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Risk factors for pulmonary disease due to culture-positive *M. tuberculosis* or nontuberculous mycobacteria in South African gold miners

P. Sonnenberg*,**,***, J. Murray***,+, J.R. Glynn*, R. Glyn Thomas++, P. Godfrey-Faussett*,#, S. Shearer‡

Risk factors for pulmonary disease due to culture-positive M. tuberculosis *or nontuberculous mycobacteria in South African gold miners. P. Sonnenberg, J. Murray, J.R. Glynn, R. Glyn Thomas, P. Godfrey-Faussett, S. Shearer. ©ERS Journals Ltd 2000.*

ABSTRACT: The aim of this study was to determine risk factors for disease due to nontuberculous mycobacteria (NTM) compared to those due to *Mycobacterium tuberculosis* in South African gold miners with pulmonary mycobacterial disease.

A case/control study comparing tuberculosis and NTM cases amongst all patients with a positive sputum mycobacterial culture in 1995 was carried out.

The 51 cases of disease due to NTM and 425 tuberculosis cases were similar with regard to age, education, home region, smoking habits and percentage of CD4 cells. After adjustment for confounders, those with NTM were more likely to have had previous tuberculosis treatment (odds ratio (OR) 3.61; 95% confidence interval (CI) 1.9–6.9), have worked longer underground (p-value for trend=0.05) or have evidence of silicosis (OR 12.6; 95% CI 2.2–71) and were less likely to drink regularly (OR 0.12; 95% CI 0.02–0.93) than patients with tuberculosis. In patients with disease due to NTM, 35.3% were human immunodeficiency virus-positive compared with 48.8% of tuberculosis patients (p=0.2) and an estimated 21% overall in the mines at the time of the study.

Previous tuberculosis treatment, silicosis and duration of underground work are even more strongly associated with disease due to nontuberculous mycobacteria than with tuberculosis. Attempts to reduce the incidence of all pulmonary mycobacterial disease in this community should address recognized risk factors and ensure that those with tuberculosis are diagnosed, treated and cured.

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*Dept of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, UK. **Epidemiology Research Unit, Medical Bureau for Occupational Diseases, Johannesburg, South Africa. ***Dept of Community Health, University of the Witwatersrand, South Africa. +National Centre for Occupational Health, Dept of Health, South Africa. ++Dept of Radiology, Rand Mutual Hospital and University of the Witwatersrand, South Africa. ‡Gold Fields of South Africa, Johannesburg, South Africa. #Zambian AIDS-related TB (ZAMBART) Project, Dept of Medicine, University Teaching Hospital, Lusaka, Zambia.

Correspondence: P. Sonnenberg, Infectious Disease Epidemiology Unit, Dept of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT UK. Fax: 441714-364230

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The incidence of pulmonary tuberculosis in South African gold miners increased from 686 per 100,000 workers in 1989 to >1,800 per 100,000 in 1995 [1]. Changes in the mine labour system in the 1970s resulted in longer service and a rise in the average age of the workforce [2]. Workers are thus exposed to risk factors, such as silica dust [3], for prolonged periods of time and show increased rates of tuberculosis associated with older age. These changes have led to a rise in tuberculosis and silicosis in the industry [4]. Recently, there has also been a dramatic increase in the seroprevalence of human immunodeficiency virus (HIV) infection, rising to >20% in some mines. Not all pulmonary mycobacterial disease is due to *Mycobacterium tuberculosis* [5] and miners may also be exposed to nontuberculous mycobacteria (NTM) in soil or water [6].

Exposure to a dusty work environment is a risk factor for the development of mycobacterial pulmonary disease, particularly that due to NTM [5, 7, 8]. A recent retrospective case/control study identified HIV infection and higher grades of silicosis as risk factors for both disease due to NTM and tuberculosis and previous tuberculosis, radiological scarring and a dusty job on diagnosis as risk factors for disease due to NTM in gold miners [9].

Although risk factors for pulmonary disease due to *M. tuberculosis* [10–12] and NTM [13–15] have been described, few studies have made a direct comparison between these groups [7, 8, 16–19], thereby estimating the relative importance of risk factors in the two groups. Previous retrospective studies, in developed countries, have been limited by possible selection and information bias, incomplete data and the lack of data on patients with HIV infection. Previous studies in gold miners [5, 9] have relied on a single culture for the diagnosis of disease due to NTM, leading to possible misclassification of some patients. In this study, analysis was restricted to patients with two or more positive NTM cultures and a wide range of risk factors were examined. The factors associated with tuberculous and nontuberculous pulmonary mycobacterial disease in South African gold miners were compared.

