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A 13-year molecular epidemiological analysis of tuberculosis in San Francisco

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SUMMARY

BACKGROUND: We examined the molecular epidemiology of tuberculosis (TB) in San Francisco during a 13-year period encompassing the peak of TB resurgence and subsequent decline to historic low levels.

OBJECTIVE: To compare rates of TB caused either by rapid progression of recent *Mycobacterium tuberculosis* infection or by reactivation of latent infection.

METHODS: All TB cases reported from 1991 to 2003 were included. Genotyping was performed to identify clustered cases.

RESULTS: The annual TB case rate decreased significantly from 50.8 to 28.8 cases/100 000 persons from 1992 to 1999 ($P < 0.0001$). After 1999, no significant decrease was observed for the population as a whole or in any subgroup examined. Similarly, the rate of clustered cases decreased significantly from 1992 to 1999 (11.4 to 3.1 cases/100 000, $P < 0.0001$). Although the rate of non-clustered cases also declined significantly (25.6 to 17.6 cases/100 000, $P < 0.0001$), there was a disproportionate reduction in clustered cases (94.7% vs. 50.8%, $P < 0.0001$). Neither clustered nor non-clustered cases decreased significantly after 1999.

CONCLUSIONS: TB case rates reached a plateau despite ongoing application of control measures implemented in 1993. These data suggest that intensification of measures designed to identify and treat persons with latent TB infection will be necessary to further reduce TB incidence.

KEY WORDS: molecular epidemiology; tuberculosis transmission; tuberculosis prevention and control

IN 1992, the tuberculosis (TB) resurgence that began in the late 1980s in the United States reached a peak. Since that time, TB cases and case rates have been declining consistently.[1] The resurgence, which was unprecedented in the modern history of TB, has been attributed to several factors. These include the deterioration of public health infrastructure due to reduced funding; increased institutionalization of persons in prisons, shelters, and residential care facilities; hospitalization of large numbers of immunocompromised persons due to the human immunodeficiency virus (HIV) epidemic; and increased immigration from countries with a high prevalence of TB.[2]

Studies utilizing a combination of conventional and molecular epidemiological methods demonstrated that a substantial and unanticipated proportion of the incident cases in urban centers resulted from recent transmission of *Mycobacterium tuberculosis* with rapid progression to clinical TB.[3–7] Such studies also helped identify high risk groups, locales of increased transmission and epidemiologic links not found in standard contact tracing.[7–13] In part based on molecular epidemiological studies, targeted interventions to interrupt ongoing transmission of *M. tuberculosis* were implemented in many urban areas.

Few longitudinal, population-based, community-wide studies have addressed the impact of TB control measures on the relative contributions of recent transmission with rapid progression to clinical TB and reactivation of latent infection to the overall burden of TB. In an area of New York City (NYC), Geng et al. showed a 31.8% decrease in TB cases due to recent transmission from 1992 to 1999.[14] However, the study was limited to one area of NYC and does not demonstrate the impact of control measures on overall TB case rates in a total health jurisdiction.

Since 1991, we have been conducting a population-based study of the molecular epidemiology of TB in San Francisco. We previously reported data from 1991 to 1997 showing that after TB control measures targeting high-risk groups to prevent transmission were instituted in San Francisco, there was a significant and ongoing decrease in both the overall incidence of TB and the rate of TB resulting from recent

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transmission.[15] In the current report we extend our analyses of conventional and molecular epidemiological trends in TB in San Francisco through the year 2003 to examine the dynamics of TB transmission in the new setting of overall low rates of TB.

METHODS

Patient population and genotyping methodology

All TB cases reported to the San Francisco Department of Public Health between 1 January 1991 and 31 December 2003 were included. The study was approved by the institutional review board of the University of California, San Francisco.

The collection of demographic information, *M. tuberculosis* isolates, genotyping methodologies and data management have been previously described.[15] In brief, isolates from all culture-positive cases were subjected to IS*6110*-based restriction fragment length polymorphism (RFLP) analysis.[16] The RFLP patterns were compared using Bioimage Whole Band Analyzer software (version 3.3, Bioimage Corp, Ann Arbor, MI).[17] Isolates with fewer than six IS*6110* hybridizing bands were further characterized with polymorphic guanine-cytosine rich sequence (PGRS) based RFLP analysis.[18] Isolates were defined as matching if the number, relative intensity and molecular weights of the IS*6110* and PGRS bands (for isolates with fewer than six IS*6110* bands) were identical.

