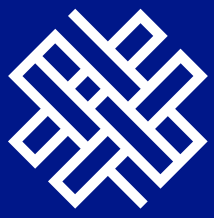
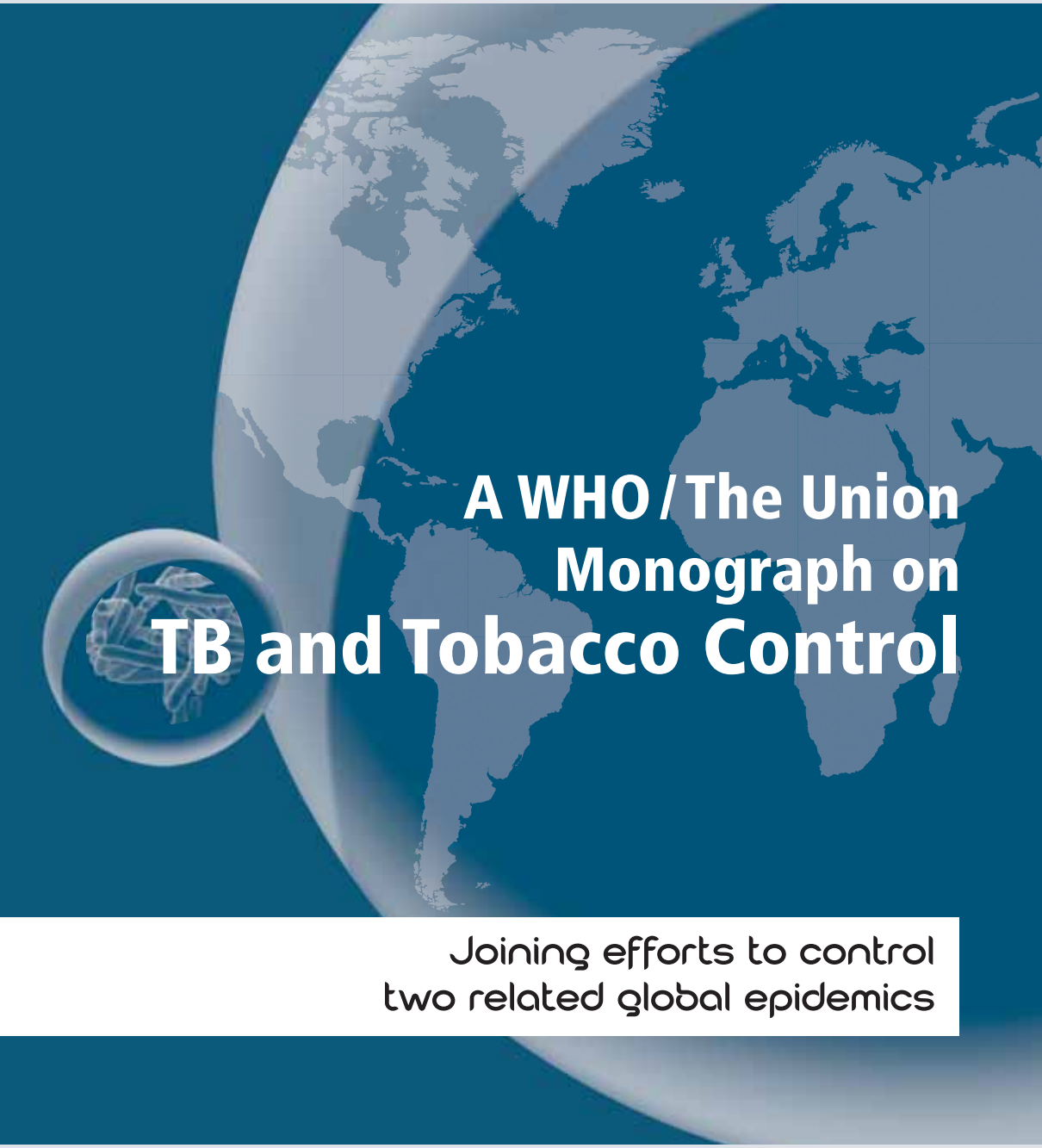


Vital Strategies

This material was produced by The International Union Against Tuberculosis and Lung Disease and is now supported by the Tobacco Control Division of Vital Strategies.

Find it at VitalStrategies.org/tobaccocontrol



A WHO / The Union Monograph on TB and Tobacco Control

Joining efforts to control two related global epidemics

World Health Organization

International Union Against Tuberculosis and Lung Disease

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A WHO/The Union
MONOGRAPH ON
TB AND TOBACCO CONTROL

Joining efforts to control two related global epidemics

World Health Organization

International Union Against Tuberculosis and Lung Disease

EXECUTIVE SUMMARY
TB AND TOBACCO

An association confirmed

Associations between tobacco use and tuberculosis (TB) outcomes have long been suspected but until recently the predominant view was that existing studies were not adequate to provide confirmation of any link. However, more recent studies and some recent reviews of existing studies have seemed to provide a better-evidenced link between active and passive tobacco smoking and a range of TB outcomes including infection, response to treatment, relapse rates and mortality.

The WHO Framework Convention on Tobacco Control (WHO-FCTC), the first international drug control treaty to consider demand on an equal footing to supply and one of the most rapidly embraced of all UN treaties, came into force in February 2005. International programmes to respond to the global TB epidemic have been evolving for many years, receiving much needed boosts from the Millennium Development Goal (MDG) of halving TB prevalence and mortality by 2015 and the establishment of the Global Fund Against Aids, Tuberculosis and Malaria (GFATM).

In 2004, WHO Tobacco Free Initiative (TFI), the WHO Stop TB! Department (STB) and the International Union Against Tuberculosis and Lung Diseases (The Union) responded to the mounting evidence of links between tobacco use and TB by collaborating to examine whether "the integration of tobacco control and respiratory care services in Primary Health Care (PHC) settings can reduce smoking and the occurrence of TB among respiratory patients". The first commitment under the collaboration was to see whether any causal associations between tobacco use and TB outcomes could be confirmed or quantified through a systematic review of the literature.

All relevant studies up to July 2005 that met a high standard of inclusion criteria were considered; following the review stages, 50 studies were reviewed in detail and scored for the strength of evidence. The review concluded that:

> "This review indicates that passive or active exposure to tobacco smoke is significantly associated with **tuberculous infection** and **tuberculosis disease**. Active smoking is significantly associated with **recurrent tuberculosis** and tuberculosis **mortality**. These effects appear to be independent of the effects of alcohol use, socioeconomic status and a large number of other potential confounders."

Joining efforts to control two global epidemics

Considerable increases in effect and efficiency had previously been found when the demonstrated associations between HIV/AIDS and TB had become the basis of joint prevention and regimes. The second phase of the WHO/The Union collaboration on tobacco and TB was to prepare a policy paper to provide guidance to managers of national TB and Tobacco control programmes to plan and implement joint tobacco control activities through the health care system within the framework of existing and evolving TB strategies. In the most developed of TB strategies currently in use, Practical Approach to Lung Health (PAL), the focus is on integrated treatment of all respiratory conditions and diseases in PHC settings.

Key elements of the policy are that the smokers among those presenting or being assessed at PHCs for TB or other respiratory diseases or conditions should be identified and offered counselling and other smoking cessation treatments. PHC facilities should operate as smoke-free environments and health staff and managers needed to be trained and supported in delivering smoking cessation treatments. The report suggests key indicators to be used in monitoring and evaluating the joint programmes. It concludes that:

> "Since there is a relation between the tobacco and the TB epidemic, the National TB programme (NTP) and the National Tobacco Control Programme have mutual concerns. Opportunities must be created within the health care system to provide every TB patient who is a smoker encouragement and help to overcome the tobacco addiction. In addition every TB patient who is not a smoker must be made aware of the consequences of being exposed to secondhand smoke. Both Programmes have a duty to support the health delivery services to fulfil the responsibility in providing such assistance in the period during which the patient is treated with anti-TB chemotherapy. Through the identification and treatment of tobacco addiction among TB patients, higher levels of lasting treatment success will be achieved. NTP should also support tobacco control beyond the clinical interventions."
>
> "In turn, any progress achieved by the National Tobacco Control Programme in implementing effective population-based policies will reduce the prevalence of smokers in the population and will have an impact on TB infection, morbidity and mortality rates."
>
> "The National Tobacco Control Programme should also contribute to improving the NTP performance stressing TB-related issues in the information and advocacy campaigns about the health dangers of tobacco use and exposure to tobacco smoke, especially in countries where pulmonary TB is highly prevalent and people have a clear perception of this disease threat."

A successful trialling of tobacco cessation treatments in conjunction with TB and respiratory health programmes will provide a basis for extending them to other health programmes where tobacco use contributes to or exacerbates the disease or condition under treatment. If identification and treatment of tobacco addiction becomes routine in programmes dealing with Maternal Health, Cardiovascular Diseases, Cancer and Diabetes it will be a significant step to such assistance being provided for any person attending a health unit for curative or preventive care.

CONTENTS

ABBREVIATIONS AND ACRONYMS

BCG	A vaccine named for ingredient bacillus Calmette-Guerin
BMI	Body mass index
CDC	Centre for Disease Control
CHD	Coronary heart disease
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
DOTS	Internationally recommended strategy for TB control prior to the introduction of the new Stop TB Strategy in 2006
GYTS	Global Youth Tobacco Survey
HIV	Human immunodeficiency viru
IARC	International Agency for Research on Cancer
The Union	International Union against Tuberculosis and Lung Diseases (Union, see below)
IVDU	Intravenous drug user
MDG	Millennium Development Goal
MOH	Ministry of health
NTP	National TB programme
OR	Odds ratio
PAL	Practical Approach to Lung health
PHC	Primary health care
PTB	Pulmonary tuberculosis
RR	Risk ratio
SES	Socioeconomic status
SHS	Secondhand smoke
STB	Stop TB!
TB	Tuberculosis
TFI	Tobacco Free Initiative (also WHO TFI)
Union	International Union against Tuberculosis and Lung Diseases
WHO	World Health Organization
WHO FCTC	WHO Framework Convention on Tobacco Control

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The preparation of this document was coordinated by Douglas Bettcher, Léopold Blanc, Annemieke Brands, Dongbo Fu, Armando Peruga, Salah-Eddine Ottmani and Karen Slama.

The section on the systematic literature review (Part I) was based on reviews and data extraction provided by Chen-Yuan Chiang, Donald A. Enarson, Anne Fanning, Prakash C. Gupta, Cecily S. Ray and Karen Slama. The text was written by Karen Slama.

The section on the joint efforts to control TB and tobacco (Part II) was prepared and written by Antonio Pio with the contribution of Salah-Eddine Ottmani and Armando Peruga.

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PREFACE

Tuberculosis and Tobacco: Joining efforts now

Past global efforts in TB control have focused on three technical interventions: case management, chemoprophylaxis of selected groups and BCG vaccination of the newborn. The pre-eminent priority has been and remains assigned to case management that comprises early detection, diagnosis and treatment of TB cases, and systematic monitoring of outcomes. Case management of infectious cases, as defined in the so-called DOTS strategy, has been shown to be the most effective intervention to reduce the TB problem in any socioeconomic setting. However, despite an impressive progress in the implementation of the DOTS strategy, a thorough analysis of the epidemiological trends pointed out that the 2015 TB-related Millennium Development Goals were unlikely to be reached in all the WHO regions unless a broader strategic approach were envisaged. Thus, in 2006, WHO and the international partners met the challenge by developing a new Stop TB strategy enhancing the DOTS reach.

The new Stop TB strategy recognizes that prevention of the most frequent risk factors is an important contributor to the sustainability of case management interventions for TB control. Although the national TB programmes (NTP) have no direct responsibility for the control and eventual elimination of the main risk factors for TB, it should play an important role in advocacy and support for all the relevant programmes and initiatives, and take an active part in any joint activities.

Available evidence shows that poverty, HIV infection and tobacco smoking are the main determinants for TB. As shown in this monograph, recent research has demonstrated that tobacco smoking is one of the most important risk factors that favours the progression from latent TB infection to pulmonary disease, increases the probabilities of relapse after TB treatment, and increases TB case fatality. Any reduction in the prevalence of tobacco smoking should be expected to bring about collateral benefits in the control of the TB problem. This document provides information on the relationship between the TB and tobacco global epidemics, and points out the need to join efforts between TB and tobacco national control programmes. The growing evidence of a possible causal association between active or passive exposure to tobacco smoke and various outcomes of tuberculosis should be reason enough to join forces in tackling both the tuberculosis and the tobacco epidemic.

There are some parallels between the tuberculosis and tobacco epidemic in terms of support by governments and donor agencies. For several decades tuberculosis had been a neglected disease affecting the poorest of the poor and support to develop and improve tuberculosis control in low income countries had only been given by a few donor agencies. Despite the fact that the WHO FCTC has became one of the most successful treaties in United Nations history, enforcement of sound tobacco control strategies is still weak in most low income countries. It is to be hoped that governments and donor agencies understand that if we wait to support and implement effective tobacco control strategies, millions of people, mainly in developing income countries, will suffer and die unnecessarily in the 21st century.

A lot has been learnt in tobacco control about the individual and social forces that can hook people to certain behaviours and lead them to believe change is impossible. Political commitment to reduce the burden of tobacco use will be a key factor as it is for tuberculosis, not least in legislative actions to increase taxes on tobacco products, institute advertising bans and mandate smoke free environments. The health care system, both public and private sector, will also play an important role in reducing tobacco use, as it does in the Stop TB campaign.

This monograph provides guidelines to managers of these two programmes on the implementation of tobacco control activities as an integral part of TB case management interventions at primary health care facilities. Further, it outlines the managerial support required in successfully adding tobacco control interventions to TB Programme activities and their proposed further extension to respiratory patients generally.

Tobacco control is needed if we want healthy populations in low income countries. The entire community is the optimal target and population health is a strong argument for government action. In light of the associations between tobacco smoking and tuberculosis, tobacco control is urgent in areas of high endemic tuberculosis infection, and access to patients in the health system offers crucial opportunities to treat tobacco use in ways that have been proved effective. Repeated brief tobacco cessation advice offered at a time when individuals are attentive to changes in their behavior to give them better health can be a potent ally for both tuberculosis treatment success and better future health for the treated patients. Health care personnel have a responsibility to contribute to tobacco control every day and not only by providing advice to patients. As non-smokers they can be a good example for their patients and for the society as a whole. They can also use their contacts and their influence to support effective legislation by advocating for sound tobacco control measures.

A world with less poverty, less HIV infection and less tobacco smoking is a world with less tuberculosis.

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Dr Nils E. Billo
Executive Director
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Dr Douglas Bettcher
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Tobacco Free Initiative
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INTRODUCTION

In HIV/AIDS and TB the world has faced two global epidemics that are significantly interlinked. The impact of the HIV epidemic in fuelling the TB epidemic in populations where there has been an overlap between those infected with HIV and those infected with Mycobacterium tuberculosis is well recognized. Identification of the HIV/AIDS and TB link raised the possibility of joint prevention and treatment regimes within the global effort to control these epidemics.

A third epidemic, tobacco use, has long been under suspicion for associations with the TB epidemic, a suspicion now fully documented in this monograph. However, the links between the global tobacco and TB epidemics have not been recognized by public health managers until very recently (1). Tobacco smoking has rarely been mentioned among the challenges identified in the documents on policies for TB control. The adverse association is also overlooked by clinicians treating tuberculosis (2).

To reverse this situation, WHO Tobacco Free Initiative (TFI) and WHO Stop TB! (STB), in collaboration with the International Union Against Tuberculosis and Lung Diseases (The Union), resolved to integrate tuberculosis (TB) and tobacco control activities within district-level health systems in 2004. Factors behind this decision included:

- The conclusion that exposure to tobacco smoke, either active or passive, can have an important impact on many aspects of tuberculosis; and that tobacco control efforts need to be fully implemented in areas where the population is at high risk of TB.
- a requirement to target risk groups such as smokers and risk factors such as tobacco use under the Stop TB Strategy designated to meet the Millennium Development Goal of halving TB prevalence and mortality from TB by 2015;
- a view that tobacco control efforts were more likely to be strengthened when incorporated into existing national, state and district level health structures and linked with existing positions and accountability processes; and
- the need to involve the governmental health sector to increase awareness among health personnel and contribute to the development of sustainable tobacco control programs at the country level.

The overall objective of the integration of TB and tobacco control efforts is to enhance their effectiveness by focusing on risk factors for TB, while enlarging the reach of tobacco control in general, and increasing intervention opportunities in existing health services as a way of reaching a large number of smokers.

This monograph first presents the magnitude and impact of the TB and tobacco global epidemics. This will familiarize unaware policy-makers, health system managers and health personnel with the severity of both epidemics and hopefully will create a sense of urgency to act and integrate TB and tobacco control efforts.

A systematic literature review on the association between tobacco and TB (qualitative and quantitative) is then introduced. It examines the associations between active and passive tobacco use and various TB outcomes including occurrence of the disease, risks of infection, mortality, treatment outcomes and relapse after treatment. The conclusions of the review lay the scientific foundations for joint action in TB and tobacco control

Finally, the basis for integrating TB and tobacco control measures in primary health care settings are proposed, particularly in developing countries. The integration policy is structured around the premise that as associations between TB and tobacco use have now been observed, TB patients who are smokers should be specifically identified and offered advice and other assistance on quitting.

The release of this monograph is expected to raise awareness on the relation between tobacco and TB occurrence in populations, help implement the integration of TB and tobacco control efforts and stimulate the development of other intervention models to integrate tobacco control measures within the health systems. Actions described in this document to integrate tobacco and TB control need to be tested in pilot sites, particularly in countries with ongoing PAL activities; this will help to broaden the scope of interventions to all respiratory conditions, including TB, within PHC settings. Lessons learnt from site-piloting will help to improve the definition and the formulation of the integration policy, develop large scale country experiences and promote field research on the integration of tobacco control within Stop TB Strategy and beyond. Furthermore, field experiences in the integration of tobacco and TB control need to be monitored, evaluated and reported in order to advocate the development and implementation of tobacco control approaches within the health systems.

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KEY EPIDEMIOLOGICAL ASPECTS OF TWO GLOBAL EPIDEMICS

1. THE TB EPIDEMIC

In 2005, the global incidence of TB was estimated at 8.8 million cases (136 per 100,000), of which 3.9 million (60 per 100 000) were pulmonary cases confirmed by direct sputum microscopy(1). Asia and sub-Saharan Africa contributed 84% of the estimated number of TB cases. The TB epidemic in sub-Saharan Africa is fuelled by HIV/AIDS epidemic. The global annual TB incidence rate was increasing at 1.5% in the mid 1990s but decreased and reached a 1.0% increase rate in 2003 and 2004, likely due to the slowing down of the HIV epidemics in sub-Sahara Africa. In 2005, the global TB incidence rate became stable or in decline in all six WHO regions. However, the total number of new TB cases is still rising slowly. It is estimated that the global incidence rate will be about 150 per 100,000 in 2015, generating more than 10 million new cases(2).

The prevalence of TB morbidity was estimated in 14.1 million cases (217 per 100,000). An estimated 1.6 million people (24 per 100 000) died from TB in 2005. Although the global annual incidence rate was increasing over previous years, the prevalence and mortality rates decreased over the period 1990-2005 in the WHO Regions of the Americas, Eastern Mediterranean, South-East Asia and Western Pacific, but increased over the same period in Europe and particularly in sub-Saharan Africa.

Several regions of the world are experiencing severe epidemics of multi-drug resistant TB (MDR-TB). There are approximately 420,000 MDR-TB cases a year, including new and previously treated cases. The highest prevalence of MDR-TB has been observed in Eastern Europe and some provinces of China.

2. THE TOBACCO EPIDEMIC

Worldwide, approximately 1.3 billion people currently smoke cigarettes or use other tobacco products, with more than 900 million tobacco users living in developing countries. The total global prevalence in smoking is 29% (47.5% of men and 10.3% of women over 15 years of age smoke)(3).

Tobacco is the second major cause of death in the world. Cigarettes kill half of all lifetime users and half of those die in middle age (35-69 years). It is currently responsible for the death of one in ten adults worldwide. Every 6.5 seconds one tobacco user dies from a tobacco-related disease somewhere in the world(3).

The death toll from tobacco consumption is now 4.9 million people a year; if action is not taken to curb the spread of tobacco use, annual deaths are expected to reach 8.3 million by 2030, of which more than 80% will be in developing countries(4).

An estimation of global tobacco deaths calculated in 2000 shows that tobacco-related diseases killed about 100 million persons in the 20th century. If current trends persist, tobacco would kill 150 million persons in the first quarter of the 21st century and 300 million persons in the second quarter.

Despite the current knowledge of the harm caused by tobacco, consumption continues to increase and the focus of the tobacco epidemic is shifting from industrialized to developing countries. The key reason for increased consumption and the shifting pattern of consumption are the marketing strategies of the tobacco industry. As some tobacco markets decline in response to effective policies, the tobacco industry has been developing new markets among young people and men and women in developing countries.

The costs of tobacco go far beyond the tragic health consequences. Tobacco is also a significant economic burden on families and societies and is a major threat to sustainable and equitable development. Tobacco contributes to the continuing poverty of low-income households and countries because money is spent on tobacco rather than on food, education and health care.

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ASSOCIATION BETWEEN EXPOSURE TO TOBACCO SMOKE AND TUBERCULOSIS: A QUALITATIVE SYSTEMATIC REVIEW

1. INTRODUCTION

High prevalence of tobacco use has been noted in studies looking at risk factors for tuberculosis (TB) since 1918 (1). The association between TB and tobacco use has, however, been widely considered up to the present day by tuberculosis experts to perhaps be a chance association (2,3). Reluctance to attribute causality to tobacco exposure is based on methodological issues. For example, lack of adjustment for important confounders such as alcohol or socioeconomic status (SES) or misclassification of patients due to poor standards for establishing tuberculosis outcomes have fuelled the debate. Tobacco control experts are concerned by the poor quality or absence of assessment of tobacco exposure in investigation of risk factors for tuberculosis outcomes. Nonetheless, particularly over the past decade, many studies have found exposure to tobacco smoke to be a significant risk factor for tuberculosis outcomes after adjustment for other risk factors. Therefore, a systematic review was undertaken to weigh the strength and quality of the evidence of a causal association between exposure to tobacco smoke and various manifestations and outcomes of tuberculosis.