Methods

Study population

The study population comprised 28,522 males working in four gold mines in Gauteng Province. The males were migrant workers from the rural areas of Southern Africa. The medical services and tuberculosis control programme have been described in detail previously [20].

All patients with at least one positive sputum mycobacterial culture in 1995 were prospectively enrolled in the study. Males clinically suspected of having tuberculosis routinely undergo at least three sputum smear examinations and a minimum of one specimen is cultured, the organism identified and tested for drug resistance. In study subjects, an attempt was made to obtain two specimens for mycobacterial culture from each patient, on different days to reduce the possibility of laboratory contamination.

On enrolment, each patient was interviewed and their medical records reviewed using a standard form. Interviews were conducted, in the patient′s own language, by the same interviewer who was unaware of whether the patient had tuberculosis or disease due to NTM. It was possible to ascertain whether a patient had previously received antituberculosis treatment, however, prior to 1991, data were unavailable as to whether treatment was for *M. tuberculosis* or an NTM. Patients classified as having previously received antituberculosis therapy included those who had had documented sputum negativity at the end of treatment, and patients who had completed treatment and were assessed as cured on the basis of clinical and radiographic findings. No patients were receiving isoniazid chemoprophylaxis or antiretroviral therapy at the time of enrolment. An assessment of prior isoniazid chemoprophylaxis could not be reliably obtained, particularly since mass prophylactic campaigns had previously been conducted in the mines. Alcohol consumption was recorded as nondrinker, weekend drinker or daily alcohol intake. Patients were classified as nonsmokers, previous smokers (stopped smoking $\geq$3 months prior to clinical symptoms) or current smokers. HIV testing was performed with consent and all patients were counselled.

Ethical approval was obtained from the Committee for Research on Human Subjects of the University of the Witwatersrand, South Africa.

Laboratory methods

Sputum smear examinations, using fluorescent microscopy and auramine staining, were performed according to standard methods [21]. Sputum specimens were inoculated into Bactec 12B vials (Becton Dickinson, Sparks, MD, USA) after appropriate decontamination using standard *N*-acetyl-cysteine/sodium hydroxide digestion and concentration [21]. Once a positive growth index was recorded, the presence of mycobacteria was confirmed using microscopy and Ziehl-Neelsen staining. Isolates of acid-fast bacilli were identified using deoxyribonucleic acid/ribonucleic acid hybridization (Gen-Probe; AccuProbe, San Diego, CA, USA) for *M. tuberculosis*, *M. kansasii* and *M. avium complex*. Standard biochemical tests and morphological assessment on a Lowenstein-Jensen slope were used to identify all other species [21].

T-cell analysis was carried out by means of flow cytometry using SimulSet monoclonal antibodies and a FACSort (Becton Dickinson, San Jose, CA, USA). The relative levels of CD4+ and D8+ lymphocytes expressed as percentages of total lymphocytes numbers, which are less variable than absolute counts, were used [22]. A CD4 percentage of >28% corresponds to an absolute CD4+ count of $\geq$500 cells·μL^{-1}, 14–28% to 200–499 cells·μL^{-1} and <14% to <200 cells·μL^{-1}.

Chest radiography

Patients underwent posteroanterior chest radiography on diagnosis. The radiographs were read jointly by two readers blinded to the culture result, HIV status and clinical data. Silicosis was assessed on serial films (diagnosis, 6 months later, 9–18 months later), using International Labour Office (ILO) standard guidelines [23]. Silicosis was recorded as present (ILO category 1/1 or higher), possible (ILO category 1/0 or 0/1) or absent (ILO category 0/0 or 0/-).

Criteria for diagnosis

Pulmonary tuberculosis was diagnosed if at least one sputum culture yielded *M. tuberculosis*. The study used a modification of the American Thoracic Society criteria for disease due to NTM [13]. A diagnosis of nontuberculous pulmonary mycobacterial disease was made if at least two sputum cultures were positive for the same nontuberculous mycobacterium. Patients were classified as "single NTM" if they yielded a single sputum culture positive for a nontuberculous mycobacterium. Patients with no chest radiographic changes were included.