Definition of clustering

Cases were defined as clustered if, within 1 year, two or more isolates from different patients contained 1) six or more IS*6110* bands in an identical pattern, or 2) five or fewer IS*6110* bands in an identical pattern and an identical PGRS pattern. For each new isolate the database was searched for the previous 1 year (from the date the specimen was collected) to identify potential matches. For each cluster the initial case was assumed to be the index case and was not counted as clustered. The 1-year period for defining clustering was chosen to enable analysis of a larger number of time periods and because our analyses have shown that most clustering occurs within 1 year.[15] In addition, in our previous report of trends in San Francisco, altering the time period for defining clustering did not significantly affect results.[15]

Statistical analysis

Annual TB case rates per 100 000 persons were calculated using San Francisco annual population estimates published by the California State Department of Finance.[19,20] Foreign- and US-born rate calculations used denominators from the US Census Bureau's count of San Francisco population in 1990 and 2000. To verify that trends were not changed by an increase in population reported in the 2000 Census, rates dependent on Census estimates were recalculated and retested with a smoothed denominator, estimated by determining the average increase per year and adding that estimate to the previous yearly estimate, creating a consistent change in the denominator. Rates among HIV-infected and homeless persons were based on San Francisco Department of Public Health estimates of those populations.[19–23] For years without a published value, denominator values for all four groups were estimated by determining the average increase per year and adding that estimate to the previous yearly estimate. A test for trend in annual TB case rates was performed using Poisson regression with a variable for calendar year, setting 1991 equal to 0 and increasing the value by 1 for each subsequent year.[24] Loss of trend was tested for by beginning with 1991 and dropping 1 year at a time until the trend was not significant. This procedure could result in a loss of significant trend due solely to too few data points, but all trends lost significance with from 7 to 4 years remaining. Difference between trends in clustered and unique case rates was assessed using Poisson regression with an interaction term for year by cluster status. Univariate predictors of clustering were assessed for significance using the χ^2 test. A multivariate logistic regression model was created by testing univariate predictors one by one using the likelihood ratio test to compare each model and retaining variables that significantly improved the likelihood ($\chi^2 > 3.84$, $P < 0.05$ with one degree of freedom). Model fit was assessed using the Hosmer-Lemeshow test for goodness-of-fit, and only models showing adequate fit ($P > 0.30$) were included in the final analysis.[25]

RESULTS

TB case rates

During the study period, 3134 cases of TB were reported to the San Francisco Department of Public Health. The annual TB case rate decreased significantly from 1992 through 1999 (from 50.8 to 28.8 cases/100 000 persons, $P < 0.0001$, Figure 1). Between 2000 and 2003, the case rate varied between 18.9 and 22.2 cases/100 000 and showed no significant downward trend. Among the subgroups studied, annual case rates decreased significantly ($P < 0.0001$) until 1996 for HIV-infected patients, 1997 for African-Americans, 1998 for Hispanics, 1999 for Whites and US-born persons, and 2000 for foreign-born persons and all other groups. Thus, in the last 4 years of the study, there were no significant declines in annual TB case rates for the population as a whole or in any subgroup examined.

During the period of the study, the percentage of reported TB cases who were foreign-born increased from 57.6% in 1991 to 77.5% in 2003. Among these cases, Asian/Pacific Islanders were the most frequent, increasing from 48.1% in 1991 to 66.9% in 2003. In each year of the study, more than 93% of Asian/Pacific