2. METHODOLOGY FOR THE SYSTEMATIC REVIEW

2.1. Selection of articles

Our research strategy aimed to review all English language journal articles on tobacco exposure and tuberculosis that met inclusion criteria. To identify relevant articles, two researchers independently examined titles of published articles in PubMed for all years up to July 2005, using the keywords "tuberculosis" and "smoking", "tuberculosis" and "tobacco", "tuberculosis" and "cigarettes". A database of over 14,000 articles about tuberculosis that has been developed for staff of the International Union Against Tuberculosis and Lung Disease (The Union), was then searched using the keywords "smoking", "risk factors", "predictors", "case management", "death", "defaulters" "definitions", "delay" and "indicators". Articles' reference lists were examined for other titles, and Google Scholar was then consulted under the terms "tuberculosis and smoking"; interesting titles were searched in the other databases and entered in the register of articles, or, if necessary, hand entered. Identified references were then more fully examined if the title or abstract indicated possible relevance, and full texts were collected for screening to be included according to inclusion criteria (given below). Each article initially chosen as acceptable for inclusion was reviewed for data extraction by three different reviewers.

2.2. Inclusion criteria

Published journal articles available in English of cohort, case-control or cross-sectional studies that included effect estimates of exposure to tobacco smoke in relation to tuberculosis outcomes: infection, tuberculosis disease, recurrent tuberculosis, treatment outcome indicators (patient delay, default, slower smear conversion, severity of disease, drug-resistant TB), tuberculosis death during or after treatment, and tuberculosis mortality were examined for inclusion. All selected articles were required to provide information on the country of study, sample size, population source, age and sex. Many studies were eliminated because results were only presented in terms of statistical significance, without an effect size calculation (odds, risk or hazard ratios). This means that many of the early studies investigating the relationship between tobacco and tuberculosis were excluded; however, several are discussed in the body of the text.

2.3. Definitions

Tobacco exposure: Tobacco smoke exposure was measured according to one or more of the following: type of exposure (active and/or passive), current and past exposure, duration and frequency of exposure and age at initial exposure. The best measures for determining reported tobacco use were defined as biochemical validation of self-report for active smoking: expired CO > 8ppm or cotinine unless nicotine replacement medication is used, and cotinine for passive exposure. Self- or family- reported exposure was considered an acceptable measure. A failure to provide an explanation of how exposure to tobacco was determined was considered unacceptable.

Outcome measures: Tuberculin skin test reaction at a specified cut-off of induration size was considered an acceptable or best measure for ***tuberculous infection***. Sputum smear positive for acid-fast bacilli and/or a culture positive for *M. tuberculosis* was considered the best measure for ***tuberculosis disease***. An acceptable measure included clinical, radiological or histological diagnosis in addition to appropriate response to anti-tuberculosis treatment. ***Recurrent tuberculosis*** was defined as recurrent active tuberculosis in a patient who was previously demonstrated to be cured of the disease. An acceptable measure of ***tuberculosis death*** during or after treatment was defined as dying with verified tuberculosis as defined above. There were few studies specifically investigating the association between tobacco smoke exposure and the transition from tuberculous infection to disease, for which the association was measured in those already infected. The association between tobacco smoke exposure and tuberculosis disease was investigated by analysing tobacco smoke exposure as a risk factor for disease without differentiating those with tuberculous infection and those without.

For ***mortality*** studies, death certificate notification, medical records or family interviews were considered acceptable sources of information, although there was disagreement among reviewers of the quality of information about tuberculosis as the cause of mortality. Mortality was not considered a 'best measure' for tuberculosis. There has been clear evidence of substantial error in routine reports of Vital Statistics Registers concerning mortality designated as being due to tuberculosis. A study from Norway (4) that reviewed and compared information from Vital Statistics and the National Disease Register demonstrated that substantial proportions (28%) of entries were not considered, on detailed review, to have active tuberculosis. Moreover, an additional substantial proportion (31%) were identified in other sources but not identified as such in the Vital Statistics Registry. Virtually the same rates of error were found (but not published) in two similar studies from Canada (5,6). Such errors have also been noted in routine (unpublished) evaluations from Uruguay and China, Province of Taiwan (personal communications). Consequently, although considered 'acceptable', these types of data are not considered 'reference standards'.

Studies were considered to demonstrate dose-effect if statistical significance was indicated for dose-effect in the study data presented. Results were considered coherent if they indicated statistically significant effect ratios for most measures of current active or passive exposure to tobacco smoke. Partial effect indicates the presence of a significant effect for a small number of the tobacco smoke exposure measures; a non-coherent effect was one that was not easily understood in the light of insignificant effects in other smoking exposure measures, or demonstrated an association in the univariate analysis but not in the multivariate analysis.

2.4. Procedures

Experts in tuberculosis control and tobacco control were invited to participate in this review as members of the steering committee[1] to oversee the protocol and the final report, with a sub-group to be involved in reviewing articles and in writing this report. The procedure for review and quality assessment and the data extraction form were approved by the steering committee prior to commencing the protocol. Article search and selection were undertaken independently by two team members (KS, BC).

Each article received three reviews. Experts did not consult with one another and reviewed articles independently, using the standard format provided. A few items were resubmitted to reviewers because no majority was reached, and then, in all cases, a majority or unanimous assessment was obtained.

In addition to information about inclusion criteria, reviewers noted all other risk factors and covariables that were measured for each study, and indicated unadjusted and adjusted results, including dose-effect. According to criteria established by the steering committee, each article was rated for quality on 25 items assessing elimination of bias in the study population, measurement of active and passive exposure to tobacco, measurement of the tuberculosis outcome, adequacy of the study design to establish a relationship between tobacco exposure and a tuberculosis outcome, adequacy of the analysis and the presentation of data for readers to draw conclusions. All items were judged either to be present, or if they were unreported or badly reported, to be absent. If the reviewer was unsure, he or she was to mark absent. Only items that clearly could not be provided were considered not applicable for assessment. Quality scores were determined by the proportion of items that were present from all those applicable. The articles whose scores were above the mean of scores were considered to be high quality.

Strength of evidence for each tuberculosis outcome was determined according to the following criteria:

- Strong evidence: generally consistent findings in at least two high-quality cohort and multiple case-control studies.
- Moderate evidence: generally consistent findings in one high-quality cohort and two high-quality case control studies or three or more high-quality case control studies.
- Limited evidence: generally consistent findings in a single cohort study or two case-control studies or multiple cross-sectional studies.
- Not enough evidence: the above conditions are not met
- Conflicting evidence: less than 75% of the studies report consistent findings.

1 N. Ait-Khaled (The Union), M Aiub Hijjar (CRHF, Ministry of Health, Brazil), C. Audera Lopez (WHO), E. Bateman (University of Cape Town), G. Battista Migliori (Fondazione S. Maugeri, Tradate, Italy), J. Becerra (CDC), D. Bettcher (WHO), N. Billo (The Union), L. Blanc (WHO), B. Callarman (The Union), C-Y. Chiang (The Union), V.L. da Costa e Silva (WHO), A.L. Davidow (New Jersey Medical School), P.D.O. Davies (Cardiothoracic Centre, Liverpool), D.A. Enarson (The Union), A. Fanning (University of Alberta), P. Gupta (Healis Institute, India), P. Hopewell (University of California, San Francisco), P. Jha (University of Toronto), A. Khalakdina (SEARO), D. Maher (WHO), S. Ottmani (WHO), M. Pai (University of California, Berkeley), C. Ray (Healis Institute, India), B. Rowe (University of Alberta), K. Slama (The Union), K.R. Smith (University of California, Berkeley), C. Torres (Colombian Pulmonary Society), J.P. Zellweger (Swiss Lung Association)

3. RESULTS

The search for articles in PubMed for all years from 1954 to July 2005 yielded 718 articles. The search of The Union database of tuberculosis articles from 1918 to July 2005 found 959 articles, of which 202 were duplicates of those already identified, for a total of 1475 published articles. Throughout this process, reference lists of articles found were also examined for titles. Google Scholar yielded over 9000 entries including many duplicates and unusable entries; from that search and from reference lists, 388 interesting titles were searched in the other databases to be entered in the register of articles, or, if necessary, hand entered, for a final list of 1,863 references. These references were examined if the title or abstract indicated possible relevance, and the full texts of 192 articles were screened for inclusion according to inclusion criteria (given above), yielding 47 articles to be reviewed by three different readers. Five more articles were excluded by the reviewers because they did not provide the information needed for inclusion, for a final selection of 42 articles containing 50 studies for data extraction. Thirty-four of the articles selected for inclusion were found in PubMed, 32 were found in The Union database of tuberculosis articles, accounting for 37 articles. All of these references were listed in Google Scholar, as were 5 additional articles, for a total of 42.

Associations: Forty-four (88%) of the studies included in the systematic review showed a significant effect of tobacco smoke exposure on a tuberculosis outcome: 8 out of 8 studies for infection, 20 out of 21 for disease, 2 out of 3 for recurrent tuberculosis, 1 out of 2 for patient delay, 2 out of 2 for default, 1 out of 3 for smear conversion, 2 out of 2 for drug resistant tuberculosis, 1 out of 2 (50%) for death after treatment, and 5 out of 5 for mortality. Among all 50 studies, twelve found a dose-effect relationship, 19 a coherent effect, and 13 found limited or partial effects. Six of the 50 studies found no significant effect. Table 1 gives an overview of the studies and examples of some effect ratios found.

In the text below the articles are grouped according to the tuberculosis outcome measured.

A summary of all of the studies, including the research question, co-variables and adjusted effects ratios of tobacco effects is presented in the Annex.

3.1. Tuberculous infection

Eight studies investigated tuberculous infection, including two that looked specifically at the role of tobacco (7,8). One study was a case-control study (7) and the other seven were cross-sectional studies (8-14). Populations were prisoners in the US (7) and Pakistan (9), nursing home residents in the UK (11), homeless people in Spain (14), migrant farm workers in the US (10), Vietnamese emigrants to Australia (12), adults living in a high tuberculosis risk area in South Africa (8) and children of TB patients in India (13). All of the studies showed some effect of tobacco exposure on the risk of tuberculous infection: one study found a significant effect only with former smokers (10), five studies found coherent effects of tobacco exposure measures (7, 8, 11, 13, 14) and two studies found a strong dose-effect relationship (9,12). Most of the studies defined tuberculin positivity at $\geq$10 mm. Anderson et al (7) included a lower cut-off ($\geq$5mm) for HIV+ patients, and Hussain et al (9) included a higher cut-off ($\geq$15mm) for BCG-vaccinated prisoners in Pakistan. Solsona et al (14) used >5mm for the BCG-vaccinated homeless. Plant et al (12) investigated risk factors for reactivity of >5mm, >10mm and >15mm. All of the studies relied on self- or family report concerning exposure to tobacco. Only one study investigated passive smoking (children under five years of age in Singh et al (13); none of the others included passive exposure to tobacco as a risk factor even in crowded settings such as prison. Most of these studies controlled for age and sex, one controlled for alcohol use (among the homeless) (14), one specifically for socioeconomic status (among prisoners in Pakistan) (9), although most of the studies used populations that were probably fairly homogenous on this measure. All co-variables used to adjust for tobacco effects are presented in the Annex.

The Anderson et al's case-control study (7) looked at the role of smoking in tuberculin conversion after non-significant tuberculin skin test (TST) reaction on admission to prison. There was a lack of two-step skin testing for 16.4% of converters incarcerated for less than 1 year prior to the retest. There was no information given about active TB cases. Smoking for more than 15 years, adjusted for age and sex, was found to be significantly related to newly acquired tuberculous infection, i.e., TST conversion, (OR 2.12, 95%CI=1.03-4.36). While all results are in the expected direction, they were not statistically significant for a dose effect.

The den Boon et al's cross-sectional study in South Africa (8), found an association between pack years and infection among adults in a high risk area. The OR for infection among smokers of >15 pack years was 1.90 (95%CI=1.28-2.81). HIV-infected individuals were excluded. BCG-vaccination was not measured; however, vaccine coverage in the country is known to be high.

Hussain et al's cross-sectional study of latent infection among male prisoners in Pakistan (9) showed a significant dose-effect of daily quantity of smoking, adjusted for age, SES and crowding on risk of tuberculous infection (1-5 cigarettes: OR 2.6, 95%CI=1.6-4.4; 6-10 cigarettes: OR 2.8, 95%CI=1.6-5.2; >10 cigarettes: OR 3.2, 95%CI=1.3-8.2).

The McCurdy et al's study of immigrant farm workers in California (10) found, in multivariate logistic regression, a statistically significant association (OR 3.1, 95%CI=1.2-8.1) of tuberculin reactivity for former smokers among migrant farm workers living in family units, but not for current smokers (OR 1.87, 95%CI=0.7-4.8). The authors of this cross-sectional study suggest that some current smokers with tuberculous infection could have dropped out from the worker population due to poor health and thus failed to be detected. They also state that the participants did not represent the entire farm worker population. Single persons were excluded; the participation rate was 44% for skin testing (296/669 residents) and 70% for the questionnaire (469/660).

In a cross-sectional study of nursing home residents by Nisar et al (11), Heaf test grade was directly related to pack years. The authors comment that "Hypersensitivity reaction remains potentially active in most elderly people, ...maintained by smoking or re-activated by infection." The reported odds ratio for current smokers was 1.59 (no 95% CIs provided).

In another cross-sectional study, Plant et al examined risk factors in infection among Vietnamese emigrants to Australia (12). The effect of smoking on reactivity to TST was measured at three cut-off points: 5mm, 10mm, and 15mm. Smoking was related to significant TST reactions at all three cut-off points, but the effect of smoking on tuberculin reactivity was greatest at 5mm. Their results showed a higher likelihood of having a 5mm induration (versus none) among those who smoke more than 6 cigarettes per day (OR 2.60, 95%CI=1.08-6.26). The authors commented that this finding lends some support to the suggestion that smoking undermines larger reactions to tuberculin and that the use of a large cut-off point for smokers may lead to under-detection of infection. They did not discuss the possibility that the significant association between tobacco smoke exposure and tuberculin skin test reactivity might be due to an association with nontuberculous mycobacteria, always a possibility when small size skin test reactions are noted. The authors do report that their setting was a high tuberculosis prevalence environment, and that their results indicate that smoking explains a large proportion of the gender differences in tuberculin reactivity. Duration of smoking was used as a continuous variable. The OR for duration was 1.12, meaning that for a one year increase in the duration of smoking, the increase in excess risk was 12%. Assuming an average duration as 10 years, the overall excess risk was 120% corresponding to an OR of 2.2. This estimation is similar to the OR of ever-smokers (2.6) suggesting study consistency.

The purpose of the cross-sectional study by Singh et al (13) was to investigate the prevalence and risk factors for transmission of infection among children in household contact with adults having pulmonary tuberculosis. Of 281 children under the age of 5 years in contact with active TB patients, 140 were in contact with sputum smear positive adults; 141 children were in contact with sputum smear negative adults (diagnosed using standard methods). After testing they were divided into those with significant tuberculin reactions (induration >10mm) cases (n=95) and those with non-significant reactions (not infected) controls (n=186) for comparisons of risk factors. (All of the children in contact with the diseased adults were x-rayed. Those found to have a significant reaction to the skin test or an abnormal x-ray were admitted and tested for disease by smear of gastric lavage and treated if they were considered to have the disease. Nine children were identified with the disease itself and were started on treatment.) Tuberculin reaction was significant on 95 out of the 281 total children (33.8%), of whom 65 were contacts of sputum smear positive patients and 30 were contacts of sputum smear negative patients. The mean duration of symptoms in the adult source cases was 7.0 and 4.7 months respectively ($p>0.05$). Among children in household contact with adult tuberculosis patients, tuberculous infection was significantly associated with contact with sputum smear positive adult cases (OR 3.2, 95%CI=1.84-5.60) and exposure to tobacco smoke (OR 2.68, 95%CI=1.52-4.71). The authors reported that children in contact with sputum smear positive smokers had a higher infection rate than those in contact with sputum smear positive non-smokers; results were confirmed by multiple logistic regression but not presented.

Solsona et al's cross-sectional study of tuberculin skin test reactivity among BCG-vaccinated homeless persons in Barcelona (14) defined smokers as those who use 10 cigarettes or more per day. It is, however, well known that smokers with little revenue are very likely to compensate for their needs by extracting large quantities of nicotine, CO and tar from each cigarette, by puffing more deeply and more frequently to the end of the cigarette, so that the number of cigarettes per day is a poor measure of tobacco smoke exposure (12). In this study, smokers (of more than 10 cigarettes per day) had an OR of 1.72 (95% CI=1.02-2.86) in multivariate logistic regression for tuberculous infection, whereas sex and alcohol were not significantly associated with infection.

Summary

All of the studies of infection found significant effects of exposure to tobacco, with odds ratios ranging from 1.03 to 3.2. Of the studies that were considered to have used the best measure for assessing infection (7,8,9,12,13), 4 found effects for exposure to active smoking with higher odds ratios for longer duration or higher consumption, and one found an effect of passive exposure. None of the studies used best measures for assessing exposure to tobacco smoke.

3.2. Tuberculosis disease

Twenty-one studies explored the relationship between tobacco smoke exposure and tuberculosis disease; nine of these studies specifically investigated the effect of exposure to tobacco smoke, the others included exposure to tobacco smoke as a potential risk factor among other variables.

Twenty of the studies found a significant effect for at least one tobacco exposure measure (16-35); all but one of these (32) found an adjusted effect. Both passive and active exposures were found to increase risk of tuberculosis. Three of the studies were cohorts (16-18), 14 were case-controls (19-32) and 4 were cross-sectional (33-36). Study populations included patients with silicosis in China, Hong Kong Special Administrative Region (Hong Kong SAR) (16), white gold miners in South Africa (exposed to silica) (17), elderly people in China, Hong Kong Special Administrative Region (Hong Kong SAR) (18), young adults in Spain (19), juvenile prisoners in Pakistan (36), children exposed to TB in

Thailand (30) and in Spain (20), patients in Thailand (23) and the USA (24), HIV-infected patients in the US (28) and in Spain (32), sanitation employees in Shanghai (35), volunteers for x-rays in the US (33) and TB patients with population controls in China (27), Estonia (21), India (26,34), Malawi (25), Mexico (29), the UK (31) and West Africa (in Guinea, Guinea Bissau and the Gambia)(22). Two studies investigated only new smear positive TB (23,33), one investigated new smear and culture positive TB (26), 7 studies included along with smear positive cases those who were defined as having tuberculosis based upon clinical, radiological or histological diagnosis and showing appropriate response to anti-TB treatment (16,21,22,31,32,35,36). The remaining studies included other pulmonary TB cases, extrapulmonary cases, non-defined cases or self-reported cases (17-20,24,25,27-30,34). Four of the studies measured passive tobacco exposure as well as active exposure (19-21,23). Two studies measured exposure of children to secondhand tobacco smoke (passive smoking) (20, 30).

The cohort study of risk for TB among silicotics by Chang et al (16), found the sample to have 9 times the risk for TB, or 5 times the risk for positive culture as in the general population. Over the course of the study, 19.7% (n=137) of the patients died. The risk was slightly higher for smokers, with exposure measured in pack years, for all TB (RR 1.012, 95%CI=1.005-1.019) but not for sputum smear positive TB.

In the Hnizdo et al's cohort of white gold miners in South Africa (17), cases with TB disease had significantly higher cumulative exposure to dust and cigarette pack-years than the rest of the cohort: (RR 1.02, 95%CI=1.01-1.03).

Leung et al (18) examined the role of smoking on the occurrence of TB disease among a cohort of elderly people in China, Hong Kong Special Administrative Region (Hong Kong SAR). Active smoking was associated with culture confirmed TB (HR 2.80, 95%CI=1.82-4.31); significant hazard ratios were also demonstrated for all pulmonary TB, new TB, and active TB. A significant dose-effect of exposure to tobacco smoke, adjusted for a large number of variables including social class and alcohol use, was also identified.

Two studies from Spain published in 1996 indicated that passive exposure to tobacco smoke (passive smoking) might be an important risk factor for tuberculosis among children or young adults. Exposure to others' smoking in Alcaide et al's study (19) was associated with TB disease in children (unadjusted OR 2.7, 95%CI=1.0-7.2) but the association was not significantly elevated when adjusted for age, sex and SES level. The combined effect of passive smoking with active smoking was associated with TB (OR 5.6, 95%CI=2.1-15.1). Active smoking was the only significant tobacco measure associated with TB in multiple logistic regression (OR 3.8, 95%CI=1.5-9.8). In the Altet et al's paper (20), adjustment for sex, age, SES variables and frequency of contact with TB produced an OR of 5.39 (95%CI=2.44-11.91) for passive smoking on young children. A dose-effect relationship for frequency of exposure was also identified. These case-control studies may have led to the inclusion of passive exposure to tobacco smoke as a potential risk factor in studies that were to follow (e.g. 21), nevertheless, many studies looking at risk factors for tuberculosis over the past 5 years still have not investigated passive exposure along with active exposure (e.g., 22).

Ariyothai et al (23) identified an association for active and passive tobacco exposure among adults after adjusting for age, alcohol use, SES, and close contact. This case-control study from Thailand excluded people who were HIV+, or who had diabetes mellitus or lung disease other than tuberculosis. While passive smoking in general was non-significantly associated with tuberculosis, higher frequency of passive exposure to tobacco smoke was significant (OR 4.62, 95%CI=1.47-14.51 for office or neighbourhood exposure >3 times/week). Current smoking was significantly related to TB

disease (OR 2.70, 95%CI=1.04-6.97) as was longer duration (OR 4.0, 95%CI=1.3-12.6 for smoking for >10 years), or having started between ages 15-20 years (OR 3.2, 95%CI=1.2-8.8). While alcohol and various other variables were also associated with the effect of tobacco use on tuberculosis, only body mass index (BMI) was found to be confounding, changing the odds ratios by more than 15%.

The Buskin et al's case-control study of TB patients in the US (24) examined several risk factors including tobacco use, however, apart from longer duration of smoking, none were significantly associated with tuberculosis. Adjusting for age and heavy alcohol use, smoking for 30 years or more was associated with TB (OR 2.6, 95%CI=1.1-5.9). Since this study provided age and sex distribution of the reference population only, risk ratios were only reported by sex.

The Crampin et al's study (25) of risk factors for TB disease in Malawi found a prevalence of only 10% smoking in the sample, yet demonstrated an adjusted risk of TB among ex-smokers (OR 1.9, 95%CI=1.1-3.5). The association was lost, however, after controlling for HIV. This case-control study used a loose matching scheme and much of the data were incomplete. The authors report that few in their sample smoked heavily, but of the 7 men who smoked at least 20 cigarettes per day, six were cases.

