Chronic airflow obstruction and respiratory symptoms following tuberculosis: a review of South African studies

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SUMMARY

BACKGROUND: There is renewed interest in the chronic respiratory sequelae of pulmonary tuberculosis (PTB), particularly chronic airflow limitation. A number of South African epidemiological studies have been published, which, although not specifically designed to examine this association, provide useful data on the nature of the relationship.

OBJECTIVE: To review population-based and occupational studies conducted in South Africa that provide estimates of the association between PTB, chronic symptoms and lung function loss.

RESULTS: Two general population and a number of occupational studies were included. Most were able to control for likely confounders. Chronic chest symptoms and lung function loss were consistently associated with PTB, whether measured by self-report or prospectively in cohort studies. Odds ratios (ORs) were higher for chronic bronchitis (range 1.5–7.2) than for asthma (range 0.7–2.2). For spirometrically defined chronic obstructive pulmonary disease, the OR range was 2.6–8.9, depending on definition. Combined obstructive/restrictive lung function loss was the most common functional outcome, with a net obstructive effect. The association of past TB with non-specific bronchial hyperresponsiveness was equivocal.

CONCLUSION: These studies add to the evidence of a strong association between PTB, even if treated, and subsequent airflow obstruction as well as restrictive loss. Unanswered questions include extent of recovery over time, effect modification by smoking and other cofactors, and degree of reversibility by treatment.

KEY WORDS: pulmonary tuberculosis; chronic obstructive pulmonary disease; lung function; occupational

THERE HAS RECENTLY BEEN increased interest in pulmonary tuberculosis (PTB) as a cause of chronic airflow obstruction.1–4 Although PTB has long been known to result in chronic respiratory symptoms and functional impairment,5–8 this relationship appears to have attracted relatively little research interest, presumably because of the declining incidence of TB in industrialised countries and the success of treatment from the 1960s onwards. Even in developing countries with rising TB burdens, the focus of TB control programmes has been on case identification and treatment completion aimed at interruption of the infectious cycle. In this context, post-treatment sequelae are likely to be regarded as a secondary phenomenon. The recent increase in interest in the association between PTB and its chronic sequelae can be attributed to efforts to measure the global burden of the major diseases, including reduced quality of life, disability and costs to the health system. A further stimulus has been the increased attention to chronic obstructive pulmonary disease (COPD), the burden of which is rising in rich and poor countries, and concomitantly an interest in non-tobacco causes of COPD.9,10 Among such non-tobacco causes, PTB is now recognised as an important contributor to chronic airflow limitation and bronchitis in countries with high TB burdens.9,10 South Africa is in the midst of a human immunodeficiency virus (HIV) driven TB epidemic, with an estimated annual incidence of smear-positive TB of 348 per 100 000 population and of all forms of TB of 948/100 000 in 2007, the highest reported country rates in the world.11 Although local population studies of COPD are scarce, a recent investigation of a heavily smoking low-income community in Cape Town revealed a very high prevalence of COPD. Using the Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition of Stage II disease and above (postbronchodilator forced expiratory volume in one second [FEV₁]/forced vital capacity [FVC] ratio < 70% and FEV₁ < 80% of predicted), 22.2% of men and 18.7% of women aged ≥40 years had COPD, the highest of all recorded country prevalence values.12,13
Despite this heavy dual burden of TB and COPD in South Africa, only a few, relatively small clinical studies have been designed to examine the association between PTB and chronic respiratory impairment. An early retrospective study of 71 patients previously treated for PTB found an excess prevalence of obstruction compared to controls, associated with greater radiological abnormality at diagnosis and amount of sputum produced at the time of assessment. Another study of 74 patients with severe active PTB found that while both FEV\textsubscript{1} and FVC improved over the course of treatment, the proportion with restrictive deficit declined while the frequency of obstructive deficit rose. Negative correlations were demonstrated between lung function and radiological abnormality at diagnosis and at treatment completion. In a recent study of 33 patients treated for an average of 20.6 months for multidrug-resistant PTB, 31 (97%) had abnormal spirometry at completion of treatment. Restriction alone and combined obstructive/restrictive deficits predominated. The duration from first diagnosis of TB to treatment completion (mean 51.8 months) was predictive of both radiological damage and lung function loss at end of treatment.