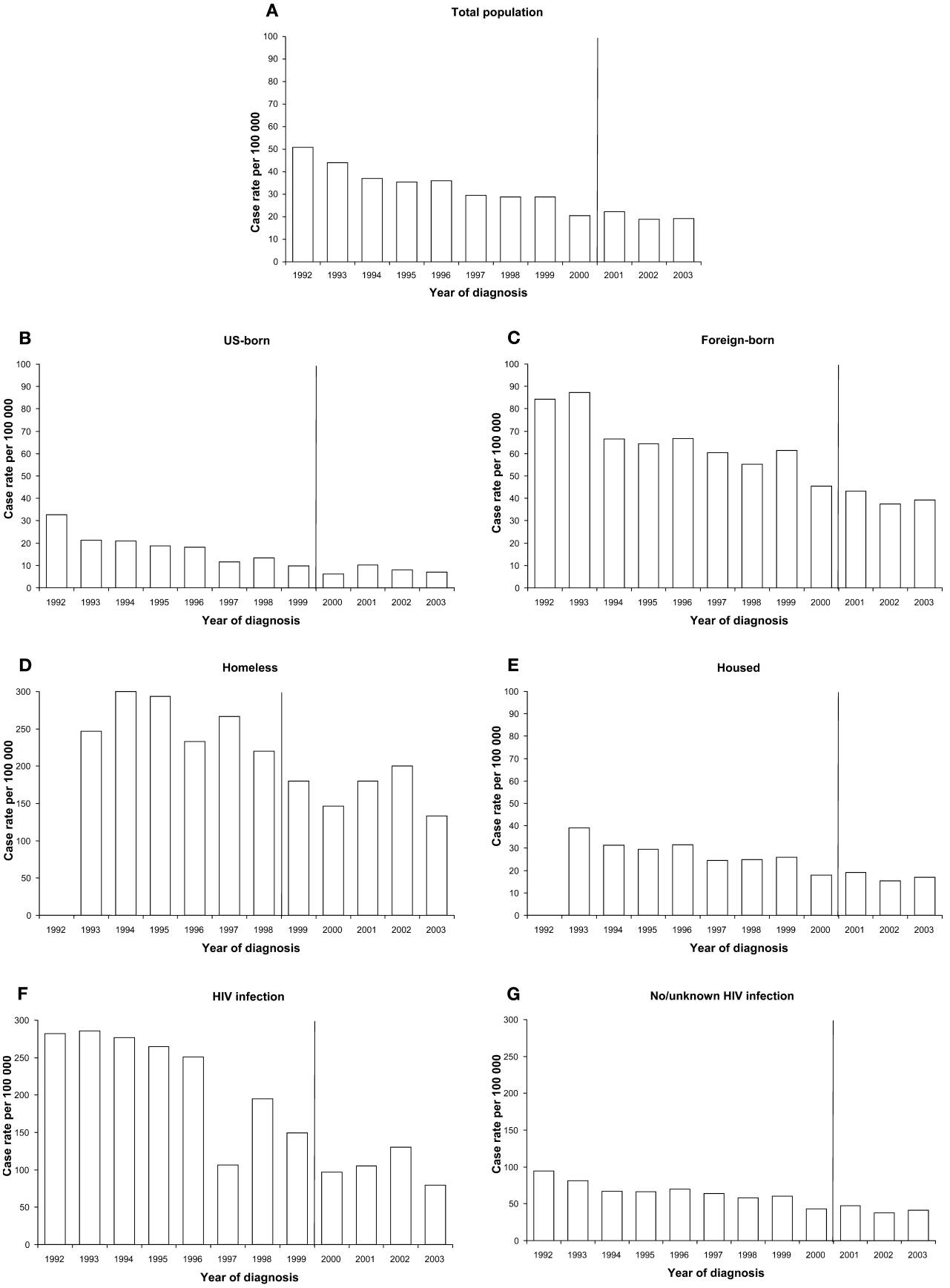

Figure 1 Overall TB case rates in San Francisco, California, 1992–2003. The case rate of TB overall and in various subgroups in San Francisco from 1 January 1992 through 31 December 2003, assessed at 1-year intervals. All A–E show a significant downward trend from 1992 (1993 in the case of homeless and housed) through 2003 ($P < 0.0001$). Vertical line signifies year where trend lost significance: bars after the line do not constitute a significant downward trend. Data on housing status were not collected prior to 1993. **A.** Population as a whole. **B.** Persons born in the US. **C.** Persons born outside the US. **D.** Persons who were homeless at any time during the year. **E.** Persons who were housed throughout the year. **F.** Persons infected with HIV. **G.** Persons negative for HIV or persons with unknown HIV status. TB = tuberculosis; HIV = human immunodeficiency virus.

