

Foci of Tuberculosis Transmission in Central Los Angeles

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To identify sites of tuberculosis transmission and to determine the contribution of HIV-infected patients to tuberculosis morbidity in an urban area, we prospectively evaluated 249 patients with culture-proven tuberculosis in central Los Angeles. Restriction fragment length polymorphism (RFLP) analysis was performed on *Mycobacterium tuberculosis* isolates to identify patients infected with the same strain. Using RFLP and clinical and epidemiologic data, we identified the most likely source case and site of transmission for 79 patients. Homelessness, birth in the United States and Native American ethnicity were independent predictors of being a source case, but HIV infection was not. Three homeless shelters were sites of tuberculosis transmission for 55 (70%) of the 79 patients. HIV-infected patients constituted 27% (66/249) of the study population, but only 17% (13/79) of patients were infected by an HIV-infected source case. We conclude that transmission of tuberculosis in central Los Angeles was highly focal, and that the major transmission sites were three homeless shelters. HIV-infected tuberculosis patients did not play a major role in spread of tuberculosis. Tuberculosis control measures targeted at specific homeless shelters can reduce tuberculosis morbidity in urban areas where homelessness is common and the incidence of tuberculosis is high. Barnes PF, Yang Z, Pogoda JM, Preston-Martin S, Jones BE, Oyata M, Knowles L, Harvey S, Eisenach KD, Cave MD. Foci of tuberculosis transmission in central Los Angeles. *AM J RESPIR CRIT CARE MED* 1999;159:1081-1086.

Tuberculosis is a major public health problem in many urban areas in the United States, and studies based on restriction fragment length polymorphism (RFLP) analysis of *Mycobacterium tuberculosis* isolates have shown that 31-54% of urban tuberculosis cases result from extensive transmission of a small number of *M. tuberculosis* strains (1-3). To devise more effective tuberculosis control measures, it is critical to identify sites where tuberculosis is frequently transmitted, as well as subpopulations of patients who contribute significantly to spread of tuberculosis. Homeless shelters, congregate living facilities, and hospitals have been identified as important sites of tuberculosis transmission in urban areas (3-8), but their contribution to tuberculosis morbidity in the population is uncertain. Patients infected with the human immunodeficiency virus (HIV) are highly susceptible to tuberculosis from recent or remote infection (5, 9), and HIV-infected patients contributed substantially to the tuberculosis epidemic in New York City in the early 1990s (2, 8, 10). However, the contribution of

HIV-infected tuberculosis patients to the spread of tuberculosis in other urban areas remains uncertain. To identify sites of tuberculosis transmission and to determine the contribution of HIV-infected patients to tuberculosis morbidity, we performed a prospective, population-based, molecular epidemiologic study of all tuberculosis patients in central Los Angeles.

METHODS

Study Subjects

From March 1994 through May 1997, one of us (M.O.) prospectively identified 289 consecutive patients with culture-proven tuberculosis living in central Los Angeles, using previously described methods (3). No viable *M. tuberculosis* isolate was available for 10 patients. Thirty patients were not interviewed because of death (10 patients), loss to follow-up (12 patients), or patient refusal (8 patients). The remaining 249 patients constitute the study population, 162 of whom were included in a prior study (3). *M. tuberculosis* was cultured from pulmonary specimens in 226 cases and from extrapulmonary sites only in 23 cases. Serologic testing for HIV infection was performed in 231 patients. Among the 18 patients who were not tested, none had HIV risk factors, their mean age was 60.7 yr, and only three patients were under 45 yr. These 18 patients were considered HIV-negative.

Interviews

Patients were interviewed before RFLP analysis to obtain information on their contacts and whereabouts during the 2 yr prior to diagnosis of tuberculosis, as previously described (3). Patients were classified as alcoholic or drug users, based on responses to questions adapted from screening instruments for alcoholism and substance abuse (11, 12). All procedures involving human subjects were approved by the institu-

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Homelessness Scores

Each patient's degree of homelessness was estimated by a "homelessness score," as previously described (3). Briefly, four points were scored for sleeping in a shelter or on the street, three points for sleeping in a residential rehabilitation program, two points for sleeping in single-resident occupancy (SRO) hotels, one point for sleeping in homes of friends or relatives, and no points for sleeping in one's own home. Patient scores were based on sleeping locations during the 2 yr prior to diagnosis of tuberculosis, weighted by the number of nights at each location.

