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A Trial of Mass Isoniazid Preventive Therapy for Tuberculosis Control

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ABSTRACT

BACKGROUND

Tuberculosis is epidemic among workers in South African gold mines. We evaluated an intervention to interrupt tuberculosis transmission by means of mass screening that was linked to treatment for active disease or latent infection.

METHODS

In a cluster-randomized study, we designated 15 clusters with 78,744 miners as either intervention clusters (40,981 miners in 8 clusters) or control clusters (37,763 miners in 7 clusters). In the intervention clusters, all miners were offered tuberculosis screening. If active tuberculosis was diagnosed, they were referred for treatment; if not, they were offered 9 months of isoniazid preventive therapy. The primary outcome was the cluster-level incidence of tuberculosis during the 12 months after the intervention ended. Secondary outcomes included tuberculosis prevalence at study completion.

RESULTS

In the intervention clusters, 27,126 miners (66.2%) underwent screening. Of these miners, 23,659 (87.2%) started taking isoniazid, and isoniazid was dispensed for 6 months or more to 35 to 79% of miners, depending on the cluster. The intervention did not reduce the incidence of tuberculosis, with rates of 3.02 per 100 person-years in the intervention clusters and 2.95 per 100 person-years in the control clusters (rate ratio in the intervention clusters, 1.00; 95% confidence interval [CI], 0.75 to 1.34; P=0.98; adjusted rate ratio, 0.96; 95% CI, 0.76 to 1.21; P=0.71), or the prevalence of tuberculosis (2.35% vs. 2.14%; adjusted prevalence ratio, 0.98; 95% CI, 0.65 to 1.48; P=0.90). Analysis of the direct effect of isoniazid in 10,909 miners showed a reduced incidence of tuberculosis during treatment (1.10 cases per 100 person-years among miners receiving isoniazid vs. 2.91 cases per 100 person-years among controls; adjusted rate ratio, 0.42; 95% CI, 0.20 to 0.88; P=0.03), but there was a subsequent rapid loss of protection.

CONCLUSIONS

Mass screening and treatment for latent tuberculosis had no significant effect on tuberculosis control in South African gold mines, despite the successful use of isoniazid in preventing tuberculosis during treatment. (Funded by the Consortium to Respond Effectively to the AIDS TB Epidemic and others; Thibela TB Current Controlled Trials number, ISRCTN63327174.)

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Tuberculosis is a leading cause of death in adults globally and was responsible for an estimated 1.4 million deaths in 2011.[1,2] Human immunodeficiency virus (HIV) infection, exposure to silica dust in ultradeep mines, and close working and living conditions predispose South African gold miners to tuberculosis.[3] Despite standard control measures and annual active case finding, the escalating prevalence of HIV (29% in 2001) intensified the tuberculosis epidemic. Case notifications exceeded 4000 per 100,000 miners in 1999[4-6] and remained high in 2008 (3000 per 100,000 miners), despite the promotion of HIV testing linked to free antiretroviral therapy (which substantially reduces the incidence of tuberculosis) and targeted isoniazid preventive therapy for miners living with HIV.[6,7]

In a trial in the 1960s in which households were randomized in Alaska, where tuberculosis was epidemic, isoniazid preventive therapy that was delivered to all household members resulted in a 55% decline in tuberculosis incidence over 6 years.[8-10] These findings led us to consider a novel intervention for gold miners. We reasoned that a community-wide intervention, which consisted of screening an entire workforce for active tuberculosis and linking that to treatment for those with active disease or a course of isoniazid preventive therapy for those without active disease, would reduce the burden of tuberculosis. Benefits would accrue both through the indirect effect of mass case finding and treatment (thus reducing transmission) and through the direct protective effect of isoniazid treatment for miners with latent infection. We evaluated this intervention in the Thibela TB study.