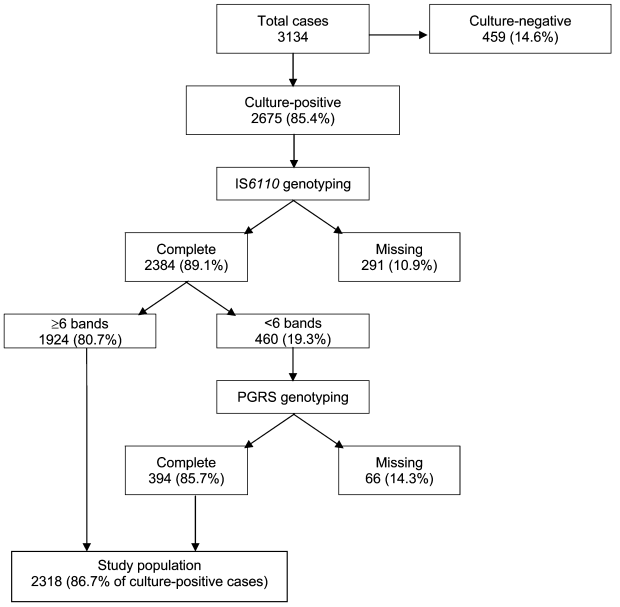

Figure 2 Genotyping flow chart. Between 1991 and 2003, 3134 tuberculosis cases were reported in San Francisco. Genotyping was performed in the 2675 (85.4%) cases with a positive culture for *M. tuberculosis.* Complete genotyping results were available for 2318 (86.7%) culture-positive cases. PGRS = polymorphic guanine-cytosine rich sequence.

Islanders with TB were foreign-born (39.9% were born in China, 31.8% in the Philippines, 12.7% in Vietnam and the remainder in 21 different countries).

Genotyping

Of the 3134 incident cases, 2675 (85.4%) had positive cultures for *M. tuberculosis* (Figure 2). IS*6110*-based genotyping was successful for 2384 (89.1%) isolates and six or more IS*6110* hybridizing bands were present in 1924 (80.7%) isolates. For the remaining 460 isolates with fewer than six bands, PGRS-based genotyping results were available for 394 (85.7%) isolates. Thus, complete genotyping results were available for 2318 (86.7%) of the culture-positive cases. Compared with patients for whom genotyping data were available, culture-positive patients without genotyping data were more likely to be aged >65 years, Asian or foreign-born and less likely to be homeless or treated at the Department of Public Health clinic ($P \leq 0.05$ for each comparison).

Clustering analysis

Of the 2318 patients with complete genotyping results, 224 were reported in 1991. In the clustering analysis, these cases were included only as a reference group for patients identified in 1992, since genotyping results from the previous year were not available for comparison. Among the remaining 2094 cases, 396 (18.9%) were clustered.

In a univariate analysis (Table), clustering was associated with being US-born, male, <55 years of age, African-American, HIV-infected and having a history of homelessness, alcohol abuse, and injection or non-injection drug use. Asian patients were significantly less likely to be in clusters compared with white patients. In the best fitted multivariate logistic regression model only age, race, place of birth, HIV status and homelessness were included to determine adjusted odds ratios (Table 1). In this model, patients who were <55 years of age ($P < 0.001$), African-American ($P = 0.003$), US-born ($P < 0.001$), HIV-infected ($P = 0.02$) or homeless ($P = 0.01$) were more likely to be in clusters.

Table Predictors of clustering

Predictor	Unadjusted RR (95%CI)	Adjusted, best fit model OR (95%CI)
Age <55 years	1.42 (1.32–1.51)	1.77 (1.29–2.43)
Male	1.11 (1.04–1.19)	
Race		
Native American Indian	1.35 (0.80–2.26)*	2.03 (0.66–6.27)
Asian/Pacific Islander	0.80 (0.71–0.90)*	0.63 (0.37–1.07)
African-American	1.23 (1.05–1.44)*	1.75 (1.20–2.55)
Hispanic (White)	0.88 (0.75–1.04)*	0.83 (0.49–1.42)
White (not Hispanic)	1.00 (reference)	1.00 (reference)
US-born	2.82 (2.53–3.15)	2.40 (1.53–3.76)
HIV-infected	2.73 (2.28–3.26)	1.46 (1.05–2.01)
Homeless	3.20 (2.63–3.90)	1.51 (1.09–2.10)
Recreational drug use (non-injection)	3.39 (2.68–4.29)	
Injection drug use	4.70 (3.38–6.54)	
Alcohol abuse	2.37 (1.88–2.97)	

* Hazard ratio (95%CI).
RR = relative risk; CI = confidence interval; OR = odds ratio; HIV = human immunodeficiency virus.