RFLP Analysis

IS6110-based and pTBN12-based RFLP analysis of *M. tuberculosis* isolates from the study patients was used to identify patients infected with the same *M. tuberculosis* strain, using published methods (3). Briefly, we considered *M. tuberculosis* isolates from different patients to represent the same strain if IS6110-based patterns revealed: (1) six or more fragments of identical size; (2) six or more fragments of identical size, except that one isolate showed one additional band or a band of different size and pTBN12-based RFLP patterns were indistinguishable; or (3) five or fewer bands of identical size and pTBN12-based RFLP patterns were indistinguishable. Two or more patients infected with the same *M. tuberculosis* strain constituted a "cluster."

Statistical Analysis

Differences in the distribution of demographic and clinical variables between patients who were or were not source cases were tested by chi square tests of association. Unconditional logistic regression was used to derive maximum likelihood odds ratios and 95% confidence intervals for risk of being a source case and the following variables: age, ethnicity, country of birth, HIV status, alcoholism, drug use, and homelessness score (13). Stepwise regression using forward and backward elimination methods were used to identify the independent variables that best predicted the likelihood of being a source case (14).

To determine if HIV-infected patients were more or less likely to be source cases than HIV-negative patients, the distribution of source case HIV status was compared with expected distributions if HIV-infected and HIV-negative source cases infected other patients at equal rates. This was done using the G statistic, equal to twice the log-likelihood ratio and approximately distributed as chi square, to assess goodness of fit (15).

RESULTS

Patient Characteristics

Of 249 tuberculosis patients, 148 (59%) were born in the United States, 83 (33%) in Latin America, 15 (6%) in Asia, and 3 (1%) elsewhere. One hundred and six patients (43%) were Latino, 102 patients (41%) were African American, 21 (8%) were non-Latino white, and 20 (8%) were other races. The mean age was 43.0 ± 13.3 (SD) yr, 212 patients (85%) were male, and 66 patients (27%) were infected with HIV. One hundred and seven patients (43%) were alcoholic and 75 patients (30%) were drug users.

RFLP Analysis

IS6110-based and pTBN12-based RFLP analysis was performed for 249 and 145 isolates, respectively. One hundred and thirteen patients were not clustered, and 136 patients were clustered in 12 clusters, each consisting of 2–51 patients.

Identification of Probable Source Cases

Because patients infected with the same *M. tuberculosis* strain rarely had personal contact but often spent time at common locations (3), we used epidemiologic data obtained by interview to identify potential source cases. For each of the 136

clustered tuberculosis patients, we attempted to identify the most likely "source case." The date of diagnosis for each patient was the date on which a clinical sample was first obtained that yielded *M. tuberculosis*. For patients in a cluster, we assumed that those in whom tuberculosis was diagnosed first were potential source cases for patients in whom tuberculosis was diagnosed later, and that the reverse was not the case. Patients were considered infectious for 1 mo prior to initiation of antituberculosis therapy because the median duration of cough in our population was 1 mo. Antituberculosis therapy rapidly reduces bacillary concentrations in sputum and greatly diminishes infectiousness (16–18). In addition, most patients with sputum acid-fast smear-positive tuberculosis were hospitalized when antituberculosis therapy was initiated. We therefore assumed that patients were not infectious after beginning treatment.

As an example of assigning source cases, consider patient A in cluster X. Potential source cases were those in cluster X for whom antituberculosis therapy was begun at least 2 wk prior to the date of diagnosis of tuberculosis in patient A. We estimated the time patient A was exposed to each potential source case by an "exposure score." Interview data included the time each patient spent at a location per month but not the number of hours shared with other patients, because there was rarely personal contact. Assuming random distributions of time spent at these locations, the number of hours shared by two patients is proportional to the exposure score, which is the product of the number of hours spent there by each patient. For example, if patients A and B spent 60 and 90 h, respectively, at location 1 during patient B's infectious period, the exposure score at location 1 is 5,400 (60×90). If patients A and B were both at more than one location during patient B's infectious period, the same calculation was performed for each location, and the numbers summed to yield the total exposure score to patient B. Because patients who are sputum acid-fast smear-positive are approximately four times more infectious than those who are sputum smear-negative (19), we divided the exposure score to sputum smear-negative patients by four, prior to comparison with sputum smear-positive patients. In comparing exposure scores to potential source cases for a given patient, the highest score was usually more than twice that of the next highest score, and the patient with the highest exposure score was considered the source case. In 26 cases, the highest exposure score was only 10–50% greater than other exposure scores. In these cases, presence and duration of cough were used to identify the probable source case. A patient with cough was considered the source case if other potential source cases had no cough. When more than one potential source case complained of cough, the one with the longest duration of cough was considered the source case. When potential source cases had the same duration of cough, the patient with the highest exposure score was considered the source case.