Methods

Study Population

The Thibela TB study was a cluster-randomized trial conducted at three gold-mining companies in South Africa.[11] We included all geographically discrete mines (to minimize between-cluster mixing) that were expected to be in operation for at least 10 years and that had a workforce of at least 1000 miners. Clusters comprised all miners (both permanent employees and temporary contract workers) at participating mines and associated hostels, where most miners lived. (For definitions of types of workers, as well as other terms used in the study, see Section S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

Randomization

Clusters were stratified into two groups according to rates of tuberculosis case notification (low or high) in 2005 (before the study was initiated). Randomization was restricted to ensure an overall balance according to mining company, province, and workforce size.[11]

Intervention

The entire workforce at each intervention cluster was encouraged to participate in the intervention.[11,12] Consenting miners were screened for tuberculosis on the basis of symptoms (cough with duration >2 weeks, unintentional weight loss, or night sweats) and chest radiography for all participants.[5,13] Miners with symptoms or abnormalities on chest radiography suggestive of tuberculosis had one sputum specimen collected for fluorescence microscopy, mycobacterial culture on liquid media, and (if positive) speciation and drug sensitivity testing.[14] Miners without active tuberculosis and no contraindications were offered a 9-month course of isoniazid (300 mg daily) with pyridoxine (25 mg daily), which was dispensed monthly by research staff who screened the miners for symptoms of tuberculosis or adverse effects.[11,15] The intervention thus included case finding for active tuberculosis at monthly dispensing visits. Tuberculin skin tests were not performed, since there was an estimated pretrial prevalence of latent tuberculosis infection of 89% among the miners.[16]

Participants who reported symptoms suggestive of hepatotoxicity discontinued isoniazid and were referred to mine health services for further assessment. Study nurses managed other possible adverse reactions using clinical algorithms and made referrals for treatment if necessary. Full details of the study design are provided in the study protocol (available at NEJM.org).

Standard of Care

In all clusters, mine health services provided comprehensive free medical care. This included tuberculosis diagnostic and treatment services, HIV testing, and antiretroviral therapy (Section S2 in the Supplementary Appendix).

STUDY ACTIVITIES AND TIMELINES

In the baseline survey, we determined the demographic characteristics, tuberculosis history, and risk factors in a random sample of approximately 1000 miners per cluster by means of interviews and standardized reading of a previous occupational health chest radiograph.[11] In intervention clusters, miners were recruited during the intervention enrollment period, with the duration of the enrollment period varying according to cluster size and continuing until all miners had the opportunity to enroll. The subsequent 9-month intervention follow-up period allowed all participants to complete 9 months of isoniazid therapy; miners who joined intervention workforces during this period were offered enrollment. Corresponding periods were defined for control clusters (Fig. 1).

After the intervention follow-up period, we measured the incidence of tuberculosis in all clusters during the 12-month measurement period for the primary outcome. At the end of the study, we measured the prevalence of tuberculosis among a consecutive sample of employees undergoing their annual medical examination. The management of suspected tuberculosis is described in Section S3 in the Supplementary Appendix.

STUDY OUTCOMES

The primary outcome was the incidence of tuberculosis (in both pulmonary and extrapulmonary forms) during the measurement period for the primary outcome. Cases were ascertained primarily from mine health service records of tuberculosis treatment, supplemented by autopsy records to ascertain tuberculosis cases that were only identified post mortem (Section S1 in the Supplementary Appendix).

Secondary outcomes included the prevalence of sputum culture–positive tuberculosis among a consecutive sample of employees (in order to avoid potential bias due to differential case ascertainment); death from any cause, as ascertained from human resource records (with a sensitivity analysis that included death and "medical boarding" [i.e., termination of employment due to ill health]); and rates of tuberculosis case notification (all treated cases reported by the mine health services). The last two outcomes were analyzed over the entire study follow-up period. We measured adherence to isoniazid treatment on the basis of monthly attendance at drug-dispensing visits, pill count, and urine testing for isoniazid in a random sample of participants (Section S4 in the Supplementary Appendix). We also collected data on factors that could have an influence on the