Statistical methods

The data were entered in duplicate and validated using Epi-Info 6.02 (Centers for Disease Control, Atlanta, GA, USA) and analysed using STATA 5.1 (Stata corporation, College Station, TX, USA). Categorical variables were analysed using the Chi-squared test if binary or the Chi-squared test for trend if ordinal. Odds ratios (ORs) with 95% confidence intervals (CIs), p-values for binary variables and p-values for linear trend (P_T) for ordinal variables are presented. The odds of developing disease due to NTM or tuberculosis in patients with various risk factors were compared using univariate analysis. In order to assess risk factors controlled for possible confounding, logistic regression analysis was performed. Age and HIV status were included in the model *a priori*. All other risk factors with a level of significance of $p<0.1$ (on univariate analysis, or on bivariate analysis in which each risk factor was controlled in turn for each other risk factor) were originally included. The final model, including significant variables at $p<0.05$, is presented. The presence of interaction in clinically relevant subgroups of patients (HIV-positive or -negative, with and without previous tuberculosis treatment, smear-positive and -negative) was determined using likelihood ratio tests.

Results

During 1995, 505 males had a sputum specimen that was positive on mycobacterial culture. Of these, 425 contained *M. tuberculosis* alone, seven both *M. tuberculosis* and an NTM in the same specimen (mixed infections), and 73 NTM alone.

Two or more samples were cultured from 69 of the 73 NTM patients. In 18 of the 73 patients, only a single culture was positive and in four patients only one specimen was available. The remaining 51 NTM patients had at least two positive cultures (15 had three or more), 48 of whom yielded the same NTM in all cultures (table 1). In the other three patients, one culture yielded a mixture of both *M. kansasii* and *M. avium-intracellulare* (MAI); in two of these, the other culture yielded *M. kansasii* alone and in the third the subsequent two cultures yielded MAI alone.

The 51 patients with two or more positive NTM cultures had significantly different clinical, laboratory and radiological features when compared to the 22 with a single positive NTM culture. They were more likely to be smear-positive, and on chest radiography had more extensive changes, upper zone involvement and cavitation (data not shown). These 22 patients were likely to have NTM infection or contamination rather than disease, and, in addition to the seven patients with mixed NTM and *M. tuberculosis* infection, were excluded from further analysis.

The risk factors for disease due to NTM *versus* tuberculosis were determined initially using univariate analysis (table 2). There were no significant differences in age (mean 40.4 *versus* 39.5 yrs; p=0.4), home region, smoking habits and percentage of CD4+ cells. Those with NTM were more likely to have a lower level of education, to be HIV-negative and to drink less than patients with tuberculosis, but these results did not reach statistical significance. Previous tuberculosis treatment, silicosis, duration of underground work and alcohol consumption were significant factors after adjustment for possible confounders (table 3). Cavitation was confounded by previous tuberculosis treatment: unadjusted OR 2.1 (95% CI 1.1–3.8) and adjusted OR 1.6 (95% CI 0.83–2.9; p=0.2). There were no significant interactions.

Secondary analysis, comparing patients with *M. kansasii* disease (n=34) and those with tuberculosis yielded broadly similar results. Eleven (32.3%) *M. kansasii* patients were HIV-positive compared with 207 tuberculosis patients (unadjusted OR 0.50 (95% CI 0.24–1.1; p=0.07). One patient with *M. kansasii* had silicosis (OR 4.4 (95% CI 0.44–44; p=0.2). On multivariate analysis (adjusting for age, HIV status, previous tuberculosis, duration of underground work and alcohol consumption) previous tuberculosis treatment (OR 2.1 (95% CI 0.98–4.4; p=0.05) and duration of underground work (OR 2.8 (95% CI 0.73–11) for 10–19 yrs and 9.3 (1.7–49) for ≥20 yrs; PT=0.006) were independent risk factors. No *M. kansasii* patients were daily drinkers (OR 0.89 (95% CI 0.43–1.8); for weekend drinkers, PT=0.06).

