.2 Gap and Purpose of Study

Multiple epidemiologic studies have reported that smoking increases the risk of TB infection, TB disease, and TB death. However, previous studies have not estimated the proportion of TB disease incidence due to smoking adjusted for age and sex. Previous studies have also not estimated the proportion of TB deaths attributable to smoking in high burden countries. This study addresses whether the changes in the global TB epidemic and changes in global smoking prevalence have impacted the relative impact of smoking on the public health burden of TB.

The specific objectives of this study are:

1. To estimate the proportion of TB disease incidence due to tobacco smoking among 32 high burden TB countries.
2. To estimate the proportion of TB deaths due to tobacco smoking among 32 high burden TB countries.

CHAPTER II

REVIEW OF LITERATURE

2.1 Epidemiology of TB and Smoking

Although incident TB is decreasing worldwide, the number of TB cases are still increasing due to better detection and reporting, and population growth. For instance, estimated TB incidence in the Pacific has remained high but stable from 2000 to 2013. Using data from the WHO annual TB surveillance for 22 Pacific island countries and territories, TB case notification rate increased by 58%, from 146 to 231 per 100,000 population in the same period (Viney et al., 2015). In another study notified TB cases increased from 24 878 in 2006 to 26 517 in 2014 (Noeske, Nana Yakam, & Abena Foe, 2016).

Globally, smoking prevalence will get worse without additional policies and strategies. MPOWER is a comprehensive set of tobacco control policies which consists of six basic strategies: monitor tobacco use, protect people from tobacco smoke, offer help to quit tobacco use, warn about the dangers of tobacco, enforce bans on tobacco advertising, promotion and sponsorship, and raise taxes on tobacco (WHO, 2008). Méndez et al. estimated that global smoking prevalence would be 22.7% by 2020 and 22.0% by 2030, however if MPOWER implemented 100% globally, the prevalence would reduce to 15.4% in 2020 and 13.2% in 2030 (Mendez, Alshanqeety, & Warner, 2013). Another study conducted

by Bilane et al. also estimated that there will be 1·1 billion tobacco smokers (95% credible interval 700 million to 1·6 billion) in 2025 globally. The authors predicted that smoking prevalence will be higher among African men and eastern Mediterranean men and women if the current trends continue. Tobacco epidemic is at risk of worsening in LMIC without effective and sustainable tobacco control measures (Bilano et al., 2015).

2.2 The Association between TB Disease and Smoking

Smoking prevalence was higher among TB patients (39.3 %) than the general population (23.95 %) (Jimenez-Fuentes et al., 2016). A study in Iran found that the prevalence of cigarette smoking was 22% among newly diagnosed TB patient vs 13.9% among the general population of Iran (Aryanpur et al., 2016). A cross-sectional study conducted in South Africa also reported that patients with active TB had very high rates of smoking (56%) prevalence (Brunet et al., 2011).

Large cross-sectional studies in south and central India conducted in 2007 and 2014, respectively, reported a positive association between smoking and TB disease. The study in south India found that smokers had a 2.1 (95% confidence interval (CI), 1.7–2.7) times higher risk of TB disease than non-smokers did which is similar with the case control study in south India (Kolappan & Gopi, 2002; Kolappan, Gopi, Subramani, & Narayanan, 2007). In addition, the study in central India reported a strong

dose response relationship between TB disease and tobacco smoking. Compared to non-smokers, the adjusted prevalence odds ratio (aOR) for mild, moderate and heavy tobacco smokers were 2.28 (95% C1 0.43–3.63), 2.51 (1.59–3.96) and 2.74 (1.60–4.69) respectively (Rao et al., 2014). A recent multicenter cross-sectional study in Spain based on 5,846 TB cases found that smoking was associated with pulmonary TB with an aOR of 1.61(95%CI: 1.16 - 2.24) (Jimenez-Fuentes et al., 2016).

Multiple case-control studies estimated the relationship between tobacco smoking and TB disease. A case-control study conducted in Hong Kong showed that TB patient were approximately 2 times more likely to have smoked than population control in both sex and all age group (Leung et al., 2003). In this study, the odds of ever smoking among TB patients were 2.44 (males) and 2.08 (females) aged 16-64 and 2.09 (males) and 2.83 (females) aged >or = 65 compared to population control.

A hospital based case-control study performed in Thailand reported that duration and amount of cigarette smoking had positive relationship with pulmonary TB (Ariyothai et al., 2004). Ariyothai et al. reported that compared to non- smoker, persons who had smoked >10 years had a higher risk of pulmonary TB (odds ratio (OR) = 2.96, 95% CI = 1.06-8.22). Those who smoked >10 cigarettes/day (OR = 3.98, 95% CI = 1.26-12.60) or >3 days/week (OR = 2.68, 95% CI = 1.01-7.09) had higher risk of pulmonary TB compared to non-smokers (Ariyothai et al., 2004).

Case-control studies conducted in India at different set up reported the association between tobacco smoking and TB disease. The study conducted at University Hospital showed a higher association than at district hospital. Compared to nonsmoker, the adjusted odds of developing pulmonary TB among smokers were approximately 4 times (aOR,3.8, 95%CI, 2.0 to 7.0; P value, <.0001) vs 2 times (aOR,1.70, 95%CI: 1.01-2.88) in University and rural hospitals, respectively (Dhamgaye, 2008; Prasad, Garg, Singhal, Dawar, & Agarwal, 2009). Prasad et al and Dhamgaye also showed amount and duration of smoking were also positively associated with pulmonary TB. The difference could be due to regional variation in smoking prevalence in India. In a large case-control study conducted in India, the prevalence risk ratio of TB disease was 2.9 (95% CI, 2.6-3.3) for ever-smokers compared with never-smokers in adult men between 35 and 69 years of age (Gajalakshmi, Peto, Kanaka, & Jha, 2003). Another case-control study in south India also found that smoking was independently associated with pulmonary TB with a strong dose response relationship (age aOR 2.24. (95% CI 1.27 to 3.94) (Kolappan & Gopi, 2002).

Although smoking is less common in African countries, some studies reported the association between smoking and TB. A multicenter case–control study conducted in three West African countries (Guinea, Guinea Bissau, and The Gambia) reported that smoking was an

independent risk factor of pulmonary TB. The adjusted OR for both current and passive smoking were aOR 2.54 (95% CI 1.77-3.66) and 1.82 (95% CI 1.05-3.15) respectively (Lienhardt et al., 2005). A case-control study in St Peter's Tuberculosis Hospital in Ethiopia reported that the odds of pulmonary TB were higher among men smokers (43%) than controls (25%) with an aOR of 2.3 (95% CI 1.1–4.8) (Ramin, Kam, Feleke, Jacob, & Jha, 2008).

Recent case-control study conducted in Istanbul (Turkey) reported that the odds of developing active TB were five times more among current smokers (OR 4.97, 95% CI: 3.2-7.5, p< 0.0001) than non-smokers (Ozturk, Kilicaslan, & Issever, 2014). The association was higher than that of from other countries (Ozturk et al., 2014). In a case-cohort study in northern California, where TB is not common, the odds of active TB in ever and past smoker were 1.34 (95% CI, 1.07- 1.66) and 1.37 (95%CI, 1.07-1.75) respectively compared to never smoker. However, among current smokers, 46.3% TB cases vs 48.9% controls were current smoker with OR of 1.26 (95% CI 0.91 to 1.7) (Smith et al., 2015). The authors concluded that ever- and former smokers were at an increased risk of pulmonary TB disease when compared with never-smokers.

