Risk Factors for Pulmonary Mycobacterial Disease in South African Gold Miners
A Case-Control Study

ELIZABETH L. CORBETT, GAVIN J. CHURCHYARD, TIM CLAYTON, PHILIP HERSELMAN, BRIAN WILLIAMS, RICHARD HAYES, DAAN MULDER, and KEVIN M. DE COCK

Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kindgom; Departments of Medicine and Occupational Health, Ernest Oppenheimer Hospital, Welkom; Epidemiology Research Unit, Johannesburg, South Africa; and Tropical Epidemiology and Public Health, Institute of Social Medicine, University of Amsterdam, The Netherlands

Pulmonary mycobacterial disease is common in miners. Risk factors for nontuberculous pulmonary mycobacterial (NTM) disease and tuberculosis (TB) in gold miners were identified in a retrospective case-control study that included 206 NTM patients and 381 TB patients of known human immunodeficiency virus (HIV) status diagnosed between 1993 and 1996. A total of 180 HIV-tested trauma/surgical inpatients were selected as control patients. Both HIV infection (odds ratio [OR] 3.6 for NTM and 4.5 for TB patients) and higher grades of silicosis (OR 5.0 for NTM and 4.9 for TB patients) were significantly more common in NTM and TB patients than in control patients. HIV prevalence rose in the control and both case groups during the study period. The overall HIV prevalence was 13.1% in NTM patients, 14.2% in TB patients, and 5.6% in control patients. Previous TB (OR 9.6), premorbid focal radiological scarring (OR 7.4) and a dusty job at diagnosis (OR 2.4) were additional significant risk factors for NTM disease. These findings suggest that the historically high incidence of NTM disease in miners is largely attributable to chronic chest disease from silica dust inhalation and prior TB. HIV infection has recently become an additional risk factor for mycobacterial disease in miners and is likely to become increasingly important as the HIV epidemic progresses. Corbett EL, Churchyard GJ, Clayton T, Herselman P, Williams B, Hayes R, Mulder D, De Cock KM. Risk factors for pulmonary mycobacterial disease in South African gold miners: a case-control study.

AM J RESPIR CRIT CARE MED 1999;159:94–99.

The South African tuberculosis (TB) incidence rates are among the highest reported worldwide (1). Gold mining is an important industry in South Africa, with approximately 300,000 currently employed men, the majority of whom are underground workers. Gold deposits are found in hard rock with a high silica content, and silicosis is a recognized occupational hazard (2, 3). Silicosis is a strong risk factor for TB (4) and has been associated with pulmonary disease caused by nontuberculous mycobacteria (NTM) (5–8). Reported TB incidence rates in currently employed miners are above the South African national rates (9) and are increasing. In South Africa, as in other parts of the world, NTM disease also appears to be common in miners (10, 11). In recent years human immunodeficiency virus (HIV) infection has become widely prevalent in South Africa (12). HIV infection predisposes to both TB and NTM disease (13, 14) and the introduction of this additional strong risk factor would be expected to result in an increase in the incidence of both diseases.

This study is a retrospective case-control investigation of the effects of HIV infection, dust exposure, silicosis, and prior TB infection on NTM disease and TB in a South African mining workforce. South African miners are mainly migrant workers from rural South Africa and neighboring countries who work and live for the majority of the year in complexes based around mine shafts, returning to their home areas for 1 to 3 mo each year. Use of commercial sex workers is common practice and the incidence of sexually transmitted diseases (STDs) in these men is extremely high (15). HIV prevalence in TB and STD patients has been increasing rapidly during the last few years (Dr. G. Churchyard, unpublished observations).

METHODS

Study Location

The case and control patients were selected from patients attending the Ernest Oppenheimer Hospital situated at Welkom in the Free State Province of South Africa. The hospital is the sole source of tertiary care for employees of Freegold, a gold mining company, and provides a centralized TB treatment program. Detailed records of

(*Received in original form March 11, 1998 and in revised form August 11, 1998*)

Elizabeth L. Corbett is supported by a Wellcome Trust Training Fellowship in Clinical Tropical Medicine.

K. M. De Cock is currently Director, Division of HIV/AIDS—Surveillance and Epidemiology, National Center for HIV, STD and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia.

Correspondence and requests for reprints should be addressed to Dr. E. L. Corbett, c/o Department of Medicine, Ernest Oppenheimer Hospital, P.O. Box 87, Welkom 9460, South Africa.

Am J Respir Crit Care Med Vol 159. pp 94–99, 1999
Internet address: www.atsjournals.org

each case of TB and NTM disease treated since 1990 have been kept on a computerized database, and separate records of all TB patients are available from 1975. The company keeps computerized demographic and employment records on all employees. All miners are screened annually with a 100-mm mini-chest radiograph. Serial radiographs are available for review. During the study period, the size of the entire workforce contracted from 82,000 to 63,000 employees, the majority of whom are black underground workers.