A study from India by Kolappan et al (26) examining the association of tobacco smoke exposure with tuberculosis disease identified cases through surveys of the entire population of 30 villages in Tamil Nadu State during 1993-96. Controls were randomly selected from these same village populations. Those still available for interview in 1998 participated in the study. Measurement of tobacco use was blinded to the disease status of patients. Among the study population (original cases + controls), 58% were smokers. Among the 85 cases there were 64 smokers, and of the 459 controls, 253 individuals smoked. No information was available on former TB patients who quit tobacco smoking. This study found smoking to have an adjusted odds ratio for smear or culture positive TB of 2.24 (95%CI=1.27-3.94) with a dose effect for both quantity and duration of smoking, adjusted for age.

A case-control study by Leung et al (27) among adults aged 14 years or more in China, Hong Kong Special Administrative Region (Hong Kong SAR) found significant effects for both men and women, older and younger groups. The weighted OR for men and women under 65 years was 2.40 (95%CI=1.71-3.39)), and for those 65 years old or over OR 2.19 (95%CI=1.6-2.98).

Lienhardt et al's study of risk factors for development of tuberculosis disease (22) was undertaken in three countries of West Africa: Guinea, Guinea Bissau and the Gambia. Cases and household controls were compared on host characteristics; cases and community controls were compared on environmental characteristics and on both host and environmental factors. The three countries were considered similar for ethnic mix, SES indicators, and geographical environment as well as a comparable burden of TB. There was an interaction between TB and country on number of adults in the home, SES variables and history of asthma, but the effect of asthma and home ownership were in the same direction in all three sites. The authors concluded that smoking was consistently associated with TB, with a dose-response effect according to duration of smoking. However, the dose-effect data was not presented in the paper. The OR for current smoking was 2.03 (95%CI=1.22-3.39).

Miguez-Burbano et al (28) examined the association between tobacco smoking and the development of tuberculosis (TB) or pneumocystis carinii pneumonia (PCP) [This is now termed *Pneumocystis jirovecí*] among HIV+ patients on treatment. The presence of tuberculosis disease was determined from hospital records and treatment response. Of the 15 cases that developed PCP, 11 had previously had TB. Most (92%, 11/12) TB cases and 70% of controls were smokers. Long-term smoking

(>20 years' use) increased risk of TB in this population three-fold (p<0.04). Cases and controls were matched on age, sex, race, income and HIV status. Nine (75%) TB cases were receiving anti-retroviral therapy (mean 19.3+15 months) – this was not adjusted but is probably a protector more than a risk factor.

The Perez Padilla et al's case-control study (29) was undertaken primarily to measure the effect of biomass fuels on TB disease risk in Mexico. Only 10% of the study sample smoked, but a modest effect was nevertheless found for smoking (ever smoking OR 1.5, 95%CI=1.0-2.3). The authors note: "Tobacco smoke, which resembles biomass smoke in several aspects can reduce several defence mechanisms that may be important against TB."

The Tekkel et al's study of risk factors in Estonia (21) found significant association for both active and passive exposure to tobacco smoke for development of TB: (Current smoking OR 4.62, 95%CI=2.44-8.73; passive smoking at home OR 2.31, 95%CI=1.25-4.24). The analysis of passive smoking does not seem to exclude active smokers and therefore may overestimate the unique effect of passive exposure to tobacco smoke.

Another case-control study from Thailand by Tipayamongkholgul et al (30) also found tobacco smoke exposure to be an important risk factor for children exposed to their parents' tobacco smoke. The children were matched on sex and age (±2yrs), and had little diversity on SES as most parents had stable incomes. The study found that regular passive smoking at close range is an important risk factor for TB disease in children, even in those who had no direct contact with TB patients (adjusted OR 9.31, 95%CI=3.14-27.58). The effect of BCG vaccination was not evaluated since non-immunized children are difficult to find in Thailand. Although the study measures could have been affected by recall bias and lack of direct observation, the results seem robust.

In the study by Tocque et al (31), interviews took place over two time periods: the first was two years before diagnosis of tuberculosis and the other was the present day. Prior to diagnosis, cases were more likely to have smoked (univariate OR 2.3, 95% CI=1.4-3.9) and were heavier smokers or had smoked longer than controls. Cases had reduced their smoking after diagnosis whereas controls did not show this behaviour change over the same interval (one month to 7 years). The authors suggest that TB patients are routinely advised to stop smoking, and that this advice seems to have been followed by a significant number of patients.

Toledo et al's case-control study of 477 HIV+ patients (32) compared cases with TB with controls who did not have TB. The association of smoking to TB (unadjusted OR 1.3, 95%CI=1.0-1.6) did not reach statistical significance (p=0.05), so it was not included in multivariate analysis.

Adelstein and Rimington's 1967 cross-sectional study of the role of smoking as a risk factor for tuberculosis (33) found a significant trend effect in rates of TB for both men and women (p<0.01 for men, p<0.001 for women). These rates were converted to odds ratios by a reviewer. The adjusted ORs rise with increased tobacco exposure categorized as 1-9 cigarettes/day (OR 2.67, 95% CI=0.99-7.21); 10-19/day (OR 4.39, 95% CI=2.22-8.66); 20 or more cigarettes/day (OR 6.26, 95% CI=3.04-12.89).

The Gajalakshmi et al's paper (34) included cross-sectional data from a large population survey in India which compared the proportion of people with self-reported TB according to their smoking status. A dose-effect in risk ratios was found for both cigarettes and the form of tobacco traditionally smoked in India, bidis. The RR, adjusted for age, educational level and tobacco chewing, increased from 2.6 (95%CI=2.2-3.1) for ≥10 cigarettes/day to 4.5 (95%CI=3.7-5.5) for ≥15 bidis/day.

The cross-sectional study by Shah et al (36) found a non-significant effect of active smoking on tuberculosis disease among young (aged 15-23 years) male prisoners in Pakistan (OR 1.59, 95%CI=0.44-5.37). The confounding effect of exposure to others' tobacco smoke was unfortunately not examined.

Yu et al's study from 1988 (35) surveyed the total work force of sanitation employees in Shanghai. Those found to have TB were compared with the rest of the workers. Types of work included auxiliary, cleaning up garbage, cleaning up faeces and administrative staff. The study showed that although male sex and older age were associated with a higher risk of tuberculosis, these differences were due in great measure to the smoking factor. Heavy smoking of >400 cigarettes per year had an OR of 2.17 (95%CI=1.29-3.63). Being an administrative staff member held a higher risk than other types of work.

3.3. Recurrent tuberculosis

In a cohort of 42,655 elderly Chinese, Leung et al 2004 (18) found that current smoking increased the risk of retreatment for TB among TB patients, hazard ratio 2.48 (95% CI=1.04-5.89), adjusted for all measured co-variates, including sex, age, several measures for socioeconomic status, alcohol use, health status, social activities, recent hospital admission and other diseases. The authors did not clearly describe whether the previous episode of tuberculosis was cured or if there had been default. Furthermore, the authors did not investigate the possibility of recurrent tuberculosis due to reinfection.

Thomas et al (47) undertook a cohort study in India to look at risk factors for relapse of tuberculosis among 503 patients with sputum smear positive pulmonary tuberculosis treated and cured under DOTS. Relapse was defined as two sputum smears positive for acid-fast bacilli by direct smear, one smear and culture positive from separate samples or two culture positive among patients followed up 6, 12, or 18 months after their original treatment. Tobacco smoke exposure was included among potential risk factors, but dose was not measured. Of the 503 patients, 62 (12%) relapsed in the 18 months following treatment; 48 (77%) of the relapses occurred during the first 6 months of follow-up. The relapse rate in the sample was 18.1% among smokers compared to 7.3% among non-smokers (OR 2.8, 95%CI=1.5-5.2). Age, sex, weight, initial smear grade and end of intensive phase sputum conversion results did not influence the rate of relapse. On stepwise logistic regression analysis, a higher relapse rate was independently associated with irregular treatment (OR 2.5) drug resistance (OR 4.8), and smoking (OR 3.1, 95%CI=1.6-6.0). Alcohol use was not found to have an independent effect. However, the authors did not perform genotyping of strains of the first and the second episode to investigate the possibility of recurrent tuberculosis due to reinfection.

In the case control study that found a significant effect of tobacco use on new tuberculosis cases, Leung et al (27) found that having previously had tuberculosis was not associated with ever smoking.

Summary

Twenty-two of the twenty-four studies looking at new and/or recurrent tuberculosis disease found a significant relationship between exposure to tobacco and disease. Of 19 studies with significant results for active exposure, odds ratios ranged from 1.012 to 6.26; of 4 studies with significant effects for passive exposure, odds ratios ranged from 1.6 to 9.3. Best measures of disease were used to assess tuberculosis in 9 studies (16,18,19,20,22,23,25,26,47). No studies used best measures to assess exposure to tobacco.

3.4. Tuberculosis characteristics and case management

Eleven studies measured the effects of exposure to active tobacco smoke on the characteristics of tuberculosis and on case management issues, but there are only a few studies in each of the categories. Many of the results come from studies that looked at other tuberculosis outcomes, and this is indicated in the Annex. Five studies (from 3 articles) were specifically interested in the role of tobacco on characteristics and case management: delay in care seeking or diagnosis (46), smear conversion (27,50) and severity of disease (27,46). Other treatment issues include default and acquired drug-resistant TB. The two studies that examined the relationship of tobacco exposure on delay (46,48) found significant and non-significant results. The two studies of default (49,54) found some effect of tobacco, but there were not enough studies to make a judgement of evidence. Three studies looked at smear conversion. A cross-sectional study (55) found effects of smoking on delayed smear conversion among new smear positive patients in South Africa, but no significant effects were found in a cohort study in Pakistan (50) or a cross-sectional study from China, Hong Kong Special Administrative Region (Hong Kong SAR) (27). A case-control study (46) and a cross-sectional study (27) found effects of exposure to tobacco smoke on various indicators of disease severity. A case-control study in Brazil (56), along with a cross-sectional study in Russian Federation (57) found small, significant associations of smoking with drug-resistant tuberculosis after treatment.

3.4.1. Delay

Altet-Gomez et al 2005 (46) measured delay in their study of the role of smoking on tuberculosis outcomes, but found no difference between smokers and non-smokers. Dos Santos et al (48) found that having given up smoking was an important factor in an unacceptable delay before seeking treatment (OR 0.58, 95%CI=0.43-0.79; p=0.0005), but the authors did not include tobacco use in the final model for adjustment.

3.4.2. Default

Chang et al's 2004 study of default (49) found an adjusted odds ratio for default by smokers of 3.00 (95% CI=1.81-6.53), controlling for age and sex. Alcohol was not found to be a significant factor. This study does not provide details of how smoking data was obtained.

The cross-sectional study by Salami et al (54) in Nigeria compares noncompliant pulmonary TB patients (case group) with compliant patients (control group) on lifestyle and other factors as taken from medical records of treated smear positive patients. Noncompliance was an important issue in this sample population: over a nine year period, patients had a very high default rate of 44.2% (769/1741) and 11.6% (202/1747) of the treated patients died. A significant odds ratio of 1.6 (95%CI=1.31-1.98; $p<0.001$) for default was found for cigarette smoking, without controlling for alcohol, but a final backward regression model did not include smoking. The authors expressed their belief that social demands/needs of patients might have led them back into smoking and drinking before completing their treatment. However, the study does not make clear whether the patients had stopped smoking or alcohol drinking during any part of their treatment.

3.4.3. Smear conversion

Abal et al's cohort study of the effect of tobacco smoking on smear conversion (50) found that smoking did not influence chances of an early sputum conversion when other factors remained stable. The authors report significant differences between smokers and non-smokers in bacillary load, far advanced radiological lesions and high initial smear positivity, but the evidence is not presented.

Leung et al 2003 (27) compared evolution of treatment response in 851 notified TB cases according to smoking status, and found no significant effect of tobacco smoking on either smear or culture conversion.

The Durban's study (55) is a cross-sectional analysis of data from a randomized controlled trial of M. vaccae in TB treatment. The objective was to find out if a dose of M. vaccae, a non-pathogenic organism, could boost the immune system and thus shorten the time to conversion to negative sputum culture for patients being given standard treatment. Covariates, including smoking, were adjusted for in the analysis. The 374 patients in the trial had newly diagnosed, sputum smear-positive pulmonary TB. The primary outcome was the time to a negative sputum culture. Ever smoking status significantly increased the amount of time it took to reach negative sputum culture: hazard ratio for smear conversion 0.58 (95% CI=0.40-0.84).

3.4.4. Disease severity

The Altet-Gomez et al's 2005 cross-sectional study of over 13,000 TB patients (46) found that smoking was related to more cavitary lesions (OR 1.9, 95%CI=1.6-2.3; $p<0.001$) and a greater likelihood of hospitalization (OR 1.8, 95%CI=1.5-2.2; $p<0.001$). These results were adjusted for age, sex, alcohol use and site of pulmonary disease.

In Leung et al's 2003 case-control study in China, Hong Kong Special Administrative Region (Hong Kong SAR) (27) looking at the relationship of tobacco use and tuberculosis, multiple regression modelling found that ever smoking significantly and independently predicted cough (OR 1.69, 95%CI=1.26-2.26), dyspnea (OR 1.84, 95%CI=1.24-2.75), upper zone involvement (OR 1.67, 95%CI=1.01-2.77), cavitation (OR 1.76, 95%CI=1.18-2.63), miliary involvement (OR 2.77, 95%CI=1.11-6.95), positive sputum culture (OR 1.43, 95%CI=1.07-1.91), and lesser likelihood of only extrathoracic TB (OR 0.31, 95%CI=0.13-0.71), independent of sex, age over 65 years, working at onset of illness, regular alcohol use, history of narcotic abuse, coexisting medical illness and absence of contact history within 5 years.

3.4.5. Acquired drug resistance

The Barroso et al's study of multidrug resistant tuberculosis (MDRTB) (56) compared TB patients who had acquired MDRTB or sensitive TB as a case-control study within a cohort. There was no information about how smoking was defined or information obtained. This study found a strong effect of a combined variable of alcohol with tobacco for both default from treatment and factors in MDRTB (OR 3.01, 95%CI=1.4-7.1). Analysis was not considered by reviewers to be well done.

Ruddy et al (57) investigated risk factors for drug resistance in Russian Federation and found that smoking was related to resistance to isoniazid (OR 3.3, 95% CI=1.2-9.2). No other associations with tobacco were found.

Summary

There were not enough studies of treatment characteristics and case management to show evidence of an effect. Of the 11 studies examined, seven found significant association with tobacco use. Three of the four high quality studies (46 delay, 46 severity, 49,57) found a significant association with tobacco use and three of the four studies that used best measures for identifying tuberculosis outcomes (47,50,54,55) found a significant association. None of the studies used best measures for assessing exposure to tobacco.

3.5. Death during and after treatment

The cohort study by Leung et al (18) of elderly Chinese in China, Hong Kong Special Administrative Region (Hong Kong SAR) looked at deaths after treatment for tuberculosis. This study found a non-significant relationship with smoking among women, but among men, the unadjusted odds ratio for smoking was 4.66 (95%CI=1.20-18.0).

The 2005 case-control study by Altet-Gomez et al (46) of 13,038 tuberculosis patients in Spain found that there was a small but insignificant difference between smokers with non-smokers in the death rate while on treatment.

3.6. Mortality

Five studies investigated the role of exposure to tobacco smoke and tuberculosis mortality in often large data sets. Reviewers felt difficulty existed in determining the accuracy of mortality rates for tuberculosis. All of the studies show strong effects of smoking on tuberculosis mortality A major challenge in using mortality rates from community sources is the potential bias of misclassification of deaths caused by COPD, definitively established as largely caused by tobacco, as tuberculosis mortality. Death certificates, medical records, obituaries and family reports may not be an adequate measure to judge the validity of assessments of mortality attributed to tuberculosis.

The Doll et al's cohort study (51) was designed to measure the excess risk of smoking for mortality among 34,000 British male doctors due to tobacco-related cancers, respiratory diseases and cardiovascular diseases. Cause of death was determined by death certificates, obituaries or family descriptions The relative risk found of dying from pulmonary tuberculosis for smokers compared to lifetime non-smokers was 2.8, with a dose effect; the RR for those who smoked more than 25 cigarettes/day was 5.0.

Gajalakshmi et al (34) compared 78,000 men on tobacco exposure measures in a case control study of those who had died from disease and widowers in urban and rural areas of India. Based on recorded cause of death, they found that smokers were over 4 times more likely to die of tuberculosis (urban area RR 4.5, 95%CI=4.0-5.0; rural area RR 4.2, 95%CI=3.7-4.8) and that one third of the excess mortality among smokers was related to respiratory diseases. The authors suggest that the effects of smoking on tuberculosis mortality are more related to the effect of smoking on disease incidence rather than fatality; this hypothesis is coherent with the results of this review.

Lam et al's case-control study (58) of deaths from all causes associated with smoking among 40,561 ethnic Chinese determined cause of death from medical registry and used informant data on smoking, drinking, employment, housing in 1988 and age, sex, birthplace, and education of both dead cases and living controls. This study found some effect among women and a strong dose-effect on mortality among men aged 35-69 years (OR 2.52, 95%CI=1.24-5.22) and among those aged 70 years or more (OR 1.63, 95%CI=1.01-2.64).

Liu et al (59) investigated the effect of smoking on mortality among 275,616 adults aged 35-69 years in China. Respiratory TB was included as a cause of death in the analysis. This was a retrospective case-control study using surrogate respondents since cases and controls both were dead persons. Controls were deaths from causes other than neoplastic, respiratory and vascular diseases. Strong dose-effect results were found for men in terms of quantity and age of starting smoking. Both women and men had higher weighted risk ratios for mortality from TB, controlling for age and residence (women RR 1.29 $\pm$0.04; men RR 1.20 $\pm$0.08).

Sitas et al's case control study (60) investigated mortality related to smoking five years prior to death, as indicated on the death certificate. The authors analysed 5% of all death certificates in the year 1995 (n=5341). Evaluation of a death notification question on tobacco use confirmed accuracy similar to 1995 national survey data, with 54% in males and 15.8% in females. This study compared cause of death between smokers and non-smokers, with cases including tobacco-related causes of death. TB deaths were included as cases. The authors state that about 20% of deaths due to tuberculosis could have been avoided if smokers had the same death rates as non-smokers. The authors state that the results are reliable and concordant with what might be expected from indirect calculations of the burden of tobacco-related disease. This is an interesting way to look at tobacco effect on TB. Controls were those whose deaths were due to causes not related to tobacco, with an odds ratio of 1.0; cases, those who died of diseases usually linked to tobacco smoking, had an odds ratio for TB of 1.61 (95%CI=1.23-2.11), similar for men and women. Odds ratios for lung cancer were 4.79, for COPD 2.53, for other lung infections 1.32.

Summary

All of the mortality studies found significant relationships with tobacco use, with risk ratios ranging from 1.02 to 6.62. One of the two studies that examined death after treatment found a significant association for men, and that study (18) was considered to have used the best measure for tuberculosis. None of the studies used best measures for assessing exposure to tobacco smoke.

4. POTENTIAL CONFOUNDERS

4.1. Tobacco and alcohol

Tobacco smoking is often associated with alcohol intake, presenting the potential for confounding. In 1961, Brown and Campbell concluded in their study of cases and controls in Queensland and Victoria (37) that smokers were in excess among tuberculosis patients because heavy drinkers were likely to be heavy smokers. They felt that this confirmed that alcohol and not smoking was more directly associated with tuberculosis. In 1963, Lewis and Chamberlain published a study of 100 TB cases and 2 control groups of 100 people each in the UK (38). The proportion of smokers in all three groups was similar, whereas the proportion of heavy drinkers was higher in the cases. They felt that this demonstrated that there was no support for the contention that smoking predisposes to TB. It should be noted that a high proportion of the control groups had smoking-related diseases other than tuberculosis. Indeed, the comparisons of OR for heavy drinking among regular smokers were similar or higher in the controls (2.88 in Brompton and 2.55 in Charing Cross than among TB cases 2.14) The validity of conclusions is questionable. These studies from the 1960s have until recently been cited (e.g. 39) as the evidence that alcohol is a risk factor for tuberculosis disease, but that smoking has no independent effect. But it should be remembered that these studies occurred in a period when tobacco use was high. In the general public in 1960 in the UK, 60% of men smoked (40); in 1964 in Australia 58% of men smoked (41). Women's rates were lower than men's rates at that time (42). In the Australia study, 91% of tuberculosis patients smoked. It was not unusual to find men who smoked 80 cigarettes or more per day. Because excessive (compared with moderate or low) use of tobacco was considered the variable of interest, rather than use compared to non-use, light smokers of up to 9 cigarettes per day were grouped with non-smokers in the control groups of these studies. This had been done in the text by Lowe in his 1956 study (43), even though his analyses had been done with non-smokers as a separate category. In the Lowe study, 2.5% of male TB patients (including only 1 of 174 male sanatorium patients) were non-smokers, and 8.1% of male controls were non-smokers. It is only over time that we have discovered that measurable differences in health outcomes can be found between very light and/or occasional smokers and non-smokers, as well as between people who are exposed to other people's smoke and those who are not exposed.

The Ariyothai et al's study (23) included in this systematic review found significant differences in risk between non-smokers and smokers of less than three cigarettes per week, and Yu et al (35) found an important effect of smoking for what were described as "heavy smokers" who smoked 400 cigarettes or more per year, (≥1.1 cigarettes per day). Five out of six studies (13,20,21,23,30) found significant differences in risk between those not exposed and those exposed to passive smoking. Investigating the effects of passive smoking is fraught with difficulty in clearly identifying non-exposed individuals (44). That is why the studies with young children are important as there is less risk of contamination of the non-exposed sample. Passive exposure to tobacco smoke is ubiquitous in many of the countries that currently have high tuberculosis rates, mirroring the environment in active smoking (few healthy men were not smokers) in which early studies were performed. Indeed, a recent study looking at sex differences in both tuberculosis rates and tobacco use has noted the presence of high tobacco smoking rates in many high burden tuberculosis countries, particularly those which have low levels of HIV/AIDS (45).

Two tuberculous infection studies (7,14) and 10 studies about tuberculosis disease (18,21-25,27,28,31,32) measured both tobacco use and alcohol use; 3 of these studies did not investigate the alcohol results as a risk factor for disease (18,27,28), but the Leung et al's study (18) adjusted for alcohol use in determining the significant effect of tobacco.