Two cohort studies conducted in Hong Kong and Taiwan reported the association between smoking and TB disease. A retrospective cohort in Hong Kong for adults aged 65 years or older showed that the risk of

pulmonary TB among current smokers were 2.87 (95% CI, 2.00–4.11) times than among never smokers (Leung et al., 2004). A prospective study in Taiwan reported that the risk of active TB in current smokers was two (1.94 95%CI (1.01-3.73) times compared with never smokers (Lin, Ezzati, Chang, & Murray, 2009). Both studies showed a statistically significant dose–response relationship and adjusted for potential confounders like socio economic status (SES), age, sex, alcohol use, marital status, and chronic disease like diabetes mellitus. Lin et al. also found that the smoking-attributable fraction of TB disease was 17%.

2.3 The Association between TB Mortality and Smoking

Studies to date showed that smoking increases poor outcome among TB patients especially death. A large retrospective case-control study in south India, compared to never-smokers, among ever-smoker men 25-69 years of age, the prevalence risk ratio of death from TB were 4.5 (95% CI, 4.0-5.0) and 4.2 (95% CI, 3.7-4.8) in urban and rural residents, respectively. The authors concluded that 61% of TB deaths are attributable to smoking, which is greater than deaths from cardio vascular disease or cancer in India (Gajalakshmi et al., 2003). A case-control study using a national representative data among men and women 30-69 years of age conducted in India reported that, compared to non-smokers, mortality from TB were significantly higher in smokers with a risk ratio of

3.0 (99% CI, 2.4 to 3.9) and 2.3 (99% CI, 2.1 to 2.6) in women and men, respectively (Jha et al., 2008).

A case-control study in Hong Kong examined all causes and specific cause mortality associated with smoking. Lam et al. reported that among men, mortality from TB in smokers was 2.54 (95% CI 1.24-5.22) times than in non-smokers. The association was not significant in women (adjusted risk ratios of 1.49, 95% CI: 0.18-12.57) (Lam, Ho, Hedley, Mak, & Peto, 2001). A large population study in China based on 15,497 TB deaths, reported that the risk ratio for TB death in smokers vs non-smokers were 1.5 (95%CI 1.4–1.6) and 1.6 (95%CI 1.5–1.7) in men and women, respectively. Jiang et al. also reported that smoking-attributable fraction of TB death were 22.5% in men and 6.6% in women (Jiang et al., 2009).

Sitas et al. conducted a case-control study in South Africa using South African death notification system. Based on 416 TB deaths, 20% of TB deaths were attributable to smoking with OR of 1.61 (95% CI, 1.23 to 2.11). TB deaths attributable to smoking was 28% among men and 7% among women (Sitas et al., 2004). A case-control study in rural Bangladesh based on 78 pulmonary TB deaths reported that 35.1% of TB mortality attributable to smoking among men 25-69 years old. The associated odds were 1.82 (99% CI, 0.7- 4.7) among ever-smoker vs

never-smoker, after adjusting for differences in age, education and use of chewing tobacco (Alam et al., 2013).

A large cohort study in India followed men 35 years and older for 13 years and estimated TB deaths among smokers. After adjusting for potential confounders (age, education, and smokeless tobacco use), the risk of death from TB among smokers were 2 times more than among non-smoker (RR 2.12, 95% CI: 1.70, 2.66). The authors reported that the risk was higher for bidi smokers (RR 2.63, 95% CI: 2.05, 3.38) than cigarette smokers (RR 1.68, 95% CI: 1.28, 2.20). Pednekar et al. concluded that 32% of TB mortality was attributable to bidi smoking (Pednekar & Gupta, 2007). However, a cohort study in Taiwan reported that smoking was not significantly associated with TB death (Hazard ratio [HR] 1.420,95% CI 0.872–2.313) when adjusted for independent prognostic factors such as age, the presence of underlying disease, symptom duration 60 days, extra-pulmonary involvement, serum albumin level >3.5 g/dl, and delayed anti-TB treatment (Wang et al., 2007). Although the study in Taiwan included all age, both sex, and shorter duration than the study in India.

2.4 Summary of literature review

Highlights from the literature review of previous studies include:

- TB incidence and smoking prevalence is changing globally
- Studies to date suggested that smoking is associated with risk of developing TB with a strong dose response relationship.
- Most Studies suggested the association between smoking and TB mortality with some controversy as reported by a cohort study in Taiwan.
- The association between smoking and TB were higher in men.

CHAPTER III

MANUSCRIPT

Introduction

Tuberculosis (TB) remains one of the leading causes of morbidity and mortality worldwide. In 2015, 10.4 million people developed active TB and 1.8 million died from the disease (WHO, 2016a). The majority of TB disease (87%) occurs in 30 high burden countries and an estimated 95% of TB cases and deaths occur in low- and middle-income countries (LMIC) (WHO, 2016a, 2016c). Currently, there are more than 1 billion tobacco users in the world and nearly 80% of them live in LMIC, where the burden of tobacco and TB related illness and death is highest (WHO, 2015c, 2016b). Tobacco is the second major cause of death in the world and kills half of all lifetime users. Annually, tobacco kills 6 million people and more than 5 million deaths are due to direct tobacco use (WHO, 2016b). The co-occurrence of both smoking and TB in LMIC is a major public health problem.

Although tobacco use is declining in many high-income countries, it is increasing in LMIC (Mendez et al., 2013) where tobacco control policies are not well established. In 2015, the World Health Organization (WHO) projected that smoking prevalence will decrease in all WHO regions except Africa and Eastern Mediterranean regions where smoking is expected to increase (WHO, 2015b). Although TB disease incidence is

declining globally, TB incidence rates are still high in African and Asian regions (Viney et al., 2015; WHO, 2013a, 2015d). However, the extent to which changes in smoking prevalence may impact changes in global TB incidence trends is largely unknown.

The risk of active TB is associated with immunosuppression and also with modifiable behaviors such as tobacco use (Maurya, Vijayan, & Shah, 2002; WHO, 2016c). Tobacco smoking approximately doubles the risk of TB infection, TB disease, and TB death (Bates et al., 2007; Lin, Ezzati, & Murray, 2007; Slama et al., 2007). Cohort studies have estimated that people who smoked tobacco are more than twice as likely to develop active TB disease compared to non-smokers (Alcaide et al., 1996; Bates et al., 2007; Leung et al., 2004). Moreover, smokers are more likely to die from TB disease than non-smokers (Gajalakshmi et al., 2003; Lin et al., 2007; Slama et al., 2007). Studies also reported that tobacco smoking increases the risk of recurrent TB after treatment completion (Mahishale, Patil, Lolly, Eti, & Khan, 2015; Yen et al., 2014). Previous reports estimated that more than 20% of adult TB cases are attributable to smoking, which is more than HIV (16%) and diabetes (15%) (Lonnroth et al., 2010; Lonnroth, Roglic, & Harries, 2014). However, previous estimates of the proportion of TB cases attributable to smoking were not adjusted for age and sex nor did they include sensitivity analyses to assess the potential bias due to smoking prevalence measurement error. In addition,

previous studies have not estimated the proportion of country specific TB deaths attributable to smoking in high burden countries.