Bacteriology

Miners presenting either with symptoms suggestive of mycobacterial disease, or who were noted to have new radiological changes at their annual medical examination were routinely screened for mycobacterial disease with sputum microscopy and culture. Sputum samples were taken on two subsequent days and were concentrated, stained with auramine O, and examined for mycobacteria using fluorescent microscopy. Positive slides were confirmed with Ziehl-Nielsen staining. Initial culture of all sputum samples was onto Lowenstein-Jensen (LJ) slopes. The number of colonies on positive LJ slopes was recorded as: scanty (1 to 20); 1+ (20 to 99); 2+ (100 to 200); 3+ (more than 200). Positive LJ slopes were sent to the South African Institute of Medical Research (SAIMR), Johannesburg, for species identification and drug sensitivity testing. The hospital policy was to send only a single LJ slope for identification per disease episode, unless further positive cultures were obtained from the patient more than 6 mo after beginning treatment. The SAIMR laboratory used standard biochemical tests to distinguish different nontuberculous mycobacterial species.

Case and Control Selection

NTM case patients. Patients from whom NTM organisms had been isolated between January 1993 and July 1996 were identified from the TB database. A total of 206 men with their first infection with one of the three most commonly identified pathogenic organisms at this location, *Mycobacterium kansasii*, *M. scrofulaceum*, and *M. avium* complex, who met the case definitions for NTM disease as outlined subsequently, and who had been HIV-tested for the first time as a result of their diagnosis of NTM disease were included as cases.

The case definitions for NTM disease were: (*1*) isolation of a fully speciated NTM organism from one or more sputum samples, plus (*2*) new chest radiograph changes compatible with NTM disease, plus (*3*) treatment with two or more antimycobacterial drugs. Past mycobacterial disease episodes were identified from the TB database and TB clinic records. HIV test dates, results, and dates of previous tests were obtained from computerized hospital records.

Mycobacterium tuberculosis case patients. Patients presenting with a first episode of culture-positive *M. tuberculosis* disease between January 1993 and July 1996 were identified from the TB database. Those who had an HIV test for the first time because of their TB were identified by comparing the diagnosis dates with the hospital HIV test records. Three hundred eighty-one TB cases were selected by random sampling of the 1,091 patients identified in this way. This number was chosen to give an estimated 2:1 TB case to control ratio.

Control patients. Patients who had been admitted to the hospital and HIV-tested between January 1993 and July 1996 because of trauma or for surgery for conditions unrelated to HIV infection were identified using International Classification of Diseases–Ninth Revision (ICD9) codes and HIV test records. Certain subgroups of patients are routinely offered HIV testing in the absence of clinical signs or symptoms suggestive of HIV disease, including patients considered to be at high risk of bacterial sepsis (e.g., acute spinal injuries and those admitted to the intensive care unit) and patients undergoing certain orthopedic procedures where knowledge of the result will influence the surgical procedure used (e.g., fractured mandible). The hospital policy is that all HIV testing is carried out with informed consent and with pre- and post-test counseling. Patients tested because of a clinical suspicion of HIV infection, and patients with a past history of NTM disease were excluded. All 180 eligible control patients were included in the study.

The incidence of sexually transmitted diseases is high and a high proportion of the mining workforce have had an outpatient HIV test (estimated at 20%). Because known HIV-positive patients would tend not to be retested when admitted to the hospital, only patients being HIV-tested for the first time were considered for inclusion as control patients and the same restriction was then applied to the case patients.

Radiography. For the NTM patients, new chest radiographic changes were assumed to be present if the patient had been referred from the occupational health service because of new radiological changes detected on an annual screening radiograph. Otherwise the presence of new radiographic changes was assessed by comparing the presentation chest radiograph with previous standard or mini-chest radiographs.

The presence of preexisting silicosis and/or apical focal scarring suggestive of old TB or progressive massive fibrosis was assessed from mini-radiographs taken at least 6 mo before the study entry date. These films were read independently by two readers unaware of the identity of the patient. If no suitable mini-radiograph was found then standard size premorbid radiographs were used instead when available. In order to minimize the risk of reading films with slowly progressing mycobacterial disease, reference to previous films was made in cases where scarring was detected. Scarring was only recorded as present if the lesion had been static for at least 12 mo. Silicosis was scored on a six-point scale modified from the International Labor Office (ILO) classification system designed for use with standard-size chest radiographs (16). Standard-size ILO reference radiographs were available for comparison. The final decisions were reached by consensus in cases of initial disagreement.

