Title

Migration-related tuberculosis among Asian immigrants in San Francisco: Treatment outcomes, 1994--1998

Author

Arai, Shoshana Rachel

Publication Date

2005

Peer reviewed|Thesis/dissertation

Migration-Related Tuberculosis among Asian Immigrants in San Francisco: Treatment Outcomes, 1994-1998

by

Shoshana Rachel Arai

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

NURSING

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Migration-Related Tuberculosis among Asian Immigrants

in San Francisco: Treatment Outcomes, 1994-1998

By

Shoshana Rachel Arai, R.N., Ph.D

Shoshana R. Arai, PhD (c)

University of California San Francisco

Migration-Related Tuberculosis Among Asian Immigrants in San Francisco: Treatment Outcomes, 1994-1998

In California, the majority of new cases of tuberculosis (TB) have been detected among the state's newly arriving immigrants, yet there are few follow-up studies on the treatment outcomes of these foreign-born populations. A historical cohort study was conducted to evaluate the treatment outcomes of 4,943 Asian immigrants who were treated for active TB disease or latent TB infections at the San Francisco TB Clinic, from 1994 to 1998. The study sample consisted exclusively of Asian newcomers from China, the Philippines and the Southeast Asian countries of Vietnam, Laos and Cambodia. Their outcomes were followed using their electronic clinic record for ten years to the year 2004. In the active disease cohort, there were 359 Asians initiated on 4-drug first line chemotherapy for pulmonary and extrapulmonary disease. The 300 immigrants with active pulmonary TB achieved 100% treatment adherence. Among the 59 immigrants with extrapulmonary TB, one person (1.7%) failed to complete treatment resulting in a 98.2% adherence rate. These high adherence rates of the active TB cohort may have been result of the chemotherapy's mandated status. Among the 4,547 Asians treated for latent tuberculosis infections, 3,576 (82.5%) completed prophylaxis treatment and 755 (17.4%) were classified as non-adherent. Controlling for years in the United States, the logistic regression analysis indicated that two factors, the immigrants' countries of origin and speaking English, were statistically significant predictors for treatment completion. Chinese immigrants were 1.3 times (AOR 1.3, 95% CI, 1.06-1.67, $p = .014$) more likely

to complete the voluntary prophylaxis treatment than immigrants from the Philippines. Immigrants who spoke English were 42% (AOR .417, 95% CI, .333-.524) less likely to complete treatment than the non-English speaking immigrants. This variation in treatment adherence suggests that clinicians' cultural assumptions about acculturation and adherence should be re-examined to identify the characteristics of the Asian population at risk for nonadherence. These findings indicate it is not the non-English speaking immigrant from China in need of drug monitoring, but in reality, it is the immigrant who speaks English and appears more acculturated who may require additional support to complete prophylaxis treatment.

Mary C White, RN, MPH, PhD

Dr. Mary C. White, Dissertation Committee Chair

Acknowledgements

It is a long list of friends and faculty that helped me throughout the years in the doctoral program. I would like to acknowledge the thoughtful mentorship that my committee chairs, Dr. Juliene Lipson and Dr. Mary C. White, provided for me for the past six years. To Joan and Kip, who generously gave me a first year scholarship to get me started, the solicitous support of the JACL, who encouraged my research among Asian immigrants, and the UCSF Nursing Alumni Scholarship Fund's financial support in my beginning years. To my daughter, Natsuko, who was willing to read and gently critiqued my lengthy drafts. To Elinor Davis who spent her weekends carefully editing my numerous revisions. To Jennifer Ginsdale, the San Francisco TB Clinic epidemiologist, who shared the clinic's elephantine database for my study. I would also like to extend a special note of appreciation to Dr. Julia Faucett who encouraged me as a neophyte summer research intern to "go- for- broke" and apply to the doctoral program.

Without their help, I would not have able to complete this long journey. I am deeply grateful for the opportunity to explore, back track and turn data upside down and find the epiphany of new realities. The process has given me the chance to look under the bedcovers, the time to frame my thoughts globally and anchor my feet to terra firma.

Thank you.

Dedication

This dissertation is dedicated to my patients, my steadfast family, and to the memories of my father, sister, Nikki and friend, Chiye.

