Twenty Years Of Molecular Epidemiology of Tuberculosis in San Francisco

Community Research in Tuberculosis: Muscogee County Revisited

RFLP as an epidemiologic tool:

Repetitive DNA Sequences as Probes for Mycobacterium tuberculosis

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Received 24 April 1986 Accepted 1 August 1986

These small segments of Mycobacterium tuberculosis DNA which are providing asochi plasmids were identified, in vivo, with DNA from clinical isolates of M. tuberculosis, via selected tandem repeats (TRD) of the complete DNA sequence. Three plasmids, each 1.8 kb in length, hybridized with M. tuberculosis DNA and were used to identify and isolate DNA from clinical specimens. These plasmids were also shown to be useful for fingerprinting studies for epidemiological studies.

Comstock GW. Public Health Reports 79: 1964; 1045-56

Community Research in Tuberculosis
Muscogee County, Georgia

Topics from among 25 peer reviewed publications:
• Value of community based research
• Prevalence and significance of radiographic findings
• Effectiveness of BCG (or lack of effectiveness)
• Interpretation of tuberculin skin test reactions
• Prognosis of solitary pulmonary nodules
• Prevalence of nontuberculous mycobacteria in culture
• Studies of isoniazid preventive therapy
• Risk of reactivation of untreated inactive tuberculosis

Muscogee and San Francisco: People

Community Research in Tuberculosis
Principles From Muscogee County

• Combining effective tuberculosis control and a basic epidemiologic study
• Broad coverage, standard procedures, quantitative independent measurements
• Based on entire population of county
• Integration of service and research
• One study to complement and reinforce findings from another
Molecular Epidemiology of TB
- Uses a “stable” biomarker to track the organism through a population.
- Assumes that there is an epidemiological link between cases from whom the “same” organism (same pattern RFLP/DNA fingerprint) is isolated.
- Assumes progression to disease within the time period between an index case and a “secondary” case.
- Cases without matching isolates (unique) assumed to result from activation of latent infection.
- Best interpreted in context of good epidemiological data.

Assessing an outbreak

THE NEW ENGLAND JOURNAL OF MEDICINE
Jan. 25, 1992

AN OUTBREAK OF TUBERCULOSIS WITH ACCELERATED PROGRESSION AMONG PERSONS INFECTED WITH THE HUMAN IMMUNODEFICIENCY VIRUS

An Analysis Using Restriction-Fragment-Length Polymorphism
Charles L. Daley, M.D., Peter M. Snider, M.D., Gregg F. Sobrero, M.D., M.P.E., Gary R. Sobrero, M.D., J. Thomas McGowan, Jr., Ph.D., William J. Jacob, Jr., M.D., and Fred C. Hummel, M.D.

Conclusions. Newly acquired tuberculous infection in HIV-infected patients can spread readily and progress rapidly to active disease. There should be heightened surveillance for tuberculosis in facilities where HIV-infected persons live, and investigation of contacts must be undertaken promptly and be focused more broadly than is usual.

An Outbreak of TB With Accelerated Progression Among Persons Infected With HIV
- TB can progress extremely rapidly through a vulnerable population (“A match on a pile of dry leaves.”)
- Source of outbreak identified (or, those who weren’t the source were exonerated.)
- Contact investigations must be undertaken promptly and be broader
- Need for surveillance in facilities for persons with HIV infection.

A broader look at the community epidemiology

THE NEW ENGLAND JOURNAL OF MEDICINE
June 16, 1994

THE EPIDEMIOLOGY OF TUBERCULOSIS IN SAN FRANCISCO
A Population-Based Study Using Conventional and Molecular Methods
Peter M. Snider, M.D., Fred C. Hummel, M.D., Sarah F. Storer, B.S., Antony Fal, M.D., John Farrow, M.D., Danielle C. Eoften, B.S., Gregg F. Sobrero, M.D., M.P.E., Charles L. Daley, M.D., and Gary R. Sobrero, M.D.

Conclusions. Despite an efficient tuberculosis-control program, nearly a third of new cases of tuberculosis in San Francisco are the result of recent infection. Few of these instances of transmission are identified by conventional contact tracing. (N Engl J Med 1994;330:1703-9.)

The Epidemiology of Tuberculosis in San Francisco: A Population-Based Study Using Conventional and Molecular Methods.