In contrast to these clinical studies, a number of epidemiological studies conducted over the past decade or so, on the association between mainly occupational and environmental risk factors and respiratory disease, have included a measure of past TB. The purpose of collecting this information was typically to control for past TB as a potential confounder rather than interest in TB per se. As a result, many of these studies would not be routinely identified in a literature search on search terms such as TB and COPD.

The objective of this report is to present, in a single review, the findings of a number of epidemiological studies in South African populations in different settings, with the purpose of contributing to our understanding of the association between PTB and chronic respiratory outcomes, including symptoms and lung function loss. Both occupationally based and general population studies are included. Most of these studies involved one or more of the authors of the current review as co-authors. The remaining studies were identified in a recent comprehensive review of respiratory research in South Africa. Measures of effect such as odds ratios derived from logistic regression modelling

### Table 1: Association between history of TB and chronic respiratory symptoms or chronic bronchitis diagnosis in South Africa (cross-sectional study unless indicated)

<table>
<thead>
<tr>
<th>Study author, year, reference</th>
<th>Type of population (n)</th>
<th>TB definition* (sample frequency)</th>
<th>Confounders/covariates controlled</th>
<th>Outcome</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
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</tr>
<tr>
<td>Ehrlich et al., 2004\textsuperscript{17}</td>
<td>National: men (5671), women (8155)</td>
<td>Past TB (2.4%)</td>
<td>Smoking, age, smoky domestic fuel, occupational exposure, education, BMI</td>
<td>Chronic bronchitis</td>
<td>Male: 4.9 (2.6–9.1) Female: 6.6 (3.7–11.7)</td>
</tr>
<tr>
<td>Ehrlich et al., 2005\textsuperscript{18}</td>
<td>National (13826)</td>
<td>Past TB (2.4%)</td>
<td>Smoking, age, sex, smoky domestic fuel, occupational exposure, race, wealth, education, medical insurance, BMI, rural residence</td>
<td>Wheeze Asthma (self-reported)</td>
<td>3.4 (2.5–4.7) 2.2 (1.5–3.2)</td>
</tr>
<tr>
<td>Jithoo, 2006\textsuperscript{19}</td>
<td>Community study (3483)</td>
<td>Past TB (9.7%)</td>
<td>Smoking, age, sex, income, education, BMI, occupational exposure, smoky domestic fuel, cannabis, alcohol use, other diseases, including asthma</td>
<td>Chronic bronchitis Wheeze plus breathlessness</td>
<td>1.5 (1.0–2.3) 1.9 (1.3–2.7)</td>
</tr>
<tr>
<td>Occupational</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Naidoo et al., 2006\textsuperscript{20}</td>
<td>Coal miners (684)</td>
<td>Past TB (doctor diagnosed) (3.0%)</td>
<td>Smoking, age, height, dust exposure</td>
<td>Chronic bronchitis Usual wheeze</td>
<td>7.2 (2.1–24.2) 8.1 (2.7–24.2)</td>
</tr>
<tr>
<td>Adams, 2007\textsuperscript{21}</td>
<td>Fish processing workers (643)</td>
<td>Past TB treatment (13%)</td>
<td>Smoking, age, sex, smoking, age, atopy</td>
<td>Chronic bronchitis Asthma symptoms\textsuperscript{1}</td>
<td>2.3 (0.8–6.8) 0.7 (0.4–1.7)</td>
</tr>
<tr>
<td>Baatjies et al., 2009\textsuperscript{22}</td>
<td>Bakery workers (517)</td>
<td>Past TB treatment (7%)</td>
<td>Smoking, age, sex, atopy</td>
<td>Chronic bronchitis Asthma symptoms\textsuperscript{1}</td>
<td>1.6 (0.4–7.6) 1.3 (0.6–3.2)</td>
</tr>
<tr>
<td>Ross et al., 2010\textsuperscript{23}</td>
<td>Gold miners (cohort 370)</td>
<td>Confirmed TB cases over 4.5 years (50%)</td>
<td>Smoking, age, silicosis, duration of employment, other respiratory diseases</td>
<td>Dyspnoea</td>
<td>2.20 (1.18–4.11)</td>
</tr>
</tbody>
</table>

\textsuperscript{1}Tuberculosis self-reported unless otherwise indicated.

\textsuperscript{2}Recent attack of asthma, or night waking with breathlessness or tight chest.