The goal of this study was to estimate the proportion of TB disease incidence due to tobacco smoking in 32 countries with a high burden of TB. Second, among the same countries, we aimed to estimate the proportion of TB deaths due to tobacco use. We estimated the proportions of TB disease and death using standard population attributable fraction calculations.

METHODS

Epidemiological Data Sources and Study Design

We used six population-based cross-sectional data sources to conduct this population attributable fraction study. We obtained TB case notification and TB mortality data from 2015 Global TB Report (WHO, 2015a). Tobacco use data came from the Global Adult Tobacco Survey (WHO, 2014), the WHO Global Report (WHO, 2015b), Tobacco Free Initiative country profiles (WHO), and the Tobacco Atlas (Atlas). We obtained population data from the United States Census Bureau (Census, 2015).

The Global TB Report has been published by WHO annually since 1997 to provide epidemiologic surveillance of the global TB epidemic and includes TB data at regional and country levels (WHO, 2016c). Global

Adult Tobacco Survey is a household survey developed in 2007 as part of the Global Tobacco Surveillance System which collects nationally representative data and includes tobacco use data on persons aged 15 years old and older. To date Global Adult Tobacco Survey includes 25 LMIC where tobacco burden is high (WHO, 2014). The 2015 WHO Global Smoking prevalence report includes estimated age specific current tobacco smoking prevalence based on Bayesian hierarchical meta-regression modelling and projected tobacco smoking prevalence trends in WHO regions (WHO, 2015b). Tobacco Free Initiative established by WHO in 1998 and provide country specific tobacco surveillance data (WHO).

Study Population Selection Criteria

Our study participants included adult male and female individuals aged 15 years and older who lived in the 32 high TB-burden countries. The 30 high TB-burden countries were defined by the 2016 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 estimated incidence rates of TB cases with at least 10,000 new cases per year (WHO, 2014). We added Uganda and Afghanistan which were not among the 30 2016 WHO countries but they were included in 2015 global TB report among the 22 high burden-TB countries (WHO, 2015a, 2016c).

Tuberculosis Incidence and Mortality

To estimate country-specific TB incidence rates, we obtained TB notification data from 2015 global TB report for the 32 highest TB-burden countries (WHO, 2015d). Although TB incidence is not directly measured at the country level, TB case notification rates are directly measured to provide proxy estimates for TB incidence rates which include notified and undiagnosed TB cases (WHO, 2015d). A TB notification indicates that TB is diagnosed in a patient and is reported within the national surveillance system to WHO (WHO, 2013b). The TB notification rate is defined as the number of new and relapse TB cases notified in a given year per 100,000 population (WHO, 2013b). In 2014, 205 countries reported TB incidence data to WHO (WHO, 2015d). We used TB notification rates for our estimates of TB incidence as it includes sex and age specific data. For countries without sex specific data (for example, Mozambique and Papua New Guinea), we used the global male to female TB case notification ratio (1.7) (WHO, 2015d). In 2014, notifications of newly diagnosed TB cases represented 63% (60%-66%) of estimated incident cases in the world (WHO, 2015d).

To determine country-specific rates of TB mortality, we used the reported percentage of patients with TB whose treatment outcome was indicated as TB deaths. A TB death was defined as a TB patient who died from any cause during treatment (WHO, 2015d). We extracted 2013 TB

mortality data from the 2015 global TB report, except for Congo (we used 2011 data) (WHO, 2013a).

Relative Risk for TB disease and TB Mortality Associated with Smoking

We obtained relative risk estimates for the association between smoking and TB incidence, and the association between smoking and TB mortality from previously published studies reported by Bates et al., Slama et al., and Lin et al. in 2007 (Bates et al., 2007; Lin et al., 2007; Slama et al., 2007; van Zyl Smit et al., 2010). The risk of TB disease in smokers versus non-smokers was 2.3 (95% CI 2-2.8) (Bates et al., 2007), 2.3 (95% CI 1.8-3.0) (Slama et al., 2007), and 2.0 (95% CI 1.6-2.6) (Lin et al., 2007). The reported risk ratios for TB mortality, comparing smokers to non-smokers, were 2.1 (95% CI 1.4-3.4) (Bates et al., 2007), 2.2 (95% CI 1.3-3.7) (Slama et al., 2007), and 2.0 (95% CI 1.1-3.5) (Lin et al., 2007). We used a relative risk of 2.3 (95% CI 1.5-2.8) for smoking associated with TB disease as reported in two systematic reviews. For TB mortality, we used a relative risk of 2.0 (95% CI 1.1-3.7) comparing smokers to non-smokers.

Smoking Prevalence

Smoking prevalence data were obtained from four previously mentioned data sources for the 32 countries (Table 1). Age and sex specific smoking prevalence data were extracted from the Global Adult Tobacco Survey for 12 countries (WHO) which was our primary data

source and from 2015 WHO global report on trends in prevalence of tobacco smoking for 14 countries (WHO, 2015b). When country data were not available in the primary data source, we checked the next available data sources as seen in Figure 1. For countries without age stratification data, we used Tobacco Free Initiative country profiles and the Tobacco Atlas to estimate smoking prevalence (Atlas; WHO) .

The smoking prevalence data used for this study was based on the definition of current tobacco use except for Afghanistan, Angola, and Central African Republic. We used current tobacco (smoked and smokeless) prevalence for Kenya and Pakistan since age distribution data were available for both types of tobacco use. For Afghanistan, Angola, and Central African Republic, we used daily tobacco use. Current tobacco use included daily smoking and occasional smoking of any type of smoked and smokeless tobacco product (Bilano et al., 2015; Prignot, Sasco, Poulet, Gupta, & Aditama, 2008). Smoked tobacco included manufactured cigarettes, bidi, hukkah (waterpipes), hand–rolled cigarettes, pipes full of tobacco, cigars, cherrots or, cigarillos, and any other. Others included dhaba (waterpipes made of bamboo) (Bilano et al., 2015).

Population Data

The 2014 age and sex specific population distributions data for 32 highest TB burden countries were extracted from the International Data Base of the United States' Census Bureau (Census, 2015).

Statistical Calculations

We calculated crude estimates of population attributable fractions (PAF) for TB disease incidence and TB mortality for the 32 countries (Figure 2) (Stevenson et al., 2007). Age and sex specific estimates and age-adjusted estimates for TB disease incidence were calculated for the 26 countries where age specific smoking prevalence were available. To calculate TB incidence PAF, we used estimated smoking prevalence, TB incidence (TB notification rate), and relative risk of TB disease comparing smokers to non-smokers. For TB mortality PAF calculation, we used estimated smoking prevalence, TB mortality rate (reported TB death rate), and relative risk of TB mortality associated with smoking.

We used the 95% confidence intervals (CI) of the relative risks from published estimates and 95% CI around smoking prevalence from WHO report to calculate the upper and lower PAF estimates for each country. We estimated the excess number of active TB cases attributable to smoking for each country in each age and sex group by multiplying age-sex specific PAFs by the corresponding country-specific reported TB cases from WHO. The number of TB deaths attributable to smoking were estimated by multiplying the PAF for each country by the number of TB deaths in the corresponding country.