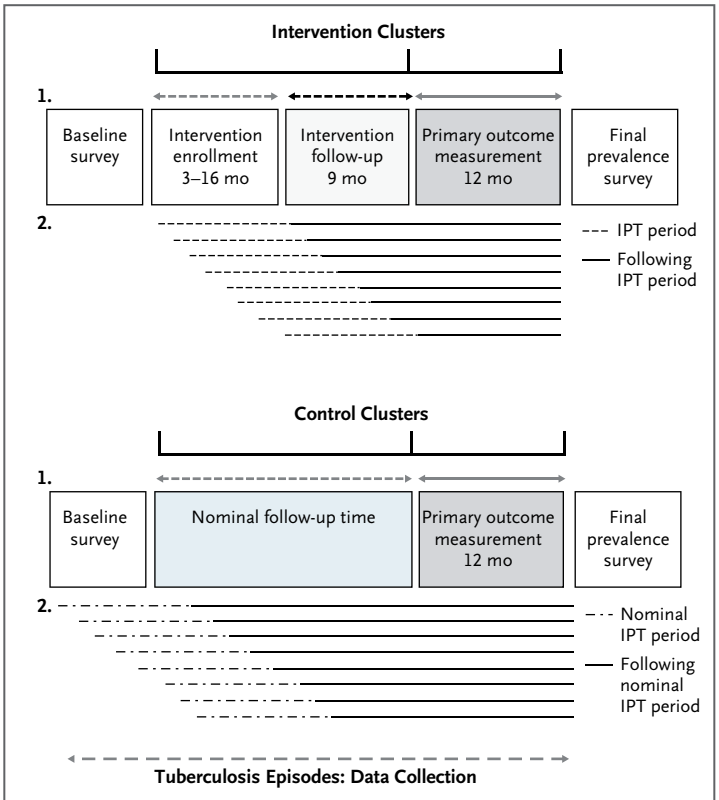

Figure 1. Study Activities and Timelines.

Shown are the study activities for intervention clusters and control clusters (labeled section 1) and horizontal lines illustrating the person-time of follow-up for isoniazid preventive therapy (IPT) in the analysis of the direct effect of isoniazid (labeled section 2). In all clusters, the baseline survey was conducted at the time of cluster enrollment, and the final prevalence survey was conducted at the end of the measurement period for the primary outcome. Incident cases of tuberculosis were ascertained during the interval between these surveys. After the baseline survey, in the intervention clusters, there was an enrollment period, after which there was a 9-month follow-up period to allow every participant to complete the 9-month course of IPT, with equivalent periods in the control clusters. There was then a 12-month period during which the primary outcome of tuberculosis incidence was measured in the intervention and control clusters. In section 2 of each part of the figure, the horizontal lines represent follow-up time for a sample of participants who were included in the cohorts contributing to the analysis of the direct effect of the intervention (see the Methods section for inclusion criteria). The time at risk was measured from the date that isoniazid was first dispensed (in the isoniazid cohort) or from the date of the baseline survey (in the control cohort) to the date that tuberculosis treatment was initiated, the date that the participant died or left the workforce, or the end of the measurement period for the primary outcome, whichever came first. The dotted lines represent the first 9-month follow-up period for these participants, and the solid lines represent the subsequent time periods.

effectiveness of the intervention (Section S5 in the Supplementary Appendix).

OVERALL EFFECT OF THE INTERVENTION

We conducted cluster-level analyses to assess the overall effect of the intervention (encompassing both direct and indirect effects of the intervention and reflecting coverage achieved)[17] with respect to the primary and secondary outcomes, as appropriate for a cluster-randomized trial with stratified design and a small number of clusters.[17] Although the intervention was offered to all miners, the analyses of the incidence and prevalence of tuberculosis and mortality were restricted to permanent employees, since the ascertainment of outcomes among contract workers, who accessed health care outside the mine, was incomplete. The analysis of the primary outcome was based on all employees in the workforce during the enrollment period (or the equivalent for control clusters) and at the start of the measurement period for the primary outcome. Person-time at risk was measured from the start of the measurement period for the primary outcome to the date on which tuberculosis treatment was initiated, the miner died, the miner left the workforce, or the end of the measurement period for the primary outcome — whichever came first. The rate of death from any cause was measured from the time of cluster enrollment to the end of the measurement period for the primary outcome. Tuberculosis case notifications were expressed as annualized rates. (Additional statistical methods are described in Section S6 in the Supplementary Appendix.)