The rate of clustered cases decreased 94.7% overall from 11.4 cases/100 000 in 1992 to 0.6 cases/100 000 in 2003 (Figure 3). In the population as a whole, the clustered case rate decreased almost every year from 1992 to 1999 and subsequently ranged from 0.6 to 2.5 cases/100 000 during the last 4 years of the study. Similarly, the clustered case rate decreased significantly in all subgroups examined until it reached a level of about 3 to 5 cases/100 000, except in HIV-infected and homeless persons. The rates of non-clustered cases also decreased significantly during the period of the study; however, there was a disproportionate reduction in the clustered cases compared with the non-clustered cases (94.7% vs. 50.8%, respectively, $P < 0.0001$).

DISCUSSION

We have been conducting a comprehensive molecular and conventional epidemiological analysis of TB in San Francisco since 1991. TB case rates declined dramatically throughout most of the 1990s in the population as a whole and in all subgroups examined. However, since 1999–2000 there has been no further

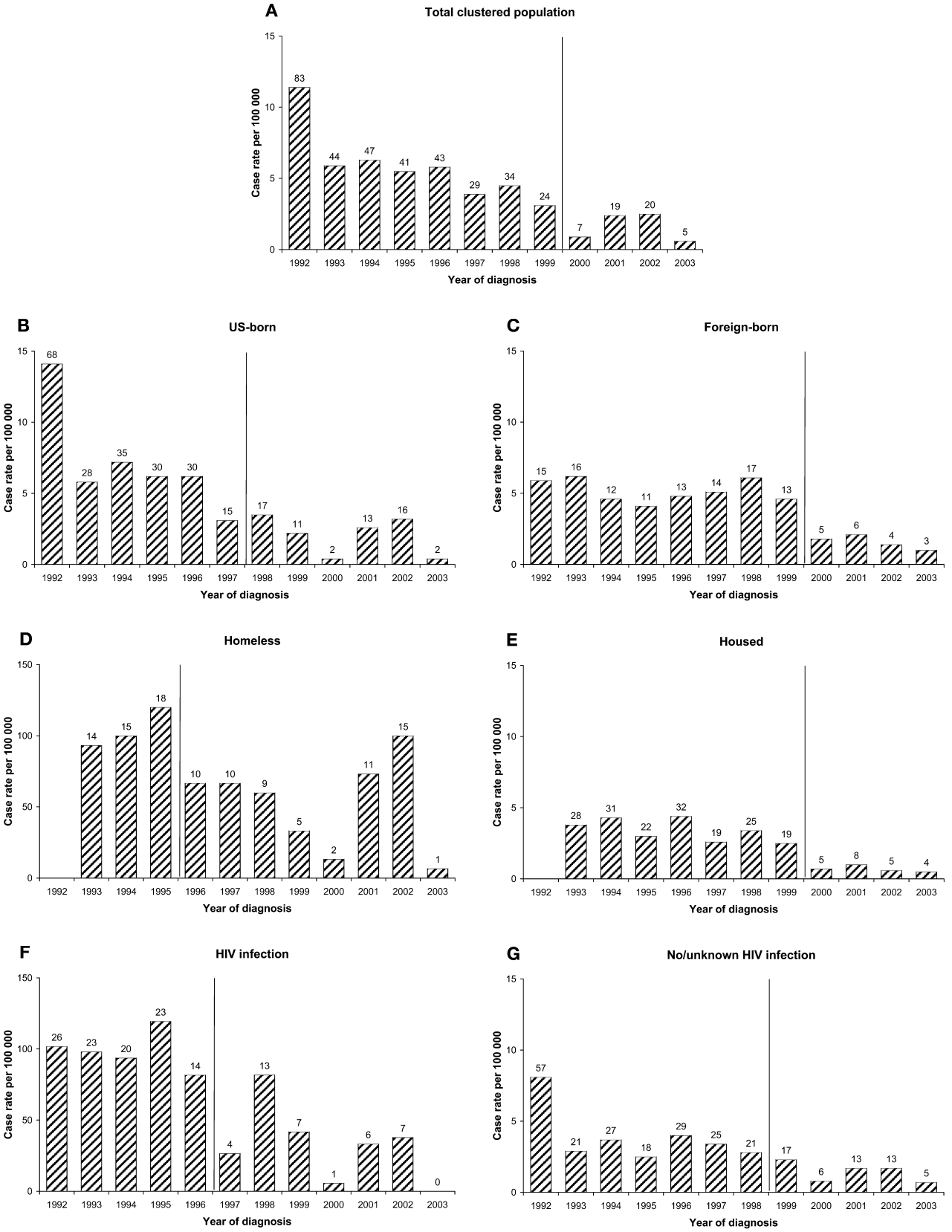

Figure 3 Clustered TB case rates in San Francisco, California, 1992–2003. The rate of clustered cases of TB overall and in various subgroups in San Francisco from 1 January 1992 through 31 December 2003, assessed at 1-year intervals, limited to those patients with known genotype. Number of cases/year (case rate numerator) is reported over each bar. All A–E show a significant downward trend from 1992 (1993 in the case of homeless and housed) through 2003 ($P < 0.0001$). Vertical lines signify year where trend lost significance: bars after the line do not constitute a significant downward trend. Cases reported in 1991 were included only as a reference group for patients identified in 1992, as genotyping results from the previous year were not available for comparison. Data on housing status were not collected prior to 1993. **A.** Population as a whole. **B.** Persons born in the US. **C.** Persons born outside the US. **D.** Persons who were homeless at any time during the year. **E.** Persons who were housed throughout the year. **F.** Persons infected with HIV. **G.** Persons negative for HIV or persons with unknown HIV status. TB = tuberculosis; HIV = human immunodeficiency virus.

decrease in overall case rates or rates of clustered cases. Moreover, there has been no significant decrease in rates for any of the subgroups examined. The disproportionate decrease in clustered cases compared with non-clustered cases suggests that much of the decline could be attributed to a reduction in the number of cases due to recent infection followed by rapid progression to clinical illness. Our data are consistent with recent national data showing that TB case rates in the US reached a plateau after the year 2000.[1]

The Institute of Medicine's report in 2000 reaffirmed a commitment to eliminating TB in the US (defined as reducing the incidence of TB to less than one case per one million population by 2010).[26] In San Francisco, intensified TB control measures were implemented in 1993.[15] These measures aim to identify and treat active TB cases and their contacts rapidly, with the goal of reducing TB transmission.[14,27,28] We have shown that between 1992 and 2000, these measures were associated with substantial progress toward the elimination target set by the Institute of Medicine. During this period, there was an average annual decline in the incidence of TB of 7% per year. The most dramatic declines in case rates were seen in HIV-infected persons, non-Hispanic whites, African-Americans, younger persons and the US-born. All of these factors have been shown to be associated with clustering.[4,5,7,14,29,30]