Occupational data. Employment records including the number of years worked and job description at study entry were obtained for all patients. The job descriptions were used to allocate men into two dust categories as follows. High dust exposure: all underground manual jobs that were predominantly concerned with the mining or initial transport of rock from the face, or manual underground jobs involving later stages of rock transport. Low dust exposure: all surface jobs, skilled jobs that were mainly or partly underground, but were not based predominantly at the rock face, and all underground jobs that were based away from the rock face and not involved with transport of rock.

Data Analysis

Data were analyzed using STATA 4.0 software. Odds ratios (OR) and 95% confidence intervals (95% CI) (Cornfield) for different risk factors were calculated in the univariate analyses. Logistic regression was used for multivariate analysis to identify independent risk factors for NTM disease and TB, and to identify differences between the NTM and TB cases. The variables included in all models were HIV status, silicosis grade, premorbid radiological scarring, previous TB treatment (NTM and control patients only), age group, employment duration group, dust level of the job at diagnosis, and a time scale representing the month of presentation. The latter was included to adjust for the disproportionate number of TB patients who were recruited in the later part of the study while HIV prevalence was increasing. p Values were derived using likelihood ratio tests.

RESULTS

In total 594 mineworkers from whom NTM organisms had been isolated from one or more sputum samples were identified during the specified time period. Four hundred six had a fully speciated NTM identified of which 273 (67.2%) were *M. kansasii* isolates, 52 (12.8%) were *M. scrofulaceum* isolates, and 24 (5.9%) were *M. avium* complex isolates. Two hundred six (59.0%) NTM case patients were identified from the 349 patients with suitable NTM organisms, including 161 (78%) with *M. kansasii*, 30 (15%) with *M. scrofulaceum*, and 15 (7%) with *M. avium* complex isolates. Each of the case patients had an HIV test for the first time at the time of diagnosis together with new chest radiograph changes and was treated with antimycobacterial drugs but had no past treatment for the same NTM organism. The HIV prevalence was 13.1% in the case patients compared with 33.3% in those who otherwise fulfilled the entry criteria but had had an HIV test before ($p < 0.001$).

Of the 161 *M. kansasii* case patients, 132 (82%) were smear-positive; 41 (25%) had between 20 and 100 mycobacterial colonies; 34 (21%) had between 100 and 200 colonies; and 22 (14%) had more than 200 colonies present on the LJ slope from which the organism was identified. Of the 30 *M. scrofulaceum* case patients, 24 (80%) were smear-positive; 10 (33%) had between 20 and 100 mycobacterial colonies; and 3 (10%) had more than 100 colonies present on the LJ slope from which the organism was identified. Of the 15 *M. avium* complex case patients, 6 (40%) were smear-positive; 3 (20%) had between 20 and 100 mycobacterial colonies; and 2 (13%) had more than 100 colonies present on the LJ slope from which the organism was identified. As outlined in the METHODS section, men who made a satisfactory response to antimycobacterial treatment did not have more than one mycobacterial isolate identified, regardless of the number of available cultures. However, 138 (87%) of the *M. kansasii*, 21 (70%) of the *M. scrofulaceum*, and 7 (47%) of the *M. avium* patients did have more than one positive mycobacterial sputum culture at the time of presentation. In addition, 19 (12%) of the *M. kansasii* and 5 (17%) of the *M. scrofulaceum* case patients had a further isolate of the same NTM species identified from follow-up sputum samples taken during the course of their treatment or on/after completion of treatment.

The HIV prevalence in the 381 TB case patients was 14.2%. This was lower than the prevalence in those who were otherwise eligible but had been excluded because of a previous HIV test (37.6%, $p < 0.001$). Three hundred thirty-three potential control patients were identified using the ICD9 admission codes and HIV test dates. After review of the case notes, 180 control patients were selected from these on the basis of the reason for HIV testing without reference to the HIV test result. The admission diagnoses in eligible control patients were predominantly trauma-related for 152 patients and elective surgery in 28. The overall HIV prevalence in patients selected as control patients was 5.6%.

No suitable mini-radiograph could be found for 50 patients (6.6% of total), of whom 32 had a standard radiograph available from which a silicosis score could be obtained, leaving 18 patients with no silicosis score (one control patient, four NTM patients, and 13 TB patients). Seventeen TB patients had only the presentation large chest radiograph available. These patients were not given any score for previous focal radiological scarring.