OR = odds ratio; CI = confidence interval; TB = tuberculosis; BMI = body mass index.
and lung function differences from linear regression modelling were extracted as reported. The use of a variety of measures of PTB and of respiratory outcomes in these studies enabled us to examine features of the relationship between PTB and COPD that are incompletely understood. These data could also contribute to a fuller accounting of the public health consequences and costs of PTB as a chronic disease in a high TB, high COPD burden country.

RESULTS

General considerations

The studies that form the subject of this review are summarised in Table 1 (symptoms) and Table 2 (spirometric measures). The majority are cross-sectional investigations of occupational populations, with two exceptions: an analysis of the relevant data from the national Demographic and Health Survey, and a Burden of Obstructive Lung Disease (BPLD) study in a low-income suburb of Cape Town. Results in one case are further analyses (Baatjies, unpublished) of data already published. The studies included adults only, except for the Demographic and Health Survey, which included adolescents aged 15–17 years.

TB as the exposure was recorded in a number of ways. The cross-sectional studies relied on an interview question regarding recall of past TB, including diagnosis or treatment. The cohort studies were able to use incident TB cases diagnosed and recorded during employment. All the studies included some statistical control for confounding. Potential confounders are those covariates that have known associations with both TB and lung function loss. These include age, tobacco use, low socio-economic status, occupational silica exposure, and smoky domestic fuel. It has also

<table>
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<tr>
<th>Study author, year, reference</th>
<th>Type of population (n)</th>
<th>TB definition* (sample frequency)</th>
<th>Confounders/covariates controlled</th>
<th>Outcome</th>
<th>Association/lung function loss OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population Jithoo, 200619</td>
<td>Community study (847)</td>
<td>Past TB (15.1%)</td>
<td>Smoking, age, sex, education, occupational exposure, BMI, smoking status, asthma</td>
<td>COPD (GOLD Stages I and II) COPD (GOLD Stages III and IV)</td>
<td>2.6 (1.5–4.6) 8.9 (4.2–18.9)</td>
</tr>
<tr>
<td>Occupational Cowie, 199824</td>
<td>Gold miners (cohort 242)</td>
<td>Confirmed TB cases over 4.5 years (22.3%)</td>
<td>Smoking, age, silicosis, smoking history, baseline FEV1</td>
<td>Average annual FEV1 excess loss</td>
<td>29 ml/year</td>
</tr>
<tr>
<td>Hnizdo et al., 200025</td>
<td>Gold miners (27 660)</td>
<td>Recorded TB cases (9.3%)</td>
<td>Age, gender, duration since TB, smoking history, atopy</td>
<td>FEV1: 1: 153 ml 2: 326 ml 3+: 410 ml FVC: 1: 96 ml 2: 286 ml 3+: 345 ml</td>
<td></td>
</tr>
<tr>
<td>Naidoo et al., 200526</td>
<td>Coal miners</td>
<td>Past TB (3.0%)</td>
<td>Smoking, age, sex, smoking history, occupation, dust exposure</td>
<td>Average FEV1, FVC excess loss</td>
<td>FEV1: 20.8% predicted FVC: 13.5% predicted</td>
</tr>
<tr>
<td>Adams, 200721</td>
<td>Fish processing workers (643)</td>
<td>Past TB treatment (13%)</td>
<td>Smoking, age, sex, smoking history, occupation, dust exposure</td>
<td>COPD (GOLD Stages II–IV) NSBH</td>
<td>4.47 (1.54–13.01) 0.81 (0.44–1.50) 8.2 (1.3 – 52.0)</td>
</tr>
<tr>
<td>Baatjies et al., 2009;22 Baatjies et al., unpublished d</td>
<td>Bakery workers (517)</td>
<td>Past TB treatment (7%)</td>
<td>Smoking, age, sex, smoking history, occupation, dust exposure</td>
<td>COPD (GOLD Stages II–IV) NSBH</td>
<td>2.3 (1.0 – 5.3)</td>
</tr>
<tr>
<td>Ehrlich et al., 201127</td>
<td>Gold miners (520)</td>
<td>Radiographic TB (19.4%)</td>
<td>Smoking, age, sex, smoking history, dust exposure, silicosis</td>
<td>Average FEV1, FVC excess loss</td>
<td>FEV1: 347 ml FVC: 264 ml</td>
</tr>
<tr>
<td>Ross et al., 201023</td>
<td>Gold miners (cohort 370)</td>
<td>Confirmed TB cases over 4.5 years (50%)</td>
<td>Smoking, age, silicosis, duration of employment, other respiratory disease, baseline lung function</td>
<td>Average annual FEV1, FVC excess loss</td>
<td>FEV1: 40 ml/year FVC: 44 ml/year</td>
</tr>
</tbody>
</table>