Table of Contents

Table of Tables

Table of Figures

Chapter 1: Introduction

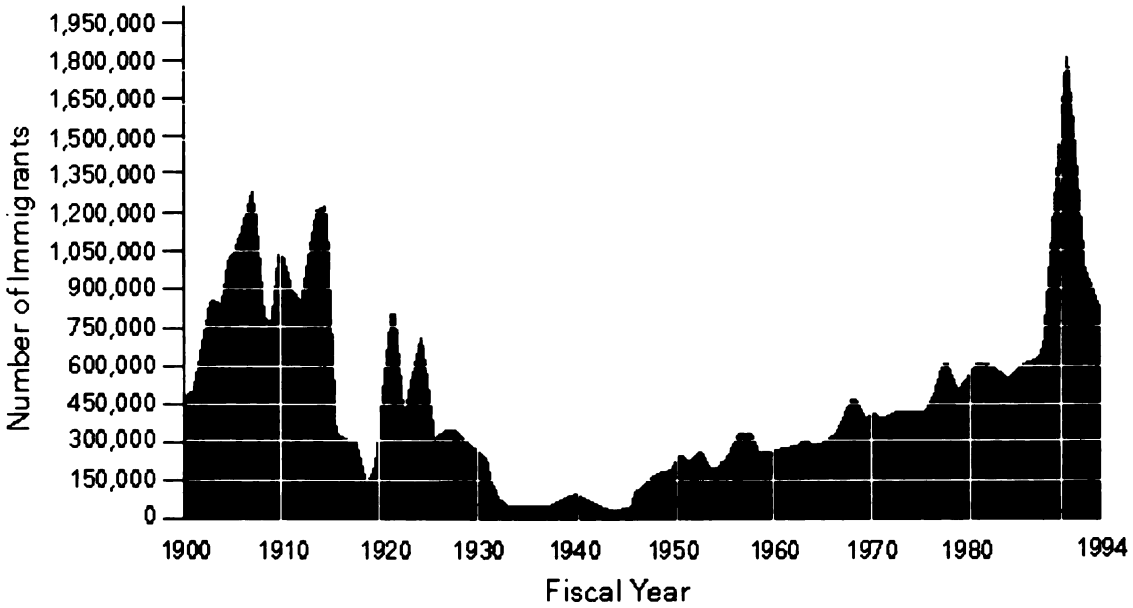
Migration-Related Tuberculosis among Asian Immigrants in San Francisco: Treatment Outcomes, 1994-1998

Tuberculosis (TB), the ancient scourge of mankind, continues to play a definitive role in the lives of immigrants in the twenty-first century. In California alone, in 2002, 75.4% of the reported active TB cases were among foreign-born persons. This retrospective study was designed to examine the phenomenon of migration-related tuberculosis. The study focused on the treatment outcomes of the Asian immigrants from TB endemic countries who were seen at the San Francisco General Hospital (SFGH) Tuberculosis Clinic from 1994 to 1998. At the SFGH TB Clinic, 7,824 Asian immigrants were screened for the presence of latent tuberculosis infections (LTBI) and active infectious TB disease during this four-year period. Eligible Asian immigrants (n = 4,943) were divided into two separate cohorts based on disease and treatment status. One cohort consisted of 396 Asian immigrants diagnosed with active pulmonary and extrapulmonary TB who received curative multi-drug antituberculosis therapy. The second cohort was composed of 4,547 Asian immigrants with LTBI who were offered and initiated on preventive prophylaxis therapy. In this dissertation, the completion rates and five-year post-treatment efficacy for the two cohorts are evaluated separately with special attention to the immigrants' countries of origin: People's Republic of China, the Republic of Philippines and the Southeast Asia region, which included the countries of Vietnam, Cambodia and Laos.

The selection of these three Asian countries/region reflects the sober reality of TB's global presence. The World Health Organization (WHO) estimates that over one-