Of the 27 NTM patients previously treated with antituberculosis therapy, three had had previous disease caused by *M. tuberculosis*, nine had yielded an NTM on culture (four *M. kansasii*, two MAI, three NTM species not identified), three had provided negative cultures and one had provided a positive smear with a contaminated culture. Data on the causative organisms were not available for 11 patients who had received treatment prior to 1991. The three NTM patients with definite silicosis were smear-negative, two had received no previous tuberculosis treatment. Two yielded *M. scrofulaceum* and one *M. kansasii* on culture. The three tuberculosis patients with silicosis were all smear-positive and none had received previous tuberculosis treatment.

Table 1. – Organism isolated and human immunodeficiency virus (HIV) status in 476 patients with pulmonary mycobacterial disease

Organism	Total n	HIV-positive n (%)
Mycobacterium tuberculosis	425	207 (48.8)
Nontuberculous mycobacteria	51	18 (35.3)
Mycobacterium kansasii	34	11 (32.3)
MAI	9	4 (44.4)
Mycobacterium abscessus	2	0 (0)
Mycobacterium scrofulaceum	3	2 (66.7)
Mixed *Mycobacterium kansasii/MAI*	3	1 (33.3)

MAI: *Mycobacterium avium-intracellulare*.

Discussion

This study aimed to identify risk factors for pulmonary disease due to NTM compared with those for pulmonary tuberculosis. The study design allowed a comparison of risk factors between the two groups, but did not provide information on risk factors for either disease in the population. Thus a finding of no difference between these groups may be due to a risk factor of similar magnitude for both tuberculosis and disease due to NTM. After adjusting for potential confounders, previous tuberculosis treatment, duration of underground work and silicosis were independent risk factors for developing disease due to NTM compared to *M. tuberculosis*. These are all strong risk factors for tuberculosis, implying a very strong association with disease due to NTM. Daily alcohol consumption was a risk factor for developing tuberculosis rather than disease due to NTM. There were no significant differences in age, home region, level of education, smoking, HIV status and level of immunity between the two groups. Similar risk factors were identified when patients with *M. kansasii* alone and those with all NTM species were compared with tuberculosis cases.

The setting and design of this study have a number of strengths. The well-resourced medical services and well-developed infrastructure provided an opportunity to study disease in a defined community with a high prevalence of mycobacterial disease and HIV infection. The prospective nature of the study ensured little missing data with most patients undergoing multiple sputum cultures. This enabled more stringent criteria to be used for disease due to NTM than have previously been used in this setting [5, 9]. The importance of requiring more than one positive NTM culture for diagnosis of disease due to NTM is highlighted by the differences found between these patients and those with only a single positive NTM culture. There is unlikely to have been bias in the selection of patients since all patients went through the same referral system.

Table 2. – Risk factorsfor pulmonary disease due to nontuberculous mycobacteria (NTM) or *M. tuberculosis* in 476 gold miners on univariate analysis

	NTM n (%)	TB n(%)	OR	95% CI	p-value
Subjects	51 (10.7)	4.25 (89.3)			
Demographic					
Age					
<40 yrs	26 (51.0)	247 (58.1)	1		
≥40 yrs	25 (49.0)	178 (41.9)	1.3	0.75–2.4	0.3
Home region					
South Africa	21 (41.2)	194 (45.6)	1		
Neighbouring countries	30 (58.8)	231 (54.4)	1.2	0.67–2.2	0.5
Education					
No formal education	23 (45.1)	150 (35.3)	1		0.09#
Primary education	22 (43.1)	190 (44.7)	0.76	0.41–1.4	
Secondary education	6 (11.8)	85 (20.0)	0.46	0.18–1.2	
Occupational					
Years underground*					
0–9	8 (15.7)	93 (21.9)	1		0.04#
10–19	20 (39.2)	208 (48.9)	1.1	0.47–2.6	
≥20	23 (45.1)	124 (29.2)	2.2	0.92–5.1	
Habits					
Smoking (n=469)+					
Nonsmoker	12 (23.5)	101 (24.2)	1		0.7#
Previous	13 (25.5)	124 (29.7)	0.88	0.39–2.0	
Current	26 (51.0)	193 (46.2)	1.1	0.55–2.3	
Alcohol (n=467)+					
Nondrinker	27 (52.9)	184 (44.2)	1		0.07#
Weekends only	23 (45.1)	186 (44.7)	0.84	0.47–1.5	
Daily	1 (2.0)	46 (11.1)	0.15	0.02–1.1	
Medical history					
Previous TB treatment					
No	24 (47.1)	317 (74.6)	1		
Yes	27 (52.9)	108 (25.4)	3.3	1.8–6.0	<0.001
Immune status					
HIV (n=475)+					
Negative	33 (64.7)	217 (51.2)	1		
Positive	18 (35.3)	207 (48.8)	0.57	0.31–1.1	0.07
CD4+% (in HIV+) (n=215)+					
>28%	9 (52.9)	94 (47.5)	1		0.4#
14–28	7 (41.2)	75 (37.9)	0.98	0.35–2.8	
<14%	1 (5.9)	29 (14.6)	0.36	0.04–3.0	
Chest radiography					
Cavitation (n=473)+					
No	19 (37.3)	232 (55.0)	1		
Yes	32 (62.7)	190 (45.0)	2.1	1.1–3.8	0.02
Silicosis (n=474)+					
No	37 (72.5)	357 (84.4)	1		0.008#
Possible	11 (21.6)	63 (14.9)	1.7	0.81–3.5	0.2
Yes	3 (5.9)	3 (0.7)	9.7	1.8–51	0.001