Both of the infection studies found a significant effect for alcohol use. One did not control for alcohol in the adjusted rate for tobacco (7), and the other (14) found an effect for tobacco, but no effect for alcohol in multivariate analysis. In the disease studies, all of the 10 studies that measured alcohol found an unadjusted association between tobacco use and tuberculosis disease and the association remained significant in 9 studies (90%) after adjustment for other variables (18, 21-25, 27, 28, 31), although in the Crampin et al's study (25), the effect of tobacco did not remain in a second adjustment for HIV. Three (43%) of the 7 studies that investigated alcohol use as a risk factor for tuberculosis disease did not find a significant univariate effect (22,24,32). The Toque et al's study (31) found that alcohol did not remain significant in multivariate analysis. All 4 studies that adjust for alcohol (18,23,24,31) found a significant adjusted effect for tobacco. It is time to lay to rest the theory that an effect measured for tobacco use is only a surrogate for a real effect of alcohol use.

4.2. Tobacco and poverty

The other major confounder that is often cited in questioning the role of tobacco in relation to tuberculosis outcomes is low socioeconomic status, or more generally, poverty. The most important evidence that tobacco is not simply a marker of poverty and is indeed an independent risk factor comes from the evolution of tobacco use in the population. Hill and Doll's British male doctor cohort (51) shows the effect of tobacco on the health of a high socioeconomic group. The risk, for smokers, of dying of tuberculosis in the 1950s in this cohort was almost four times greater than for non-smokers (52). From time-trend indicators available in many rich countries, cigarette smoking was more heavily represented in the richer strata before being adopted by poorer classes in their societies. When that was the case, it was necessary to have a high rate of tuberculosis to see a relationship with tobacco. The current preponderance of smokers among the poor in many rich countries is being reproduced in other countries in the world, but the transition is only now occurring in some places, which means that there is great variability in the proportions of smokers according to socioeconomic class in Eastern and Southern Europe, Africa and Asia, even in the face of traditional smoking such as bidis or kretek cigarettes which are already widespread in poor social groups. Poverty sets the stage for respiratory infection (53) so it is of course important to measure how or if smoking and poverty interact in relation to tuberculosis. In the present review, level of education or income were the most frequent indicators of socioeconomic class, but other indicators measured

include type of residence, ownership, number of people per room, etc. Twenty-one studies in this review which found an independent effect for exposure to tobacco smoke also examined the independent effect of at least one measure of socioeconomic status: 15 studies adjusted for the socioeconomic measure that was significantly related to the tuberculosis outcome (9,18-23,28-31,34,35,58,60), 6 studies did not show a significant adjusted effect for the SES measure taken (8,10,12,24,25,33).

4.3. Tobacco and sex

In some of the studies included in this review, a stronger relationship was found between exposure to tobacco and the tuberculosis outcome among men than among women. Although there is a levelling of rates of tobacco use among men and women in some industrialized countries, the general trend in most high burden tuberculosis countries today is what was common elsewhere in the past; a higher proportion of men than women smoke, and among smokers, men smoke for longer and with greater intensity than women. It has been noted in some countries that the differences in tuberculosis disease rates by sex begin to be seen in age cohorts when young men start smoking. A recent article (45) presents evidence for the hypothesis that the differences in tuberculosis rates among men and women are influenced by the gender differences in tobacco use.

5. QUALITY ASSESSMENT FOR DETERMINING LEVELS OF EVIDENCE

Levels of evidence

All of the quality scores are presented in Table 1. The items used for quality assessment are presented in Table 2. The range of possible scores is from 0-100. The mean score for studies of infection was 76.25, for studies of disease 76.45, for studies of death or mortality 74.07, and for disease characteristics and case management issues, 66.68. Using the quality assessment procedure, the conditions are met for the following levels of evidence of a causal relationship between exposure to tobacco smoke and the measured tuberculosis outcomes. Table 3 summarises the following results.

5.1. Strong evidence

- TB disease: Two high quality cohort studies, 9 high quality case-control studies, 2 high quality cross-sectional studies show at least one statistically significant relationship between TB disease and passive or active exposure to tobacco smoke; 7 of the above studies show a dose effect. Seven out of 8 other studies also show significant effects.

5.2. Moderate evidence

- Recurrent tuberculosis: Two high quality cohort studies found an effect of smoking on re-treatment and relapse. One other study did not identify an association.

5.3. Limited evidence

- Infection: One high quality case-control study and 4 high-quality cross-sectional studies show high odds ratios for infection among those exposed actively or passively to tobacco smoke. Three other studies also show an effect.
- Mortality: 2 high quality case-control studies show high risk ratios for smokers of mortality from tuberculosis, as do the 3 other studies looking at the issue of mortality.

5.4. Not enough evidence

There is insufficient evidence from the material reviewed for measuring an effect of tobacco smoking on the following outcomes:

- Default: Two studies showed a significant association.
- Drug resistant TB: Two studies showed significant effects.
- Severity of disease: Two studies showed significant effects.
- Patient delay: One study showed a significant association, the other high quality study did not.
- Smear conversion: One study showed significant effects, but two others did not.
- Death during or after treatment: One high quality cohort study found a significant effect of tobacco use on death after treatment among men, but not among women. The other study did not find a significant effect.

6. DISCUSSION

6.1 Principal findings

This systematic review used predefined methods to identify the available evidence regarding the association between tobacco exposure and tuberculosis. The inclusion criteria of this systematic review demanded a certain quality of data presentation, so the evidence required to evaluate the strength of the relationship between exposure to tobacco smoke and tuberculosis outcomes is particularly rigorous. This review indicates that passive or active exposure to tobacco smoke is significantly associated with ***tuberculous infection*** and ***tuberculosis disease***. Active smoking is significantly associated with ***recurrent tuberculosis*** and tuberculosis ***mortality***. These effects appear to be independent of the effects of alcohol use, socioeconomic status and a large number of other potential confounders. Although none of the studies used biological validation of reported exposure to tobacco smoke, excess risk of tuberculosis outcomes was found in all but 6 studies – tuberculosis disease (36), recurrent disease (27), smear conversion (27,50), delay (46) and death during or after treatment (46).

Studies are emerging that indicate biological mechanisms that are possibly underlying the association of exposure to tobacco smoke with tuberculosis outcomes (12,63) and other infections (64,65). These studies reinforce the evidence in this review for the associations found.

The majority of studies measured active smoking. There are few available studies looking at the impact of exposure to passive smoking, which is a difficult exposure measure particularly among adolescents and adults. Because they more often stay at home, infants and children are probably less likely than adults to be at risk of misclassification in exposure to secondhand tobacco smoke. It is therefore notable that the studies of children show strong excess risk of tuberculous infection or tuberculosis disease through exposure to others' tobacco smoke.

6.2. Limitations of existing original studies

The results described here are tempered by the methodological limitations of the included studies. Most provide a detailed accounting of the criteria used to determine the tuberculosis outcome, and best measures of tuberculosis disease were assessed to be present in 19 studies. However, the tobacco exposure measures are often weak: many studies define smoking as simply present or absent, no dose measures (consumption, duration of use) of active smoking or other tobacco use are taken,

and some studies do not even indicate the procedure undertaken for assessing smoking status. When duration and consumption rates are measured at all, they are often collapsed into pack years, which may mask a dose effect. In clinical trials that investigate tobacco use, biochemical validation is customary because a certain percentage of individuals will not provide accurate information about their tobacco use status (66). Only one of the studies in this review noted that they may not have adequately measured the true extent of active smoking in the chosen population (10). Many studies missed the opportunity to investigate exposure to others' tobacco smoke, even in populations where close proximity to smokers would be expected to subject them to high levels of passive smoking. The non-identification of non-smokers exposed to tobacco smoke could lead to underestimation of the effect of tobacco smoke on tuberculosis in those settings.

6.3. Limitations of the review process

This systematic review has some limitations that warrant discussion. First, due to time and funding restrictions, the review did not include papers in languages other than English. We are aware of several non-English language studies that also showed significant effects of exposure to tobacco on tuberculosis outcomes (egg. 61,62). Consequently, these findings may underestimate the magnitude of the association. On the other hand, some published studies that have measured smoking in relation to tuberculosis outcomes may have been missed if they did not include tobacco in the keywords or the abstract. Nevertheless, the evidence of an association between tobacco smoke exposure and disease is unlikely to be altered in any meaningful way by the inclusion of such studies.

Second, our understanding of the relationship between exposure to tobacco and tuberculosis treatment and case management is limited by the inclusion criteria, but can be strengthened by new cohort and case-control trials.

Third, we acknowledge the limits of this review concerning mortality. Three early mortality studies that found higher risk ratios among smokers for tuberculosis (67-69) were not included in this review because they were published as chapters or books. All 10 of the studies known to us (34,51,58-60,67-71) that provide effect ratios of the association between exposure to tobacco smoke and population mortality rates have found a significant effect; these data are not well represented in this systematic review.

This qualitative review attempted to remain as objective as possible in determining the strength of evidence of an association between exposure to tobacco smoke and tuberculosis outcomes, and our quality assessment is concerned with this question, not the overall quality of the study in question. The classic cohort study initiated by Doll and Hill of male British doctors carried out over 50 years has been a model for identifying disease mortality risks of smoking. As well as reports that have been made at each 10-year follow-up period, numerous other articles have described the study results. Tuberculosis was prevalent in the UK when the cohort study began, and deaths attributed to tuberculosis were found to be more frequent among smokers than among non-smokers. Follow-up reports included tuberculosis specifically or collapsed it into respiratory diseases. The reviewers were dismayed that this study was not included in the high quality studies, and requested a second round of reviews, which again provided a score that was lower than the mean. This is an indication that our quality scores are extremely severe with non-validated tuberculosis outcomes.

6.4. Recommendations for research

There is a clear need for more research, particularly high quality cohort and case control studies that examine the role of passive or active exposure to tobacco smoke in excess rates of tuberculous infection, increased severity of disease, smear conversion, relapse and other treatment outcomes. While there are numerous studies about tuberculosis disease, few focus on smear or culture positive tuberculosis, or specifically investigate transition to disease from infection. Studies should also investigate possible interactions of nicotine and other tobacco components on anti-tuberculosis drug effects.

There is sufficient evidence to indicate that studies of risk factors for tuberculosis outcomes should include measures of passive and active exposure to tobacco smoke. Researchers looking at the effects of exposure to tobacco smoke need to be attuned to the criteria for identifying tuberculosis and to seek an approach to validate the precision of reported tuberculosis mortality from large population surveys where the possibility of misclassification may be large.

An ideal study would validate self-reported exposure to tobacco smoke with biochemical verification of at least a subsample of the study population, and measure consumption rates, duration of use, lifetime use, age of initiation and, for ex-smokers, length of abstinence. Rates should be measured in relation to sex, age socioeconomic status and alcohol use. Studies of passive exposure to tobacco should use biochemical validation and indicate the source, duration and frequency of exposure as well as the age of earliest exposure. Cohort studies of the association of passive and active exposure to tobacco smoke and tuberculous infection of people similarly exposed to tuberculosis are needed. An ideal study related to tuberculosis disease would be a cohort or case-control study of verified smear or culture positive tuberculosis within a population of infected individuals measured over time and compared on tobacco exposure.

This review provides evidence of an independent effect of exposure to tobacco on tuberculosis outcomes, and it would be useful to have similar reviews of the independent effects on tuberculosis of alcohol and poverty.

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Author, year (reference)	Study Design	Tuberculosis outcomes	Tobacco exposure effect[1]	Adjusted tobacco effect ratio[2] (+95%CI)	Quality Score[3]	High quality[4]
Abal et al, 2005 (50)	Cohort	Smear conversion	Active ns	ns	63.64	
Adelstein & Rimington, 1967 (33)	Cross-section	Disease	Active+++	20+ cigarettes/day ORs M 6.56 F 6.38	**78.95**	*
Alcaide et al, 1996 (19)	Case-control	Disease	Active+++ Passive ns Active+passive ++	OR 3.6 (1.5-2.2) Daily & passive OR 5.6 (2.1-15.1)	**85.71**	*
Altet et al, 1996 (20)	Case-control	Disease	Passive+++	OR 5.21 (2.31-12.62)	**100.00**	*
Altet-Gomez et al, 2005 (46)	Case-control Case-control Cohort	1 Delay 2 Severity 3 Death after	1 Active ns 2 Active + 3 Active ns	ns More cavitary lesions OR 1.9 (1.6-2.3) ns	**70.59** **70.59** 70.59	* *
Anderson et al, 1997 (7)	Case-control	Infection	Active+	>15 years' smoking OR 2.12 (1.03-4.36)	**89.47**	*
Ariyothai et al, 2004 (23)	Case-control	Disease	Active+++ Passive ±	OR 2.70 (1.04-6.97) Office exp >3/wk OR 4.62 (1.47-14.51)	**85.71**	*
Barosso et al, 2003 (56)	Case-control	MDRTB	Alcohol & tobacco++	OR 3.01 (1.4-7.1)	61.11	
Buskin et al, 1994 (24)	Case-control	Disease	Active+	>30 years' smoking OR 2.6 (1.1-5.9)	**83.33**	*
Chang et al, 2001 (16)	Cohort	Disease	Active+	RR 1.012 (1.005-1.019) p=0.019	**80.95**	*
Chang et al, 2004 (49)	Case-control	Default	Active++	OR 3.44 (1.81-6.53)	**70.59**	*
Crampin et al, 2004 (25)	Case-control	Disease	Active+	Ex-smokers OR 1.9 (1.1-3.5)	**77.78**	*
den Boon et al, 2005 (8)	Cross-section	Infection	Active+++	>15 pack years OR 1.90	**89.47**	*
Doll et al, 1999; Doll, 1954 (51)	Cohort	Mortality	Active+++	>25 cigarettes/day RR 5.0	61.90	
dos Santos et al, 2005 (48)	Cross-section	Delay	Active +	Stopped smoking OR 0.58 (0.43-0.79)	65.00	

Author, year (reference)	Study Design	Tuberculosis outcomes	Tobacco exposure effect[1]	Adjusted tobacco effect ratio[2] (+95%CI)	Quality Score[3]	High quality[4]
Durban Immunotherapy Trial Group, 1999 (55)	Cross-section	Smear conversion	Active++	Hazard ratio smoking 0.58 (0.40-0.84)	66.67	
Gajalakshmi et al, 2003 (34)	Cross-section Case-control	1 Disease, 2 Mortality	1 Active+++ 2 Active++	≥10 cigarettes/day RR 2.6 (2.2-3.1) RR 4.5 (4.0-5.0)	73.68 73.68	
Hnizdo & Murray, 1998 (17)	Cohort	Disease	Active+	Pack years OR 1.02 (1.01-1.03)	61.90	
Hussain et al, 2003 (9)	Cross-section	Infection	Active+++	>10 cigs/day OR 3.2 (1.3-8.2)	**78.95**	*
Kolappan & Gopi, 2002 (26)	Case-control	Disease	Active+++	OR 2.24 (1.27-3.94)	**85.00**	*
Lam et al, 1998 (58)	Case-control	Mortality	Active+++	Men 35-69 yrs RR 2.54 (1.24-5.22)	**77.78**	*
Leung et al, 2003 (27)	Case-control Case-control Case-control	1 Disease 2 Recurrent TB 3 Severity 4 Smear conversion	1 Active ++ 2 Active ns 3 Active ++ 4 Active ns	<65 years old OR 2.40 (1.71-3.39) ns Cavity OR 1.76 (1.08-2.63) ns	61.11 61.11 61.11 61.11	
Leung et al, 2004 (18)	Cohort Cohort Cohort	1 Disease 2 Relapse 3 Death after treatment	1 Active+++ 2 Active ++ 3 Active++	Hazard ratio 2.87 (2.00-4.11) OR 2.48 (1.04-5.89) Men OR 4.66 (1.20-18.0	**80.95** **80.95** **80.95**	* * *
Lienhardt et al, 2005 (22)	Case-control	Disease	Active++	OR 2.03 (1.22-3.39)	72.22	
Liu et al, 1999 (59)	Case-control	Mortality	Active+++	Men RR 1.20 (+.04) WomenRR 1.29 (+.08)	**88.89**	*
McCurdy et al, 1997 (10)	Cross-section	Infection	Active+	Ex-smoker OR 3.11 (1.20-8.09)	52.94	
Miguez-Burbano, 2003 (28)	Cross-section	Disease	Active+	>20 years' smoking 3x	68.42	
Nisar et al, 1993 (11)	Cross-section	Infection	Active++	Unadjusted OR 1.59	66.67	
Perez-Padilla et al, 2001 (29)	Case-control	Disease	Active++	OR 1.5 (1.0-2.3)	66.67	

Author, year (reference)	Study Design	Tuberculosis outcomes	Tobacco exposure effect[1]	Adjusted tobacco effect ratio[2] (+95%CI)	Quality Score[3]	High quality[4]
Plant et al, 2002 (12)	Cross-section	Infection	Active+++	OR 2.31 (1.58-3.38)	**82.35**	*
Ruddy et al, 2005 (57)	Cross-section	MDRTB	Active+	Resistance to H OR 3.3 (1.2-9.2)	**72.22**	*
Salami et al, 2003 (54)	Cross-section	Default	Active+	Unadjusted OR 1.61 (1.31-1.98)	63.16	
Shah et al, 2003 (36)	Cross-section	Disease	Active ns	ns	57.89	
Singh et al, 2005 (13)	Cross-section	Infection	Passive++	OR 2.68 (1.52-4.71)	**88.24**	*
Sitas et al, 2004 (60)	Case-control	Mortality	Active++	OR 1.61 (1.23-2.11)	64.71	
Solsona et al, 2001 (14)	Cross-section	Infection	Active++	OR 1.72 (1.02-2.86)	61.90	
Tekkel et al, 2002 (21)	Case-control	Disease	Active++ Passive++	OR 4.62 (2.44-8.73) OR 2.31 (1.25-4.24)	55.00	
Tipayamongkholgul et al, 2005 (30)	Case-control	Disease	Passive++	OR 9.31 (3.14-27.58)	**100.00**	*
Tocque et al, 2001 (31)	Case-control	Disease	Active+	≥30 years' smoking OR 2.3 (1.2-4.2)	**89.47**	*
Toledo et al, 2000 (32)	Case-control	Disease	Active+	Unadjusted OR 1.3 (1.0-1.6)	57.89	
Yu et al, 1988 (35)	Cross-section	Disease	Active+++	OR 2.17 (1.29-3.63)	**83.33**	*

1 Tobacco effect: ns non-significant, ±some effect, but not coherent, + limited or partial effect, ++coherent effect, +++strong dose-effect
2 Selected example
3 Percentage of quality aspects present among total possible
4 Ranking for strength of evidence evaluation, high quality marked by *
For more information see Appendix

TABLE 2. ITEMS FOR QUALITY ASSESSMENT

1. Study population

a. Cases and controls were drawn from the same population
b. Co-variates were designated
c. Eligibility criteria were specified
d. Attrition rate was similar in each group in cohorts

2. Assessment of exposure to tobacco smoke

a. Smoking status was defined
b. Smoking status was validated by more than self-report
c. Quantity consumed was measured
d. Duration of use was measured
e. Those who assessed smoking status did not know the tuberculosis outcome

3. Assessment of Passive smoking

a. Passive smoking exposure was clearly defined
b. A valid measurement was used to determine passive exposure
c. Non-exposure was unlikely to be misclassified

4. Assessment of tuberculosis outcome

a. A valid definition was used for the tuberculosis outcome
b. Assessment of the outcome was reproducible
c. A valid measurement of the tuberculosis outcome was used
d. Those who assessed the tuberculosis outcome did not know the individual's tobacco use history

5. Study design

a. The design was adequate to measure an association
b. Information was given about those lost to follow-up
c. Effect of co-variables was measured
d. Follow-up was long enough for outcomes to occur
e. Results were consistent with data

6. Analysis and data presentation

a. Appropriate analysis was performed
b. Dose-effect calculations were made
c. Adjustment for confounders was presented
d. Importance of loss to follow-up on outcomes was described

TABLE 3. MEASURING THE STRENGTH OF EVIDENCE: NUMBER OF STUDIES SHOWING SIGNIFICANT EFFECTS OF TOBACCO USE ON TUBERCULOSIS OUTCOMES AND NON-SIGNIFICANT RESULTS

Number of studies	Tuberculosis outcome	High quality studies			Other studies			Strength of evidence
		Co-hort	Case-control	Cross-section	Co-hort	Case-control	Cross-section	
8	**Infection**	–	**1**	**4**	–	–	3	**Limited**
	Significant	–	–	–	–	–	–	
	Non-sig							
21	**TB Disease**	**2**	**8**	**2**	1	6	1	**Strong**
	Significant	–	–	–	–	–	1	
	Non-sig							
3	**Recurrent TB**	**2**	–	–	–	–	–	**Moderate**
	Significant	–	–	–	–	1	–	
	Non-sig							
2	**Patient Delay**	–	–	–	–	–	1	Not enough
	Significant	–	**1**	–	–	–	–	
	Non-sig							
2	**Default**	–	**1**	–	–	1	–	Not enough
	Significant	–	–	–	–	–	–	
	Non-sig							
3	**Smear conversion**	–	–	–	–	–	1	Not enough
	Significant	–	–	–	1	–	1	
	Non-sig							
2	**Severity**	–	**1**	–	–	1	–	Not enough
	Significant	–	–	–	–	–	–	
	Non-sig							
2	**Drug resistant tuberculosis**	–	–	**1**	–	1	–	Not enough
	Significant	–	–	–	–	–	–	
	Non-sig							
2	**Death during/ after treatment**	**1**	–	–	–	–	–	Not enough
	Significant	–	–	–	–	1	–	
	Non-sig							
5	**Mortality due to tuberculosis**	–	**2**	–	1	2	–	**Limited**
	Significant	–	–	–	–	–	–	
	Non-sig							

TUBERCULOSIS AND TOBACCO: JOINING EFFORTS TO CONTROL TWO GLOBAL EPIDEMICS

The systematic review presented in the previous chapter demonstrated that there are adverse associations between the global tuberculosis and tobacco epidemics, in that active and passive exposure to tobacco smoke is associated with TB infection, disease and mortality. While the review had limitations and further research is clearly warranted into aspects of the association and into the biological mechanisms linking tobacco exposure to TB outcomes, the association itself is now beyond doubt.