Sensitivity Analysis

We estimated the amount of systematic error due to misclassification of smoking prevalence using the 95% CI around point estimates of smoking prevalence for each country. We recalculated PAF for each country using the smoking prevalence confidence interval range and compared the result with PAF calculation (the association between TB disease and TB death in smokers vs. non-smoker).

RESULTS

In 2014, there were an estimated 3.4 billion people over the age of 15 years in the 32 high burden TB countries. In these high TB burden countries during 2014, over 4.5 million developed TB disease and 163,000 died from TB. The estimated crude prevalence of smoking in the 32 countries was 21.8% (N=731 million) with a higher prevalence among men (39.2%) compared to women (4.1%).

The crude proportion of TB disease incidence attributable to tobacco smoking was 19.9% (894,891 excess cases) and the age-adjusted proportion was 17.7% (759,846 excess cases) (Table 2). The country-specific proportion of TB disease attributable to tobacco smoking ranged from 5.0% (95%CI, 2.1-6.5%) in Ethiopia to 31.7% (95%CI, 16.0-37.8%) in Russia (Table 2). Smoking-attributable TB disease was higher among men (30.5%) than among women (4.7%) (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 0.5% in Nigeria to 22.0% in Russia (Table 3).

Overall, 15.0% (95% CI 1.9%-31.6%) of TB deaths (an estimated 24,773 reported deaths) in adults aged 15 years and 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% to 51.4%) in Russia. Russia (28.1%), Indonesia (25.8%), and Sierra Leone (24.2%) were the top 3 countries with the highest proportion of TB deaths attributable to tobacco smoking (Table 4). Although the proportion of TB cases [14.2% (95% CI, 6.4% -17.7%)] 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 are highest because of its population size.

In sensitivity analysis accounting for smoking prevalence misclassification, we found that with the lowest estimates of smoking prevalence, the proportion of TB disease incidence attributable to smoking was 16.3% and the lowest proportion of TB deaths attributable to smoking was 12.1%. The highest estimated proportion of TB disease incidence and TB deaths attributable to smoking were 23.4% and 18.0%, respectively. (Table 5).

DISCUSSION

Overall, we found that tobacco smoking accounted for an estimated 17.7% of TB disease incidence and 15.0% for TB mortality in 32 high burden TB countries. The proportion of TB disease attributable to smoking was more than six times higher in men compared with women. The larger proportion of TB disease due to smoking in men compared with women demonstrates the disparity of smoking prevalence among men and women. Our results suggest that strong tobacco control policies and programs in LMIC, and specifically within TB control programs, would help reduce the global burden of TB.

Previous studies from individual countries have estimated the proportion of TB incidence attributable to smoking and reported findings consistent with our results. For example, a 2009 study from Taiwan reported that 17% of TB cases were attributable to smoking (Lin et al., 2009). Another study conducted in India reported that 14% of TB cases were attributable to smoking (Kolappan et al., 2007). Our findings suggested that smoking accounted for more TB disease among men than among women across countries, a result consistent with a study from Hong Kong that reported 33% of TB cases attributable to smoking among men and 9% in women (Leung et al., 2004).

In most countries, smoking prevalence among TB patients is higher than the general population. For example, 43% of men with TB disease in

Ethiopia were ever smoker and 56% of TB patients in South Africa were current smokers (Brunet et al., 2011; Ramin et al., 2008). According to our study, tobacco smoking was responsible for nearly 18% of TB disease in 32 high TB burden countries. Our estimate is lower than a 2010 study by Lonnroth et al, which estimated that 21% of TB disease incidence was attributable to smoking among 22 high TB burden countries (Lonnroth et al., 2010). Our study included 10 additional countries than the previous study and we adjusted for age, which may partially explain our lower estimate of the proportion of TB due to smoke. Moreover, the Lonnroth et al study used smoking prevalence data from 2008 and the global prevalence of smoking decreased between 2008 and 2014 when our smoking prevalence estimates were measured. For example, from 2008 to 2014 smoking prevalence in Russia and China reduced by 10% (49.0% to 39.1%) and 6% (34.5% to 28.1%), respectively (Lonnroth et al., 2010).

Although only an ecologic-level hypothesis, it is plausible that the global reduction in smoking prevalence during the past decade also reduced TB incidence rates. For example, the reduction in smoking prevalence in Russia and China correlated with reductions in TB incidence during the past 10 years. The TB incidence rate per 100,000 population per year reduced from 107 to 84 in Russia and from 97 to 68 in China between 2008 and 2014 (WHO, 2011, 2014, 2015d).

Previous studies from individual countries have reported smoking-attributable TB mortality. For example, 25%, 32%, and 35% of TB deaths in men were attributable to smoking in South Korea, India, and Bangladesh, respectively (Alam et al., 2013; Jee et al., 2009; Pednekar & Gupta, 2007). In South Africa, TB mortality attributable to smoking was 20% in both sexes (Sitas et al., 2004), which is modestly higher than our estimate of 16%, likely due higher smoking prevalence estimates used by Sitas et al. A study in China (Jiang et al., 2009) also showed high rate of TB mortality attributable to smoking which is in agreement with our study. Jiang et al estimated that TB deaths in 22.5% of men and in 6.6% of women were attributable to smoking.

Our findings indicated that smoking has an important effect on TB disease incidence and TB mortality. The estimated proportion of TB disease attributable to diabetes and HIV is likely less than the proportion due to smoking. Incorporating all risk factors including smoking in TB prevention program is therefore essential. The considerable impact of smoking on TB epidemics highlight the importance of promoting smoking cessation in people at risk of TB, especially in LMIC where the prevalence of smoking and the burden of TB are highest.

Our study had a number of limitations. First, this study relied on reported TB cases that underestimated the excess number of TB cases and deaths caused by tobacco smoking. Although an estimated 63% of

TB cases were reported to WHO in 2014, only an estimated 50% of TB cases were reported among the 32 high burden countries (WHO, 2015d). However, low report rates did not affect the estimates of population attributable fraction. 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 across countries and it did not provide dose rate and duration of exposure to smoke. Although most countries used WHO guidelines to collect smoking prevalence data, study participants could underreport their tobacco use especially for products other than cigarettes in developing countries. The estimates used for this study were based on the most current and reliable nationally representative data source, a strength to our study. Further, we applied sensitivity analysis for smoking prevalence and adjusted for age to improve estimates.

Conclusion

Smoking plays a substantial role in the global TB pandemic, including increasing the risk of TB disease and TB death in high TB burden countries. Smoking cessation efforts need to be incorporated in TB programs to reduce TB mortality. In addition, strong and coordinated global tobacco control efforts are needed from every country and

especially in high burden countries to avert TB disease and death due to smoking.