The patient characteristics of the NTM and TB case patients and the control patients are shown in Table 1. The numbers of cases and controls recruited each year and their HIV prevalence are shown in Table 2. The HIV prevalence increased in each group from the earlier to the later period of the study, with a more rapid rise in the case patients than the control patients. The proportion of TB case patients recruited in the later period of the study was higher than that of NTM or control patients. The mean ages of the HIV-positive and HIV-negative NTM cases were 42.5 and 44.1 yr, respectively ($p = 0.240$), 39.8 and 42.4 yr, respectively, for the TB cases ($p = 0.031$), and 34.7 and 39.2 yr, respectively, for the control patients ($p = 0.104$). There was a higher proportion of NTM and TB cases compared with control patients in the older age groups and longer employment duration groups. There was a higher prevalence of HIV infection, silicosis, and prior focal radiological scarring in the NTM and TB case patients than in the control patients. Silicosis increased in prevalence with increasing age in each group. Univariate OR, CI, and p values for risk factor prevalence in case patients compared with control patients are shown in Table 3.

Multivariate OR, 95% CI, and p values of risk factor prevalence for cases compared with control patients are shown in Table 4. A time scale representing the month of diagnosis was included in both models in addition to the variables shown in Table 4. For the NTM cases, premorbid focal radiological scarring, a past history of TB, HIV infection, silicosis, a dusty job at diagnosis, and duration of service were significant risk factors for disease when compared with control patients. For the TB cases compared with controls, HIV infection, probable, early and high-grade silicosis and duration of employment were significant risk factors.

Univariate and multivariate OR, 95% CI, and p values of risk factor prevalence for NTM cases compared with TB cases are shown in Table 5. Only NTM case patients with no known history of past TB treatment were included in this comparison. Focal radiological scarring and a dusty job at the time of diagnosis were significantly more prevalent in the NTM case patients in both the univariate and multivariate analyses.

TABLE 1

NTM AND TB CASE AND CONTROL PATIENT CHARACTERISTICS

Characteristic	NTM Cases (*n = 206*)	TB Cases (*n = 381*)	Controls (*n = 180*)
Age group			
< 35 yr	28 (13.6)*	73 (19.2)*	61 (33.9)*
35–44 yr	80 (38.8)	163 (42.8)	71 (39.4)
⩾ 45 yr	98 (47.6)	145 (38.1)	48 (26.7)
Employment duration			
< 10 yr	21 (10.2)	65 (17.1)	70 (38.9)
10–14 yr	35 (16.7)	64 (16.8)	42 (23.3)
15–19 yr	68 (33.0)	141 (37.0)	39 (21.7)
⩾ 20 yr	82 (39.8)	111 (29.1)	29 (16.1)
Occupation at diagnosis			
Driller	31 (15.1)	56 (14.7)	33 (18.3)
Mining team	89 (43.2)	150 (39.4)	65 (36.1)
Scraper winch	31 (15.1)	43 (11.3)	19 (10.6)
Rock transport (underground)	22 (10.7)	41 (10.8)	11 (6.1)
Other underground	26 (12.6)	62 (16.3)	34 (18.9)
Surface	7 (3.4)	29 (7.6)	18 (10.0)
Dusty job at diagnosis	184 (89.3)	307 (80.6)	138 (76.7)
HIV-positive	27 (13.1)	54 (14.2)	10 (5.6)
Silicosis grade†			
None	96 (47.8)	198 (53.8)	142 (79.3)
Possible	20 (10.0)	50 (13.6)	19 (10.6)
Probable	15 (7.5)	40 (10.9)	8 (4.5)
Early	40 (19.9)	37 (10.1)	6 (3.4)
High-grade	30 (14.9)	43 (11.7)	4 (2.2)
Silicosis prevalence (probable/early/high) by age group†			
< 35 yr	5 (19.2)	7 (10.1)	1 (1.6)
35–44 yr	20 (25.3)	41 (25.3)	7 (10.0)
⩾ 45 yr	60 (62.5)	72 (52.6)	10 (20.8)
Prior focal radiological scarring‡	107 (53.0)	46 (13.1)	10 (5.6)
Past history of TB treatment	97 (47.1)	NA	10 (5.6)

* Number (%).
† From radiographs of 201 NTM patients, 368 TB patients, and 179 control patients.
‡ From radiographs of 202 NTM patients, 351 TB patients, and 179 control patients.

TABLE 2

HIV PREVALENCE BY YEAR OF DIAGNOSIS IN NTM AND TB CASES AND CONTROL PATIENTS

	NTM Cases		TB Cases		Control Patients	
Year of Presentation	n	HIV-positive	n	HIV-positive	n	HIV-positive
1993	63	3 (4.8)*	64	3 (4.7)*	47	2 (4.3)*
1994	62	12 (19.4)	117	11 (9.4)	45	2 (4.4)
1995	61	7 (11.5)	135	26 (19.3)	62	4 (6.5)
1996 (January–July only)	20	5 (25.0)	65	14 (21.5)	26	2 (7.7)
Total	206	27 (13.1)	381	54 (14.2)	180	10 (5.6)

* Number (%).