The recognition of associations between the HIV/AIDS and TB epidemics was followed by concerted efforts to integrate interventions at both the clinical and strategic levels, which have since been reflected in the new Stop TB Strategy and the Global Plan to Stop TB 2006-2015 as well as the strategic framework to control TB/HIV.

The recognition of associations between the TB and tobacco epidemics likewise makes it imperative to carefully consider exposure to tobacco in efforts to reduce risks for tuberculosis. Both tuberculosis and tobacco use demand concerted and effective responses. Tobacco control efforts need to be fully implemented everywhere, and as the review indicated, another reason for urgency has been found for such efforts in areas where the population is at risk for tuberculosis.

This chapter explores the possibilities and advantages of joint initiatives on TB and tobacco control. Its objectives are:

- to describe the scope of TB and tobacco control programmes in order to find points of common action between both programmes, and
- to propose the active clinical and managerial involvement of the TB national programmes in tobacco control, mostly in primary health care settings.

1. TUBERCULOSIS CONTROL AND THE STOP TB STRATEGY

A strategy for effective TB control, called DOTS, was developed in the early 1990s by WHO, other international cooperation agencies, The Union and other NGOs.

These institutions established the Stop TB Partnership in 2000 and developed an inter-agency global programme to accelerate the expansion of the DOTS strategy and improve the quality of TB control services(1). The specific interventions to control TB are case management, chemoprophylaxis in selected population groups and BCG vaccination of the newborn.

Case management that comprises case finding, diagnosis and treatment is the most effective, feasible and affordable intervention for TB control in all situations. The fundamental case finding method in limited resource settings is direct sputum smear microscopy and the most recommended treatment is patient-centred short-course chemotherapy. To be effective the case management intervention should be implemented in such way that at least 70% of the estimated incidence of smear positive cases are detected and 85% of these cases are cured after treatment.

Despite remarkable progress made in achieving the targets of the case management intervention, a 2005 analysis of the foreseeable trends of the problem indicated that the DOTS strategy alone was not sufficient to achieve the 2015 TB-related Millennium Development Goals (MDG). A revised strategy, addressing the major constraints to achieving global TB control targets and enlarging the DOTS reach, has been developed(2,3).

The new Stop TB Strategy has six principal components:
Pursue quality DOTS expansion and enhancement aimed at improving case finding and cure through an effective patient-centred approach to reach all patients, especially the poor. To this end, the strategy now emphasizes:

- political commitment at national and local levels with increased and sustained financing to support TB control and increasing the competence and availability of human resources to undertake DOTS tasks;
- strengthening the laboratory network capacity for sputum smear microscopy and phased introduction of culture and drugs susceptibility testing;
- standardized short-course chemotherapy with a major focus on patient support to ensure adherence to treatment;
- national drug management systems that guarantee regular supply of quality-assured drugs;
- a system to closely monitor programme performance and periodically evaluate achievement of TB-related epidemiological MDGs.

Address TB/HIV, MDR-TB and other challenges by:

- scaling up implementation of TB/HIV collaborative activities in countries with a high burden of TB/HIV, particularly in Africa;
- implementing preventive and restorative strategies to combat mycobacterial resistance to TB drugs, including careful introduction of second-line drugs with laboratory support to stop the circulation of resistant strains;
- designing programmes to control TB in high risk groups such as household contacts, prisoners, migrants and displaced populations.

Contribute to health systems strengthening by:

- actively participating in efforts to improve system-wide policy. Human resources, financing, management, service delivery, and information systems;
- sharing innovations that strengthen systems, including the Practical Approach to Lung health (PAL). PAL aims at improving the quality of respiratory care in PHC settings as well as the efficiency of care delivery system to manage acute and chronic respiratory conditions, including TB. PAL implies standardization of clinical care procedures and coordination among the various components of the district health system;
- adapting innovations from other fields.

Engage all health care providers, public, non-governmental and private by scaling up approaches on a public-private mix (PPM) to ensure adherence to the International Standards of TB Care. Depending on the setting, this approach may include health services under insurance schemes, health systems for prisons, army and security forces, NGO health facilities, private companies' health services, private clinics and the informal private health care sector.

Empower people with TB and affected communities to contribute to effective care by facilitating case finding, improving access to diagnostic services, fostering a patient-centred approach to treatment that motivates patient's compliance, reducing stigma and enhancing political commitment. In many countries, civil society is regarded as an essential partner in providing support to patients and their families.

Enable and promote research for the development of new drugs, diagnostics and vaccines. Operational research is also addressed to improve programme performance.

2. TOBACCO CONTROL AND THE WHO TOBACCO FREE INITIATIVE

The Tobacco Free Initiative (TFI) was established by WHO in 1998 to focus international attention, resources and action on the global tobacco epidemic and to coordinate tobacco control activities with the member states, other international agencies and NGOs. The same year, the United Nations (UN) established an Ad Hoc Inter-Agency Task Force on Tobacco Control, chaired by WHO, to coordinate tobacco control work carried out by 17 agencies of the UN system and two organizations outside the UN system.

In 1999 WHO started to work towards an international treaty that would respond to the globalization of the tobacco epidemic. The spread of the tobacco epidemic is exacerbated by a variety of complex factors with cross-border effects, including trade liberalization, direct foreign investment, global marketing, transnational tobacco advertising, promotion and sponsorship, and the international movement of contraband and counterfeit cigarettes. In 2003 this international treaty, The WHO Framework Convention on Tobacco Control (WHO FCTC), was adopted by the world assembly. Today the WHO FCTC has already been ratified by more than 140 countries(4).

The WHO FCTC sets standards and guidelines for interventions to reduce the demand for tobacco and interventions to reduce the supply in order to decrease tobacco consumption, nicotine addiction and exposure to tobacco smoke. Set out below are the measures identified as the most effective and feasible interventions for tobacco control.

2.1. Core interventions to reduce demand(5)

Applying price and tax increases

Raising the real price of tobacco and tobacco products - primarily through tax increases - is the single most effective measure to reduce consumption. There is a clear inverse relationship between tobacco taxes and tobacco consumption. As a general approximation, for every 10% increase in cigarette taxes, there is about a 2-4% reduction in consumption in high-income countries and 6-8% reduction in low- and middle-income countries. Young people and low-income smokers are two to three times more likely to quit or smoke less than other smokers after price increases(6).

Providing protection from exposure to tobacco smoke

Smoke-free policies in public places and workplaces not only protect non-smokers from second-hand smoke and create a non-smoking social norm in which adolescents grow, they also reduce tobacco consumption by 3-4% at least in high income countries(7). Therefore, the creation of 100% smoke-free environments is an essential component of any strategy to control tobacco use. Legislative and administrative measures should be adopted and enforced in order to provide 100% smoke-free environments in all indoor workplaces, public transport and public places.

Banning tobacco advertising, promotion and sponsorships

Direct and indirect advertising of tobacco products attracts new smokers, most commonly from among the ranks of the young. It encourages smokers to smoke more, reduces their will to quit smoking, and induces ex-smokers to resume smoking. It furthermore helps create an environment of social normalcy of the use of tobacco and promotes political opposition to tobacco control among the beneficiaries of marketing expenditures, mainly the media. The only effective measure that can be applied to tobacco advertising and promotion is a comprehensive ban of every form of promotion of the tobacco products(8,9). National-level studies before and after advertising bans found a decline in tobacco consumption of up to 16%(10,11,12,13).

Regulating the packaging and labelling of tobacco products

Each tobacco product package should carry large, clear and visible health warnings, using rotating messages, on the harmful effects of tobacco use. Half of the smokers intending to quit or reduce their consumption were motivated to do so by warnings on cigarette packets in Canada. The display of prominent health warnings on tobacco packages becomes an effective vehicle for health promotion messages. Seen by every smoker several times a day, packages are a communication tool that reaches every tobacco consumer giving education about the harmful effects of tobacco use(14). In addition, tobacco products should not use any term, descriptor, trademark, figurative or any other sign that directly or indirectly creates the false impression that a particular tobacco product is less harmful than other tobacco products. These may include terms such as "low tar", "light", "ultra-light" or "mild".

Raising public awareness of tobacco risks

Large and sustained information and advocacy campaigns increase public awareness of the health risks of smoking and of secondhand smoke, the addictive nature of tobacco and the benefits of quitting tobacco. This intervention includes effective and appropriate training or sensitization and awareness programmes on tobacco control addressed to health community and social workers.

Treating tobacco dependence

In view of the addictiveness of tobacco products, many tobacco-users will need support in quitting. Support for treatment of tobacco dependence refers to a range of techniques including motivation, advice and guidance, counselling, telephone and internet support, and appropriate pharmaceutical aids, all of which aim to encourage and help tobacco users to stop using tobacco and to avoid subsequent relapse. The success of these interventions is substantially enhanced when they are part of a comprehensive tobacco control strategy(15).

2.2. Core interventions to reduce supply

Controlling the illicit trade of tobacco products.

Cigarette smuggling causes considerable harm: international brands become available at very affordable prices for low-income consumers and illegal cigarettes evade legal regulations and do not pay taxes. Efforts to curb illicit trade usually require the coordination of law enforcement and customs agencies.

For tobacco control to succeed, a comprehensive approach, using a mix of the core interventions, is needed. In low- and middle-income countries, as well as in any high-income country, price measures and smoke-free environments are the most cost-effective way of reducing consumption, followed by non-price measures such as comprehensive bans on tobacco advertising and promotion, strong warning labels and dissemination of information.

3. ACTIVE INVOLVEMENT OF TB CONTROL PROGRAMME IN TOBACCO CONTROL

The major scope of action of the TB and tobacco control programmes are quite different. TB control focuses primarily on case management intervention which takes place within the health system and mainly in the context of the delivery of health care services. Tobacco control is a combination of mostly population-based interventions to disincentivate tobacco use by means of communication, advocacy, taxation, legislation and law enforcement. However, tobacco control also offers individually-based interventions through the health care system, where TB control is most likely to occur.

For a TB control programme to be effective, the health care system cannot be indifferent to tobacco control efforts. The TB programme can involve itself in tobacco control both in the clinical setting where TB patients are diagnosed and treated and outside the clinical setting.

3.1. Inside the clinical setting

In the clinical setting three types of actions should be considered: providing treatment of tobacco dependence for TB patients, making the clinic where TB patients are treated for tobacco dependence smoke free and taking managerial decisions to overcome barriers in the health system to institute treatment for tobacco dependence.

3.1.1. Treatment services

The range of effective treatments for tobacco dependence include brief routine advice to stop by health-care professionals, more intensive support to quit (given individually or in groups), and pharmacological approaches. The specific combination of treatments depends on the patient's needs. Brief routine advice and some pharmacological treatments can be offered routinely by the medical staff in charge of managing TB patients in primary health care services.

3.1.1.1. Brief routine advice

Routine advice is predicated on the basis that every patient should be asked if he or she smokes and those who smoke should be advised to quit. People who smoke should be asked how interested they are in quitting and if so, assistance should be provided. People who are not ready to quit should be asked to consider the possibility and encouraged to seek help in the future. Advice to stop smoking should be sensitive to the individual's preferences, needs and circumstances.

A number of programmes have adopted the brief intervention methodology called "Five As Approach". It consists of five steps: **A**sk, **A**dvice, **A**ssess, **A**ssist and **A**rrange. It takes between 5 and ten minutes to implement for each patient. Box 1 presents the five steps of this brief intervention adapted to the TB programme.

STEP 1. **Ask** if the patient smokes.

The initial primary intervention for smoking cessation in a health unit setting is systematic identification of smokers. This is important among new TB and other respiratory condition patients. Every such patient should be questioned on their tobacco use and a record created on whether the patient never smoked or whether the patient is a current daily, or current occasional or a former smoker.

STEP 2. **Advise** the patient to quit.

Although any health professional has the duty to advise any smoker who is a patient attending a health unit, the responsibility is more imperative for health professionals taking care of patients who suffer from conditions or problems closely related to tobacco smoking. Pulmonary TB is a case in point because of the benefits for the effective treatment and lasting cure of TB;

Every TB patient who smokes should be offered counselling. Simple advice from a clinician has been shown to increase abstinence rates significantly (by 30%) compared to no advice(16). There is a strong dose-response relationship between the intensity of tobacco dependence counselling and its effectiveness. Every TB patient who smokes should also be informed of the damage that the smoke he/she generates can do to others.

After being advised, each identified smoker should be followed up by querying and recording the patient's current willingness to stop smoking and with the diagnosis of tobacco addiction(17).

STEP 3. **Assess** the patient's willingness to quit
Ask each patient if he or she wants to quit and if the patient is willing to quit within the next month, proceed to the next step. For patients unwilling to quit tobacco use when they are informed of the TB diagnosis and treatment, the health professionals should promote more intense motivation to quit. The patient may have fears or concerns about quitting at the same time that she/he is distressed for the fact of suffering from a stigmatic disease and starting a long treatment; the patient may also be demoralized because previous quit attempts had failed and may feel that it is almost impossible to stop smoking; generally, the patient has no confidence in their ability to quit. The patient may respond to counselling by the health professional developed around the "Five Rs": relevance, risks, rewards, roadblocks and repetition. (See Box 3).

STEP 4. **Assist** the patient in making a quit attempt
A smoker suffering from a lung-related disease experience such as TB is frequently motivated to quit smoking; health professionals should strengthen such motivation, provide advice on cessation, agree on a quit date and propose and provide treatment. By quitting, the patient will directly benefit because the risks of future relapse will be less and the probability of disease among the infected household relatives are likely to decrease in a tobacco free environment. Smokers also benefit in other ways from quitting smoking, such as improved senses of smell and taste and increases in disposable income. Such "rewards" are listed in Box 3.

STEP 5. **Arrange** for taking the matter up again on the occasion of the next visit for TB treatment follow-up (see Box 2).

All health professionals attending TB patients should be able to Assist and Arrange. However, professionals of the same unit may want to consider assigning such cessation activities to a specific member of the staff at the health unit.

If the TB patient is a non-smoker, the health professional can also offer a brief routine intervention to help address exposure to SHS. The health professional can take the following steps:
STEP 1. **Ask** if the patient is exposed to SHS and record their response.
STEP 2. **Advise** the patient about the dangers of SHS.
STEP 3. **Assess** the patient's possibility to remove him/herself from an indoor environment polluted with SHS, especially at home
STEP 4. **Assist** the patient in making an attempt to make their daily life environment smoke-free, especially at home by talking to family members.

3.1.1.2. Intensive support
In urban health centres or hospitals with a large number of TB patients under treatment, it might be feasible to organize sessions of group counselling about smoking cessation or provide more intensive behavioural interventions to patients highly addicted or with co-morbidities to improve quit rates. Such interventions required specialized health professionals and are outside the scope of this monograph.

Box 1: The "Five As" Counselling Approach. Guidelines for health professionals taking care of TB patients To Ask, To Advise, To Assess	
Ask about tobacco use	Smoking is an important aspect of a TB patient's status and it is therefore relevant to find out whether the patient is a current or a former smoker, or has never smoked. • Ensure that tobacco use status is queried and documented for every new or relapse TB patient when the diagnosis is made and the TB treatment is started. • Register the information on tobacco use (current daily, current occasional, former, never) in the patient's TB Treatment Card.
Advise to quit	If the TB patient does smoke, find out that she/he is aware of the value of stopping and the health risks associated with continuing smoking, including for the present TB disease. Quitting is even more important when the patient is a pregnant woman or if the patient has associated conditions such as HIV infection, diabetes, asthma, chronic bronchitis or COPD. • Help TB patients who smoke to understand how the health harm of smoking applies to them. • It is important to the patient to attempt to quit at the same time she/he starts treatment for TB. Cutting down is not enough. • To quit will be very important for the lasting success of the TB treatment. • It has many other health benefits for the patient and for the family. • It also brings economic savings.
Assess willingness to make a quit attempt	Assess the smoker's motivation to stop: • Ask every new or relapse tobacco user TB patient if she or he is willing to make a quit attempt at this time, within the next few days. • Review reasons for quitting (health, risks for children and others in home, cost, psychological freedom from dependence). • Foster confidence that the patient is able to quit. • Communicate care and concern. • In a clear and strong manner advise the tobacco user TB patient to quit. • Ask then directly whether the patient is willing to quit.

Box 2: The "Five As" Counselling Approach. Guidelines for health professionals taking care of TB patients To Assist, To Arrange

Assist in quit attempt	Counsel the patient about a plan to quit smoking: • Set a stop date within the next week and stop completely that day. Total abstinence is essential. Not even a single cigarette after the quit date should be tried. • Review past experience and learn from it what helped and what did not help, what led to relapse, what triggers smoking: emotional distress, wanting to feel better, temptation or urges, social pressure. • Alcohol often leads to relapse. Review its use. Plan to limit or abstain while quitting smoking. • Request relatives who accompany the patient understanding and support. Smokers at home should quit with the patient or not smoke in her/his presence. • Anticipate likely difficulties and nicotine withdrawal symptoms during the critical first few weeks (irritability, headache, dizziness). Plan how to cope with them. • Ask to remove cigarettes and ash trays from home
Arrange follow-up	Follow-up is important in maintaining motivation and providing support. • If the TB patient has to visit the health unit every day for the supervised intake of TB drugs, set a day after one week to talk again about the quit attempt. • Schedule subsequent talks every month during the 6- or 8-month period of the TB treatment. • If tobacco use has occurred, review circumstances and start total abstinence again. Failures can be used as a learning experience.

Box 3: The "Five Rs" Counselling Approach for patients unwilling to quit smoking. Guidelines for health professionals taking care of TB patients

Relevance	• Encourage the patient by stressing that quitting will be beneficial for the permanent cure of TB. • Personal motivated information has the greatest impact because it is relevant to the patient's disease and to the health of the household contacts, especially if there are children. • Quitting is even more important when the patient is a pregnant woman or the patient has associated conditions such as HIV infection, diabetes, asthma, chronic bronchitis or COPD.
Risks	• First of all point out the risks of continuing to smoke for a TB patient: risks of relapse especially within the first 6 months after treatment has been completed. • The risks for disease among the household contacts who are already infected, especially children, if they are exposed to a tobacco environment at home. • The risks of worsening associated conditions when they are present in TB patients and/or household members: harm to pregnancy, increased susceptibility to respiratory infections for a HIV-positive patient, cardiovascular complications of diabetes, exacerbations of asthma, chronic bronchitis or COPD. • Long term risks: heart attacks, strokes, lung and other cancers, long term respiratory disability and need for long term care.
Rewards	Ask the patient to mention potential benefits of stopping tobacco use beyond the benefits related to her/his TB disease. Underscore the most relevant ones, for instance: • Feel better about oneself at the same time that TB is being cured and perform better in physical activities • Save money • Food will taste better and the sense of smell will be improved • Integration with non-smokers • Set a good example for children
Roadblocks	Ask the patient to mention obstacles to quitting. Often obstacles include • Withdrawal symptoms • Fear of failure • Weight gain • Depression and missing the enjoyment of tobacco
Repetition	• The motivational counselling. should be repeated often for patients who remain unmotivated to quit tobacco use. • If the patient has to attend daily or three times a week the health unit for the supervised TB drug intake, it is easy to arrange for counselling sessions, at least once a month. • For a patient whose treatment is supervised outside the health unit, the counselling session should be provided each time she / he attends for clinical and bacteriological follow-up.

3.1.1.3. Pharmacological interventions

Many patients can successfully quit smoking with the help of the counselling by health professionals. However, many smokers can't and could benefit from pharmacotherapy, if available and affordable. Pharmacological therapy may be relevant for TB patients who might suffer from withdrawal symptoms together with the disease symptoms that will still be present for several weeks after the start of TB treatment.

There is a wide range of medication options that have been proved effective for both men and women. However, special consideration should be given to some patient groups before using pharmacotherapy. Some patients may have medical contraindications (see below under each drug). Two groups of patients should be considered for pharmacological treatment with great care: pregnant women and adolescents.

Whenever possible, pregnant women smokers should be offered intensive counselling, psychosocial support and pregnancy-specific self-help materials. Quitting at any point in pregnancy can yield benefits to the fetus and expectant mother. Pharmacotherapy may be considered for pregnant women smokers who have been unable to quit using psychosocial interventions.

Counselling and behavioural interventions shown to be effective with adults should be considered for use with child and adolescent smokers. However, the content of these interventions should be adapted to the psychological young age of the smoker. If there are signs of obvious nicotine dependence, some pharmacotherapy may be used.

For optimal effectiveness, drug therapy always requires counselling and behavioural support. For any population, the cost of short-term pharmacotherapy is much less than the cost of long-term smoking.

Nicotine replacement therapy

Nicotine replacement therapy refers to medication containing nicotine that is intended to replace, at least partially, the nicotine formerly obtained from tobacco and thereby making it easier to abstain from tobacco use. This medication reduces general withdrawal symptoms and provides some effects for which the patient previously relied on smoking such as handling stressful or boring situations. Usually the replacement medication can be discontinued within three months after smoking cessation.

There are several replacement therapy delivery systems. The efficacy of the various products is similar. Thus the prescription will be based on availability, cost and patient's preference.

- Transdermal patch, with varying doses and different durations of wear (i.e. 16 or 24 hours). They may produce local skin reactions (erythema, mild edema) and sleep disturbance if a 24-hour patch is used. Rotation of patch sites may help limit skin irritation. There are high-doses patches for heavy and more nicotine-dependent tobacco users.
- Chewing gum that is intermittently chewed and held in the mouth over 30 minutes. There are 2-mg and 4-mg dosage forms. A gum should be chewed on a fixed schedule, for instance, 10 times a day.
- Lozenge that dissolves in the mouth over approximately 30 minutes. There are 2-mg and 4-mg formulations. It does not require chewing.
- Sublingual tablet, 2-mg dosage, to be held under the tongue where the nicotine is absorbed sublingually.

- Oral vapour inhaler comprises a mouthpiece and a plastic cartridge containing nicotine. The majority of nicotine is not inhaled but delivered into the oral cavity. Very little nicotine is delivered to the lungs. Frequent puffs are required, between 6 and 16 cartridges a day containing 10 mg nicotine.
- Nicotine nasal spray, a multi-dose bottle with a pump mechanism fitted to a nozzle that delivers the nicotine into the nose. Each spray contains 0.5 mg of nicotine. The dosage is one to two sprays per hour in each nostril, with a maximum of 40 doses per day. The most common adverse reaction is nasal and throat irritation.