Lists of Tables

Table.3.1: Country specific current tobacco smoking prevalence data

Global Adult Tobacco Survey (WHO)	**Global Tobacco Prevalence Report (WHO)**	**Tobacco Free Initiative (WHO)**	**The Tobacco Atlas**
Bangladesh	Cambodia	DR of Korea	Afghanistan [a]
Brazil	Congo	Papua New Guinea	Angola [a]
China	Ethiopia		CAR [a]
India	Lesotho		DR Congo
Indonesia	Liberia		
Kenya [b]	Mozambique		
Nigeria	Myanmar		
Pakistan [b]	Namibia		
Philippines	Serra Leon		
Russia	South Africa		
Thailand	Tanzania		
Vietnam	Uganda		
	Zambia		
	Zimbabwe		

a. Daily tobacco use
b. Smoke and smokeless tobacco use
DR, Democratic Republic, CAR; Central African Republic

Table 2: Estimated proportion of TB disease attributable to tobacco smoking among adults in 32 high burden TB countries

Country	Smoking prevalence [a]	Crude PAF% TB disease [b] (95% CI)		Age adjusted PAF% [c] (95% CI)		Excess number of TB cases [d]
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)	18.3	(9.1-21.9)	32987
Brazil	17.2	18.3	(7.9-23.1)	18.2	(8.0-28.0)	13052
Cambodia	21.2	21.6	(9.6-27.1)	17.9	(8.6-21.8)	5555
CAR	8.6[e]	10.0	(4.1-13.0)			
China	28.1	26.8	(12.3-33.0)	22.2	(11.3-26.4)	181158
Congo	13.9	15.3	(6.5-19.6)	13.8	(6.3-17.2)	522
DRC	6.4	7.7	(3.1-10.1)			
Ethiopia	4.3	5.3	(2.1-7.0)	5.0	(2.1-6,6)	5205
India	14.0	15.4	(6.5-19.7)	14.2	(6.4-17.7)	215352
Indonesia	34.8	31.2	(14.8-37.9)	24.8	(13.2-29.1)	74391
Kenya	11.6	13.1	(5.7-175)	12.1	(5.4-15.2)	9810
Lesotho	22.6	22.7	(10.2-28.3)	18.8	(9.4-22.4)	1567
Liberia	12.1	13.6	(5.7-17.5)	13.3	(5.9-16.8)	221
Mozambique	18.9	19.7	(8.6-24.9)	18.0	(8.2-22.3)	5140
Myanmar	20.0	20.6	(9.1-26.0)	21.1	(9.9-26.0)	21556
Namibia	21.6	21.9	(9.8-27.4)	20.2	(9.2-25.0)	1607
Nigeria	3.9	4.8	(1.9-6.4)	9.9	(4-13.1)	8521
North Korea	20.1	20.7	(9.1-26.0)			
Pakistan	19.1	19.9	(8.7-25.1)	17.3	(8.1-21.3)	48697
PNG	26.3	25.5	(11.6-31.5)			
Philippines	28.3	26.9	(12.4-33.1)	24.0	(11.7-29.1)	11295
Russia	39.1	33.7	(16.4-40.6)	31.8	(16.0-37.8)	31260
Sera Leone	31.9	29.3	(13.8-35.8)	27.0	(13.0-32.7)	1974
South Africa	19.4	20.1	(8.84-25.4)	19.1	(8.7-23.7)	52377
Tanzania	16.3	17.5	(7.5-22.2)	11.6	(5.2-14.5)	6378
Thailand	24.0	23.8	(10.7-29.6)	24.0	(18.6-51.9)	8210
Uganda	10.1	11.6	(4.8-15.0)	10.8	(4.6-13.7)	4400
Vietnam	23.8	23.6	(10.6-29.4)	19.5	(9.8-23.3)	9724
Zambia	14.6	16.0	(6.8-20.4)	14.7	(6.6-18.4)	4926
Zimbabwe	14.6	16.0	(6.8-20.4)	14.5	(6.6-17.0)	3960
Weighted Average	21.8	19.9	(8.9-24.9)	17.7	(8.6-21.9)	759846

a. Current tobacco smoking prevalence1(WHO, 2015b, 2016c)
b. TB disease incidence attributable to smoking calculated based on RR 2.3 (95%CI, 1.5-2.75) (crude) (Bates et al., 2007; van Zyl Smit et al., 2010)
c. TB disease incidence attributable to smoking calculated based on RR 2.3 (95%CI, 1.5-2.75) (age adjusted)
d. Number of excess cases based on age adjusted PAF except some countries with no age specific data
e. Daily smoking prevalence (Atlas)

PAF (Population Attributable Fraction), CAR (Central African Republic), DRC (Democratic Republic of Congo), CI (Confidence interval), PNG (Papua New Guinea)

Table 3: Estimated number and proportion of TB disease attributable to tobacco smoking by sex among adults in 32 high burden TB countries

	Men				Women			
Country	TB cases[a]	PAF% 95%CI[b]		Excess TB cases	TB cases[a]	PAF%[b] 95%CI		Excess TB cases
Afghanistan	6966	22.9	(10.3-28.6)	1598	11890	3.5	(1.4-4.7)	418
Angola	12488	17.8	(7.7-22.6)	2228	8649	2.0	(0.8-2.7)	176
Bangladesh	110196	36.8	(18.3-43.9)	40500	70547	1.9	(0.7-2.6)	1349
Brazil	48489	21.9	(9.7-27.4)	10631	23113	14.6	(6.1-18.6)	3363
Cambodia	16346	34.5	(16.9-41.5)	5647	14663	4.5	(1.8-5.9)	656
CAR	2637	17.1	(7.4-21.8)	452	2042	1.9	(0.7-2.6)	39
China	566364	40.7	(20.9-48.1)	230781	248755	3.0	(1.2-4.0)	7526
Congo	2308	25.5	(11.6-31.5)	588	1465	2.2	(0.8-2.9)	32
DRC	41153	15.6	(6.6-19.9)	6413	30748	1.5	(0.6-2.1)	472
Ethiopia	56799	9.5	(3.9-12.4)	5411	46876	0.6	(0.2-0.9)	303
India	1010620	24.0	(10.8-29.8)	242613	503218	3.6	(1.4-4.8)	18282
Indonesia	177044	46.6	(25.1-54.0)	82419	122592	3.4	(1.3-4.5)	4157
Kenya	49810	19.9	(8.7-25.1)	9908	31036	5.5	(2.2-7.3)	1715
Lesotho	4803	37.5	(18.8-44.7)	1802	3543	0.6	(0.2-0.9)	23
Liberia	1126	23.3	(10.5-29.1)	263	531	3.5	(1.4-4.7)	19
Mozambique	16834	30.0	(14.2-36.6)	5054	11784	7.3	(3.0-9.6)	866
Myanmar	65260	32.9	(15.9-39.8)	21502	36727	9.6	(3.9-12.5)	3538
Namibia	4724	30.2	(14.3-36.8)	1427	3241	12.5	(5.2-16.1)	405
Nigeria	52028	8.7	(3.5-11.3)	4510	33863	0.5	(0.2-0.7)	175
North Korea	55627	36.3	(18.0-43.4)	20212	33374	0.0	0.0	0
Pakistan	141052	29.2	(13.7-35.8)	41256	140120	7.0	(2.8-9.2)	9824
PNG	8799	32.7	(15.7-39.5)	2873	6159	15.7	(6.7-20.6)	966
Philippines	32479	38.3	(19.3-45.5)	12431	14486	10.5	(4.3-13.6)	1517
Russia	69153	43.9	(23.1-51.3)	30360	29280	22.0	(9.8-27.5)	6442
Sera Leone	4635	39.3	(20.0-46.6)	1824	2683	15.8	(6.7-20.1)	423
South Africa	157748	29.4	(13.8-35.9)	46344	116441	9.2	(3.8-12.0)	10720
Tanzania	33213	27.3	(12.6-33.6)	9070	21895	4.7	(1.9-6.2)	1031
Thailand	24613	37.7	(18.9-44.9)	9285	9662	3.3	(1.3-4.4)	316
Uganda	26702	18.6	(8.1-23.5)	4972	14169	3.4	(1.3-4.5)	480
Vietnam	37267	38.1	(19.2-45.3)	14209	12518	1.8	(0.7-2.4)	224
Zambia	20472	24.7	(11.2-30.6)	5052	13024	4.9	(2.0-6.5)	644
Zimbabwe	15723	26.7	(12.3-32.9)	4196	11640	2.5	(1.0-3.4)	295
Weighted Average[c]	2872945	30.5	(14.9-36.9)	876578	1630361	4.7	(1.9-6.2)	76935