third of the world's population in developing countries, approximately 2,000,000,000 people, are currently infected with *Mycobacterium tuberculosis* bacillus (*WHO Report 2002 Global Tuberculosis Control*, 2002). To understand tuberculosis both as a disease and social phenomenon, it is helpful to briefly review the epidemiologic and politically charged history of immigrants and refugees from developing countries and how they have impacted the distribution of TB in the United States. The rising proportion of TB among the foreign-born populations has not been an isolated trend or a new event in the history of TB in the United States. This rise in foreign-born TB case rates follows in the wake of the global movements of immigrants and refugees from TB-burdened regions to the low-prevalence industrialized countries, such as Great Britain, Australia, Denmark, the Netherlands, Italy, Canada and Switzerland (Bennett et al., 2001; Camie et al., 2001; Codecasa et al., 1999; Heath, Roberts, Winks, & Capon, 1998; Kumar, Watson, Charlett, Nicholas, & Darbyshire, 1997; Lange, Mortensen, & Viskum, 1986; Pedersen & Revsbech, 1999; Ravessoud & Zellweger, 1992; Raviglione, Snider, & Kochi, 1995; *Report from the British Thoracic and Tuberculosis Association: Tuberculosis among immigrants related to length of residence in England and Wales.*, 1975; Verver, Bwire, & Borgdorff, 2001; J. S. Wang, Allen, Chao, Enarson, & Grzybowski, 1989; J.S. Wang, Allen, Enarson, & Grzybowski, 1991). The U.S. has not been exempt from this pattern, since the turn of the century; increases in U.S. TB rates have closely followed the waves of immigrants arriving in the United States. Figure 1 illustrates the sharp fluctuations in immigration over the past century. However, a direct comparison of migration fluctuations and TB rates is only a crude indicator. This paper will discuss the multiple

Figure 1. Immigrants admitted to the United States during fiscal years 1900-1994



Note. U.S. Department of Justice, Immigration and Naturalization Services, Statistical Yearbook of the Immigration and Naturalization, 1996. Washington, D.C: U.S. Government Printing Office, 1997.
Secondary source: "Recommendations for Prevention and Control of Tuberculosis among Foreign-born Persons. Report of the Working Group on Tuberculosis among Foreign-born Persons," 1998, MMWR, 47, (p. 23).

Historical Background: Asian Migration to the United States

The first Asian immigrants in the late 1800s faced a social milieu that had already been hardened by decades of hostile nativist anti-immigration politics. The nativists in the 1900s drew on the high incidence of tuberculosis among European immigrants to justify their attempts to restrict the entrance of the Irish, Bohemians, Poles, Italians and most eastern European Jews to the United States (Fix, Passel, Enchautegui, & Zimmermann, 1994). Early population estimates of Chinese, Japanese and South Asians from India residing in the United States vary considerably, with the exception of the earliest mortality census reports (*Mortality Statistics: 1906*, 1908).[1] Often the Asian immigrants were classified in state and local public health records under "colored" instead of their actual residency status as foreign-born immigrants. By the time the Chinese Exclusion Act first passed in 1882 an estimated 300,000 Chinese had entered and worked on the west coast. The U.S. Immigration and Naturalization Act of 1924, which established the national origins quota system that specifically restricted the number of immigrants from China and Japan followed this exclusion act and further limited the growth of their communities (Hing, 1993). As their numbers slowly rose, like the earlier

[1] The tracking of nativity of the decedent and, later, the country of birth of the parents was discontinued in 1933 and 1937, respectively, as the number of births to white foreign-born or mixed heritage parents decreased from 53% of all the white births in 1915 to 9.5% in 1940 (Dunn, 1943). The mortality reports were the first national attempt to classify the "colored" population by racial descent. In contrast, the white population was classified by residency status into four categories: (1) native, meaning both parents were native; (2) one or both parents foreign; (3) parentage unknown and parentage not stated and (4) foreign-born. According to the early mortality census reports, the native white U.S.-born, as well as the subcategories and foreign-born, constituted approximately 85% to 89% of the overall population. The term "colored" included the remaining percentage, most of which were the Negroes, Indians, Chinese and Japanese. The early census reports kept unusually detailed accounts on the Asian deaths, for example, the 1906 census listed: 917 Chinese, 478 Japanese, 5 Hawaiians, 3 Koreans, 3 Filipinos, 2 East Indians, and 1 Hindoo (sp) (*Mortality Statistics: 1906*, 1908).

European immigrant groups[2], the Asian immigrants became the targets of nativist backlash. In 1876, the 30,000 Chinese immigrants living in the segregated Chinatown section of San Francisco, referred to as a "cesspool," became the scapegoats during an outbreak of smallpox.[3] More public health denouncements arose in the 1920s and 1940s when the TB mortality rates of the Chinese residents, restricted to living within the crowded confinement of Chinatown, were estimated to be three times higher than the city average (Shah, 2001). Chinatown was described in the press as the epicenter for TB in San Francisco. By 1939, campaigns were launched to support public housing as a solution to destroy "Chinatown's breeding grounds for white plague (TB) germs" (Kraut, 1995; Shah, 2001 p. 238).