*TB self-reported unless otherwise indicated.
†Included 9 cases on treatment.
‡Results reported are additional analyses that were not included in original article, which are cited here for study details.
COPD = chronic obstructive pulmonary disease; OR = odds ratio; CI = confidence interval; TB = tuberculosis; BMI = body mass index; GOLD = Global Initiative for Chronic Obstructive Lung Disease. See text for definition of stages; FEV1 = forced expiratory volume in 1 s; HIV = human immunodeficiency virus; FVC = forced vital capacity; NSBH = non specific bronchial hyperresponsiveness (provocative concentration of methacholine causing a ≥20% fall in FEV1 < 8 mg/ml).
been suggested that HIV infection may have an inde- pendent effect on chronic airflow limitation.\textsuperscript{32} Of these confounders, age and tobacco use were controlled for in all of the studies. Almost all the studies presented were of socio-economically homogeneous groups, other than the Demographic and Health Survey, where socio-economic status was controlled via a number of indicator variables. Domestic fuel exposure was recorded in only a few studies, but is closely associated with socio-economic status and region of residence, and is likely to be reasonably homo- geneous within a given workforce in the occupation-based studies. HIV infection was recorded in two studies,\textsuperscript{23,25} but was not examined as a confounder in these investigations.

**Tuberculosis and symptom outcomes**

The results were consistent in finding an elevated prevalence of respiratory symptoms among those with a past history of TB compared to those without such a history. Most of the odds ratios (ORs) exceed 2, and in some cases they reached very high values. The association between PTB and cough and phlegm was highly consistent. There was somewhat less consistency with regard to asthma, with two of the workforce studies recording no association when asthma was defined as a recent attack or nocturnal waking with breathlessness and a tight chest (including Baatjies, unpublished)\textsuperscript{21,22} (Table 1).

**Tuberculosis and spirometric outcomes**

These studies were similarly consistent in finding associations between PTB and lung function loss. Three cross-sectional studies found very strong associations when COPD was measured using the definition of GOLD Stage II and above.\textsuperscript{19,21,22} In addition, Jit hoo used as outcomes mild/moderate COPD (GOLD Stages I and II, i.e., FEV\textsubscript{1}/FVC < 70%, 80% > FEV\textsubscript{1} ≥ 50% of predicted) and, separately, severe/very severe COPD (Stages III and IV, i.e., FEV\textsubscript{1}/FVC < 70%, FEV\textsubscript{1} < 50% of predicted). The OR increased from 2.6 to 8.9 on the more severe definition.\textsuperscript{19}

Where both FEV\textsubscript{1} and FVC were measured, the loss was appreciable in both indices, of the order of 30 to 45 ml per year (when measured over time), or between 100 and 350 ml when measured once off. While the net effect was that of obstruction, mixed obstruction/restriction was apparent whenever FVC was measured. The study by Hnizdo et al. is important in that it was able to show progressive loss of lung function with each of one, two or three or more episodes of past PTB in a historical cohort of working miners.\textsuperscript{24} This report also showed that the loss was greatest in the first 6 months after the last episode of TB, and appeared to stabilise by 13 – 18 months. This suggests that there is some recovery in lung function in the first year or so after treated tuberculous disease.

Of the two studies that measured non-specific bron- chial hyper responsiveness as the outcome, one found no association with past TB,\textsuperscript{21} while the other found a moderately strong although imprecise association (OR 2.3, 95% confidence interval [CI] 1.0 – 5.3; Baatjies, unpublished). This uncertain finding contrasts with the very strong association between past TB and COPD on the GOLD definition in both of these studies.