TABLE 3

UNIVARIATE OR, CI, AND SIGNIFICANCE OF RISK FACTOR PREVALENCE IN THE CASE PATIENTS COMPARED WITH CONTROL PATIENTS

	NTM Cases		TB Cases	
Risk Factor	OR	95% CI	OR	95% CI
HIV-positive	2.6	1.22–5.38	2.8	1.33–6.1
Silicosis				
None	1	$p_T < 0.001$*	1	$p_T < 0.001$
Possible	1.6	0.79–3.07	1.9	1.07–3.34
Probable	2.8	1.13–6.80	3.6	1.62–7.89
Early/high-grade	10.4	5.08–21.09	5.7	2.87–11.46
Focal radiological scarring	19.0	9.59–37.70	2.6	1.20–5.60
PMH of TB treatment	15.1	7.64–29.93	NA	—
Dusty job at diagnosis	2.5	1.46–4.44	1.3	0.82–1.94
Employment group				
< 10 yr	1	$p_T < 0.001$	1	$p_T < 0.001$
10–14 yr	2.8	1.43–5.39	1.6	0.98–2.75
15–19 yr	5.8	3.11–10.88	3.9	2.39–6.35
⩾ 20 yr	9.4	4.94–17.98	4.1	2.43–7.00
Age group				
< 35 yr	1	$p_T < 0.001$	1	$p_T < 0.001$
35–44 yr	2.5	1.42–4.25	1.9	1.24–2.98
⩾ 45 yr	4.5	2.53–7.83	2.5	1.58–4.04

Definition of abbreviation: PMH = past medical history.
* p Values for trend shown for variables with more than two categories.

TABLE 5

COMPARISON OF RISK FACTOR PREVALENCE BETWEEN NTM PATIENTS WITH NO PAST HISTORY OF TB TREATMENT (n = 109) AND TB PATIENTS—UNIVARIATE- AND MULTIVARIATE-ADJUSTED OR, CI, AND SIGNIFICANCE LEVELS

	Univariate		Multivariate	
Risk Factor	OR	95% CI	OR	95% CI
HIV-positive	1.0	0.53–1.78	1.2	0.58–2.36
Silicosis				
None	1	$p_T = 0.02$*	1	$p_T = 0.91$
Possible	0.6	0.28–1.42	0.5	0.21–1.16
Probable	0.8	0.35–1.70	0.6	0.26–1.52
Early/high-grade	1.9	1.18–3.16	1.1	0.60–2.02
Focal radiological scarring	4.2	2.58–6.99	4.0	2.33–6.86
Dusty job at diagnosis	2.1	1.11–4.16	2.3	1.10–4.82
Employment group				
< 10 yr	1	$p_T = 0.03$	1	$p_T = 0.13$
10–14 yr	1.0	0.46–2.24	1.1	0.46–2.68
15–19 yr	1.0	0.48–1.89	1.1	0.49–2.53
⩾ 20 yr	1.9	0.97–3.61	1.9	0.78–4.37
Age group				
< 35 yr	1	$p_T = 0.23$	1	$p_T = 0.28$
35–44 yr	0.9	0.46–1.56	0.7	0.31–1.37
⩾ 45 yr	1.3	0.71–2.31	0.6	0.27–1.37

* p Values for trend shown for variables with more than two categories.

DISCUSSION

This study was designed to investigate the predominant risk factors for pulmonary NTM disease and TB in this population. The study design may have influenced the results for two main reasons. First, the control group includes trauma patients injured at work, which may have resulted in a bias toward men employed in heavy manual jobs, making the differences in occupational histories between the cases and control patients difficult to interpret. Second, restricting entry into the study to men who had not previously been HIV-tested will probably have led to relatively low HIV prevalence in both cases and control groups. This step was necessary because symptomatic STDs are sufficiently common to mean that a substantial proportion of the workforce has had an outpatient HIV test (estimated at 20%). The control patients were selected from men who had been HIV-tested in the hospital. Including men who had previously been HIV-tested would have resulted in a selection bias away from known HIV-positive men (who would tend not to be retested on admission). However, only including men with no previous HIV test will have selected mainly men who have not had a symptomatic STD or any manifestation of HIV infection, and who are therefore from a relatively low HIV risk group. In order to make the cases compatible with the control patients, the same entry criteria were applied to the cases, who were therefore restricted to men having a first HIV test as a result of their TB or NTM disease. The effect of this can be seen by comparing the HIV prevalence in the TB and NTM patients who were excluded because of having had a prior HIV test with those selected as cases (37.6% compared with 14.2% for TB patients, and 33.3% compared with 12.0% for NTM patients).