Of the 136 clustered patients, 39 source cases were identified for 79 patients. Compared to the 57 patients for whom no source case was identified, the 79 patients had significantly higher homelessness scores, were more likely to be born in the United States and to be African American. The two groups were similar in age and in the prevalence of HIV infection, alcoholism and drug use (data not shown).

The source cases for 75 patients were sputum acid-fast smear-positive, and the source cases for four patients were sputum acid-fast smear-negative and culture-positive. None of the patients with positive cultures from extrapulmonary sites only were identified as source cases. Six source cases each infected 4–8 patients, 10 patients each infected 2–3 patients, and

TABLE 1
RELATIONSHIP OF DEMOGRAPHIC AND CLINICAL VARIABLES TO SOURCE CASE STATUS

Variable	Source Cases n = 39; n (%)	Not Source Cases n = 210; n (%)	Univariate Odds Ratio (95% Confidence Interval)
Age, yr			
16–33	5 (13)	55 (26)	1.0
34–40	8 (21)	50 (24)	1.8 (0.5–5.7)
41–49	10 (26)	53 (25)	2.1 (0.7–6.5)
50–66	16 (41)	52 (25)	3.4 (1.2–9.9)
Ethnicity			
Latino	8 (21)	98 (47)	1.0
Non-Latino white	3 (8)	18 (9)	2.0 (0.5–8.4)
African American	24 (62)	78 (37)	3.8 (1.6–8.9)
Asian	1 (3)	14 (7)	0.9 (0.1–7.5)
Native American	3 (8)	2 (1)	18.4 (2.7–126.5)
Country of birth			
Foreign	2 (5)	99 (47)	1.0
United States	37 (95)	111 (53)	16.5 (3.9–70.2)
HIV-infected			
No	32 (82)	151 (72)	1.0
Yes	7 (18)	59 (28)	0.6 (0.2–1.3)
Alcoholic			
No	21 (54)	121 (57)	1.0
Yes	18 (46)	89 (43)	1.2 (0.6–2.3)
Drug user			
No	28 (68)	146 (67)	1.0
Yes	11 (32)	64 (33)	1.0 (0.5–2.1)
Homelessness score			
0	1 (3)	75 (36)	1.0
0.1–1.00	1 (3)	35 (17)	2.1 (0.1–35.3)
1.01–2.00	7 (18)	37 (18)	14.2 (1.7–119.6)
2.01–3.00	6 (15)	19 (9)	23.7 (2.7–208.7)
3.01–3.99	11 (28)	17 (8)	48.5 (5.9–401.8)
4.00	13 (33)	27 (13)	36.1 (4.5–289.3)

23 patients each infected one patient. Source cases were significantly more likely to be older than 50 yr, African American or Native American, born in the United States, and to have higher homelessness scores (Table 1). HIV infection, alcoholism, and drug use were unrelated to source case status. To identify independent predictors of being a source case, unconditional logistic regression analysis was performed. Higher homelessness scores (odds ratio, 1.9 for every increase of 1 in homelessness score; 95% confidence interval, 1.4–2.7), birth in the United States (odds ratio, 9.1; 95% confidence interval, 2.0–55.6), and Native American ethnicity (odds ratio, 15.1; 95% confidence interval, 1.6–145.0) were the only independent factors associated with being a source case. Age, ethnicity, alcoholism, drug use, and HIV status were not associated with being a source case (data not shown).

Contribution of HIV-infected Patients to Disease Transmission

In central Los Angeles, HIV infection was not associated with clustering (3) and was not associated with being a source case. However, we considered the possibility that tuberculosis patients were more likely to have been infected by HIV-infected source cases. In the total population of 249 patients, 66 (27%) were infected with HIV. Of the 79 patients for whom a source case was identified, only 13 (17%) were infected by an HIV-infected source case ($p = 0.13$, log likelihood ratio test for goodness-of-fit). Most HIV-infected and HIV-negative patients were infected by HIV-negative source cases (Table 2).