Non-nicotine medications

The non-nicotine medications are indicated in those patients who are unable to tolerate, who have failed or who do not want to use nicotine replacement products. The use of these drugs requires experience and their prescription is not recommended for non-specialized medical professionals

- Bupropion Hydrochloride Sustained Release formulation is a non-nicotine aid to smoking cessation originally developed and marketed as an antidepressant. It is contraindicated in patients with a seizure disorder, or bulimia or anorexia nervosa.
- Clonidine is an alpha-2-adrenergic agonist used as an antihypertensive medication, but also documented as an effective second-line medication for smoking cessation because it diminishes some tobacco withdrawal symptoms. However its usefulness is limited by a high incidence of side effects.
- Nortriptyline is an antidepressant that may be efficacious, as second line pharmacotherapy for smoking cessation. It has important side effects.
- Varenicline represents an entirely new class of drug with probably a different mechanism of action than either nicotine replacement therapy or bupropion. It provides clinicians and smokers with pharmacological alternatives. It is a partial agonist that binds to a specific nicotinic acetylcholine receptor, the alpha4 beta2 subtype(18). Varenicline is associated with higher smoking cessation rates than placebo and may produce better cessation rates than bupropion, a first-line–approved smoking cessation drug. Importantly, varenicline represents a third class of drug

3.1.2. Delivering TB services in smoke-free environments

The TB control community must promote and enforce a policy of smoke-free environments for all places where services are delivered to TB suspects and TB patients: waiting room, outpatient room, room for directly observed treatment, hospital ward, TB laboratory, TB registry room. This policy should be followed in the health services of the Ministry of Health and other ministries, social security facilities and the offices of NGOs, and should be strongly recommended for the private companies health services and private clinics treating TB patients. If the smoke-free environment policy has not yet been adopted by the health authorities of the different institutions that provide TB care services, the NTP must be a strong advocate for the adoption of that policy in any health service.

3.2. Managerial support to the Stop TB implementation of tobacco control activities in primary health care settings

The NTP and the National Tobacco Control Programme should collaborate in areas of mutual concern in their support to general health service providers. A collaborative approach of the NTP and the National Tobacco Control Programme should use available health care providers throughout the whole health system to ensure integrated care of TB and smoking cessation.

3.2.1. Policy development and planning

The Ministry of Health should establish coordination mechanisms between the Technical Advisory Groups of the NTP and the National Tobacco Control Programme[2] as well as between the Inter-Agency Coordinating Committees of both Programmes . A Working Group with representatives of the two Technical Advisory Groups will have the responsibility of:

- developing technical and operational policies for the identification of smokers and treatment of tobacco dependence among TB patients in primary health care settings;
- planning the managerial support to enable health care providers to perform these activities, solve problems and achieve the objectives;
- building the institutional capacity necessary to ensure the sustainability of the joint activities of the NTP and the National Tobacco Control Programme.

The participation of all the institutions and organizations, including the private sector (with the exception of the tobacco industry and its allies) , in the joint activities of the two national Programmes will be secured through the review of the policies and action plans by the two Inter-Agency Coordinating Committees. The members of both Committees will bring together a variety of experience in technical, managerial and communication matters and ensure the linkages among the MOH, other ministries, social security agencies, cooperation agencies, NGOs, health professional associations and the private sector. These Committees shall always act to protect the policies and plans with respect to tobacco control from commercial and other vested interests of the tobacco industry.

The **policy document** should include information on:

- The magnitude of the TB and the tobacco use problem in the country. The relationship between tobacco use and the TB epidemiological problem. The prevalence of tobacco smokers in the general population as well as among the new and relapse cases of TB in the country.
- The national strategies for the control of TB and the control of tobacco use.
- The objectives of the joint activities of the NTP and the National Tobacco Control Programme.
- The technical guidelines for the identification of smokers and treatment of the nicotine dependence (counselling, behavioural therapy, pharmacotherapy) that can be used by the health care providers who diagnose and treat TB at first level health facilities and first referral hospitals.
- The availability of specialized referral services for intensive treatment of nicotine dependence in the health system of the country.
- The information system that should be implemented to gather data to measure selected indicators for monitoring and evaluating the tobacco control activities carried out by the Stop TB programme.
- Guidelines on how to implement a smoke free policy in the premises where TB patients are treated.

The **action plan** can be a chapter or annex of the NTP plan or an independent document with cross references to it. Tobacco dependence assessment and treatment among TB patients should be an integral element of the new strategy to control TB. The action plan should describe the managerial process to implement the guidelines recommended in the policy document, first in the infrastructure of the MOH, and subsequently in the health services that take care of the TB patients of

2 For the purpose of this monograph National Tobacco Control Programme refers to formal or informal governmental structure or structures with responsibility in tobacco control. Given the recent emphasis in tobacco control, not all countries have a formally structured National Tobacco Control Programme and when they have it the degree of development varies considerably across countries.

other ministries, social security agencies, NGOs and the private sector. The action plan should specify the coordinating mechanisms at regional and district levels, the responsibilities of the NTP and the National Tobacco Control Programme in the managerial activities to implement the plan (training, supervision, logistics, communication, monitoring, evaluation), the share of the budgetary needs and the timetable for implementation.

The policy document and the action plan can be prepared as working documents to be presented to a national seminar of:

- Programme managers and technical staff of the NTP and the National Tobacco Control Programme and other related departments such as Primary Health Care, Health Education and Chronic Diseases.
- Managers of other ministries health services: Education, Justice (prisons), Social Welfare, Armed and Security Forces.
- Pneumonologists and public health experts from academic societies, health sciences schools, communication schools and health professional associations.
- Representatives of the management of health services in social security agencies, NGOs and large private corporations.
- Representatives of international and national cooperation agencies.

The seminar can review the policy document and the action plan and make recommendations on them to the MOH, other ministries and other relevant institutions that provide health care to TB patients.

3.2.2. Training on joint activities of the NTP and the National Tobacco Control Programme

Successful implementation of the joint activities of the NTP and the National Tobacco Control Programme depends largely upon the availability of human resources with the knowledge and skills to:

- Identify tobacco smokers and treat nicotine addiction among TB patients at first level health facilities and first referral hospitals and elsewhere in the health system.
- Provide technical, operational and budgetary support from the managerial levels to health professionals at the services delivery level regarding the joint activities of the two programmes.

The TB training courses for health centre and health post staff, for district level managers and for central level programme managers should include a module addressing the knowledge and skills needed to perform the activities at each level related to the joint activities for TB and tobacco control. The content of the module should be consistent with the national guidelines of both Programmes as included in this monograph concerning the joint activities. The module should be developed in such a way that it can be used as an integral part of the corresponding TB courses or as a separate material to be used in courses especially organized to train in TB and tobacco control joint activities.

In training staff responsible for the delivery of health care, a major emphasis should be laid on raising awareness of the benefits of smoking cessation interventions. This should include developing an understanding of the behavioural changes needed in health units to implement the recommended methods of assessing the smoking behaviour of TB patients, providing advice on quitting smoking and assisting patients to quit smoking. Trainers should have experience in tobacco dependence treatments. The main areas of expertise are:

- Knowledge of smoking and the damage it does.
- An understanding of addiction and the ways it can be treated.
- An understanding of the psychology of behavioural change.
- Skills in using a patient-centred approach and counselling.

The teaching methods should be participatory with experiential exercises and role plays. The WHO publication "Encouraging stopping smoking"(19) or the generic course on Helping Smokers Change(20), developed by the WHO Regional Office for Europe, can be taken as a model to be adapted to any country conditions.

The module for training managerial staff at district level should provide information about the epidemiological relationship between smoking and TB and the policies on smoking cessation interventions. The module should include training in skills for planning and implementing the introduction of these policies in the TB case management services, supervision of the health unit staff and monitoring of the activities.

The module for training staff at central level should provide the knowledge and skills included in the module for district level staff, plus information on planning, budgeting and evaluation at national level, coordination among different ministries and agencies, development of educational materials, advocacy and promotion on smoking and TB.

Health professionals have an important role as models for patients. Health professionals who smoke and who provide services to TB patients should participate in cessation treatment programmes to stop their own tobacco addiction permanently.

3.2.3. Supervision of tobacco control activities among TB patients

Supervision is an extension of training and should be intensified after training to ensure that the health workers are implementing the skills taught in the training courses. Supervision of joint TB and tobacco control activities should be included in the checklist for supervision of the TB control programme at the district managerial level and at all health units delivering diagnostic and treatment services to TB patients.

3.2.4. Counselling methods

An important component of the tobacco control intervention in health delivery services is counselling to encourage patients who are smokers to quit and patients who are non-smokers to avoid exposure to SHS by creating smoke-free environments at home and at work.

Effective communication with patients and others such as their families depends on their ability to understand the terms used by the health professional and to respond in words understood by the health professional. Ethnographic and other sociocultural studies can provide guidance on the local terms used by people regarding smoking, what they know about the health effects of smoking and their attitudes towards tobacco use.

Effective communication also requires that the health professional treats the smokers with respect and understanding, listens to them and expresses interest in both their recovery from TB and their quitting smoking. If the patients feel that they are understood, it will be easier for them to ask questions about issues they do not understand.

Health professionals can be provided with printed materials like brochures displaying the steps of the "5 As" to identify TB patients who are smokers and assist them to quit, and the steps of the "5 Rs" to motivate patients who are reluctant to quit.

The NTP and the National Tobacco Control Programme should also produce educational materials addressed to TB patients who smoke.

3.2.5. Monitoring, evaluation, surveillance and operational research

Monitoring, evaluation, surveillance and operational research are major managerial activities of the NTP and the National Tobacco Control Programme.

Monitoring

The main objectives of monitoring are to verify whether the health units carry out the identification and assessment of smoking patterns among new and recurrent TB cases and whether they implement the smoking cessation treatments as specified in the national policies on joint activities of TB and tobacco control.

The first step in a monitoring plan is the selection of key indicators. The second step is to identify a source of information within the information system or to establish an evaluation method (or procedure) such as regular surveys to measure the selected indicators. The most relevant indicators are:

- Number and percent of health units with at least one health professional formally trained on smoking assessment and cessation treatments.
- Number and percent of health professionals dealing with TB cases at primary health care settings who have been formally trained in smoking assessment and cessation treatments.
- Number and percent of new and recurrent pulmonary TB patients whose smoking has been assessed and registered.
- Number and percent of new and recurrent pulmonary TB cases who are current smokers and who have been given brief routine counselling to quit smoking.
- Number and percent of new and recurrent pulmonary TB cases who are current smokers who have been given both brief routine counselling and pharmacotherapy to quit smoking.

The health professional should register the information of the smoking behaviour of pulmonary TB cases, the acceptance or non acceptance to make a quitting attempt, and the cessation treatment given on the TB Treatment Card. This information may be reported to the District TB Register to facilitate the tabulation of data.

Evaluation

The main objective of evaluation is to measure the success rate of the smoking cessation treatments among pulmonary TB patients at the end of the TB chemotherapy, and if it is feasible, at the end of the first year after TB treatment completion through, for example, a survey. The main indicators that can be measured from the information registered on TB Treatment Cards are:

- Number and percent of pulmonary TB cases who received brief routine counselling as smoking cessation treatment and were non-smokers at the end of TB treatment.
- Number and percent of pulmonary TB cases who received brief routine counselling plus pharmacotherapy as smoking cessation treatments and were non-smokers at the end of TB treatment.

The following indicators should be measured through special surveys designed to follow-up TB patients after treatment:

- Number and percent of pulmonary TB cases who received brief routine counselling as smoking cessation treatment and were non-smokers one year after the end of TB treatment.
- Number and percent of pulmonary TB cases who received brief routine counselling plus pharmacotherapy as smoking cessation treatments and were non-smokers one year after the end of TB treatment.

Another evaluation indicator is:

- Number and percentage of health units attending TB patients that are completely smoke-free

Surveillance

Surveillance is the managerial activity addressed to document and analyse the situation and trends of the epidemiological indicators related to risk factors, occurrence and spread of disease that are pertinent to effective control. The main epidemiological indicators, related to tobacco smoking and TB, are:

- Prevalence of daily and occasional smoking among new and recurrent pulmonary TB cases. This indicator can be measured from the information registered in the TB Treatment Cards
- Prevalence of non-smokers among new and recurrent TB cases that report breathing SHS in indoor workplaces, public places, or homes during the last 7 days. This indicator can be measured from the information registered in the TB Treatment Cards
- TB relapse rates during the first year after completion of TB treatment among smokers, non-smokers and smokers who quit during treatment. This information has to be collected through special surveys.

Operational research

Special research studies can be carried out to measure evaluation and surveillance indicators when the information needed cannot be reliably obtained from the information system. For instance:

- Awareness of the health risks associated with tobacco use among the TB patients at the start and at the end of chemotherapeutic treatment
- Prevalence of TB among contacts of smear positive pulmonary TB cases comparing contacts of homes where nobody smokes with contacts of homes where there is at least one smoker.

The special research studies should be undertaken with the participation of scientific and academic institutions that can assist in designing, implementing and analysing research projects. These institutions can also provide equipment and technology needed for research such as statistical software and other computer tools.

3.2.6. Extending tobacco control through the Stop TB strategy

In view of the excellent progress made in expanding the DOTS strategy within the health system of more than 180 countries, Stop TB is being called on to play a spearhead role in the introduction of tobacco control activities in the case management of TB patients in the health care delivery units. The aim is the gradual extension of counselling and nicotine dependence treatment activities from TB patients to other respiratory patients through the Practical Approach to Lung Health (PAL).

PAL is a syndromic approach to the management of patients with respiratory symptoms, intended for implementation by multi-purpose health workers, nurses, doctors, and managers in PHC settings in low-and middle income countries. The objectives of PAL are to improve the quality of respiratory case management for the individual patients and to improve the efficiency and cost-effectiveness of respiratory care within district health systems. Key components of PAL are the standardization of health service delivery through the development and implementation of clinical practical guidelines, coordination among different levels of health care and the integration of TB control programmes with the organization and management of general health services.

A number of countries which have achieved a high degree of success in implementing the Stop TB strategy have started to plan and implement PAL activities within their primary health care systems. Tobacco smoke is one of the most important air pollutants affecting the integrity of the respiratory host defence and predisposing to frequent respiratory infections, in particular pneumonia, and to chronic respiratory diseases.

Therefore, identification of smokers and cessation treatments are essential components of the PAL strategy included in the WHO (21,22) and the national PAL guidelines(23).

By far the most important cause of chronic bronchitis and COPD is tobacco smoking. Quitting smoking is the most important measure in the treatment of these chronic respiratory diseases.

Smoking is a common contributory factor that increases the risk of developing asthma in susceptible patients and in triggering asthma exacerbations. Therefore identification of smokers and treatment of tobacco dependence is of paramount importance in the case management of asthma.

If tobacco control activities are successfully implemented at primary health care services through the Stop TB strategy namely through the PAL strategy, they can gradually be extended to other patients under the technical responsibility of other programmes such as Maternal Health, Cardiovascular Diseases, Cancer and Diabetes until encompassing any person attending a health unit for curative or preventive care.

3.3. Engaging in tobacco control beyond the clinical setting

Health professionals and their organizations can significantly contribute to improving the health status of their patients beyond the health care services. All health professionals -individually and through their professional associations- have a prominent role to play in tobacco control. They have the trust of the population, the media and opinion leaders, and their voices are heard across a vast range of social, economic and political arenas.

At the individual level, health professionals should be tobacco free role models and peers can encourage each other to this end. They should help educate the population on the harm of tobacco use and exposure to secondhand smoke.

At the community/local level, health professionals can initiate or support some of the policy measures described above, by engaging, in efforts to: promote smoke-free workplaces and smoke-free public transport; persuade local governments to ban tobacco advertising and promotion; and to make cultural and sports events tobacco-free.

At the national and international levels, health professionals and their organizations can add their voice and their weight to national and global tobacco control efforts like tobacco tax increase campaigns and become involved at the national level in promoting the WHO Framework Convention on Tobacco Control (WHO FCTC) and the development of a national plan of action for tobacco control.

In addition, health professional organizations can show leadership and become a role model for other professional organizations and society by embracing the tenants of the Health Professional Code of Practice on Tobacco Control.

4. CONCLUSIONS

Since there is a relation between the tobacco and the TB epidemic, the NTP and the National Tobacco Control Programme have mutual concerns. Opportunities must be created within the health care system to provide every TB patient who is a smoker encouragement and help to overcome the tobacco addiction. In addition every TB patient who is not a smoker must be made aware of the consequences of being exposed to secondhand smoke. Both Programmes have a duty to support the health delivery services to fulfil the responsibility in providing such assistance in the period during which the patient is treated with anti-TB chemotherapy. Through the identification and treatment of tobacco addiction among TB patients, higher levels of lasting treatment success will be achieved. NTP should also support tobacco control beyond the clinical interventions.

In turn, any progress achieved by the National Tobacco Control Programme in implementing effective population-based policies will reduce the prevalence of smokers in the population and will have an impact on TB infection, morbidity and mortality rates.

The National Tobacco Control Programme should also contribute to improving the NTP performance stressing TB-related issues in the information and advocacy campaigns about the health dangers of tobacco use and exposure to tobacco smoke, especially in countries where pulmonary TB is highly prevalent and people have a clear perception of this disease threat.

Code of practice on tobacco control for health professional organizations

Preamble: In order to contribute actively to the reduction of tobacco consumption and include tobacco control in the public health agenda at national, regional and global levels, it is hereby agreed that health professional organizations will:

- Encourage and support their members to be role models by not using tobacco and by promoting a tobacco-free culture.
- Assess and address the tobacco consumption patterns and tobacco-control attitudes of their members through surveys and the introduction of appropriate policies.
- Make their own organizations' premises and events tobacco-free and encourage their members to do the same.
- Include tobacco control in the agenda of all relevant health-related congresses and conferences.
- Advise their members to routinely ask patients and clients about tobacco consumption and exposure to tobacco smoke, using evidence-based approaches and best practices, give advice on how to quit smoking and ensure appropriate follow-up of their cessation goals.
- Influence health institutions and educational centres to include tobacco control in their health professionals' curricula, through continued education and other training programmes.
- Actively participate in World No Tobacco Day every 31 May.
- Refrain from accepting any kind of tobacco industry support – financial or otherwise – and from investing in the tobacco industry, and encourage their members to do the same.
- Ensure that their organization has a stated policy on any commercial or other kind of relationship with partners who interact with or have interests in the tobacco industry through a declaration of interest.
- Prohibit the sale or promotion of tobacco products on their premises, and encourage their members to do the same.
- Actively support governments in the process leading to signature, ratification and implementation of the WHO Framework Convention on Tobacco Control.
- Dedicate financial and/or other resources to tobacco control – including dedicating resources to the implementation of this code of practice.
- Participate in the tobacco-control activities of health professional networks.
- Support campaigns for tobacco-free public places.

Adopted and signed by the participants of the WHO Informal Meeting on Health Professionals and Tobacco Control; 28-30 January 2004; Geneva, Switzerland.

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Author, year, place, (ref.)	Research question	Measure of TB outcome	Study numbers and population source	% M	Age	Co-variables measured
TUBERCULOUS INFECTION Case-control studies						
*Anderson et al, 1997, USA (7)	Role of smoking in TB infection among prisoners	TST >10mm or >5mm for HIV+	233 prisoners in South Carolina 116 infection 117 controls	95% men	Range 17-54; mean: 30.5 years	Age, sex, race, HIV, alcohol use, drug use, SES crowding, disease history, exposure to TB; active smoking, quantity, duration smoked
Cross-sectional studies						
*den Boon et al, 2005; South Africa (8)	Role of smoking in TB infection	TST >10mm	2401 adults from high risk urban communities	38% men	≥15 years	Age, sex, BMI, SES, quantity and duration of smoking in pack years
*Hussain et al, 2003; Pakistan (9)	Risk factors, prevalence of TB infection in prisoners	TST ≥10mm ≥15mm for BCG-vaccinated	425 male prisoners in North West Frontier Province	100% men	Range 18-60; mean: 35 yrs	Age, SES (education) Crowding, duration of incarceration, sharing of personal effects, contact with TB in prison, BCG scar; Tobacco quantity
McCurdy et al, 1997; USA (10)	Factors in tuberculin reactivity	TST ≥10mm	296 migrant farm workers tested for reactivity to PDP	41% men	All ages, mean: 27.9 years	Age, sex, SES (education) place of birth, language, crowding, years in agriculture, n° months lived in US during past year; Past and current smoking
Nisar et al, 1993; UK (11)	Factors in tuberculin reactivity	TST (Heaf test) ≥10mm	2635 residents of nursing homes in Liverpool	25% men	Range 22-104, median age: 83 years	Age, sex, crowding, length of stay in nursing home, general well-being, prior TB, cough, general mental state, immunosuppressive medication; Current and past smoking, pack years

Author, year, place, (ref.)	Significant factors	Adjusted Tobacco effects	Adjustment for co-variates (X=present)				
			Age	Sex	Alcohol	SES	Other
TUBERCULOUS INFECTION Case-control studies							
*Anderson et al, 1997, USA (7)	Unadjusted: Older age, formerly unemployed risky living conditions, alcohol use, longer duration of smoking	Current smoking: ns Quantity since incarceration: ns Quantity before incarceration: ns Duration ≤15 years: ns Duration >15 years: OR 2.12 (1.03-4.36); p<0.05	X	X	–	–	Risky living conditions; race
Cross-sectional studies							
*den Boon et al, 2005; South Africa (8)	Higher income; Adjusted significant factors: male sex, ages 25-34, 35-44, 45-54; pack years of smoking	< 5 pack years: OR 1.77 (1.33-2.35) 5-15 pack years: OR 1.77 (1.25-2.50) >15 pack years: OR 1.90 (1.28-2.81)	X	X	–	–	–
*Hussain et al, 2003; Pakistan (9)	In multivariate logistic regression: Ages 34-42 or >42 yrs; illiterate, >2 yrs' incarceration, <60 ft² (5.5m²) accommodation, tobacco quantity	1-5 cigarettes/day OR 2.6 (1.6-4.4) 6-10 cigarettes/day OR 2.8 (1.6-5.2) >10 cigarettes/day OR 3.2 (1.3-8.2) Dose-effect	X	X	–	X	Crowding
McCurdy et al, 1997; USA (10)	In multivariate logistic regression for observed reactivity: only former smoking; age, sex, place of birth ns	Multivariate logistic regression for observed reactivity: Current smoker OR 1.87 (0.73-4.80) ns Former smoker OR 3.11 (1.20-8.09)	X	X	–	–	Place of birth
Nisar et al, 1993; UK (11)	Younger age, males sex, smoking, current and past smoking, pack years (graphical data)	Heaf test positivity (unadjusted) Ex-smokers: 1.20 Current smokers: 1.59 95% confidence intervals not given	–	–	–	–	–