a. Number of TB cases reported in 2014 among men and women in each country (WHO, 2015a)
b. Confidence interval calculated based on RR 2.3 (95%CI, 1.5-2.75) (van Zyl Smit et al., 2010)
c. The weighted average calculated based on the number of TB cases
PAF (Population Attributable Fraction), CI (confidence interval), CAR (Central African Republic), DRC (Democratic Republic of Congo), PNG (Papua New Guinea)

Table 4: Estimated proportion and number of TB deaths attributable to tobacco smoking among adults in 32 high burden TB countries

Country	Crude PAF % TB Mortality (95% CI [a])		Number of Deaths attributable to smoking	Number of TB deaths [b]
Afghanistan	11.5	(1.3-26)	22	189
Angola	8.4	(0.9-19.9)	18	211
Bangladesh	18.7	(2.25-38.3)	1352	7230
Brazil	14.7	(1.7-31.7)	841	5728
Cambodia	17.5	(2.1-36.4)	101	620
CAR	7.9	(0.9-18.8)	18	234
China	21.9	(2.73-43.1)	1788	8151
Congo	12.2	(1.4-27.3)	12	75
DRC	6.0	(0.6-14.7)	173	2876
Ethiopia	4.12	(0.43-10.4)	142	3110
India	12.3	(1.4-27.4)	7436	60554
Indonesia	25.8	(3.4-48.4)	1547	5993
Kenya	10.4	(1.2-23.9)	504	4,851
Lesotho	18.4	(2.21-38.0)	237	1168
Liberia	10.8	(1.2-24.6)	8	232
Mozambique	15.9	(1.9-33.8)	549	1717
Myanmar	16.7	(2.0-35.1)	680	4079
Namibia	17.8	(2.1-36.8)	92	478
Nigeria	3.8	(0.4-9.5)	193	5153
North Korea	16.7	(2.0-35.2)	447	2670
Pakistan	16.0	(1.9-34.0)	451	2812
PNG	20.8	(2.6-41.5)	125	598
Philippines	22.1	(2.8-43.3)	207	939
Russia	28.1	(3.8-51.3)	2490	8859
Sera Leone	24.2	(3.1-46.3)	56	220
South Africa	16.3	(1.9-34.4)	3051	19193
Tanzania	14.0	(1.6-30.6)	463	3306
Thailand	19.4	(2.3-39.3)	464	2399
Uganda	9.2	(1.0-21.4)	305	3270
Vietnam	19.2	(2.3-39.1)	287	1494
Zambia	12.7	(1.4-28.3)	230	1675
Zimbabwe	12.7	(1.4-28.3)	388	2736
Weighted Average	15.0	(1.9-31.6)	24773	162785

a. TB death attributable to smoking calculated based on relative risk 2.0 (1.1-3.7) (Lin et al., 2007; Slama et al., 2007
b. Number of reported deaths: multiplying the cohort number of TB cases by the percent of death in each country from WHO report(WHO, 2015d)

PAF (Population Attributable Fraction), CAR (Central African Republic), DRC (Democratic Republic of Congo), CI (Confidence interval), PNG (Papua New Guinea)

Table 5. Sensitivity analysis for proportion of TB disease and deaths attributable to tobacco smoking based on smoking prevalence

Country	Smoking Prevalence (95% CI) [a]		PAF% TB disease (95% CI) [b]		PAF % Tb Mortality (95% CI) [b]	
Afghanistan	13.0	(16.1-14.4)	14.4	(11.3-17.3)	11.5	(8.9-13.9)
Angola	9.2	(5.8-14.1)	10.7	(7.0-15.5)	8.4	(5.5-12.4)
Bangladesh	23.0	(19.4-28.6)	23.0	(20.1-27.1)	18.7	(16.2-22.2)
Brazil	17.2	(14.2-21.4)	18.3	(15.6-21.8)	14.7	(12.4-17.6)
Cambodia	21.2	(16.2-27.3)	21.6	(17.4-26.2)	17.5	(13.9-21.4)
CAR	8.6	(5.1-12.3)	10.0	(6.2-13.8)	7.9	(4.9-11.0)
China	28.1	(22.2-32.8)	26.8	(22.4-29.9)	21.9	(18.2-24.7)
Congo	13.9	(9.9-18.3)	15.3	(11.4-19.2)	12.2	(9.0-15.5)
DRC	6.4	(4.3-9.2)	7.7	(5.3-10.7)	6.0	(4.1-8.4)
Ethiopia	4.3	(3.0-5.6)	5.3	(3.8-6.8)	4.1	(2.9-5.3)
India	14.0	(10.7-16.9)	15.4	(12.2-18.0)	12.3	(9.7-14.5)
Indonesia	34.8	(28.4-42.9)	31.2	(27.0-35.8)	25.8	(22.1-30.0)
Kenya	11.6	(6.9-17.9)	13.1	(8.2-18.9)	10.4	(6.5-15.2)
Lesotho	22.6	(16.6-29.4)	22.7	(17.7-22.7)	18.4	(14.2-22.7)
Liberia	12.1	(6.5-20.8)	13.6	(7.8-21.3)	10.8	(6.1-17.2)
Mozambique	18.9	(12.2-27.7)	19.7	(13.7-26.5)	15.9	(10.9-21.7)
Myanmar	20.0	(16.1-29.6)	20.6	(17.3-27.8)	16.7	(13.9-22.8)
Namibia	21.6	(15.5-28.8)	21.9	(16.8-27.0)	17.8	(13.4-22.2)
Nigeria	3.9	(3.9-3.3)	4.8	(4.1-5.5)	3.8	(3.2-4.3)
North Korea	20.1	(15.1-27.3)	20.7	(16.4-26.2)	16.7	(13.1-21.4)
Pakistan	19.1	(15.7-27.0)	19.9	(17.0-26.0)	16.0	(13.6-21.3)
PNG	26.3	(17.5-37.5)	25.5	(18.5-32.8)	20.8	(14.9-27.3)
Philippines	28.3	(23.2-33.2)	26.9	(23.2-30.1)	22.1	(18.8-24.9)
Russia	39.1	(31.6-46.4)	33.7	(29.1-37.6)	28.1	(24.0-31.7)
Sera Leone	31.9	(22.0-42.3)	29.3	(22.2-35.5)	24.2	(18.0-29.7)
South Africa	19.4	(15.5-24.1)	20.1	(16.8-23.9)	16.3	(13.3-19.4)
Tanzania	16.3	(11.7-21.3)	17.5	(13.2-21.7)	14.0	(10.5-17.6)
Thailand	24.0	(20.2-28.1)	23.8	(20.8-26.8)	19.4	(16.8-21.9)
Uganda	10.1	(7.3-13.6)	11.6	(8.7-15.0)	9.2	(6.8-12.0)
Vietnam	23.8	(19.8-29.2)	23.6	(20.5-27.5)	19.2	(16.5-22.6)
Zambia	14.6	(10.0-19.5)	16.0	(11.5-20.2)	12.7	(9.1-16.3)
Zimbabwe	14.6	(10.8-18.5)	16.0	(12.3-19.4)	12.7	(9.7-15.6)
Weighted Average	21.8	(17.2-26.3)	19.9	(16.3-23.4)	15.0	(12.1-18.0)