*: surface workers (one (2.0%) NTM and 11 (2.6%) tuberculosis (TB)) were regarded as having spent 0 yrs underground; +: data not available for all subjects; #: p-value for linear trend. The baseline group is used as reference; hence, the odds ratio (OR)=1 and no confidence interval (CI) is given. For binary variables, a single p-value is given; for ordinal variables, a p-value for trend is given. CI: confidence interval; HIV: human immunodeficiency virus; CD4%: percentage of CD4+ cells; HIV+: HIV-positive

Interviews and chest radiograph reading were conducted in a blinded manner using a structured format.

There may be limitations to the generalizability of these results as the study population was restricted to working males. High-risk groups, such as persons with advanced silicosis, end-stage acquired immune deficiency syndrome or older workers who may have left on pension and subsequently developed disease, were not included, resulting in a "healthy worker effect".

The strongest risk factor for the development of pulmonary disease due to an NTM compared to *M. tuberculosis* was a history of previous tuberculosis treatment, an association that has been well-described [13–15]. The 53% of NTM patients with a history of tuberculosis treatment are a mixture of those with previous *M. tuberculosis*, perhaps with residual lung damage with cavitation, and chronic nontuberculous pulmonary mycobacterial disease which had not responded to therapy.

The finding that patients with disease due to NTM were more likely to show cavitation than those with tuberculosis was confounded by the effects of previous tuberculosis treatment. Patients with previous tuberculosis may exhibit cross-immunity to other mycobacteria, and *vice versa* [24, 25] which may provide some protection against acquiring NTM infection or developing disease due to NTM. On the other hand, previous tuberculosis with residual lung

Table 3. – Risk factors for pulmonary disease due to nontuberculous mycobacteria compared to that due to *M. tuberculosis* using logistic regression analysis

	Adjusted values		
	OR	95% CI*	p-value
Previous TB treatment			
No	1		
Yes	3.61	1.9–6.9	<0.001
Alcohol			
Nondrinker	1		0.06^{+}
Weekends only	0.91	0.48–1.7	0.8
Daily	0.12	0.02–0.93	0.04
Silicosis			
No	1		0.03^{+}
Possible	1.4	0.62–3.0	0.5
Yes	12.6	2.2–71	0.004
Years underground			
0–9	1		0.05^{+}
10–19	1.1	0.43–2.8	0.8
≥20	3.2	0.95–10.8	0.06
HIV			
Negative	1		
Positive	0.67	0.35–1.3	0.2

*: adjusted for age and the other variables in the table; $^{+}$: p-value for trend. The baseline group is used as reference; hence, the odds ratio (OR)=1 and no confidence interval (CI) is given. For binary variables, a single p-value is given; for ordinal variables, a p-value for trend is given. TB: tuberculosis; HIV: human immunodeficiency virus.

damage may predispose to disease due to NTM as NTM thrive in old cavities [13–15]. It is possible that the effect of cavitation on mycobacterial disease may be modified by a patient's HIV status [24], since both immunity to mycobacteria and tissue destruction are cell-mediated; however, it was not possible to assess this due to small numbers. The temporal relationship between cavitation and disease due to NTM also needs to be considered, since cavities may be the result of NTM infection itself. The diagnostic criteria for disease due to NTM rely on the isolation of NTM from repeated sputum samples, and using criteria dependent on sputum diagnosis may lead to a biased selection of patients with cavitary disease [17].