These data demonstrate that HIV-infected patients are clearly not more likely to be source cases than HIV-negative patients. In contrast, they suggest that HIV-infected patients may be less likely to be source cases. We therefore evaluated the distribution of factors that would reduce the transmission

potential of tuberculosis in HIV-infected patients. In comparing HIV-infected and HIV-negative patients, there were no differences in the percentages of patients with cough, the duration of cough, the mean homelessness score, or the duration of time spent at homeless shelters (data not shown). The only difference between the groups was that sputum acid-fast smears were positive in 50% (33/66) of HIV-infected patients and in 61% (111/183) of HIV-negative patients ($p = 0.04$, Fisher exact test).

Identification of Probable Sites of Tuberculosis Transmission

Based on the analysis outlined above, we identified the most likely source cases for 79 patients. For each of these 79 pa-

TABLE 2
SOURCE CASES FOR PATIENTS WITH AND WITHOUT HIV COINFECTION

Cluster(s)	Source Case HIV+	Source Case HIV–	Source Case Unknown
A (n = 34)*	3	21	10
HIV+ (n = 7)	0	5	2
HIV– (n = 27)	3	16	8
B (n = 51)	9	33	9
HIV+ (n = 16)	1	9	6
HIV– (n = 35)	8	24	3
Nine other clusters (n = 51)	1	12	38
HIV+ (n = 11)	0	3	8
HIV– (n = 40)	1	9	30

* Cluster A corresponds to cluster 4.1, and cluster B corresponds to cluster 21 in a previous publication (3).

tients, we determined the most likely site where tuberculosis was transmitted. The transmission site was considered to be the location that contributed the most to the exposure score between the source case and the infected case, which was a measure of the time shared by the patients during the source case's infectious period. Among the 79 patients, the site of transmission was shelter 1 in 36 (46%) cases, shelter 2 in 11 (14%) cases, shelter 3 in 8 (10%) cases, and other locations in the remaining 24 (30%) cases. These other locations included a shelter, two residential rehabilitation facilities, three SRO hotels, two soup kitchens, a bar, an all-night theater, three street corners, an alley, and two small parks.

Our analysis to identify source cases was based on several assumptions. We assumed that tuberculosis patients were not source cases for patients in whom tuberculosis was diagnosed at an earlier date. This may be incorrect if patients in whom tuberculosis was diagnosed later were symptomatic for prolonged periods. To determine if this assumption affected our results, we first identified all 19 clustered patients who were symptomatic for 3 mo or more. These patients were considered to be potential source cases for patients who were exposed to them while they were symptomatic, even if their date of diagnosis preceded that of the patient with prolonged symptoms. Exposure scores and duration of cough were then used to reassign source cases, as outlined above. This reanalysis changed the assigned source cases for 10 patients. However, shelters 1, 2, and 3 remained the sites of transmission for 55 (70%) of 79 patients.

Another assumption we made was that for a given patient, potential source cases were considered to be those for whom antituberculosis therapy was started at least 2 wk prior to the diagnosis of tuberculosis in that patient. It could be argued that this period should have been longer. In the 79 pairs of infected cases and source cases, the period between initiation of antituberculosis therapy in the source case and diagnosis of tuberculosis in the infected case was 2-3 wk in only four patients, 4-8 wk in 11 patients, and more than 8 wk in 64 patients. We substituted 8 wk for 2 wk as the cut-off period for identifying potential source cases, then used exposure scores and duration of cough to reassign source cases, as outlined above. Source cases were identified for a total of 72 patients. Shelters 1, 2, and 3 were identified as the transmission sites for 54 (75%) of 72 patients.

We assumed that patients were infectious for 1 mo before beginning antituberculosis therapy. To determine if this assumption affected our results, we reassigned source cases after considering each patient to be infectious for the period during which they complained of cough. Shelters 1, 2, or 3 were identified as transmission sites for 55 (71%) of 78 patients.