However, our data suggest that the limits of these TB control measures emphasizing prevention of transmission as well as treatment of HIV infection may have been reached. Despite ongoing application of control measures, no progress toward elimination has been made in the past 4 years. Since 2000, the average annual reduction in TB incidence has been only 0.06%/year. Overall case rates varied non-significantly from 18.9 to 22.2 cases/100 000 and clustered case rates from 0.6 to 2.5 cases/100 000. The plateau in case rates suggests that with the current mix of measures there is a level below which ongoing transmission of *M. tuberculosis* will not consistently decline. Below this level, the variation in annual clustered case rates will be related to sporadic TB outbreaks that are likely to continue to occur.

In addition, it appears that recent transmission with rapid progression to active disease is no longer a major component of the pathogenesis of TB in San Francisco. Throughout the course of the study, a progressively greater proportion of cases developed as a consequence of reactivation of latent infection, and accounted for more than 85% of cases in the last 2 years of the study. In view of the increased importance of reactivation as the dominant pathogenic mechanism by which TB develops, it is unlikely that in cities such as San Francisco overall TB case rates will decline further unless more effective control measures to identify and treat latent TB infection (LTBI) are applied.

In the US, more than 50% of incident TB cases occur in persons born outside of the country, generally in persons from parts of the world where the prevalence of TB is high.[31] Our data have consistently shown that foreign birth is associated with reactivation of LTBI as the pathogenic mechanism for developing TB. In the final year of our study nearly 80% of TB cases occurred in the foreign-born, and 77% of these cases resulted from reactivation of latent infection. Moreover, in our studies, there has been very little clustering among foreign-born persons as well as almost no transmission between US-born and foreign-born persons.[32,33] Improved control of the TB epidemic in developing countries may be needed to achieve elimination of TB in the US.

The failure of TB case rates to decline in the last 4 years of our study could possibly be explained by increased numbers of immigrants arriving in San Francisco, an increasing prevalence of HIV infection or an increase in the prevalence of other demographic characteristics known to be associated with TB infection. However, there are no data to suggest that any of these factors is playing a significant role. It is also important to note that case rates, especially for the HIV-infected and homeless populations, may be either too high or too low due to errors in population estimates. In addition, as previously noted, our study may have underestimated the true rate of clustering by using a 1-year interval to define a cluster and by requiring that genotyping patterns be identical to be considered matching. Counteracting this possible effect, the characteristics of the 15% of incident cases that did not have genotyping performed suggest that they are less likely to be in clusters; thus, were they included in the analysis, the overall rate of clustering would likely be even lower.