Small PM, et al. NEJM. 1994; 330: 1537
TB Control Interventions: 1992-3

- Intensified contact investigations
- Expanded use of directly observed therapy
- Developing an HIV related TB prevention program
- Screening for TB and use of treatment of LTBI among persons in correctional facilities, residential care facilities, and SRO hotels
- Intensified hospital infection control


The Homeless


60% of the cases had clustered patterns of RFLP, thought to represent recent transmission of infection with rapid progression to disease. Seventy-seven percent of African-American cases were clustered, and 88% of HIV-seropositive cases. The high rate of tuberculosis in the homeless was due to recent transmission in those HIV-positive and nonwhite. Control measures in the homeless should include directly observed therapy and incentive approaches, treatment of latent tuberculous infection in those HIV-seropositive, and screening in hotels and shelters.

Differences in Contributing Factors to TB Incidence in U.S.-born and Foreign-born Persons

Chin DP, et al. AJRCCM. 1998; 158:1797

Predictive Value of Contact Investigation for Identifying Recent Transmission of Mycobacterium tuberculosis

MARCUS A. BHINE, PHILIP C. HOPWELL, E. ANTONIO RUIZ, L. MAHA KARAMAWA, CEDILDA F. SANCHEZ, and PETER M. SMALL

Cases of tuberculosis in San Francisco between 1991 and 1996 with positive cultures who had been previously identified as contacts ("contact cases") to active cases ("index cases") were studied. Of 11,271 contacts evaluated, there were 66 pairs of culture-positive index and contact cases. DNA fingerprints were available for both members of these pairs in 14 instances (82%). The index and contact cases were infected with the same strain of Mycobacterium tuberculosis in 13 instances (79%); 95% CI: 56 to 82%); 16 pairs (30%) were infected with unrelated strains. Unrelated infections were more common among foreign-born (risk ratio [RR] = 5.22; p < 0.001), particularly Asian (RR = 3.89; p = 0.002) contacts. Contact investigation is an imperfect method for detecting transmission of M. tubercu-

Transmission of Mycobacterium tuberculosis from patients smear-negative for acid-fast bacilli

M A Biline, S S Klans, H Sakamoto, F C Megan, J Pera de Leon, C I Daley, P M Small

Findings: 1574 patients with culture-positive tuberculosis were reported and DNA fingerprints were available for 1350 (86%) of these patients. Of the 71 clusters of patients infected with strains that had matching fingerprints, 28 (30% [95% CI 28–82]) had a smear-negative putative source. There were 183 smear-negative cases in these 71 clusters, of whom a minimum of 32 were attributed to infection by smear-negative patients (17% [12–24]). The relative transmission rate of smear-negative compared with smear-positive patients was calculated as 0.22 (95% CI 0.16–0.32). Sensitivity analyses and stratification for HIV-1 status had no impact on these estimates.

Changes over a 13 year period

IMPACT OF CURE RATE ON INCIDENCE OF TUBERCULOSIS IN SAN FRANCISCO

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


Department of Medicine and Epidemiology, Infectious Diseases Unit, California, San Francisco, USA

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.
Overall, Clustered, and Unique Case Rates: 1992-2005

Clustered and Unique Rates

Program interventions

Cattamanchi A, et al. IJTLD, 2006

Clustered and Unique Case Rates: Foreign-born and US-born

Foreign-born

United States-born

Cattamanchi A, et al. IJTLD, 2006 in press

Variable Host-Pathogen Compatibility in M. Tuberculosis

a

b Geographic origin of lineages

Gagneux S, et al. PNAS 2006

Secondary Case Rate Ratio

\[ SR = \frac{n_S \text{Line} / n_U \text{Line}}{n_S \text{Line} \text{Y} / n_U \text{Line} \text{Y}} \]

Where:

- \( n_S \text{Line} \) = no. of secondary (clustered) cases for lineage X
- \( n_S \text{Line} \text{Y} = \) no. of secondary (clustered) cases for lineages Y+Z
- \( n_U \text{Line} \) = total number of unique-index cases for lineage X
- \( n_U \text{Line} \text{Y} = \) total number of unique-index cases for lineages Y+Z

Secondary Case Rate Ratio by Lineage and Race/Ethnicity

Gagneux S, et al. PNAS 2006
Effects of Drug Resistance on Clustering of M. Tuberculosis