DIRECT EFFECT OF THE INTERVENTION

In a post hoc analysis estimating the direct protective effect of isoniazid, we analyzed two cohorts comprising all employees who were included in the baseline survey, excluding those who were receiving tuberculosis treatment or isoniazid preventive therapy at the time of the baseline survey; the isoniazid cohort included employees to whom isoniazid preventive therapy was dispensed at least once in intervention clusters as part of this study, and the control cohort included those who were in control clusters (Fig. 1). The time at risk was measured from the date that isoniazid was first dispensed in the isoniazid cohort or from the date of the baseline survey in the control cohort to the date on which tuberculosis treatment was initiated, the employee died, the employee left the workforce, or the end of the measurement period for the primary outcome — whichever came first.

We compared the incidence of tuberculosis between the isoniazid cohort and the control cohort, stratified into three periods: the first 9-month period, reflecting the duration of the intended administration of isoniazid preventive therapy; and two subsequent periods (>9 to 18 months and ≥18 months), assessing the durability of effect. Adjusted and sensitivity analyses were conducted (Section S7 in the Supplementary Appendix).

STUDY OVERSIGHT

The study was approved by the ethics committees at the University of KwaZulu-Natal and the London School of Hygiene and Tropical Medicine and by the South African Medicines Control Council and the South African Safety in Mines Research Advisory Committee. Miners who participated in the intervention and prevalence surveys provided written or witnessed oral informed consent. The authors designed the study and vouch for the completeness and accuracy of the data presented. The isoniazid that was used in the study was donated by Sanofi-Aventis, which had no other role in the study.

STATISTICAL ANALYSIS

With 15 clusters, we estimated that the study had a power of 80% to detect a 40% lower incidence of tuberculosis during the measurement period for the primary outcome in the intervention clusters than in the control clusters, assuming a coefficient of variation of 0.25, a harmonic mean workforce size of 2000, and a rate of tuberculosis incidence in the control clusters of 2 cases per 100 person-years. We estimated that the study had the same power to detect a 55% lower prevalence of tuberculosis in the intervention clusters at the end of the study, assuming 1.5% prevalence in control clusters and a coefficient of variation of 0.3, with a harmonic mean of 750 employees per cluster.[11]

RESULTS

STUDY POPULATION

Fifteen clusters underwent randomization: eight clusters to the intervention and seven to control (Fig. 2). Among 78,744 miners (40,981 in the in-

Figure 2. Study Population and Analyses of Primary and Secondary Outcomes.

Workforce turnover (migration in and out of the companies) in the intervention and control clusters was calculated from monthly payroll records provided throughout the study period. In the analysis of the primary outcome of tuberculosis incidence, employees were excluded if they were not in the workforce during the enrollment period (3224 in the intervention clusters and 3831 in the control clusters) or if they were contract workers (6667 and 3645, respectively). In the analysis of the secondary outcome of tuberculosis prevalence, employees were excluded if they had cultures that were contaminated (165 in the intervention clusters and 241 in the control clusters) or if they had incomplete laboratory data (11 in each group). A restricted analysis of tuberculosis prevalence excluded 1626 employees in the intervention group who were not in the workforce during the intervention enrollment period and 1100 employees in the control group who were not in the workforce during the equivalent period in control clusters.

tervention clusters and 37,763 in the control clusters), 95.9% were men, and the median age was 41 years. The median cluster size was 4391 miners (range, 2727 to 11,325) in the intervention clusters and 5887 miners (range, 1305 to 10,014) in the control clusters.

Among 13,958 miners (7561 in the intervention clusters and 6397 in the control clusters) in the baseline survey, 2.6% had definite silicosis (Section S1 in the Supplementary Appendix). A total of 12.5% reported having had previous active tuberculosis, 13.6% reported being HIV-positive, 2.7% reported receiving previous or current antiretroviral therapy, and 0.5% reported receiving previous or current isoniazid preventive therapy, with similar rates in the two study groups (Table 1). Mean rates of tuberculosis case notification in the 12 months before cluster enrollment were slightly lower in the control clusters than in the intervention clusters.