In summary, after peaking in the early 1990s, there was a dramatic and rapid decline followed by a plateau in TB case rates in San Francisco. To advance toward the overall elimination of TB in San Francisco, our data indicate the need for more effective diagnosis and treatment of LTBI. This will require increased outreach to and screening within immigrant communities, more accurate diagnostic tests for LTBI, and, ideally, shorter and safer drug regimens for treatment of LTBI.[26,34]

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RÉSUMÉ

CONTEXTE : Nous avons examiné l'épidémiologie moléculaire de la tuberculose (TB) à San Francisco pendant une période de 13 ans, comportant le pic de résurgence de la TB et le déclin ultérieur vers les faibles niveaux historiques.

OBJECTIF : Comparer les taux de tuberculose causés soit par la progression rapide d'une infection récente par *Mycobacterium tuberculosis*, soit par la réactivation d'une infection latente.

MÉTHODES : On a inclus tous les cas de tuberculose signalés entre 1991 et 2003. Le génotypage a été pratiqué pour l'identification des cas regroupés en grappes.

RÉSULTATS : Le taux annuel des cas de TB a diminué de façon significative de 50,8 à 28,8 cas/100.000 personnes entre 1992 et 1999 ($P < 0{,}0001$). Après 1999, on n'a plus observé aucune diminution significative dans l'ensemble de la population, ni dans aucun des sous-groupes examinés. De la même manière, le taux de cas regroupés

en grappes a diminué de façon significative entre 1992 et 1999 (de 11,4 à 3,1 cas/100.000, $P > 0,0001$). Quoique l'on ait observé également un déclin significatif des cas non-regroupés en grappes (de 25,6 à 7,6 cas/100.000, $P < 0,0001$), la réduction des cas en grappes est disproportionnée (94,7% vs. 50,8%, $P < 0,0001$). Après 1999, on n'a plus observé de décroissance significative des cas, qu'ils soient ou non regroupés en grappes.

CONCLUSION : Les taux de cas de TB ont atteint un plateau malgré l'application courante des mesures de contrôle mises en œuvre en 1993. Ces données suggèrent que l'intensification des mesures élaborées pour identifier et traiter des personnes atteintes d'infection tuberculeuse latente seront nécessaires pour réduire davantage l'incidence de la TB.

RESUMEN

MARCO DE REFERENCIA : Se estudió la epidemiología molecular de la tuberculosis (TB) en San Francisco durante un período de 13 años, el cual abarcó el punto máximo del resurgimiento de la TB y su posterior disminución a niveles considerablemente bajos.

OBJETIVO : Comparar las tasas de TB causada por la evolución rápida de una infección reciente por *Mycobacterium tuberculosis* o por la reactivación de infecciones tuberculosas latentes (ITBL).

MÉTODOS : Se incluyeron en el estudio todos los casos de TB declarados entre 1991 y 2003. Se realizó el genotipado de las cepas para descubrir los casos asociados en conglomerados.

RESULTADOS : Entre 1992 y 1999, la tasa anual de TB disminuyó en forma significativa de 50,8 a 28,8 casos/100 000 habitantes ($P < 0,0001$). Después de 1999, no se observó una disminución significativa en la población en general ni en ningún subgrupo examinado. Se presentó igualmente una disminución considerable de la tasa de casos en conglomerados entre 1992 y 1999 (de 11,4 a 3,1 casos/100 000 ; $P < 0,0001$). Si bien la tasa de casos independientes también disminuyó en forma significativa (de 25,6 a 17,6 casos/100 000 ; $P < 0,0001$), la reducción fue desproporcionada para los casos asociados en conglomerados (94,7% contra 50,8% ; $P < 0,0001$). Después de 1999 no hubo una disminución significativa de los casos independientes ni de los casos en conglomerados.

CONCLUSIONES : Las tasas de TB alcanzaron una meseta pese a la aplicación de las medidas de control puestas en práctica en 1993. Estos datos indican que será necesaria la intensificación de las medidas que buscan identificar y tratar a las personas con ITBL a fin de reducir aún más la incidencia de TB.