TABLE 4

MULTIVARIATE-ADJUSTED OR, CI, AND SIGNIFICANCE OF RISK FACTOR PREVALENCE IN THE CASE PATIENTS COMPARED WITH CONTROL PATIENTS

	NTM Cases		TB Cases	
Risk Factor	OR	95% CI	OR	95% CI
HIV-positive	3.6	1.35–9.82	4.5	2.12–9.57
Silicosis				
None	1	$p_T < 0.001$*	1	$p_T < 0.001$
Possible	1.2	0.51–3.07	1.6	0.86–2.90
Probable	1.4	0.44–4.22	2.8	1.24–6.46
Early/high-grade	5.0	2.02–12.32	4.9	2.32–10.58
Focal radiological scarring	7.4	3.24–16.73	1.8	0.81–3.80
PMH of TB treatment	9.6	4.19–22.09	—	—
Dusty job at diagnosis	2.4	1.06–5.45	1.0	0.62–1.62
Employment group				
< 10 yr	1	$p_T < 0.001$	1	$p_T < 0.001$
10–14 yr	2.6	1.09–6.24	1.9	1.07–3.36
15–19 yr	5.6	2.27–14.00	4.4	2.45–7.75
⩾ 20 yr	7.1	2.70–18.79	3.6	1.84–7.12
Age group				
< 35 yr	1	$p_T = 0.39$	1	$p_T = 0.79$
35–44 yr	0.7	0.30–1.55	1.1	0.65–1.98
⩾ 45 yr	0.6	0.26–1.60	0.9	0.48–1.73

Definition of abbreviation: PMH = past medical history.
* p Values for trend shown for variables with more than two categories.

Despite these limitations, HIV infection is clearly a significant risk factor for both TB and NTM disease in this working population. It is likely that the relatively low OR for HIV found in this study reflect both the early stage of the HIV epidemic and the unusually high incidence of mycobacterial disease in HIV-negative patients due to the high prevalence of other strong risk factors that are rare in other populations. The rising prevalence of HIV infection among the control patients between 1993 and 1996 suggests that HIV infection is likely to make an increasingly important addition to the already high rates of occupational mycobacterial disease as the South African HIV epidemic progresses.

Silicosis remains the other major risk factor for TB, with a progressive rise in the OR for TB with increasing silicosis grades. Increased susceptibility to TB from very early silicosis has been noted before (17). Silicosis prevalence in South African gold miners seems to have increased over the last two decades, probably as a result of changes in work practices resulting in an increased duration of employment for the workforce as a whole (18, 19). The prevalence of silicosis reported here is high in both cases and control patients, and is considerably higher than that reported from this same location in the 1980s (2). However the two studies are not directly comparable as there is considerable interobserver variation in silicosis reporting (3) and the control patients used here were not a random cross-section. Another factor that will have increased the apparent prevalence of silicosis from this site is an improvement in the radiological quality of the miniature radiographs from the introduction of better X-ray techniques. Increasing the resolution of the radiographs is likely to have resulted in an increased sensitivity, especially for early cases of silicosis. The silicosis prevalence reported here in the control patients are similar to those reported in an autopsy survey of miners dying of trauma which covered the period of 1975–1991 and noted a rise both in the median age at death and in silicosis prevalence from the earlier to the later years of the study (19).

A past history of TB, premorbid focal radiographic scarring, silicosis, HIV infection, and a dusty job at diagnosis are the significant risk factors for NTM disease identified here. After adjusting for silicosis a dusty job remained a significant risk factor for NTM disease, but not TB. Miners working in dusty environments have been shown to have symptoms of chronic bronchitis, with lung function changes comparable to those in smokers (20). Past TB, bronchiectasis from other causes, chronic bronchitis, and other types of chronic lung disease have been reported with high frequency in both mining and nonmining patients with pulmonary NTM disease (8). The findings taken overall suggest that an intact bronchial tree and sputum clearance mechanisms are important first-line defenses against pulmonary NTM disease.

Past TB treatment and focal radiological scarring had the highest OR in both the univariate and multivariate analyses, and were each present in about half of the NTM case patients. Prior focal radiological scarring was initially intended to identify patients with old TB scarring, but the radiological appearances of progressive massive fibrosis can be indistinguishable from TB scarring. Focal scarring was strongly correlated with a past history of TB treatment ($p < 0.001$), but was also correlated with silicosis grading ($p < 0.001$), with the prevalence of focal scarring in patients with no known history of previous TB treatment increasing from 8.6% in those with no silicosis to 32.3% in those with high-grade silicosis. Thus prior focal radiological scarring probably represents a composite score of these two separate pathologies.