In identifying source cases, we considered patients who were sputum acid-fast smear-positive to be four times more infectious than those who were sputum smear-negative. We varied this number from three to seven and again reassigned source cases, but this had no significant effect on the results (data not shown). In summary, when several assumptions made to identify potential source cases were varied within reasonable bounds, this did not significantly affect our major finding that shelters 1, 2, and 3 were the major sites of transmission of tuberculosis.

Characteristics of Shelters that Were Major Transmission Sites

Because transmission of tuberculosis for 70% of patients occurred at only three shelters, we compared the characteristics of these shelters with those of other indoor locations where the homeless slept. Some homeless persons slept at shelters

that provided beds on a first-come first-served basis. Others enrolled in residential rehabilitation programs that focused on eliminating substance abuse and on assisting persons to become self-sufficient. These programs ranged from 7 wk to 2 yr in duration.

Eight shelters provided sleeping locations for an average of 821 people per night (Table 3). Five hundred and ninety-five persons slept in three rooms in shelter 1, and 15-98 persons slept in one room in shelters 2, 3, and 4. No shelters screened their occupants for tuberculosis. Of 12 residential rehabilitation programs that provided shelter for a total of 1,063 persons, the number of persons per room was substantially lower than in shelters 1 through 4. Seven of the 12 programs screened all enrollees with a tuberculin skin test and, if indicated, a chest radiograph. These seven facilities housed 878 (83%) of the persons enrolled in residential rehabilitation programs. None of the 12 rehabilitation programs were major sites of tuberculosis transmission, whereas three of the seven shelters (1, 2, and 3) were major sites of tuberculosis transmission. Shelters 1, 2, and 3 provided sleeping locations for 86% of persons who slept at shelters. Upper-air germicidal ultraviolet light was not installed in any shelters or rehabilitation programs.

DISCUSSION

The findings in this report demonstrate two important features of tuberculosis transmission. First, during a period when no large tuberculosis outbreak was recognized in central Los Angeles, transmission of tuberculosis was extraordinarily focal, with three homeless shelters serving as probable transmission sites for 70% of 79 patients for whom source cases were identified. Second, unlike the case in New York City, HIV-infected tuberculosis patients did not play a major role in spread of tuberculosis. This finding confirms that the transmission dynamics of tuberculosis vary geographically, and that local public health authorities must use their knowledge of tuberculosis epidemiology to identify high-risk populations and

TABLE 3
SLEEPING LOCATIONS USED BY HOMELESS PERSONS
IN CENTRAL LOS ANGELES

Location	Mean Number of Occupants	Number of Sleeping Rooms	Tuberculosis Screening
Shelter			
1	595	3	No
2	98	1	No
3	15	1	No
4	62	2	No
5	27	13	No
6	10	10	No
7	8	3	No
8	6	1	No
Rehabilitation program			
1	190	83	Yes
2	185	22	Yes
3	130	24	Yes
4	128	19	Yes
5	110	34	Yes
6	90	2	No
7	85	58	Yes
8	50	2	No
9	50	25	Yes
10	25	3	No
11	12	1	No
12	8	8	No

tuberculosis transmission sites. The focal nature of tuberculosis transmission, predominantly at homeless shelters that housed large numbers of persons who were not screened for tuberculosis, suggests that control measures targeted at these locations should reduce tuberculosis morbidity in urban areas where homelessness is common and the incidence of tuberculosis is high.

In our study population, 136 patients were in 12 clusters, and a standard assumption is that one patient in each cluster developed tuberculosis from remote infection, whereas the remaining 124 patients developed tuberculosis from recent infection (1–3). Alternatively, all clustered patients were recently infected by source cases that were not included in the study. A shortcoming of our study is that source cases and sites of transmission were identified for only 79 of these 124 patients. However, even if shelters 1, 2, and 3 were not transmission sites for any of the 45 patients for whom no source case was identified, these shelters were transmission sites for 55 (44%) of 124 patients. Because our study did not include patients with tuberculosis infection, the extent of tuberculosis transmission that we observed represents only the tip of the iceberg. Many persons at shelters 1, 2, and 3 were probably recently infected with *M. tuberculosis*, did not develop disease during the study period, but remain at risk for future development of tuberculosis.