PARTICIPATION IN THE INTERVENTION

In eight intervention clusters, 27,126 miners (66.2% [range according to cluster, 54.5 to 97.4]) enrolled in the study (Fig. S1 and S2 in the Supplementary Appendix). Of these miners, 3467 (12.8%)

Table 1. Characteristics of Study Participants Who Completed the Baseline Survey.*

Characteristic	Control Clusters (N = 6397)	Intervention Clusters (N = 7561)	Total (N = 13,958)
	number/total number (percent)		
Age group			
18–29 yr	732/6349 (11.5)	746/7504 (9.9)	1,478/13,853 (10.7)
30–39 yr	1590/6349 (25.0)	1801/7504 (24.0)	3,391/13,853 (24.5)
40–49 yr	2742/6349 (43.2)	3343/7504 (44.5)	6,085/13,853 (43.9)
50–70 yr	1285/6349 (20.2)	1614/7504 (21.5)	2,899/13,853 (20.9)
Male sex	6246/6395 (97.7)	7380/7561 (97.6)	13,626/13,956 (97.6)
Country of birth			
South Africa	3532/6396 (55.2)	4272/7561 (56.5)	7,804/13,957 (55.9)
Lesotho	1609/6396 (25.2)	2071/7561 (27.4)	3,680/13,957 (26.4)
Mozambique	823/6396 (12.9)	806/7561 (10.7)	1,629/13,957 (11.7)
Other	432/6396 (6.8)	412/7561 (5.4)	844/13,957 (6.0)
Residence in hostel	3838/6396 (60.0)	4391/7558 (58.1)	8,229/13,954 (59.0)
History of working underground	6249/6397 (97.7)	7379/7560 (97.6)	13,628/13,957 (97.6)
Medical history			
Current receipt of tuberculosis therapy	119/6396 (1.9)	160/7560 (2.1)	279/13,956 (2.0)
Previous tuberculosis	734/6381 (11.5)	1006/7553 (13.3)	1,740 /13,934 (12.5)
HIV-positive by self-report	301/2325 (12.9)	380/2689 (14.1)	681/5,014 (13.6)
Previous or current use of isoniazid preventive therapy	37/6395 (0.6)	38/7560 (0.5)	75/13,955 (0.5)
Previous or current use of antiretroviral therapy	176/6386 (2.8)	199/7544 (2.6)	375/13,930 (2.7)
Silicosis†			
None	5779/6127 (94.3)	6488/6774 (95.8)	12,267/12,901 (95.1)
Possible or probable	166/6127 (2.7)	134/6774 (2.0)	300/12,901 (2.3)
Definite	182/6127 (3.0)	152/6774 (2.2)	334/12,901 (2.6)

* During the 12 months before cluster enrollment, there were 1437 treated tuberculosis cases among 39,175 miners in the intervention clusters and 1168 cases among 36,030 miners in the control clusters, for rates of tuberculosis case notification of 3668 and 3242 per 100,000 person-years, respectively.
† Silicosis was graded according to the modified International Labour Organization scale.

did not start isoniazid preventive therapy; the most common reason was a diagnosis of active tuberculosis (in 971 miners) or suspected tuberculosis (in 734). Isoniazid preventive therapy was initiated by 23,659 miners (87.2% [range according to cluster, 81.9 to 92.8]); isoniazid pills were dispensed for 6 months or more to 54.5% of these miners (range according to cluster, 34.9 to 79.2) (Fig. S1 in the Supplementary Appendix). The mean proportion of miners in intervention clusters who were given isoniazid pills each month during the first 9 months after cluster enrollment was 33.5% (range according to cluster, 9.8 to 65.4) (Fig. S3 in the Supplementary Appendix). More details about adherence are provided in Section S4 in the Supplementary Appendix.