Although mining has long been associated with NTM disease, this is the first detailed investigation of NTM disease risk factors, and goes some way to explaining the historically high incidence rates on a combination of silicosis and high TB incidence rates, with the additional possibility that chronic bronchitis from exposure to dust may be contributing to NTM disease. It is also possible that miners may have a greater occupational exposure to potentially pathogenic environmental mycobacteria than workers in less dusty occupations. HIV infection has now been added to these long-standing risk factors. Using the multivariate OR, the population attributable fractions for the significant NTM disease risk factors are respectively: past history of TB treatment, 42%; focal radiological scarring, 46%; early/high grade silicosis, 28%; dusty job, 52%; and HIV infection, 9%. The figure for HIV infection will be an underestimate because of the case and control selection bias discussed previously. Silicosis may predispose to NTM disease both directly and indirectly, by predisposing to TB which is itself a strong risk factor for NTM disease.

A high proportion of patients with a past history of TB is a consistent feature of NTM disease case series from around the world (8, 21). The data from this study illustrate the strength of this association. The association is likely to be at least in part a causal one, due to predisposition to NTM disease from post-tuberculous bronchiectasis. However, the ability to respond to mycobacterial antigens is in part genetically determined (22), and so it is also possible that previous TB disease (as opposed to asymptomatic infection) is simply acting as a marker for genetically poor mycobacterial responders. This latter hypothesis is consistent with the observation that the incidence of HIV-negative NTM disease does not seem to have fallen in the United States following the reduction in TB incidence rates, but the proportion of NTM patients with no known risk factor for NTM disease has increased (23).

One notable negative finding is that age has not been identified here as an independent risk factor for TB. There were small but significant age differences between the TB and NTM cases and control patients, but duration of employment and silicosis, which are both strongly age-associated, were sufficient to account for the increased ages of the cases in the multivariate analyses for both TB and NTM. This may simply reflect the choice of control patients, and is in contrast to several other studies of TB in miners from South Africa where increasing age has been identified as an important independent risk factor for TB (18, 24, 25). However, because of the association between age, cumulative silica dust exposure, and silicosis, interpretation of age-related changes in TB susceptibility in miners is difficult regardless of the study design.

The two main conclusions concerning the gold mining industry in South Africa are as follows. First, dust control regulations need to be reassessed, taking into account the recent changes in employment patterns, the mounting evidence that silicosis prevalence is increasing, and the onset of the HIV epidemic. Despite the numerous regulations addressing dust levels, there is no systematic monitoring of silicosis prevalence and morbidity in South Africa, although annual chest radiograph screening is compulsory for all mine workers. Directly monitoring and reporting early silica-induced morbidity in addition to silica dust exposure would allow time trends to be identified more confidently, at an earlier stage and, if linked to employment data, could facilitate the introduction of more effective control measures by identifying high-risk occupations.

Second, the impact of HIV infection on the preexisting tuberculosis problems in mineworkers is likely to be severe. Mineworkers live in close contact with one another both at work and in the hostels in which most of them live for the majority of their working years. HIV-infected mineworkers will not only be at high risk of reactivational TB but will also be at high risk of exogenous reinfection because of their social conditions. As HIV infection becomes more prevalent this may result in a situation akin to that seen in HIV housing facilities and inpatient wards, where the combination of high TB prevalence and high individual susceptibility to infection has resulted in nosocomial epidemics (26). TB control, STD control, and HIV and silicosis prevention must become high priorities for all those concerned with the health of mineworkers. The possibility that TB and other opportunistic infections may accelerate the course of HIV infection (27) adds to the gravity of the situation. Finally, the possibility of NTM disease must be considered by physicians treating former mineworkers for TB, especially those with a past history of TB treatment or evidence of old TB scarring on their chest radiographs.

***Acknowledgment*:** The authors give many thanks to Carol Van Blommestein, who manages the TB database and helped with patient identification and microbiological data; Jake Mjandana and Tuso Ramolahloane for locating the mini-radiographs used in the study; and Hetta Steyn and Louis Von Rensberg for supplying occupational records.