Reference | Odds Ratio
--- | ---
Godfrey-Faucett\(^1\) | 1.49 (0.68-3.26)
Single-drug resistant | 1.49 (0.68-3.26)
MDR 0.27 (0.09-0.83) | 1.49 (0.68-3.26)
Van Soolingen\(^2\) | 0.7 (0.5-0.9)
INH resistant | 0.7 (0.5-0.9)
Garcia-Garcia\(^3\) | 8.14 (0.5-27)
MDR 0.16 (0.4-0.6) | 8.14 (0.5-27)
Other resistance | 1.14 (0.5-2.7)

\(^1\)Lancet 2000;356:1066, \(^2\)JID 1999;180:726, \(^3\)Arch Int Med 2000;160:630

Effects of Any Drug Resistance on Generation of Secondary Cases

![Graph showing the effects of drug resistance on secondary cases](image)

Community-Based Molecular Epidemiology of TB in San Francisco: 1991-2010

- Total cases: 4,058
  - Pulmonary: 3288 (81%)
  - Extra-pulmonary: 770 (19%)
- Total culture positive: 3728 (86%)
- Culture positive: 408 (60%)
- IS6110 & PGRS genotyping: 2524 complete data

- Population:
  - Chinese: 583 (25%)
  - Filipino born: 403 (16%)
  - Mexican born: 272 (11%)
  - US born: 716 (36%)
  - Others: 556 (20%)

- Lineage:
  - Euro-American: 791 (48%)
  - East Asian: 791 (48%)
  - Afro-Caribbean: 394 (24%)
  - East African Indian: 35 (1%)
  - West African f: 1 (1%)

Burgos M, et al. JID. 2003; 188:1878-84
Twenty Years of Molecular Epidemiology of Tuberculosis in San Francisco

![Graph showing the frequency of TB lineages by place of birth.]

**Frequency of TB lineages by place of birth**

<table>
<thead>
<tr>
<th>Lineage</th>
<th>POB/Lineage</th>
<th>China</th>
<th>Philippines</th>
<th>Latin America</th>
<th>United States</th>
</tr>
</thead>
<tbody>
<tr>
<td>East-Asian</td>
<td>401/585</td>
<td>20/409 (5.2%)</td>
<td>14/272 (5.1%)</td>
<td>99/755 (11.9%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(68.8%)</td>
<td>(5.1%)</td>
<td>(11.9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Euro-American</td>
<td>141/583</td>
<td>24/409 (5.7%)</td>
<td>251/272 (92.3%)</td>
<td>613/755 (81.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(24.2%)</td>
<td>(5.7%)</td>
<td>(92.3%)</td>
<td>(81.2%)</td>
<td></td>
</tr>
<tr>
<td>Indo-Oceanic</td>
<td>41/583</td>
<td>365/409 (89.0%)</td>
<td>7/272 (2.9%)</td>
<td>52/755 (6.9%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(7%)</td>
<td>(89.0%)</td>
<td>(2.9%)</td>
<td>(6.9%)</td>
<td></td>
</tr>
</tbody>
</table>

**Effect of Drug Resistance on Transmissibility and Pathogenicity of Mycobacterium tuberculosis**
- CDC-TBESC Task Order 8
  - CDC PI: Patrick Moore
  - TBESC PI: Jenny Flood, California DHS
  - Ed Graviss, Methodist Hospital Research Institute, Houston, TX.
- CDC-Universal Genotyping program
  - California DHS TB Branch and Mycobacterial Diseases Laboratory: Jenny Flood, Ed Desmond

**Lineage-specific Prevalence and Transmission of M. Tuberculosis**

A collaboration with
- CDC TBESC Task Order 2
  - CDC PI: Mary Reichert
  - TBESC PI: Tim Sterling
- UCSF
  - PI: Phil Hopewell
- Health departments: Arkansas, New York, Tennessee, Maryland, Georgia, New Jersey, San Francisco

**Conclusions of Studies Reviewed**
- Targeted interventions have decreased incidence and disproportionately decreased clustering.
- There is little interaction between the epidemics in US-born and foreign-born populations.
- Transmission from smear-negative cases is less but still important compared with smear positive cases.
- An important % of contacts have disease as the result of infection from sources other than the index case.
- Pleural tuberculosis is a result of recent infection.
- There may be specific adaptation of pathogens to racial/ethnic groups.
- Mutations that result in nonfunctional kat G cause a reduction in pathogenicity of M. tb.