OVERALL EFFECT OF THE INTERVENTION

Among 63,174 employees who were included in the primary outcome analysis, there were 1743 cases of tuberculosis (887 in the intervention clusters and 856 in the control clusters), for an incidence of tuberculosis of 3.02 and 2.95 cases per 100 person-years, respectively (rate ratio in the

intervention clusters, 1.00; 95% confidence interval [CI], 0.75 to 1.34; P=0.98) (Table 2, and Table S1 in the Supplementary Appendix). After adjustment for individual-level variables (sex, age, and surface or underground work) and cluster-level variables (prevalence of silicosis, prevalence of receipt of antiretroviral therapy, pretrial rates of tuberculosis case notification, and randomization stratum), there was no significant between-group difference in tuberculosis incidence (adjusted rate ratio, 0.96; 95% CI, 0.76 to 1.21; P=0.71). The results were similar when the analysis was restricted to definite or probable tuberculosis cases (Table 2).

The prevalence of tuberculosis was similar in the intervention clusters and the control clusters. A total of 166 of 7049 employees (2.35%) in the intervention clusters and 119 of 5557 employees (2.14%) in the control clusters had sputum cultures that were positive for *Mycobacterium tuberculosis* (prevalence ratio, 1.05; 95% CI, 0.60 to 1.82; P=0.86); there was little change in the prevalence ratio after adjustment for potential confounders (adjusted prevalence ratio, 0.98; 95% CI, 0.65 to 1.48; P=0.90) or when the analysis was restricted to employees who were in the workforce during the main enrollment period (Table 2). The rates of death from any cause and of tuberculosis case notification did not differ significantly according to study group (Table S2, Fig. S4, and Section S8 in the Supplementary Appendix). Data on factors that could have had an influence on the effectiveness of community-wide isoniazid preventive therapy are described in Section S9 in the Supplementary Appendix.

DIRECT EFFECT OF THE INTERVENTION

A total of 4646 employees in the intervention group and 6263 in the control group met the inclusion criteria for the isoniazid and control cohorts and were included in the analysis of the direct effect of the intervention. (Fig. S5 in the Supplementary Appendix). Baseline characteristics were gener-

Table 2. Overall Effect of Community-wide Isoniazid Preventive Therapy: Tuberculosis Incidence and Prevalence.

Outcome	Control Clusters		Intervention Clusters		Rate Ratio (95% CI)*			
	Cases	Rate	Cases	Rate	Unadjusted	P Value	Adjusted†	P Value
	no./no. of person-yr	*per 100 person-yr‡*	*no./no. of person-yr*	*per 100 person-yr‡*				
Primary outcome: tuberculosis incidence§								
Any	856/29,014	2.95	887/29,352	3.02	1.00 (0.75–1.34)	0.98	0.96 (0.76–1.21)	0.71
Definite or probable	656/29,014	2.26	703/29,352	2.40	1.07 (0.70–1.64)	0.72	1.04 (0.73–1.48)	0.80
					Prevalence Ratio (95% CI)*			
	no. of cases/ total no.	*%‡*	*no. of cases/ total no.*	*%‡*				
Secondary outcome: tuberculosis prevalence¶								
All employees	119/5557	2.14	166/7049	2.35	1.05 (0.60–1.82)	0.86	0.98 (0.65–1.48)	0.90
Employees in workforce at the time of cluster enrollment	97/4457	2.18	128/5423	2.36	1.05 (0.62–1.78)	0.85	1.01 (0.66–1.55)	0.94

* Comparisons are for the intervention clusters versus the control clusters.
† Rate ratios were adjusted for individual-level variables (sex, age, and surface or underground work) and cluster-level variables (prevalence of silicosis and antiretroviral therapy, rate of tuberculosis case notification during the 12 months before cluster enrollment, and randomization strata).
‡ Rates per 100 person-years and percentages were calculated among all employees regardless of cluster.
§ The analysis of incidence during the 12-month measurement period for the primary outcome was restricted to employees who were in the cluster during the intervention enrollment period and the equivalent time for control clusters.
¶ The analysis of prevalence at the end of the study excluded employees with contaminated cultures, incomplete laboratory results, or both.