The rehabilitation programs in central Los Angeles provided shelter for many homeless persons but were not important sites of tuberculosis transmission, probably because most of them screened enrollees for tuberculosis and because few persons slept in the same room. Of the three homeless shelters that were major sites of tuberculosis transmission, one housed 595 occupants in three rooms and another housed 98 occupants in one room. Because no shelters screened their occupants for tuberculosis, large shelters were more likely to admit someone with tuberculosis, who had the potential to infect large numbers of persons sleeping in the same room. Interventions focused on these locations are likely to significantly reduce transmission of tuberculosis. One logistically simple intervention is installation of upper-air germicidal ultraviolet light in homeless shelters (20), but the efficacy of ultraviolet light remains controversial. Alternatively, case-finding can be done by screening shelter occupants with chest radiographs or sputum acid-fast smears and mycobacterial cultures. Sputum analysis allows rapid detection of acid-fast smear-positive patients. However, 50% of tuberculosis patients are smear-negative, and these patients may be difficult to locate when culture results are available. Chest radiography is advantageous because it permits rapid identification of most infectious tuberculosis patients. Screening chest radiography of 9,877 homeless patients in Los Angeles yielded 42 tuberculosis cases, or 425 cases per 100,000 (21). This rate is more than 50 times that in the United States population, and screening is likely to be cost-effective, although formal cost-benefit analyses have not been performed. A substantial proportion of tuberculosis cases among the homeless arise from reactivation of remote infection and are avoidable only through preventive therapy. Therefore, if public health resources are adequate, tuberculin skin testing in shelters should be performed, in combination with directly observed preventive therapy (22).

Our identification of probable source cases was based on assumptions that reflect our understanding of how tuberculosis is transmitted. Nevertheless, because there was no direct contact between most patients, our conclusions regarding source cases must be regarded as tentative. Given this caveat, our analysis showed that the homelessness score, birth in the United States, and Native American ethnicity were the only indepen-

dent predictors of being a source case. Tuberculosis patients with high homelessness scores were by definition more likely to sleep at homeless shelters and therefore more likely to infect many individuals. Persons born in the United States may be more likely to use shelters than foreign-born persons. In our population, among patients with homelessness scores of 3 or greater, persons born in the United States spent 10.8 ± 11.6 nights per month in shelters, whereas foreign-born persons spent 3.5 ± 6.2 nights per month there ($p < 0.05$, Wilcoxon rank-sum test). No conclusions can be made regarding Native American ethnicity and source case status, because only five Native American patients were in the study population.

We found that HIV-infected patients did not play a major role in the spread of tuberculosis. HIV infection was not associated with clustering (3) or with being a source case, and patients were less likely to have been infected by HIV-infected source cases than by HIV-negative source cases. Our findings differ from those in New York City, where HIV-infected patients contributed substantially to the tuberculosis epidemic (2, 8, 10). This difference in tuberculosis transmission dynamics may be due to several factors. First, only 4% of tuberculosis patients in Los Angeles are intravenous drug users (Laura Knowles, unpublished data), whereas the comparable figure in New York City is 22% (23). Second, the HIV seroprevalence among drug users is much lower in Los Angeles than in New York City (24, 25). Congregation of drug users, many of whom were HIV-infected, in "shooting galleries" was common in New York, and probably facilitated transmission of tuberculosis in a highly susceptible population. Finally, the reduced transmission potential of tuberculosis among HIV-infected tuberculosis patients in Los Angeles may have resulted in part from the increased frequency of negative sputum acid-fast smears in these patients. Other investigators have noted that, compared with HIV-negative tuberculosis patients, HIV-infected tuberculosis patients are more likely to have negative sputum acid-fast smears (26–28), perhaps because the bacillary burden in sputum of HIV-infected patients is lower (29). Although HIV-infected patients may be less likely to infect others, a high priority must nevertheless be given to treatment and prevention of tuberculosis in this population, because the risk of progression from tuberculosis infection to disease is extremely high (5, 9) and because tuberculosis adversely affects mortality (30), probably through enhancing HIV replication and accelerating progression of HIV disease (31, 32).

In summary, we found that a substantial proportion of tuberculosis morbidity in central Los Angeles was attributable to transmission at one of three homeless shelters. Limiting transmission of tuberculosis depends on local efforts to identify high-risk populations and tuberculosis transmission sites. In urban locations where homelessness and tuberculosis are common, public health authorities should consider interventions such as case-finding based on screening chest radiographs, use of upper-air germicidal irradiation at tuberculosis transmission sites, and targeted application of preventive therapy.

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