Sex differences in the epidemiology of tuberculosis in San Francisco

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SUMMARY

Setting: Worldwide differences in sex-specific tuberculosis case rates remain fundamentally unexplained.

Objective: To explore various factors that may explain sex differences in tuberculosis incidence rates for San Francisco from 1991–1996.

Design: A retrospective epidemiologic analysis of sex-specific tuberculosis incidence rates in San Francisco from 1991–1996. Stratified analyses were performed on age at diagnosis, racial/ethnic group, human immunodeficiency virus (HIV) status, and place of birth. Molecular fingerprinting with IS\textsubscript{6110} data was used to study sex differences in the incidence of disease for recently transmitted and reactivated cases of tuberculosis.

Results: In the study period, the male to female incidence rate ratio was 2.1 (95%CI 1.9–2.3). Stratified analyses revealed differences in sex-specific rates after the age of 14 and the highest male:female ratios were seen in the US-born, white, and black populations. High ratios were also observed for cases with clustered fingerprints, similar to those observed for the US-born population. In sub-populations with predominantly reactivated cases of tuberculosis, ratios were also above unity after adolescence, but the effect was less pronounced.

Conclusion: The ongoing transmission of tuberculosis in the US-born population is one of the factors that explains the difference in sex-specific rates of disease in San Francisco. Observed differences in tuberculosis rates between the sexes may be due to a difference in transmission dynamics rather than diagnosis or reporting biases.

Key Words: tuberculosis; sex; gender; epidemiology

The reasons for global sex differences in the epidemiology of tuberculosis are largely unknown. An international research meeting on gender and tuberculosis in 1998 reported that tuberculosis is now the single biggest infectious killer of women in the world, and the leading cause of death among women of reproductive age. In general, a higher proportion of male case notifications exists worldwide, but a breakdown of case rates by geographic region reveals variable male to female rate ratios. For instance, in Zambia, Uganda, and Congo, incidence and mortality rates in young females are higher than or equal to those in males of the same age.

Two reviews published in the last year detail the current status of global sex differences in tuberculosis. Two hypotheses to explain such variability have been presented: 1) under-diagnosis or under-reporting of tuberculosis in females, and 2) real differences in infection with Mycobacterium tuberculosis and/or progression to active disease. The first hypothesis encompasses socio-cultural factors including stigmatization of females with tuberculosis and impaired access to health care. The second hypothesis reflects socio-cultural and biologic factors that influence opportunities for exposure to M. tuberculosis and conditions that foster progression and reactivation. We have explored the latter hypothesis in San Francisco, where diagnosis and reporting of tuberculosis cases is not expected to vary for males and females.

Current tuberculosis epidemiology in San Francisco represents a blend of ongoing transmission in the US-born and reactivation disease in the foreign-born, and we have assessed how sex differences in tuberculosis rates varied according to the different transmission dynamics in these two populations. The use of molecular fingerprinting, which helps distinguish recent spread from reactivation of latent infection, permitted a refined understanding of sex differences in tuberculosis case rates.

Study Population and Methods

The study population included all reported cases of tuberculosis (pulmonary and extra-pulmonary) in...
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San Francisco from 1 January 1991 through 31 December 1996. The data were collected as part of an ongoing study combining conventional and molecular epidemiology with approval from the human subjects research committees at the University of California at San Francisco, the San Francisco Department of Public Health, and Stanford University. Data collected for each patient included sex at birth, age at diagnosis, race/ethnicity, and country of birth. We use the term ‘sex’ in reference to the biologic distinction between males and females rather than ‘gender’, which incorporates socially-defined behavioral, cultural, and psychological characteristics. Human immunodeficiency virus (HIV) testing was not performed on all individuals, so patients were classified as HIV-positive, HIV-negative, or HIV unknown. Because the HIV unknown patients had demographic characteristics placing them at very low risk for HIV infection (e.g., elderly, foreign-born, female), we considered them as HIV-negative for the purposes of statistical analysis (data not shown).

Isolates of culture-positive cases sent to the Stanford Center for Tuberculosis Research were fingerprinted according to standardized techniques. Secondary typing was performed on isolates with <6 copies of IS6110 using Smal digests and hybridization with the consensus PGRS (polymorphic guanine-cytosine-rich) sequence. DNA fingerprints were compared with computer-assisted visual matching. Cases sharing identical patterns were assigned as members of clusters, inferred to represent groups of individuals involved in chains of transmission with rapid progression to disease.

Average annual incidence rates of tuberculosis were calculated using cases reported in the study period as numerators and 1990 San Francisco population data as denominators. To calculate the incidence of tuberculosis for the HIV-positive population, 1996 estimates of HIV prevalence for San Francisco were used as denominators. Denominators for the HIV-negative population were calculated by subtraction. It is recognized that HIV prevalence data are only estimates and that the prevalence of HIV infection in San Francisco may have varied somewhat during the study period. These data are used to estimate the interaction of tuberculosis and HIV infection, recognizing that inferences based on HIV data may be relatively limited.