References

1. Department of National Health and Population Development. 1995. Tuberculosis update. *Epidemiol. Comments* 22:13–17.
2. Cowie, R. L., and M. G. Van Schalkwyn. 1987. The prevalence of silicosis in the Orange Free State. *J. Occ. Med.* 29:44–46.
3. Becklake, M. R. 1992. The mineral dust diseases. *Tuber. Lung Dis.* 73: 13–20.
4. Cowie, R. L. 1994. The epidemiology of tuberculosis in gold miners with silicosis. *Am. J. Respir. Crit. Care Med.* 150:1460–1462.
5. Snider, D. E. 1978. The relationship between tuberculosis and silicosis. *Am. Rev. Respir. Dis.* 118:455–460.
6. Rosenzweig, D. Y. 1967. Silicosis complicated by atypical mycobacterial infection. Transactions of the 26th VA–Armed Forces Pulmonary Disease Research Conference, U.S. Government Printing Office, Washington, DC. 47.
7. Bailey, W. C., M. Brown, H. A. Buechener, H. Weill, H. Ichinose, and M. Ziskind. 1974. Silico-mycobacterial disease in sandblasters. *Am. Rev. Respir. Dis.* 110:115–125.
8. Falkinham, J. O. 1996. Epidemiology of infection by nontuberculous mycobacteria. *Clin. Microbiol. Rev.* 9:177–212.
9. Leon, R., A. Davies, M. Salomon, and J. Davies. 1995. Leon Commission of Enquiry into Safety and Health in the Mining Industry. Government Printers, Pretoria, South Africa.
10. Cowie, R. L. 1990. The mycobacteriology of pulmonary tuberculosis in South African gold miners. *Tubercle* 71:39–42.
11. Kaustova, J., M. Chmelik, D. Ettlova, V. Hudec, H. Lazarova, and S. Richtrova. 1995. Disease caused by *Mycobacterium kansasii* in the Czech Republic: 1984–89. *Tuber. Lung Dis.* 76:205–209.
12. McIntyre, J. 1996. HIV/AIDS in South Africa—a relentless progression? *S. Afr. Med. J.* 86:27–28.
13. De Cock, K. M., B. Soro, I. Malick Coulibaly, and S. B. Lucas. 1992. Tuberculosis and HIV infection in Sub-Saharan Africa. *J.A.M.A.* 268: 1581–1587.
14. Nightingale, S. D., L. T. Byrd, P. M. Southern, J. D. Jockusch, S. X. Cal, and B. A. Wynne. 1992. Incidence of *Mycobacterium avium-intracellulare* complex bacteraemia in human immunodeficiency virus–positive patients. *J. Infect. Dis.* 165:1082–1085.
15. Campbell, C. M., and B. W. Williams. 1996. Academic research and HIV/AIDS in South Africa. *S. Afr. Med. J.* 86:55–60.
16. International Labor Office. 1980. Guidelines for the Use of ILO Classification of Radiographs of Pneumoconioses. Rev. ed. International Labor Office, Geneva.
17. Sluis-Cremer, G. K. 1980. Active pulmonary tuberculosis discovered at post-mortem examination of the lungs of black mineworkers. *Br. J. Dis. Chest.* 74:374–378.
18. Leger, J. P. 1992. Occupational disease in South African mines—a neglected epidemic? *S. Afr. Med. J.* 81:197–201.
19. Murray, J., D. Kielowski, and P. Reid. 1996. Occupational disease trends in black South African gold miners: an autopsy based study. *Am. J. Respir. Crit. Care Med.* 153:706–710.
20. Cowie, R. L., and S. K. Mabena. 1991. Silicosis, chronic airflow limitation and chronic bronchitis in South African gold miners. *Am. Rev. Respir. Dis.* 143:80–84.
21. O'Brien, R. J., I. J. Geiter, and D. E. Snider. 1987. The epidemiology of nontuberculous mycobacterial disease in the United States: results from a national survey. *Am. Rev. Respir. Dis.* 135:1007–1014.
22. Shaw, M. A., A. Collins, C. S. Peacock, E. N. Miller, G. F. Black, D. Sibthorpe, Z. Lins-Lainson, J. J. Shaw, F. Ramos, F. Silveira, and J. M. Blackwell. 1997. Evidence that genetic susceptibility to *M. tuberculosis* in a Brazilian population is under oligogenetic control: linkage study of the candidate genes NRAMP1 and TNFA. *Tuber. Lung Dis.* 78:35–45.
23. Prince, D. S., D. D. Peterson, R. M. Steiner, J. E. Gottlieb, R. Scott, H. L. Israel, W. G. Figueroa, and J. E. Fish. 1989. Infection with *Mycobacterium avium* complex in patients without predisposing conditions. *N. Engl. J. Med.* 321:863–869.
24. Cowie, R. L., M. E. Langton, and M. R. Becklake. 1989. Pulmonary tuberculosis in South African gold miners. *Am. Rev. Respir. Dis.* 139: 1086–1089.
25. Kleinschmidt, I., and G. J. Churchyard. 1997. Variation in tuberculosis incidence rates in subgroups of South African gold miners. *Occup. Environ. Med.* 54:636–641.
26. Daley, C. L., P. M. Small, G. F. Scheter, G. K. Schoolnik, R. A. McAdam, W. R. Jacobs, and P. C. Hopewell. 1992. An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus. *N. Engl. J. Med.* 326:231–235.
27. Whalen, C., C. R. Horsburgh, D. Hom, C. Lahart, M. Simberkoff, and J. Ellner. 1995. Accelerated course of human immunodeficiency virus infection after tuberculosis. *Am. J. Respir. Crit. Care Med.* 151:129–135.