Author, year, place, (ref.)	Research question	Measure of TB outcome	Study numbers and population source	% M	Age	Co-variables measured
TUBERCULOUS INFECTION Cross-sectional studies						
*Plant et al, 2002; Australia (12)	Predictors of TST reactivity	TST: >5 mm >10 mm >15 mm	1395 Vietnamese emigrants entering Australia	24% men	Range 16-81 mean: 29.1 years	Age, sex, BMI, SES (education); English proficiency, crowding, home living conditions, prior TB, contact TB; Past and current smoking, quantity and duration of smoking, abstinence duration
*Singh et al, 2005, India (13)	Risk factors, prevalence of TB infection in children	TST ≥10mm	281 children <5 years old of parents with TB 140 smear – 141 smear+	54% boys	Means Cases: 3.2 yrs Control 3.5 yrs	Age, sex, BCG, height, weight, TB symptoms, degree of malnutrition, TB in household; Exposure to passive smoking
Solsona et al, 2001; Spain (14)	Factors and prevalence of TB infection among the homeless in Barcelona	TST: >5 mm for BCG vaccinated	447 people entering homeless shelters	88% men	Range 14-69 Means: M:45.6 F:40.5 years	Age, sex, alcohol use, IVDU; current smoking

Author, year, place, (ref.)	Significant factors	Adjusted Tobacco effects	Adjustment for co-variates (X=present)				
			Age	Sex	Alcohol	SES	Other
TUBERCULOUS INFECTION Cross-sectional studies							
*Plant et al, 2002; Australia (12)	Age, male sex, productive cough, ever smoking (past+current), duration of smoking, ≥6 cigarettes/day,	Adjusted Odds ratios TST 5mm: Ever smoker OR 2.31 (1.58-3.38) p<0.001 Years (duration) of smoking OR 1.09 (1.04-1.14) p<0.01 ≥6 cig/day OR 2.60 (1.08-6.26) p<0.05 Adjusted odds ratios TST 10mm Ever smoker: OR 1.53 (1.13-2.09) p<0.01 Years (duration) of smoking: OR 1.04 (1.02-1.07) p<0.01 Adjusted odds ratios TST 15mm Years (duration) of smoking: OR 1.03 (1.004-1.06) p<0.05 Dose-effect	X	–	–	–	Age squared
*Singh et al, 2005, India (13)	Multivariate logistic regression: Age <2 yrs severe malnutrition, No BCG scar, contact with smear+ adult, exposure to passive smoking	Exposure to passive smoking OR 2.68 (1.52-4.71) p=0.0003	X	X	–	–	Malnutrition Smear positivity of parent with TB, no BCG scar
Solsona et al, 2001; Spain (14)	Older age, male sex, alcohol use, current smoking. IVDU too infrequent to calculate. In multivariate logistic regression, alcohol and sex were not significant	In multivariate logistic regression Smoker OR 1.72 (1.02-2.86)	X	X	X	–	–

Author, year, place, (ref.)	Research question	Measure of TB outcome	Study numbers and population source	% M	Age	Co-variables measured
TUBERCULOSIS DISEASE Cohort studies						
*Chang et al, 2001; China, Hong Kong Special Administrative Region (Hong Kong SAR), China (16)	Risk factors for tuberculosis among silicotics	New PTB: smear + and other criteria	707 patients with silicosis	99% men	Range 29-84 mean: 53 yrs; median 60.5 years	Age, sex, work history, exposure to silica, history of TB; diabetes mellitus, lung/other cancers, partial gastrectomy, chronic renal failure; Current and past smoking, pack years
Hnizdo et al, 1998; South Africa (17)	Prevalence and risk factors for TB in relation to silicosis and exposure to silica	New PTB smear +, other criteria; Other PTB	115 TB cases among white male gold miners (exposed to silica)	100% men	Range 45-83 years mean birth yr 1919	Age, exposure to silica dust and duration of exposure, silicosis; Current smoking, pack years
*Leung et al, 2004; China, Hong Kong Special Administrative Region (Hong Kong SAR), China (18)	Role of smoking on TB among the elderly in China, Hong Kong Special Administrative Region (Hong Kong SAR)	New PTB: Smear +, other criteria; extra-pulmonary TB	42,655 elderly in health services	73% men	65+ mean: 73 yrs	Sex, age, SES (education, spending/mo, public financial aid, work status, housing,), language, marital status, alcohol use, self-rated health status, social activities, hospital admission within 12 months, diabetes mellitus, COPD, hypertension, heart disease, CVD; current and past tobacco smoking

Author, year, place, (ref.)	Significant factors	Adjusted Tobacco effects	Adjustment for co-variates (X=present)				
			Age	Sex	Alcohol	SES	Other
TUBERCULOSIS DISEASE Cohort studies							
*Chang et al, 2001; China, Hong Kong Special Administrative Region (Hong Kong SAR), China (16)	Logistic regression: No history of TB, progressive massive fibrosis, small opacity, caisson work, smoking in pack years	Logistic regression on all significant variables: Adjusted RR for smoking in pack years: All TB: RR 1.012 (1.005-1.019) p=0.019 Smear+TB: RR 1.009 (0.997-1.018)	ns	ns	–	–	All significant variables included in logistic regression
Hnizdo et al, 1998; South Africa (17)	Adjusted RR for PTB, whole cohort: silicosis, cumulative exposure to silica dust, smoking in pack years	Risk ratio of cumulative smoking (measured in pack years) in this population for PTB: 1.02 (1.01-1.03)	X	–	–	–	Cumulative exposure to dust, radiologically diagnosed silicosis
*Leung et al, 2004; China, Hong Kong Special Administrative Region (Hong Kong SAR), China (18)	Not measured: all included in adjusted Hazard ratio for tobacco effect	Adjusted hazard ratio for current smokers Pulmonary TB: 2.87 (2.00-4.11) New TB-no past treatment 2.61 (1.80-3.80) Active TB 2.63 (1.87-3.70) Culture confirmed TB 2.80 (1.82-4.31) Quantity Active Culture+ ≤4 cig/day 1.00 1.00 5-9 cig/day 1.45 3.61 10-14 cig/day 2.29 5.08 ≥15 cig/day 2.80 5.32 χ^2 for trend p=0.01 Dose-effect	X	X	X	X	All others

Author, year, place, (ref.)	Research question	Measure of TB outcome	Study numbers and population source	% M	Age	Co-variables measured
TUBERCULOSIS DISEASE Case-control studies						
*Alcaide et al, 1996; Spain (19)	Role of smoking as risk factor for TB in young adults	New PTB: Smear+, other criteria; Other PTB	92 close contacts of TB cases and TST>5mm: 46 cases with TB, 46 control with no sign of TB disease	52% men	Range 15-24 years	Age, sex, SES (occupation, social class index) Active and/or passive exposure, quantity smoked
*Altet et al, 1996; Spain (20)	Role of passive smoking in TB disease among children	New PTB: smear+, smear–, other criteria; Other PTB	188 children in close contact with TB cases for at least 6 months; TST >10mm, no BCG 93 cases with TB, 95 control with no sign of disease	51% boys	Range 0-14 years	Age, sex, SES (father's, mother 's occupations, own family home, n° rooms), crowding, past respiratory disease, cavity or not, AFB grading, frequency of contact, TB in household, relation index case to child, smoking occurs at home (Exclusion of those with other disease)
*Ariyothai et al, 2005; Thailand (23)	Role of smoking in TB in adults >15 in Thailand	New PTB: Smear +,	200 patients: 100 TB cases and 100 controls, other patients matched for sex	63% men	15+ means: cases: 32.9, control 33.6 years	Age, SES (education, income, occupation) alcohol use, marital status, BMI, HIV, diabetes mellitus, crowding at home, home environment, n° family members, TB in household, BCG scar; Active and passive smoking, ever smoking, duration, consumption

Author, year, place, (ref.)	Significant factors	Adjusted Tobacco effects	Adjustment for co-variates (X=present)				
			Age	Sex	Alcohol	SES	Other
TUBERCULOSIS DISEASE Case-control studies							
*Alcaide et al, 1996; Spain (19)	In multiple logistic regression with age, sex, SES, tobacco measures, only active smoking significant: OR 3.8 (1.5-9.8) p<0.01	Adjusted ORs. Active Smoking (daily+occ) OR 3.6 (1.5-2.2) p<0.01 Smoking daily OR 3.5 (1.3-9.3) p<0.01 Passive smoking OR 2.5 (1.0-6.2) ns Active smoking (daily + occ) + passive: OR 5.1 (2.0-13.2) p<0.01 Active daily smoking+passive OR 5.6 (2.1-15.1) p<0.001 Dose-effect	X	X	–	X	–
*Altet et al, 1996; Spain (20)	Father's manual occupation; younger age, exposure to tobacco	Adjusted ORs Passive smoking: OR 5.21 (2.31-12.62) Both parents smoke: OR 7.40 (2.81-20.09) In multiple logistic regression Passive smoking OR 5.39 (2.44-11.91) p<0.00005. Passive exposure/day 1-20 cigarettes: OR 1.61 (0.66-2.63) ns 21-40 cigarettes: OR 3.95 (1.59-9.80) p<0.01 >40 cigarettes: OR 7.76 (3.40-17.60) p<0.001 Dose-effect	X	X	–	X	Close contact with TB, housing, crowding, n° children, n° family members who smoke
*Ariyothai et al, 2005; Thailand (23)	Age, alcohol use, house environment, TB in family, BMI, BCG scar, current smoking, started smoking younger age, smoked over 10 years, smoked more than 10 cigarettes per day, smoke >3 days/week	Adjusted OR Passive smokers OR 2.37 (0.94-6.01) ns .Ex-smokers OR 2.88 (0.85-9.78) ns. Current smokers OR 2.70 (1.04-6.97). Age started 15-20: OR 3.2 (1.2-8.8). Smoked >10 years: OR 4.0 (1.3-12.6). Smoke >3 days/week OR 2.7 (1.01-7.1). Among passive smokers. Outdoor exposure>3 time/week OR 3.1 (1.07-9.17) Office neighbourhood exposure >3 times/week: OR 4.62 (1.47-14.51) Dose-effect	X		X	X	Close contact with TB; Only house environment and BMI changed the odds ratios for tobacco to a great extent

Author, year, place, (ref.)	Research question	Measure of TB outcome	Study numbers and population source	% M	Age	Co-variables measured
TUBERCULOSIS DISEASE Case-control studies						
*Buskin et al, 1994; USA (24)	Risk factors for TB in adults 15+	New PTB: smear+, other criteria, non-defined TB	696 patients: 151 cases with TB; 545 control patients	Similar to gen pop.	17 years	Age, sex, SES (education, income, type of residence), race, BMI, quantity of alcohol consumed, HIV, pancreatitis, pneumoconiosis, diabetes mellitus, partial gastrectomy, TB in household, Current and past smoking, duration and quantity
*Crampin et al, 2004; Malawi (25)	Risk factors for tuberculosis related to gender	New PTB: Smear positive, other criteria; extra-PTB	606 people with data on smoking history: 185 cases with new TB 421 controls from general population	46% men	15+ years	Age, sex, SES (education, occupation, household possessions score) marital status, crowding: household size score, TB identified in household, Other contact with TB cases, HIV/AIDS, alcohol use, exposure to biomass cooking fuels, burning insect repellent; Current smoking and quantity
*Kolappan et al, 2002; India (26)	Role of smoking in TB among male adults 20-50 in India	New PTB: Smear+, culture+	544 men from 30 villages in Tamil Nadu: 85 cases of new smear ot or culture positive TB 459 controls	100% men	15+ means: cases: 32.9, control 33.6 years	Age; Current smoking, quantity and duration, age of initiation, type of smoking (bidi or cigarette)

Author, year, place, (ref.)	Significant factors	Adjusted Tobacco effects	Adjustment for co-variates (X=present)				
			Age	Sex	Alcohol	SES	Other
TUBERCULOSIS DISEASE Case-control studies							
*Buskin et al, 1994; USA (24)	Longer duration of smoking	Adjusted for age and heavy alcohol use 30+ years' smoking OR 2.6 (1.1-5.9) All other tobacco measures (current and past smoking, quantity, shorter duration) ns	X	–	X	–	–
*Crampin et al, 2004; Malawi (25)	Adjusted OR HIV+, Marital status (single), moved in last 5 years, higher housing construction score, higher household size score, occupation, lower household possessions score, TB identified in household, current or past use of alcohol, frequent smoked fish, past smoking, biomass fuel exposure	Risk for TB adjusted for age, sex, area: Ex-smoking: OR 1.9 (1.1-3.5) Adjusted for age, sex, area, HIV, no smoking variable remains significant.	X	X	–	–	Area
*Kolappan et al, 2002; India (26)	Current smoking, quantity and duration	Adjusted OR for smear or culture positive pulmonary TB: Smoking: OR 2.24 (1.27-3.94) $p<0.05$ 1-10 cigarettes/day OR 1.75 11-20 cigarettes/day OR 3.17 >20 cigarettes/day OR 3.68 χ^2 linear trend, $p< 0.0001$ <10 years' smoking OR 1.72 11-20 years OR 2.45 >20 years OR 3.23 χ^2 linear trend, $p<0.0001$ Dose-effect	X	–	–	–	–

Author, year, place, (ref.)	Research question	Measure of TB outcome	Study numbers and population source	% M	Age	Co-variables measured
TUBERCULOSIS DISEASE Case-control studies						
Leung et al, 2003; China (27)	Role of smoking in adult PTB in China, Hong Kong Special Administrative Region (Hong Kong SAR)	New PTB: smear+, other criteria, other PTB	8686: 851 notified TB cases;7835 gen. house-hold survey controls	50% men	14+ years	Stratified for age and sex. Race weight, SES (employment status, type of occupation), contact with TB, alcohol use, IVDU, previous TB, symptoms, smoking
Lienhardt et al, 2005; Guinea, Guinea Bissau, the Gambia (22)	Risk factors for TB in adults 15+ in Guinea, Guinea Bissau and the Gambia	New PTB: smear+, other criteria, other PTB	2325 TB cases and community controls; 1370 for which smoking data available 688 case of new PTB, 688 controls	56% men	Means: Guinea 29.1 years Guinea Bissau 34.6 years Gambia 31.1 years	Age-matched, sex, SES (education, type of school, income, house ownership, items owned, occupation), marital status, alcohol use, drug use, tea in groups, religion, crowding: (n° of people, adults/ room, type of walls, floors, ceilings, n° windows, water source, electricity, latrine in or out of house, waste disposal, HIV, Diabetes mellitus, history and treatment of asthma and worms anaemia, TB contact; Active smoking, ever smoking
Miguez-Burbano et al, 2003; USA (28)	Role of tobacco on respiratory infection in HIV+ patients receiving treatment	New PTB: smear+, other criteria, other PTB	39 HIV+ patients nested in cohort of 259 patients: 12 cases with TB, 27 controls	58% men	Range 32-54 years	Matched on age, sex, race, income. Alcohol, drug use, tobacco variables

Author, year, place, (ref.)	Significant factors	Adjusted Tobacco effects	Adjustment for co-variates (X=present)				
			Age	Sex	Alcohol	SES	Other
TUBERCULOSIS DISEASE Case-control studies							
Leung et al, 2003; China (27)	Only tobacco variables were analysed	Odds ratio of smoking, cases vs controls Men: <65yrs > 2.44 p<0.001; 65yrs 2.09 p<0.001 Females: 2.08 p=0.041; 2.83 p<0.001 M&F weighted: 2.40 (1.71-3.39) p<0.001; 2.19 (1.6-2.98) p<0.001	X	X	–	–	–
Lienhardt et al, 2005; Guinea, Guinea Bissau, the Gambia (22)	Male sex, family history of TB, HIV, history of asthma, 6-10 or >10 adults in household, non-ownership of house, single, active smoking, ever smoking	Odds ratios in Multivariate model for new PTB: Past smoking: 1.53 (1.11-2.10) Current smoking: 2.03 (1.22-3.39) p<0.0003 Dose-effect by duration reported, but no data given	X	–	–	X	Close contact with TB, HIV+, history of asthma, marital status, n° adults in household, BCG scar, ownership of house
Miguez-Burbano et al, 2003; USA (28)	Not given, Duration of smoking	>20 years' smoking: 3x risk of TB, p=0.04	X	X	–	X	Race

Author, year, place, (ref.)	Research question	Measure of TB outcome	Study numbers and population source	% M	Age	Co-variables measured
TUBERCULOSIS DISEASE Case-control studies						
Perez-Padilla et al, 2001; Mexico (29)	Risk of biomass cooking on PTB and factors affecting that risk	New PTB: smear+, other criteria, other PTB	833 patients: 288 TB cases 545 controls: ear, nose, throat patients from same health care service	52% men	Means: Cases 41.6 years Control 36.4 years	Age, sex, SES (occupation, incomeper dependent, education), crowding, place of birth, residence, cooking with wood stove; current and past smoking, pack years, passive smoking
Tekkel et al, 2000; Estonia (21)	Risk factors for pulmonary TB in Estonia	New PTB: The Union standard case reporting	496: 248 TB cases,248 matched population controls	72% men	15+ years median 30-49 years	Matched on sex, ethnicity, birthplace. Age, BMI, SES (education, income, occupation, previous years' economic situation), alcohol use, any drug abuse, other hazardous contacts, crowding: in institution or own home, water sup-ply, sewage system, heating source, diabetes mellitus, otherlung disease, TB identified in household, other contact with TB; current and past active smoking, current and past passive smoke exposure
*Tipayamongkholgul et al, 2005; Thailand (30)	Factors associated in develop-ment of TB among BCG vaccinated children in Thailand	New PTB cases and Extra-pul-monary TB cases diagnosed in govern-ment hos-pital	260 patients: 130 TB cases and 130 control orthopedic patients from same hospitals	58% men	<15 years	Matched for sex and age (±2 years). Underlying disease (measles, chicken pox), birth-weight, nutritional status, SES (each parent's education, family income), crowding in home and bedroom, TB identified in house-hold, degree of exposure to passive smoking

Author, year, place, (ref.)	Significant factors	Adjusted Tobacco effects	Adjustment for co-variates (X=present)				
			Age	Sex	Alcohol	SES	Other
TUBERCULOSIS DISEASE Case-control studies							
Perez-Padilla et al, 2001; Mexico (29)	Exposure to biomass smoke, place of birth, residence, level of education, ever smoking, pack years	In model of risk of biomass smoke exposure, on TB, independent risk of Ever smoking OR 1.5 (1.0-2.3) Pack years OR 1.03 (1.0-1.06)	X	X	–	X	Place of birth, urban, or rural, crowding
Tekkel et al, 2000; Estonia (21)	Divorced or widowed, less education, low income, unemployment, previous imprisonment, residence, heating source, alcohol use, inadequate food, weight loss, TB in household or other contact; active and passive smoking	Adjusted odds ratios Past smoking OR 2.27 (1.00-5.14) Current smoking OR 4.62 (2.44-8.73) Passive smoking at home OR 2.31 (1.25-4.24) Passive smoking at work or at home and at work ns	–	X	–	X	Place of birth, marital status
*Tipayamongkholgul et al, 2005; Thailand (30)	History of TB contact, >5 persons per room, close exposure to passive smoking	Adjusted odds ratios stratified for contact with TB patient Close or very close exposure to passive smoking OR 9.31 (3.14-27.58) p=0.0001	X	X	–	X	For those unexposed to TB: Average n° people/room, Frequency of illness

Author, year, place, (ref.)	Research question	Measure of TB outcome	Study numbers and population source	% M	Age	Co-variables measured
TUBERCULOSIS DISEASE Case-control studies						
Toque et al, 2001; UK (31)	Lifestyle risk factors for TB among adults in Liverpool, UK followed up over time	New PTB: smear+, other criteria	310 patients: 112 TB cases, 198 general practice patients as controls	55% men	Median 55 yrs	Matched on post-code, birthdate (+3 yrs), ethnic origin. Age, sex, SES (employment status, income, home ownership, own luxury items, 1 or more bathrooms), race, nutrition, exercise, alcohol use, vitamin supplements, going outdoors, BCG, holiday or lived abroad, diabetes mellitus, presence of disease, gastrectomy, hypertension, gastric-acid inhibitors,; Active, ever smoking, duration, age of initiation
Toledo et al, 2000; Brazil (32)	Risk factors for TB among HIV infected persons	New PTB: smear+, other criteria	477 HIV+ patients 135 with TB 342 controls	91% men	16-61 years mean: 33.2 years	Matched on age. Sex, race, BMI, SES (income), city of residence, marital status, alcohol use, use of ARV drugs, PPD reactivity, anergy, CD4 count, lymphoadenopathy, respiratory anomalies, Current and past smoking
TUBERCULOSIS DISEASE Cross-sectional studies						
*Adelstein et al, 1967; UK (33)	Role of smoking as a risk factor for TB disease	New TB: smear+	76,589 volunteers for mass miniature x-ray	57% men	15+ years	Age, sex, SES (occupation, address), marital status, medical history; Current and past smoking, quantity, length of abstinence

Author, year, place, (ref.)	Significant factors	Adjusted Tobacco effects	Adjustment for co-variates (X=present)				
			Age	Sex	Alcohol	SES	Other
TUBERCULOSIS DISEASE Case-control studies							
Toque et al, 2001; UK (31)	Unadjusted: Alcohol drinker at time of first interview, non-white race, non-UK birth, lived abroad, no holiday last 10 years, fewer dairy products, fewer salads, vegetables, less high blood pressure, gastric-acid inhibitor intake, lived with someone with TB, ever smoking, duration, quantity of smoking. Multivariate logistic regression: Visitors from country of birth outside UK, lack of dairy products, little time spent outdoors, duration of smoking	Multivariate logistic regression model Smoke >30 years: OR 2.3 (1.2-4.2)	X	X	–	X	Residence, ethnicity
Toledo et al, 2000; Brazil (32)	Unadjusted OR: less income, AID related complex, past history of pneumonia, past hospitalization, lymphoadenomegaly, respiratory anomalies, ARV use, tobacco use; Stratified analysis: Income, past hospitalization, no ARV use	Unadjusted OR Smoking variable: OR 1.3 (1.0-1.6) p=0.05 Tobacco not retained for multivariate analysis	–	–	–	–	–
TUBERCULOSIS DISEASE Cross-sectional studies							
*Adelstein et al, 1967; UK (33)	Rates of TB per 1000 for age, sex, smoking status: older men have higher rates, among smokers of 20cig+/day, higher rates for women than for men	Rates of TB per 1000 All ages Males Females No smoking: 0.42 0.42 1-9 cig/day: 0.62 0.87 10-19 cig/day: 2.03 1.60 20+ cig/day: 2.67 3.52 χ^2 for trend: p<0.01 p<0.001 OR* Unadjusted Adjusted 1-9/day 2.42 1.68 10-19/day 4.43 4.16 20+/day 6.56 6.38 *Calculated by reviewer Dose-effect	X	X	–	–	–