Incidence rates of clustered and unique cases of tuberculosis were calculated using cases with clustered or unique isolates as numerators and US Census Bureau population data as denominators. Sex-specific rate ratios were then calculated. Throughout the paper, the term ‘ratio’ will refer to the ratio of male:female incidence rates of tuberculosis. A significance level of 0.05 was used to define statistically significant P values.

### RESULTS

For the study period, the average annual incidence rate was 57.3/100 000 for males and 26.8/100 000 for females (Table). A plot of age-specific incidence rates revealed that until the age of 24, incidence of tuberculosis in males and females was similar (Figure 1). After age 25, incidence in males was generally two to three times higher than in females. Stratification of rates on place of birth revealed a dramatic difference in ratios for the US-born and foreign-born populations (Figure 2). In both groups, the ratio was near unity until age 14. The ratio then increased dramatically in the US-born population, reaching a maximum

### Table Sex-specific incidence rates and ratios in San Francisco, 1991–1996

<table>
<thead>
<tr>
<th>Race/ethnicity</th>
<th>Male Rate (n)</th>
<th>Female Rate (n)</th>
<th>Ratio (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>57.3 (1247)</td>
<td>26.8 (582)</td>
<td>2.1 (1.9, 2.3)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>92.4 (563)</td>
<td>60.2 (393)</td>
<td>1.5 (1.3, 1.7)</td>
</tr>
<tr>
<td>Black</td>
<td>95.7 (224)</td>
<td>30.4 (73)</td>
<td>3.1 (2.3, 4.0)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>56.8 (167)</td>
<td>19.9 (57)</td>
<td>2.8 (2.0, 3.7)</td>
</tr>
<tr>
<td>White</td>
<td>24.1 (287)</td>
<td>4.9 (56)</td>
<td>4.8 (3.6, 6.3)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–14</td>
<td>7.3 (26)</td>
<td>7.8 (27)</td>
<td>0.9 (0.5, 1.5)</td>
</tr>
<tr>
<td>15–24</td>
<td>19.5 (64)</td>
<td>16.5 (51)</td>
<td>1.1 (0.7, 1.5)</td>
</tr>
<tr>
<td>25–44</td>
<td>54.2 (568)</td>
<td>23.8 (218)</td>
<td>2.2 (1.8, 2.5)</td>
</tr>
<tr>
<td>45–64</td>
<td>74.7 (348)</td>
<td>27.7 (130)</td>
<td>2.6 (2.1, 3.1)</td>
</tr>
<tr>
<td>65+</td>
<td>89.8 (241)</td>
<td>37.2 (156)</td>
<td>2.3 (1.8, 2.7)</td>
</tr>
<tr>
<td>Place of birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>32.6 (519)</td>
<td>8.5 (139)</td>
<td>3.8 (3.1, 4.5)</td>
</tr>
<tr>
<td>Foreign</td>
<td>96.6 (713)</td>
<td>54.5 (438)</td>
<td>1.7 (1.5, 1.9)</td>
</tr>
<tr>
<td>HIV status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>209.6 (337)</td>
<td>424.3 (29)</td>
<td>0.5 (0.3, 0.8)</td>
</tr>
<tr>
<td>Negative*</td>
<td>41.9 (910)</td>
<td>22.8 (553)</td>
<td>1.8 (1.6, 1.9)</td>
</tr>
<tr>
<td>Fingerprint status†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clustered</td>
<td>19.3 (450)</td>
<td>5.5 (134)</td>
<td>3.4 (2.8, 4.0)</td>
</tr>
<tr>
<td>Unique</td>
<td>21.8 (509)</td>
<td>11.0 (267)</td>
<td>1.9 (1.6, 2.2)</td>
</tr>
</tbody>
</table>

* Includes those whose HIV status was unknown.
† Fingerprint data available only on a subset of cases with positive cultures and DNA fingerprinting performed.
of 8.0 (95% confidence interval [CI] 4.5–13.8) in the 45–64 year age group. In the foreign-born population, the ratios were less remarkable, with a high of 2.8 (95% CI 2.2–3.4) in the elderly.

To explore these sex differences in age-specific incidence rates, ratios were stratified on race/ethnicity and HIV status. In all racial/ethnic groups, childhood rates were near unity and ratios in the elderly were near 2.0 (Figure 3). Differences were most marked between the ages of 25 and 64 in whites and blacks. By contrast, the ratios for Asians, who comprise the majority of foreign-born cases, did not vary dramatically across age groups with a maximum of 2.4 (95% CI 1.9–3.0) in the elderly.