a. Point estimate and 95% CI for smoking prevalence from WHO report (WHO, 2015b)
b. 95%CI for PAF calculated based on 95% CI for smoking prevalence
PAF (Population Attributable Fraction), CAR (Central African Republic), DRC (Democratic Republic of Congo), CI (Confidence interval), PNG (Papua New Guinea)

Figure 1: Smoking prevalence data sources in order of priority

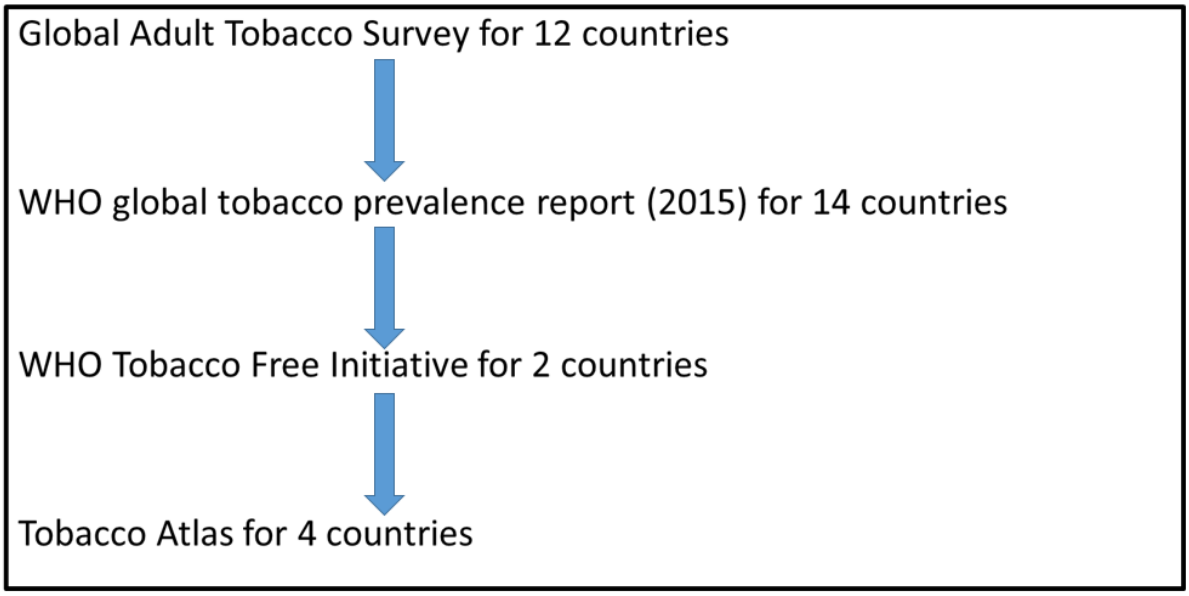

Figure 2: Population Attributable Fraction (PAF): definition and formula

The proportion by which the incidence rate of the outcome of interest (TB disease and TB mortality) in the entire population would have been reduced if the exposure of interest (smoking) were eliminated.

$$PAF = \frac{Pe(RR-1)}{1+Pe(RR-1)}$$

Where Pe = prevalence of exposure (smoking)

RR is the relative risk for the outcome (TB disease and TB mortality)

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APPENDICES

Notified adult tuberculosis (TB) cases, TB deaths, and smoking prevalence in 32 high TB burden countries

Country, Year [a]	Population (2014) [b]	Smoking Prevalence [c]	Number of notified TB cases [d]	Number of TB deaths
Afghanistan, 2013				
Male	9,346,537	22.9	6,966	
Female	9,103,091	2.8	11,890	
Overall	18,449,628	13.0	18,856	189
Angola, 2013				
Male	5,444,937	16.7	12,488	
Female	5,392,622	1.6	8,649	
Overall	10,837,559	9.2	21,137	211
Bangladesh, 2009				
Male	53,537,731	44.7	70,547	
Female	59,005,538	1.5	110,196	
Overall	112,543,269	23	180,743	7,230
Brazil, 2010				
Male	73,337,384	21.6	484,89	
Female	74,633,794	13.1	231,13	
Overall	148,971,178	17.2	71,602	5,728
Cambodia, 2014				
Male	5,031,918	39.1	16,346	
Female	5,542,136	3.4	14,663	
Overall	10,574,054	19.5	31,009	620
CAR, 2013				
Male	1,538,351	15.9	2,637	
Female	1,597,701	1.5	2,042	
Overall	3,136,052	8.6	4,679	234
China, 2010				
Male	574,572,913	52.9	566,364	
Female	553,862,448	2.4	248,755	
Overall	1,128,435,361	28.1	815,119	8,151
Congo, 2013				
Male	1,370,639	35.5	2,308	
Female	1,374,544	1.7	1,465	
Overall	2,745,183	18.5	3,773	75
DRC, 2009				
Male	21,789,564	14.2	41,153	

Female	22,280,946	1.2	30,748	
Overall	44,070,510	6.4	71,901	2,876
Ethiopia, 2013				
Male	26,649,453	8.9	56,799	
Female	27,299,308	0.5	46,876	
Overall	53,948,761	4.7	103,675	3,170
India, 2010				
Male	454,657,918	24.3	1,010,620	
Female	429,621,617	2.9	503,218	
Overall	884,279,535	14	1,513,838	60,554
Indonesia, 2011				
Male	93,002,868	67	177044	
Female	94,103,687	2.7	122592	
Overall	187,106,555	34.8	299636	5,993
Kenya, 2014				
Male	12,955,774	19.1	49,810	
Female	13,123,504	4.5	31,036	
Overall	26,079,278	11.6	80,846	4,851
Lesotho, 2013				
Male	637,600	51.7	4,803	
Female	665,126	0.4	3,543	
Overall	1,302,726	25.4	8,346	1,168
Liberia, 2013				
Male	1,149,168	25.9	1,126	
Female	1,175,485	2.6	531	
Overall	2,324,653	14.2	1,657	66
Mozambique, 2013				
Male	6,416,394	32.7	16,834	
Female	7,082,374	6.1	11,783	
Overall	13,498,768	18.8	28,617	1,717
Myanmar, 2013				
Male	20,208,558	37.8	65,260	
Female	20,829,928	8.2	36,727	
Overall	41,038,486	20	101,987	4,079
Namibia, 2013				
Male	757,230	37	4,724	
Female	743,215	11.7	3,241	
overall	1,500,445	23.8	7,965	478
Nigeria, 2012				
Male	51,199,237	7.3	52,028	
Female	49,451,476	0.4	33,863	
Overall	100,650,713	3.9	85,891	5,153
North Korea, 2014				