Motivating these past public health campaigns that frequently targeted migrant populations was the desire to prevent transmission to the mainstream population. In general, even though the increased rates of tuberculosis were observed in immigrant populations, significant transmission to native-born populations was not reported (Chin et al., 1998; Wilson, 1992). Some of the fervor of these anti-immigrant sentiments gradually receded in the late 1940s as fewer immigrants were admitted under the exclusion acts. Moreover, for the first time, limited chemotherapies (streptomycin in 1944; p-aminosalicylic acid in 1949) were available to treat TB. These drug treatments were followed by the discoveries of isoniazid (1952), pyrazinamide (1954), ethambutol (1962) and rifampin (1963). Since then, TB control strategies have relied almost

---

[2] The foreign-born immigrants frequently cited by the nativist groups as threats to public health were the Irish, Bohemians, Italians and most eastern Europeans (Ott, 1996).

[3] The white residents in San Francisco blamed the outbreak of smallpox on the Chinese. Approximately 1,646 cases of smallpox were reported to the San Francisco Health Office between May 19, 1876 and July 1, 1987; 482 died, including 77 Chinese.

exclusively on the effectiveness of chemotherapy as the means to eradicate TB as a threat to public health. In recognition of the primacy of drug treatment over all other forms of therapy, Johnston and Wildrick (1974) unequivocally stated, "The treatment of tuberculosis can be summed up in one word: chemotherapy." (Johnston, 1974, p.649).

Asian Migration to the United States in the 20th Century

The effectiveness of the national TB control strategy was tested in the 1980s when immigration climbed to almost ten million, the highest peak in U.S. history. The Asian population in the United States dramatically increased during this influx of recent immigrants from one million in 1965 to seven million by 1990. The initial wave of 262,602 Southeast Asian (SEA) refugees fleeing the aftermath of the Vietnam War foreshadowed a major epidemiological shift in the nation's TB prevalence [4] patterns. The SEA refugees who entered the United States from 1979 to 1980 had stunning estimates of active tuberculosis as high as 1,138 per 100,000 persons (CDC, 1981b; Powell, Brown, & Farer, 1983). In contrast, the comparative TB case rate for U.S.-born persons in 1980 was 12.3 per 100,000 (CDC, 1980b). Initially, the high disease estimates reported among these refugees were seen as evidence of faulty overseas screening procedures (Minh, Prendergast, & Engle, 1982; Powell et al., 1983).

---

[4] In epidemiology, the measures of disease frequency most commonly used are prevalence and incidence. Prevalence quantifies the proportion of individuals in a population who have the disease at a specific time and provides an estimate of the probability or risk that an individual will be ill at a point in time. In contrast, incidence quantifies the number of new cases of disease or events that develop in a population of individuals at risk during a specified time interval (Gordis, 2000; Hennekens & Buring, 1987). In some of the reports on the TB epidemiology of immigrants who acquired their latent TB infections (LTBI) in their countries of origin and subsequently the LTBI developed into active disease, the terms prevalence and incidence have been used interchangeably. In some of the older studies on reactivation, instead of the term LTBI, the participants' TB status has been described simply as active or inactive TB. Adding to this ambiguity, among immigrants it has been difficult to identify the specific time when they were infected with TB. Therefore, immigrants with LTBI that later develop into cases of reactivated TB should be reported as prevalence, not as an incidence. In this dissertation, to clarify the measure of disease frequency the term "proportion" of individuals at risk or ill will be reported.

Follow-up studies on the SEA refugees suggested that the greater risk factor for tuberculosis among immigrants from developing countries was actually posed by the endemic high proportion of active and latent tuberculosis infections (LTBI) that existed in their countries of origin (Enarson, 1984; Enarson, Sjogren, & Grzybowski, 1980; Jasmer, Nahid, & Hopewell, 2002; Talbot, Moore, McCray, & Binkin, 2000). Later microbiological epidemiological studies confirmed that the majority of TB cases among foreign-born persons were likely to be the result of reactivation of a remotely acquired infection, with only a small percentage of the TB infections occurring as a result of recent transmission after their arrival in the United States (CDC, 1998a; Chin et al., 1998; El Sahly et al., 2001; McKenna, McCray, & Onorato, 1995; Tornieporth et al., 1997; Zuber, McKenna, Binkin, Onorato, & Castro, 1997; Vos, 2004)

Parallel populations at risk for tuberculosis in the United States.