Author, year, place, (ref.)	Research question	Measure of TB outcome	Study numbers and population source	% M	Age	Co-variables measured
TUBERCULOSIS DISEASE Cross-sectional studies						
Gajalakshmi et al, 2003 (Population Survey); India (34)	Association smoking on TB rates in the population	Self-reported TB	305,819 adults in a population survey	100% men	35-69 years	Age, SES (education), past and current smoking, smokeless use, quantity
Shah et al, 2003; Pakistan (36)	Risk factors of TB in juvenile prisoners	New PTB: smear+, other criteria	75 male juvenile prisoners 15 with TB 60 controls	100% men	Range 15-23 Mean: 17.7 years	Nationality, residence, SES (education, father's occupation), crowding: institutional and former living quarters, n° family members in household, TB identified in house-hold, TB contacts in prison, smoking
*Yu et al, 1988; China (35)	Risk factors for TB among sanitary workers in Shanghai, China	New PTB: Smear+, Smear-, other criteria	30,289 sanitation employees	57% men	<30, 50+ years	Age, sex, SES (type of work, area of residence); crowding, , TB identified in household, other exposure to TB, persons at risk, smoking quantity
RECURRENT TUBERCULOSIS Cohort studies						
*Leung et al, 2004; China (cited above for disease) (18)	Role of smoking on tuberculosis outcomes among elderly Chinese	Retreat-ment of TB	42,655 elderly health service attendees in China, Hong Kong Special Administrative Region (Hong Kong SAR)	35% men	Mean: 73 years	Sex, age, SES (education, spending/mo, public financial aid, work status, housing,), language, marital status, alcohol use, self-rated health status, social activities, hospital admission within 12 months, diabetes mellitus, COPD, hypertension, heart disease, CVD; current and past tobacco smoking
*Thomas et al, 2005; India (47)	Predictors of relapse among PTB patients in DOTS	Relapse to PTB 6, 12 or 18 months after treatment	503 smear+ PTB patients	76% men	Range <45, 45+ years	Age, sex, initial weight, SES (education, occupation), alcohol use, drug regularity, drug sensitivity profile, smear conversion at 2 months,initial smear grading

Author, year, place, (ref.)	Significant factors	Adjusted Tobacco effects	Adjustment for co-variates (X=present)				
			Age	Sex	Alcohol	SES	Other
TUBERCULOSIS DISEASE Case-control studies							
Gajalakshmi et al, 2003 (Population Survey); India (34)	Only tobacco variables were analysed	Risk ratios for TB standardized for age, education level, tobacco chewing: Cigarettes: <10/day RR 1.7 (1.4-2.2) >10/day RR 2.6 (2.2-3.1) Bidis <15/day RR 2.9 (2.4-3.6) >15/day RR 4.5 (3.7-5.5) Dose-effect	X	X	–	X	Tobacco chewing
Shah et al, 2003; Pakistan (36)	Adjusted odds ratios: Family history of TB	Adjusted OR : no significant findings for smoking OR 1.59 (0.44-5.37) ns	Not reported				
*Yu et al, 1988; China (35)	Male sex and older age (due to tobacco use), contact with TB, Tobacco consumption	Binomial regression models for TB disease adjusted ORs: Heavy smoking (>400 cig/year) OR 2.17 (1.29-3.63) Smoking at age 50+: OR 2.138 p<0.01 Female smoker: OR1.447 p<0.01 Dose-effect	X	X	–	X	All other co-variates measured
RECURRENT TUBERCULOSIS Cohort studies							
*Leung et al, 2004; China (cited above for disease) (18)	Not measured: all included in adjusted Hazard ratio for tobacco effect	Hazard ratio for current smoking Retreatment for TB: 2.48 (1.04-5.89)	X	X	X	X	All other measured co-variates
*Thomas et al, 2005; India (47)	Stepwise logistic regression found relapse independently associated with irregular treatment, drug resistance, smoking	Unadjusted OR for relapse Smoking: 2.8 (1.5-5.2) p=0.0001; Stepwise logistic regression of smoking, alcohol, drug regularity, drug sensitivity. Smoking: OR 3.1 (1.6-6.0)	–	–	X	–	Drug regularity, drug sensitivity

Author, year, place, (ref.)	Research question	Measure of TB outcome	Study numbers and population source	% M	Age	Co-variables measured
RECURRENT TUBERCULOSIS Case-control study						
Leung et al, 2003; China (cited above for disease) (27)	Role of smoking in adult PTB in China, Hong Kong Special Administrative Region (Hong Kong SAR)	New PTB: smear+, other criteria, other PTB	8686: 851 notified TB cases;7835 gen. house-hold survey	50% men	14+ yrs	Stratified for age and sex. Race, weight, SES (employment, type of occupation), contact with TB, alcohol use, IVDU, symptoms, smoking
TUBERCULOSIS TREATMENT VARIABLES DELAY Case control study						
*Altet-Gomez et al, 2005; Spain (46)	Role of smoking on tuberculosis outcomes	New PTB: smear+; Extra-pulmonary TB	13,038 TB patients	68% men	14+ years median 25-44 years	Age, sex, alcohol use, IVDU, HIV, other pulmonary disease, severity of TB, cavitary lesions, diagnostic delay, length of hospitalization
Cross-sectional study						
Dos Santos et al, 2005; Brazil (48)	Risk factors for treatment delay in Recife	Unacceptable delay >60 days	1105 TB patients	67% men	18+ years median 18-39 years	Age, sex, SES (literacy, income, employment), marital status, alcohol use, crowding: n° persons per household, contact with TB, HIV, haemoptysis, symptom profiles; Current and past smoking
DEFAULT Case-control studies						
*Chang et al, 2004; China (49)	Risk factors for default under DOTs treatment in China, Hong Kong Special Administrative Region (Hong Kong SAR)	Default during TB treatment	408 TB patients 102 defaulters, 306 controls	86% men	Range 15-90 years Mean: 49 yrs	Matched on age and sex. SES (residency, type of employment, unemployment), alcohol use, opiate abuse history, marital status, race, BMI, treatment for HIV, chronic diseases, hospitalization prior to TB treatment, TB treatment side effects, intermittent dose taking, poor adherence 1st 2 months

Author, year, place, (ref.)	Significant factors	Adjusted Tobacco effects	Adjustment for co-variates (X=present)				
			Age	Sex	Alcohol	SES	Other
RECURRENT TUBERCULOSIS Case-control study							
Leung et al, 2003; China (cited above for disease) (27)	Unadjusted Odds ratios for ever smoking and previous TB	No significant effect foundt	X	X	–	–	–
TUBERCULOSIS TREATMENT VARIABLES DELAY Case control study							
*Altet-Gomez et al, 2005; Spain (46)	Results in terms of smoking and TB Male sex, age <65, heavy alcohol, IDVU	There was no difference in delay in diagnosis p=0.2	X	X	X	–	Pulmonary infection site
Cross-sectional study							
Dos Santos et al, 2005; Brazil (48)	Unadjusted OR Unemployment, no weight loss, health district of treatment, Having quit smoking	OR for unacceptable delay Having given up smoking: OR 0.58 (0.43-0.79) p=0.0005 Tobacco was not included in multivariate analysis	ns	ns	ns	ns	Unemploy-ment, weight loss, health district of treatment
DEFAULT Case-control studies							
*Chang et al, 2004; China (49)	Predictive of default p<0.05: History of opiate use, retreatment, initial hospitalization prior to treatment, extent of disease (upper right lobe), use of fixed dose combinations, treatment side effects, poor adherence 1st 2 months, ever smoker. Alcohol not significant Model 1: Ever smoker, retreatment, poor adherence 1st 2 months, treatment side effects Model 2: Ever smoker, Retreatment.	Logistic risk models of default: Model1 based on patient characteristics, initial TB characteristics, and treatment-related factors, Current smokers OR 3.00 (1.41-6.39) p=0.004 Model 2 based on factors available at registration Current smokers OR 3.44 (1.81-6.53) p<0.001 Ex-smokers OR 2.48 (1.09-5.64) p=0.03	X	X	–	–	–

Author, year, place, (ref.)	Research question	Measure of TB outcome	Study numbers and population source	% M	Age	Co-variables measured
DEFAULT Cross-sectional study						
Salami et al, 2001; Nigeria (54)	Risk factors for non-compliance with treatment	Default	1530 smear+ TB patients	52% men	15+ yrs	Age, sex, SES (education, unemployment, occupation), marital status, urban or rural, distance from clinic, in- or out-patient care, Alcohol, HIV, Diabetes mellitus, COPD, bronchial asthma, extent of TB disease at diagnosis, heart failure, previous default, form of TB, free treatment or not, complications of TB; smoking
SMEAR CONVERSION Cohort studies						
Abal et al, 2005; Kuwait (50)	Effect of cigarette smoking on sputum smear conversion in adults	Smear conversion after 2 months' treatment	339 smear+ TB patients in treatment	79% men	All ages	Age, sex, nationality, alcohol use, IVDU, diabetes mellitus, albumin level, TB disease factors: extent of radiological lesions, initial bacillary load; drug regimen, Active smoking, quantity smoked
Cross-sectional study within case-control						
Leung et al, 2003; China (cited above for disease) (27)	Role of smoking in adult PTB in China, Hong Kong Special Administrative Region (Hong Kong SAR)	New PTB: smear+, other criteria, other PTB	8686: 851 notified TB cases; 7835 gen. house-hold survey controls	50% men	14+ yrs	Stratified for age and sex. Race weight, SES (employment status, type of occupation), contact with TB, alcohol use, IVDU, previous TB, symptoms, smoking
Cross-sectional study within a cohort						
Durban, 1999; South Africa (55)	RCT of immuno-therapy with M. *vaccae* during TB treatment	Smear conversion after 2 months' treatment	347 newly diagnosed smear+ patients	70% men	Range 18-65 years Mean 32 yrs	Age, sex, BMI, HIV, BCG scar, smear and culture positivity, chest radiograph grade, smoking

Author, year, place, (ref.)	Significant factors	Adjusted Tobacco effects	Adjustment for co-variates (X=present)				
			Age	Sex	Alcohol	SES	Other
DEFAULT Cross-sectional study							
Salami et al, 2001; Nigeria (54)	Unadjusted: Younger age, old age, male sex, unemployment, unmarried, pre-vious default, mild TB disease, alcohol use, smoking	Unadjusted for non-compliance Smoking: OR 1.61 (1.31-1.98) p<0.001 Final backward regression model best predicting default did not include smoking	–	–	–	–	–
SMEAR CONVERSION Cohort studies							
Abal et al, 2005; Kuwait (50)	Comparing smokers and non-smokers: significant factors in smear conversion: Non-Kuwaiti origin, sputum status	Ever smoking OR 0.472 (0.21-1.06) ns	Not reported				
Cross-sectional study within case-control							
Leung et al, 2003; China (cited above for disease) (27)	Unadjusted Odds ratios for ever smoking Smear conversion: ns Culture conversion: ns	No significant effect found	X	X	–	–	–
Cross-sectional study within a cohort							
Durban, 1999; South Africa (55)	HIV+, age, BMI, smear positivity, smoking,	Hazard ratio for smear conversion Smoking: 0.58 (0.40-0.84) p=0.004	X	X	–	–	All measured co-variates

Author, year, place, (ref.)	Research question	Measure of TB outcome	Study numbers and population source	% M	Age	Co-variables measured
SEVERITY OF TUBERCULOSIS Case-control study						
*Altet-Gomez et al, 2005; Spain (cited above for delay) (46)	Role of smoking on tuberculosis outcomes	New PTB Smear+; Extra-pulmonary TB	13,038 TB patients: 4557 smokers 8481 non-smokers	68% men	14+ years median 25-44 years	Age, sex, alcohol use, IVDU, HIV, other pulmonary disease, severity of TB, cavitary lesions, diagnostic delay, length of hospitalization
Cross-sectional within case-control study						
Leung et al, 2003; China (cited above for disease,) (27)	Role of smoking in adult PTB in China, Hong Kong Special Administrative Region (Hong Kong SAR)	Severity of TB disease smokers/ non-smokers	8686: 851 notified TB cases; 7835 gen. house-hold survey controls	50% men	14+ years	Stratified for age and sex. Race weight, SES (employment status, type of occupation), contact with TB, alcohol use, IVDU, previous TB, symptoms, smoking
DRUG RESISTANT TUBERCULOSIS Case-control study						
Barosso et al, 2003; Brazil (56)	Risk factors for multi-drug resistant TB	Multidrug resistance	319 TB patients 134 MDRTB cases 185 controls (retroactive)	62% men	Means: Cases 39.8 years Control 41.2 years	Matched on age, sex, residence. SES (education, income, water, sanitation), crowding in home, alcohol use, IVDU, TB identified in household, HIV, COPD, Diabetes mellitus, psychi-atric disease, lung cavities, treatment variables, smoking
Cross-sectional study						
*Ruddy et al, 2004; Russia (57)	Risk factors for drug resistance	resistance to isoniazid, rifampicinany resistance, MDRTB new cases	600 MDRTB patients from among smear + TB patients	93% men	18+ years Mean: 36yrs Median 27-47 years	Age, sex, recreational drugs, institutional living or not, HIV, COPD, TB disease variables, current TB treatment, past current smoking

Author, year, place, (ref.)	Significant factors	Adjusted Tobacco effects	Adjustment for co-variates (X=present)				
			Age	Sex	Alcohol	SES	Other
SEVERITY OF TUBERCULOSIS Case-control study							
*Altet-Gomez et al, 2005; Spain (cited above for delay) (46)	Results in terms of smoking and TB Male sex, age <65, heavy alcohol, IDVU,	Adjusted OR effect of smoking More cavitary lesions OR 1.9 (1.6-2.3) p<0.001 By cohort logistic regression model: More hospitalization OR 1.8 (1.5-2.2) p<0.001	X	X	X	–	Pulmonary infection site
Cross-sectional within case-control study							
Leung et al, 2003; China (cited above for disease,) (27)	Not measured, ever smoking compared with other risk factors in multiple regression modelling	Ever smoker Ors for: Cough 1.69 (1.26-2.26) p<0.001 Dyspnea 1.84(1.24-2.75)p=.002 Only EPT 0.31 (0.13-0.71) p=.006 Upper zone involvement 1.67 (1.01-2.77) p=0.047. Cavity 1.76 (1.18-2.63) p=0.005 Miliary involvement 2.77 (1.11-6.95) p=0.030 Positive sputum smear 1.32 (0.98-1.78) ns Positive sputum culture 1.43 (1.07-1.91) p=0.015	X	X	X	–	Absence of contact: Working at onset of illness, history of narcotic abuse, co-existing medical illness
DRUG RESISTANT TUBERCULOSIS Case-control study							
Barosso et al, 2003; Brazil (56)	Multiple linear logistic regression factors for MDRTB: Sanitation connection, n° previous treatments, irregular treatments, lung cavitation,alcoholism + smoking	Multiple linear logistic regression for MDRTB alcoholism+tobacco OR 3.01 (1.4-7.1) p=0.007	X	X	X	–	Sanitation connection, n° previous treatments, irregular treatments, lung cavitation
Cross-sectional study							
*Ruddy et al, 2004; Russia (57)	Mulitvariate analysis of factors for any drug resistance: male sex, previous TB treatment> 4 weeks, current TB treatment, fibrocavity TB, accompanying COPD, HIV+, history of imprisonment, smoking, drug use	Resistance to isoniazid Smoking OR 3.3 (1.2-9.2) p=0.021 No other significant results for smoking	–	X	–	–	previous TB treatment > 4 weeks, current TB treatment, fibrocavity TB, COPD, HIV, history of prison, drug use

Author, year, place, (ref.)	Research question	Measure of TB outcome	Study numbers and population source	% M	Age	Co-variables measured
DEATH DURING OR AFTER TUBERCULOSIS TREATMENT Cohort studies						
*Leung et al, 2004; China (cited above for disease and relapse) (18)	Role of smoking on tuberculosis outcomes over 2 years among elderly Chinese	Tuberculosis mortality after treatment	42,655 elderly health service attendees in Hong Kong of which 1347 deaths	35% men	65+ years	Sex, age, SES (education, spending/mo, public financial aid, work status, housing,), language, marital status, alcohol use, self-rated health status, social activities, hospital admission within 12 months, diabetes mellitus, COPD, hypertension, heart disease, CVD; current and past tobacco smoking
Case-control studies						
Altet-Gomez et al, 2005; Spain (cited above for delay, severity) (46)	Role of smoking on tuberculosis outcomes	New PTB: Smear+; Extra-pulmonary TB	13,038 TB patients 4557 smokers 8481 non-smokers	68% men	14+ years median 25-44 years	Age, sex, alcohol use, IVDU, HIV, other pulmonary disease, severity of TB, cavitary lesions, diagnostic delay, length of hospitalization
MORTALITY DUE TO TUBERCULOSIS Cohort study						
Doll, 1999 (51)	Role of tobacco in disease mortality	Mortality due to PTB	Deaths in cohort of 34000 British male doctors over 40 years according to smoking status	100% men	35+ years	Cause of death of smokers and non-smokers
Case-control studies						
Gajalakshmi et al, 2003; India (cited above for disease) (34)	Association smoking and mortality	Mortality from PTB from records	78,000 males 43,000 cases who died of disease; 35,000 widowers	100% men	25+ years	Age, SES (education), current and past smoking, smokeless tobacco, quantity smoked

Author, year, place, (ref.)	Significant factors	Adjusted Tobacco effects	Adjustment for co-variates (X=present)				
			Age	Sex	Alcohol	SES	Other
DEATH DURING OR AFTER TUBERCULOSIS TREATMENT Cohort studies							
*Leung et al, 2004; China (cited above for disease and relapse) (18)	Only tobacco variables were analysed	Unadjusted Odds ratios TB followed by death among males according to smoking status (Females ns) Males Ex-smoker 4.13 (1.19-14.4) Current smoker 4.66 (1.20-18.0)	–	–	–	–	–
Case-control studies							
Altet-Gomez et al, 2005; Spain (cited above for delay, severity) (46)	Results in terms of smoking and TB: Male sex, age <65, heavy alcohol, IDVU	Deaths among smokers and non-smokers with TB were 7.9% and 8.7%, not statistically different p=0.09	X	X	X	–	Pulmonary infection site
MORTALITY DUE TO TUBERCULOSIS Cohort study							
Doll, 1999 (51)	RR higher for smokers for 22 specific diseases, including pulmonary tuberculosis	Standardized for age and year of observation, risk ratio of death from pulmonary tuberculosis compared to lifelong non-smoker All Smokers: RR 2.8 Ex-smokers: RR 2.0 1-14 cigs/day: RR 1.8 >25 cigs/day: RR 5.0 Dose effect	X	X	–	–	–
Case-control studies							
Gajalakshmi et al, 2003; India (cited above for disease) (34)	Only tobacco variables were analysed	Risk ratios of association with TB mortality Urban area RR 4.5 (4.0-5.0) Rural area RR 4.2 (3.7-4.8)	X	X	–	–	–

Author, year, place, (ref.)	Research question	Measure of TB outcome	Study numbers and population source	% M	Age	Co-variables measured
MORTALITY DUE TO TUBERCULOSIS Case-control studies						
*Lam et al, 2001; China (58)	Association smoking and mortality	Mortality due to TB from records	40,561 notified deaths in 1998 in China, Hong Kong Special Administrative Region (Hong Kong SAR) 27,507 cases who died; 13,054 living controls who registered death	47% men	35+ years	Age, sex, birthplace, SES (education, housing type, occupation, employment status), alcohol use; smoking 10 years previously, quantity smoked
*Liu et al, 1998; China (59)	Association smoking and mortality	Recorded cause of death	275,616 deaths of people whose smoking status known	61% men	35-69 years	Age 35-69, stratified for sex, stratified for urban or rural
Sitas et al, 2004; South Africa (60)	Association smoking and mortality	Mortality due to TB on death certificate; smoking status 5 yrs prior to death	5341 deaths: 4,295 cases of deaths from causes linked to smoking; 1,952	55% men	25+ years	Standardization of age, sex, education, ethnicity, disease

Author, year, place, (ref.)	Significant factors	Adjusted Tobacco effects	Adjustment for co-variates (X=present)				
			Age	Sex	Alcohol	SES	Other
MORTALITY DUE TO TUBERCULOSIS Case-control studies							
*Lam et al, 2001; China (58)	Only tobacco variables were analysed	Adjusted for age and education: Smoking men aged 35-69: RR 2.54 (1.24-5.22) Smoking men aged >70: RR 1.63 (1.01-2.64) Ages 35-69 >70 Quantity M F M F 1-14/day 1.02 2.37 1.31 1.03 15-24/day 2.93 ns 1.42 ns >25/day 6.62 ns 3.26 5.22 rend p<0.001 ns p<0.01 ns Dose-effect	X	–	–	X	–
*Liu et al, 1998; China (59)	Only tobacco variables were analysed	Weighted Risk ratios for TB mortality Men RR1.20 (+.04) Women RR 1.29 (+.08) Men: Quantity Urban Rural 1-19/day 1.24 (+.06) 1.01 (+.06) 20 /day 1.48 (+.07) 1.23 (+.05) >20/day 2.03 (+.04) 1.57 (+.15) Age started smoking <20 1.86 (+.08) 1.25 (+.06) 20-24 1.42 (+.06) 1.18 (+.05) >25 1.22 (+.06) 1.12 (+.06) Dose-effect for men	X	X	–	–	Residence
Sitas et al, 2004; South Africa (60)	Only tobacco variables were analysed	OR for TB mortality Smoking males OR 1.7 Smoking females OR 1.5 Smoking all OR 1.61 (1.23-2.11)	X	X	–	X	Ethnicity

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