Table 3. Direct Effect of Isoniazid Preventive Therapy as Shown by Tuberculosis Incidence, According to the Time Interval after Enrollment.*

Time Interval	Control Cohort (N=6263)		Isoniazid Cohort (N=4646)		Rate Ratio (95% CI)			
	Cases	Rate†	Cases	Rate†	Unadjusted	P Value	Adjusted‡	P Value§
	no./no. of person-yr	*per 100 person-yr*	*no./no. of person-yr*	*per 100 person-yr*				
Overall	382/13,776	2.77	175/9163	1.91	0.77 (0.52–1.15)	0.18	0.82 (0.58–1.15)	0.23
0–9 mo¶	133/4,564	2.91	37/3358	1.10	0.38 (0.19–0.75)	0.01	0.42 (0.20–0.88)	0.03
>9–18 mo	115/4,243	2.71	74/3156	2.34	0.97 (0.57–1.65)	0.89	0.93 (0.53–1.61)	0.93
>18 mo	134/4,970	2.70	64/2649	2.42	0.83 (0.54–1.27)	0.35	0.95 (0.62–1.46)	0.95

* The direct effect of the intervention was estimated by comparing the incidence of tuberculosis in the isoniazid cohort with that in the control cohort. Each cohort included all employees who participated in the baseline survey, excluding those receiving tuberculosis treatment or isoniazid preventive therapy at the time of the baseline survey. The isoniazid cohort consisted of employees in the intervention clusters to whom isoniazid preventive therapy was dispensed at least once as part of the study. The control cohort consisted of employees in the control clusters. Incidence was measured from the time of enrollment, which was defined as the date when isoniazid preventive therapy was first dispensed (in the isoniazid cohort) or employees participated in the baseline survey (in the control cohort), to the end of the measurement period for the primary outcome.

† Rates per 100 person-years were calculated among all employees regardless of cluster.

‡ Rate ratios were adjusted for sex, age, previous tuberculosis, antiretroviral therapy, silicosis on chest radiography, country of origin, residence, and randomization stratum.

§ P=0.02 for the interaction between study cohort and time interval.

¶ Isoniazid preventive therapy was dispensed during the first 9 months of the study.

ally similar in the two cohorts (Table S3 in the Supplementary Appendix). Over the entire follow-up period, the incidence of tuberculosis was 1.91 cases per 100 person-years in the isoniazid cohort (with 175 episodes per 9163 person-years) and 2.77 cases per 100 person-years in the control cohort (with 382 episodes per 13,776 person-years) (adjusted rate ratio, 0.82; 95% CI, 0.58 to 1.15; P=0.23) (Table 3). During the first 9-month period, the incidence of tuberculosis was 58% lower in the isoniazid cohort than in the control cohort (adjusted rate ratio, 0.42; 95% CI, 0.20 to 0.88; P=0.03) but subsequently was similar in the two cohorts (P=0.02 for the interaction between the cohort and follow-up period). The adjusted rate ratios for the isoniazid cohort versus the control cohort were 0.93 (95% CI, 0.53 to 1.61; P=0.93) for the period from 9 to 18 months and 0.95 (95% CI, 0.62 to 1.46; P=0.95) for the period of more than 18 months. Sensitivity analyses are provided in Table S4 and Section S10 in the Supplementary Appendix.

DISCUSSION

In gold mines, in which a tuberculosis epidemic has been unresponsive to conventional control measures, we evaluated a community-level intervention that was specifically targeted at interrupting the transmission of tuberculosis. After screening miners for active disease, we aimed to offer treatment for either active or latent tuberculosis to all members of the community simultaneously. In the pre-HIV era, several cluster-randomized trials of isoniazid preventive therapy were conducted in Native Alaskan households,[10] Greenland villages,[18] and Tunisian city blocks.[19] In these studies, there was no attempt to interrupt transmission abruptly by coupling tuberculosis screening with preventive therapy for all community members, and the randomization of clusters appears to have been primarily for logistic convenience, rather than with a specific intention of achieving a mass effect. Our intervention did not reduce either the incidence or prevalence of tuberculosis or the rate of death from any cause, findings that contrasted with the apparent success of the intervention in Alaska (but not in either Greenland or Tunisia, where the lack of success was attributed to an inadequate dose of isoniazid) (Section S11 in the Supplementary Appendix).[8,20]