**Modifiers of lung function loss attributable to tuberculosis**

Increased lung function loss with advanced radiologi- cal disease was established in the early literature.\textsuperscript{5 – 8,14} The association of lung function loss with radiologi- cal change was confirmed in the study by Ross et al.\textsuperscript{23} It is of interest that in this study miners with TB who 1) self-presented as opposed to being detected via annual screening, or 2) had a positive as opposed to a negative sputum smear at diagnosis, had greater lung function loss even after controlling for degree of radiological zonal involvement at diagnosis. This sug- gests that features of disease severity other than extent of radiological change are related to subsequent lung function loss. Cavitation may be one such feature.\textsuperscript{33}

It is likely that among gold miners the co-existence of silica dust load in the lung and/or the presence of silicosis contributes to the excess lung function loss of TB. However, the interaction between silicosis and TB is difficult to measure because gold miners with both diseases are required by South African law to be barred from dusty work which, in many cases, would result in their leaving the industry.\textsuperscript{34}

Two studies measured HIV infection status. In the large longitudinal study of gold miners,\textsuperscript{25} the loss of lung function in relation to PTB was not influenced by HIV status. A smaller gold miner study measured HIV infection only among those diagnosed with PTB, with no difference in subsequent lung function loss between HIV-positive and -negative patients.\textsuperscript{23} Interaction between TB and smoking was not formally examined in any of these studies.

**Attributable fractions**

The two population studies were able to compute population attributable fractions (PAF):

\[ p(POR - 1)/[p(POR - 1) + 1] \]

where \( p \) = prevalence odds ratio and \( P \) = popula- tion prevalence of the risk factor.

For chronic bronchitis, the national survey calculated a PAF due to TB of 10% among both men and women.\textsuperscript{17} In the smaller community study of COPD, the PAF due to TB was 24.9% for GOLD Stage II or higher.\textsuperscript{19}

**DISCUSSION**

The findings of these studies are concordant with those of large population studies conducted in Latin
However, the studies reviewed have a number of limitations. Cross-sectional studies of occupational groups suffer from healthy worker survivor effects, through which workers with TB and chronic respiratory illness are selected out of the workforce. However, one would predict that the bias, if any, would be to attenuate any relationship between TB and chronic respiratory illness in the survivor cohort left behind. Cross-sectional studies of two chronic disease processes are also limited in their ability to demonstrate that chronic symptoms or lung function impairment were not present before the episode of TB, or even that the direction of causation is not from COPD to TB. However, where cohort studies were able to separate TB and the measurement of lung function in time, excess decline in lung function among those with past TB was consistently demonstrable.

All of the retrospective studies, whether cross-sectional or cohort, are at risk of symptom over-reporting, i.e., participants with a past history of TB might be expected to over-report current symptoms. There is no support for this bias from the lung function studies, which show effects of TB on lung function loss commensurate with the increased symptom prevalence.

The pathophysiology of these functional sequelae of TB is speculative, but it is likely to be heterogeneous given the spectrum of presentation of active disease and the variety of clinical and radiological sequelae of PTB, including parenchymal fibrosis, chronic bronchitis, bronchiectasis and emphysema. Epidemiological studies are limited in their ability to reflect these distinctions, although some of the findings might suggest routes for further investigation.

While the net effect of TB appears to be obstructive, a restrictive component is clearly also present. In their study of active TB, Plit et al. found that FVC improved to a greater degree than FEV₁ over the course of treatment, implying that successful treatment may prevent restrictive sequelae to a greater degree than obstructive loss.

With regard to obstruction, the findings are consistent with non-reversible obstruction, with a full range of symptoms from productive cough to wheezy breathlessness. The evidence on past TB as a cause of non-specific bronchial hyper responsiveness remains somewhat weak. However, this relationship needs further study, as it has implications for treatment.

There is terminological uncertainty regarding what post-tuberculous lung disease should be called. The GOLD Report is concerned primarily with COPD caused by inhaled particles and gases. Some authors have argued for an aetiologically based definition of COPD, so that, for example, post-tuberculosis COPD would be distinguished from tobacco-induced COPD. Such an approach would be useful for public health purposes, so as to direct attention to preventable causes. It might also play a role in clinical management, although current COPD management protocols do not distinguish between different aetiologies, relying rather on demonstration of symptom relief and reversibility of obstruction to guide treatment. A number of questions remain. Only one study in this review measured the degree of the recovery of lung function following treatment and was able to show some improvement in lung function up to 13–18 months following treatment. However, further longitudinal studies are indicated over an extended period to chart changes in the balance between obstruction and restriction as well as long-term functional impairment. Interactions between TB and co-factors such as age, sex, smoking, HIV and other risk factors need large enough samples to be able to examine effect modification using formal statistical methods. The interaction with smoking is of particular interest, because it is a modifiable risk factor. Although a recent study from China which examined this formally found no interaction, this needs replication. Among many possible mechanistic pathways, identification of the extent of reversible inflammatory responses that may provide treatment options is perhaps the most immediate task.