Male	8,957,144	43.9	55,627	
Female	9,790,762	0	33,374	
Overall	18,747,906	20.1	89,001	2,670
Pakistan, 2014				
Male	67,153,607	31.8	141,052	
Female	63,627,058	5.8	140,120	
Overall	130,780,665	19.1	281,172	2,812
PNG, 2014				
Male	2,186,176	37.3	8,799	
Female	2,075,539	14.5	6,159	
Overall	4,261,715	26.3	14,958	598
Philippines, 2010				
Male	32,498,235	47.7	32,479	
Female	32,774,610	9	14,486	
Overall	65,272,845	28.3	46,965	939
Russia, 2009				
Male	53,950,453	60.2	69,153	
Female	65,194,863	21.7	29,280	
Overall	119,145,316	39.1	98,433	8,859
Sera Leone, 2013				
Male	1,590,157	56.4	4,635	
Female	1,746,240	12.9	2,683	
Overall	3,336,397	34.4	7,318	220
South Africa, 2013				
Male	18,630,731	31.9	157,748	
Female	1,924,5128	7	116,441	
Overall	3,7875,859	18.9	274,189	19,193
Tanzania, 2014				
Male	13,553,042	28.8	33,213	
Female	13,950,255	3.9	21,895	
Overall	27,503,297	16.3	55,108	3,306
Thailand, 2011				
Male	27,179,252	46.6	24,613	
Female	28,616,175	2.6	9,662	
Overall	55,795,427	24	34,275	2,399
Uganda, 2013				
Male	9,127,278	17.5	26,702	
Female	9,311,383	3.1	14,169	
Overall	18,438,661	10.3	40,871	3,270
Vietnam, 2010				
Male	34,766,213	47.4	37,267	
Female	35,908,364	1.4	12,518	
Overall	70,674,577	23.8	49,785	1,494
Zambia, 2013				

Male	3,921,346	27.1	20472	
Female	3,960,921	4.7	13024	
Overall	7,882,267	15.9	33496	1675
Zimbabwe, 2015		16.50		
Male	4,200,258	31.2	15,723	
Female	4,285,381	2.1	11,640	
Overall	8,485,639	16.5	27,363	2,736
Total	3,359,683,285	21.7	4,504,212	162,821

a. Smoking prevalence data year
b. Population age 15 years and up (Census, 2015)
c. Prevalence of current tobacco smoking (Atlas; WHO, October 2015)
d. New and relapse pulmonary TB (bacteriologically confirmed and clinically diagnosed) and Extra-pulmonary TB cases reported to WHO.(WHO, 2015d)
PAF (Population Attributable Fraction), CAR (Central African Republic), DRC (democratic Republic of Congo), PNG (Papua New Guinea)

Estimated proportion of active TB attributable to smoking with age distribution for some countries.

Countries with age and sex	Smoking Prevalence [a]	Active TB PAF (%) (95% CI) [b]		Excess number of TB cases
Brazil				
Men age in year				
15-24	14.8	16.1	(6.9-20.6)	1,234
25-44	22.5	22.6	(10.1-28.3)	4,773
45-64	28.1	26.8	(12.3-33.0)	3,943
>65	17.3	18.4	(8.0-23.2)	537
Women age in year				
15-24	6.4	7.7	(3.1-10.1)	343
25-44	14.5	15.9	(6.8-20.2)	1,529
45-64	17.9	18.9	(8.2-23.9)	1,144
>65	9.3	10.8	(4.4-14.0)	163
Over all(crude)		18.3	(7.9-23.1)	13,085
Age Adjusted		18.2	(7.9-22.9)	13,666
China				
Men age in year				
15-24	33.6	30.4	(14.4-37.0)	24,719
25-44	59.3	43.5	(22.9-50.9)	64,513
45-64	63	45.0	(24.0-52.4)	93,386
>65	40.2	34.3	(16.7-41.3)	43,864
Women age in year				
15-24	0.7	0.9	(0.4-1.2)	407
25-44	1.6	2.0	(0.8-2.7)	1,575
45-64	3.2	4.0	(1.6-5.3)	3,043
>65	6.7	8.0	(3.2-10.5)	3,983
Over all(crude)		26.8	(12.3-33.0)	218,093
Age Adjusted		22.2	(11.3-26.4)	235,490
India				
Men age in year				
15-24	9.7	11.2	(4.6-14.5)	19,007
25-44	27.0	26.0	(11.9-32.1)	98,604
45-64	37.4	32.7	(15.8-39.6)	106,147
>65	31.0	28.7	(13.4-35.2)	29,904
Women age in year				18,282
15-24	0.3	0.4	(0.1-0.5)	536
25-44	2.1	2.7	(1.0-3.5)	5,505
45-64	5.7	6.9	(2.8-9.1)	7,340
>65	9.9	11.4	(4.7-14.8)	3,492

Over all(crude)		15.4	(6.5-19.7)	233,095
Age adjusted		14.2	(6.4-17.7)	270,534
Indonesia				
Men age in year				
15-24	51.7	40.2	(20.5-47.5)	10,822
25-44	73.3	48.8	(26.8-56.2)	34,305
45-64	72.4	48.5	(26.6-55.9)	30,246
>65	61.2	44.3	(23.4-51.7)	9,413
Women age in year				
15-24	0.1	0.1	(0.0-0.2)	33
25-44	1.7	2.2	(0.8-2.9)	1,059
45-64	5.8	7.0	(2.8-9.2)	2,872
>65	6.7	8.0	(3.2-10.5)	850
Over all(crude)		31.1	(14.8-37.8)	93,332
Age adjusted		24.8	(13.1-29.1)	89,599
Kenya				
Men age in year				
15-24	4.9	6.0	(2.4-7.9)	490
25-44	23	23.0	(10.3-28.7)	6775
45-64	36.2	32.0	(15.3-38.8)	3370
>65	30.9	28.7	(13.4-35.1)	759
Women age in year				
15-24	0.7	0.9	(0.3-1.2)	60
25-44	2.7	3.4	(1.3-4.5)	594
45-64	10.9	12.4	(5.2-16.0)	685
>65	21.7	22.0	(9.8-27.5)	388
Over all(crude)		13.1	(5.5-16.9)	10,594
Adjusted		12.1	(5.4-15.2)	13,121
Russia				
Men age in year				
15-24	46.1	37.5	(18.7-44.7)	1,731

25-44	68.3	47.0	(25.5-54.4)	18,326
45-64	62.4	44.8	(23.8-52.2)	10,044
>65	40.3	34.4	(16.8-41.4)	1,074
Women age in year				
15-24	55.7	42.0	(21.8-49.4)	1,414
25-44	31.3	28.9	(13.5-35.4)	4,636
45-64	18.2	19.1	(8.3-24.2)	1,311
>65	2.9	3.6	(1.4-4.8)	105
Over all(crude)		33.7	(16.4-40.6)	33,172
Adjusted		31.8	(16.0-37.8)	38,640

a. Current tobacco smoking prevalence(WHO, October 2015)
b. TB disease incidence attributable to smoking by age group