The relationship between silicosis and tuberculosis is well recognized [5, 26, 27]. There is also an increased susceptibility of persons with silicosis to other mycobacterial diseases, in particular *M. kansasii* and MAI [9, 26]. In the present study, radiological evidence of silicosis was an independent risk factor for nontuberculous compared to tuberculous pulmonary disease, even though the number with silicosis was small. The diagnosis of silicosis in the presence of active mycobacterial disease is difficult since tuberculous nodulation may be indistinguishable from silicotic nodulation [28]. Silicotic changes are unlikely to develop within a short period of time and, therefore, an assessment of the radiograph obtained 6 months after therapy was initiated is probably a good reflection of the presence of silicosis at the onset of mycobacterial disease. Silicosis was assessed on a single radiograph in 50 patients who died or left the mine before a 6-month film could be exposed (seven NTM,43 tuberculosis). The classification of study subjects as "no silicosis" (37 patients) was probably reliable, whereas those with "possible silicosis" may have been misclassified due to the presence of active mycobacterial disease (two NTM, 11 tuberculosis). However, if these patients with "possible silicosis" were to be reclassified, even in the most extreme scenario (all NTM patients as "no silicosis" and all tuberculosis patients as "silicosis"), patients with NTM would be twice as likely to have silicosis as those with tuberculosis.

The finding that those who have spent longer underground are more likely to develop disease due to NTM than tuberculosis may have several explanations. First, the risk of tuberculosis may be increased in those exposed to silica dust even without radiological evidence of silicosis [29]. This raises the possibility that silica dust exposure, even without radiological evidence of silicosis, may also be a risk factor for nontuberculous pulmonary mycobacterial disease. Secondly, working underground also increases the risk of other respiratory conditions, such as chronic bronchitis, which may predispose to disease due to NTM [15].

Cigarette smoking and heavy alcohol consumption are risk factors for tuberculosis [11, 12]. Smoking is a potential risk factor for nontuberculous pulmonary mycobacterial disease since smoking predisposes to lung disease [11]; *M. avium* has been recovered from tobacco and cigarettes, and so smokers may experience greater exposure to NTM [30]. In the present study, the proportion of smokers was similar among the tuberculosis and NTM patients. Patients with disease due to NTM were less likely to be daily alcohol drinkers than those with tuberculosis. It is possible that the response to the question about alcohol consumption was not reliable, since 44% of males claimed to be nondrinkers, a figure that appears to be high for this community. There is no reason for tuberculosis and NTM patients to differ in their answers due to their disease status; the resultant nondifferential misclassification of exposure would shift the OR towards unity and the true difference may be larger than was estimated. The increased risk of tuberculosis in heavy drinkers is probably due to a combination of social factors and impaired immune function.

The immune response to mycobacterial infection is predominantly cell-mediated; thus, any agent which lowers cell-mediated immunity may predispose to mycobacterial infection and disease. HIV-infected patients are at high risk for tuberculosis [10] and both pulmonary and disseminated disease due to NTM [13]. The risk of disease due to NTM is particularly high in patients with a CD4+ lymphocyte count of <200 cells·μL^{-1} [13]. In the present study, 35.3% of patients with disease due to NTM and 48.8% of tuberculosis patients were HIV-positive. The estimated seroprevalence of HIV infection in this mining community at the time of the study was 21%, suggesting that HIV infection is a risk factor for both tuberculosis and disease due to NTM in this community.

The emphasis of a tuberculosis control programme should be to ensure that patients are diagnosed early and complete therapy with a bacteriological cure. Since previous tuberculosis is a risk factor for disease due to nontuberculous mycobacteria, this strategy would reduce the incidence of all mycobacterial disease. Attempts to control mycobacterial disease should also address the recognized risk factors for disease in this community. Prevention of

silicosis, through reduction of dust generation and improved ventilation underground, may reduce both tuberculous and nontuberculous disease [26].

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