We can use available data to address some of the possible reasons for the lack of effect in our study. For isoniazid preventive therapy to have a population-level effect on tuberculosis rates, it must have a direct effect. Among employees who started isoniazid preventive therapy, the incidence of tuberculosis was reduced by 58% during the 9-month treatment period, in keeping with a very high prevalence of latent tuberculosis

infection and protection against disease due to recent infection. The effect was lost immediately after treatment was discontinued, consistent with findings regarding the limited durability of isoniazid preventive therapy among HIV-infected adults in sub-Saharan Africa.[21-25]

To interrupt tuberculosis transmission, we needed to rapidly find and treat all cases of infectious tuberculosis and achieve high retention of miners receiving isoniazid preventive therapy in order to prevent reactivation. Participation in the intervention and retention in the study were variable across clusters. In our best-performing cluster with excellent participation and retention, the modest effect on case notifications was not durable (Fig. S3 in the Supplementary Appendix). In other mines, intervention enrollment took longer, and retention was lower than desirable. Thus, the proportion of miners taking isoniazid simultaneously was suboptimal. The effectiveness of community-wide isoniazid preventive therapy may have been compromised through post-treatment reinfection — within or outside the mines — in miners who had taken isoniazid. Transmission in the mines is probably more important, since 60% of miners lived in hostels and mixed predominantly with miners from the same mine. The duration of infectiousness, and thus the risk of transmission, could be reduced by minimizing the time from diagnosis to the initiation of tuberculosis treatment; potential ways to achieve this could include the use of more sensitive tools for routine annual screening, such as the automated Xpert MTB/RIF assay (which tests for the presence of *M. tuberculosis* [MTB] and resistance to rifampin [RIF]).

We can speculate about the role of other factors that may have compromised the intervention, although our data with respect to these factors are limited. The rapid waning of individual protection may have been due to reactivation of inadequately treated latent tuberculosis infection or reinfection caused by high rates of ongoing transmission. Gold miners in South Africa have a high prevalence of HIV and silicosis, both of which are strong risk factors for tuberculosis, particularly if the conditions are combined.[3] Although antiretroviral therapy reduces the individual risk of tuberculosis, the population-level effect depends on treatment coverage, which is determined by eligibility criteria, uptake, retention, and adherence.[26,27] Initiating antiretroviral therapy early and maximizing coverage may further reduce population-level vulnerability to HIV-associated tuberculosis. Intensification of dust control to minimize silicosis is critical but unlikely to have a short-term effect on rates of tuberculosis case notification.

Our study has several limitations. First, we were unable to determine the prevalence of HIV, which compromised our ability to adjust for HIV effects. Second, the relatively small numbers of clusters limited the study power; however, the consistent lack of effect across various outcomes (tuberculosis incidence and prevalence, mortality, and trends in case-notification rates) strongly suggests that the observed lack of population-level effect was not due to chance. Third, routine tuberculosis-control programs differed according to the mining company (e.g., in the frequency of active case finding); however, the intervention and control clusters were balanced according to company to minimize bias. Finally, there were limitations with respect to the analysis of direct effect, which are described in Section S12 in the Supplementary Appendix.

In conclusion, we found that a 9-month course of community-wide isoniazid preventive therapy did not improve tuberculosis control in South African gold mines. The best achievable implementation of the intervention is unlikely to have substantially changed the result, given that the best-performing cluster had excellent uptake and retention, but the intervention nevertheless had a modest and short-lived effect. Contributing factors include increased vulnerability to tuberculosis due to HIV infection and silicosis, along with the ongoing transmission of tuberculosis. Tuberculosis infection control and strategies for controlling HIV and exposure to silica dust should be expanded. Systems that minimize the time from a positive microbiologic result to tuberculosis treatment are needed. Continuous isoniazid preventive therapy should be considered for persons at highest risk for tuberculosis (i.e., those with HIV infection or silicosis) along with strategies to maximize retention.[21,28-30] Mathematical modeling may help identify combinations of strategies that are more likely to control tuberculosis in gold mines.

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