The ratio was 0.5 (95% CI 0.3–0.8) in the HIV-positive population (Table). Joint stratification on HIV status and race/ethnicity revealed that Asian and black HIV-positive males had lower tuberculosis incidence rates than HIV-positive females, with ratios of 0.8 (95% CI 0.3–0.2) and 0.6 (95% CI 0.3–1.0), respectively (Figure 4a). For the HIV-negative population, the ratio ranged from a low of 1.5 (95% CI 1.3–1.7) in Asians to a high of 2.6 (95% CI 1.8–3.5) in blacks (Figure 4b).

To examine sex differences in the incidence of tuberculosis according to recently transmitted infection and reactivation disease, we analyzed fingerprint data for the study population. Fingerprint data were available for 85% (1361/1598) of culture-positive cases, with 584 (43%) of cases belonging to a cluster. Analysis restricted to cases with unique isolates revealed a ratio consistently at unity until the age of 25 (Figure 5), after which a ratio near 2.0 was observed for the 25–44 and 45–64 year age groups. By contrast, the incidence of cases with clustered fingerprints tended to be higher in males, with a ratio of 3.3 (95% CI 2.5–4.2) in the 25–44 year age group and 3.8 (95% CI 2.4–5.7) in the 45–64 year age group.

**DISCUSSION**

We found that, after childhood, the incidence of tuberculosis was consistently higher in males. Sixty to ninety per cent of cases occurred in males, depending
ences in rates should be the focus of further analyses.

sex differences in tuberculosis rates, i.e., sex differ-
bias in diagnosis and reporting.

may serve as an important indicator of potential
port the notion that differences in childhood rates
ability in rates between the sexes in adulthood, sup-
female children. Our data, which showed great vari-
are much lower than those in young males, suggesting
been noted in studies of other countries. In some
observed in other California jurisdictions, and has
been observed historically in the US, is currently
the US-born population has been largely
constitute 80% of the US-born tuberculosis cases in
San Francisco, and represent those at highest risk for
recently transmitted infection. In contrast, the foreign-
born population of San Francisco has been largely
spared from ongoing transmission, and a less marked
predominance of male cases is observed. This sug-
gests that either antecedent infection or progression
to disease is slightly greater in males of this group.
Observed differences in tuberculosis rates between
males and females in a population may therefore be
due to differences in transmission dynamics rather
than (or in conjunction with) under-diagnosis and
under-reporting in females. The degree to which this
difference is biological or cultural in origin remains to
be elucidated.

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References


RÉSUMÉ

CADRE: Fondamentalement, les différences observées dans le monde entier dans les taux de morbidité tuberculeuse spécifiques au sexe restent inexplicées.

OBJECTIF: Explorer divers facteurs qui pourraient expliquer les différences dans les taux d’incidence de la tuberculose à San Francisco entre 1991 et 1996, d’après le sexe.


RÉSULTATS: Pendant la période d’étude, le ratio des taux d’incidence hommes/femmes est de 2,1 [IC 95% 1,9–2,3]. Les analyses stratifiées ont mis en évidence des différences dans les taux spécifiques au sexe après l’âge de 14 ans et les ratios hommes/femmes les plus élevés ont été observés dans les populations nées aux Etats-Unis, blanches ou noires. De la même manière que celles observées dans les populations nées aux Etats-Unis, des ratios élevés ont également été observés dans les cas où les empreintes digitales montrent des grappes. Dans les sous-groupes de population où il s’agit de manière prédominante de cas de tuberculose par réactivation, les ratios sont également supérieurs à l’unité après l’adolescence, mais cet effet est moins prononcé.

CONCLUSION: La transmission continue de Mycobacterium tuberculosis dans la population née aux Etats-Unis est un des facteurs explicatifs de la différence des taux de maladie spécifiques au sexe à San Francisco. Les différences observées en ce qui concerne les taux de tuberculose entre les sexes pourraient être dues à une différence de la dynamique de transmission plutôt qu’à des biais de diagnostic ou de déclaration.
ciones de la configuración haploespecífica del ADN agrupadas, similares a aquellas observadas en la población nacida en EEUU. En las sub-poblaciones con casos de tuberculosis predominantemente reactivada, las relaciones eran también superiores a la unidad después de la adolescencia, pero el efecto era menos pronunciado.

CONCLUSIÓN: La trasmisión continua de Mycobacterium tuberculosis en la población nacida en EEUU es uno de los factores que explica la diferencia en las tasas por sexo en San Francisco. Las diferencias en las tasas de tuberculosis entre los sexos pueden ser debidas a diferencias en la dinámica de la trasmisión más bien que a sesgos de diagnóstico o de notificación.