In this discussion of migration-related TB, it is important to address to some extent the overlapping association between ethnicity and the immigrant populations. Although this dissertation focuses on immigrant populations, the resurgence of tuberculosis in United States arises from two parallel epidemiological cohorts described by Hopewell (1998): (1) a growing number of foreign-born immigrants arriving from countries with a high proportion of tuberculosis disease, and (2) the U.S.-born minority and marginalized communities. These two at-risk subpopulations, who frequently may reside in the same urban neighborhoods in the United States, have marked differences in significant confounding factors, such as the social burdens of social isolation, overcrowding and homelessness (Leonhardt, Gentile, Gilbert, & Aiken, 1994), reported substance abuse, and/or incarceration and, significantly, differing rates of human

immunodeficiency virus (HIV) co-infection (Brudney & Dobkin, 1991; De Bruyn et al., 2001; El Sahly et al., 2001; Geng et al., 2002; Hopewell, 1998). Furthermore, molecular epidemiological studies on the U.S.-born disadvantaged groups using restriction fragment length polymorphism molecular analyses (RFLP) have identified that their disease exposure was the result of recent local community transmission, as opposed to the delayed reactivation of latent infections found among the immigrants (McConkey et al., 2002; Small et al., 1994). The recent infections among the U.S.-born have also resulted in a higher transmission disease index, with more secondary cases being generated by this population than by the immigrants with reactivated infections (Borgdorff, Behr, Nagelkerke, Hopewell, & Small, 2000; Borgdorff, Veen, Kalisvaart, Broekmans, & Nagelkerke, 2000; Chin, 1998; El Sahly, 2001).

However, the foreign-born population in the United States includes many individuals who enter as tourists, students, other residents and undocumented workers who are not medically screened. Therefore, in Tornieporth et al.'s study (1997) reporting that the foreign-born patients in New York City were six times less likely to be infected with HIV than the U.S.-born patients, there was a small percentage of foreign-born TB patients who were HIV seropositive. In the study, 13 (76%) of the 17 foreign-born TB and HIV positive patients originated from Caribbean and Central/South America countries and had cluster patterns that suggested that they acquired the infection after they arrived in the U.S. (Tornieporth, 1997). The overlapping in social factors characteristic of the two parallel populations is evident in the distribution of TB infection in incarcerated populations in the correctional system. The Saunders et al. (2001) study on the inmate population at a federal detention center in San Diego, California observed

that not only were the foreign-born inmates 5.9 times more likely to have positive tuberculin skin test (TST) than the U.S.-born inmates, but they also accounted for 60% of the recently diagnosed tuberculosis cases.

Significance of the Study

With new arrivals entering daily, the TB infected foreign-born individuals, in 2003, constituted 53 percent, the majority of active TB cases in the United States (CDC, 2003a). An overseas birthplace, as an epidemiological environmental factor, continues to influence the varying rates of TB among the Asian immigrants, particularly those migrating from China, Philippines, India, Vietnam, and Korea, the five largest contributors to the Asian-born U.S. population. Zuber, McKenna and McCray (1998), using data from 1975 to 1995, estimated the long-term impact cumulative case count among the Vietnamese refugees to average 1,494 cases per 100,000 persons during the first 22 years after their arrival (532/100,000 in the first year and 962/100,000 thereafter).

Studies on Southeast Asians in the 1980s indicated that immigrants and refugees who have the combination of positive tuberculosis skin tests (TST) and chest x-ray abnormalities have been associated with a 6-fold or greater increase in risk for developing active TB (Nolan & Elarth, 1988).[5] This observation was made with the understanding that treatment of inactive or latent tuberculosis was not routinely a requirement for entry or resettlement. Thus, persistently elevated rates of tuberculosis resulting from reactivation of those with old inactive disease and untreated LTBI should be expected in migrant populations who originate from TB prevalent regions of the world

[5] Persons at highest risk for the reactivation of LTBI have been those with HIV co-infection, which is associated with a 100-fold increase in risk. Other high risk predisposing situations are those in which individuals' systemic or local immunity has been compromised, i.e., cancer chemotherapy, long term systemic corticosteroids use, transplantation and end stage renal disease (Schwartzman, 2002).

and are TST positive (Gushulak, 1998). This finding was evident in Nelson's (1997) study on health status of 99 new Vietnamese immigrants in 1994 to 1995, that reported 70% (66/99) had positive TST (Nelson, Bui, & Samet, 1997).

The objective of this retrospective study is to evaluate the efficacy of past anti-TB strategies used to treat one of today's high-risk populations in the U.S. Elevated case rates and high prevalence of LTBI still persist among the migrating Asians who are no longer entering as refugees fleeing the wartime conditions and refugee camps of 1975-1980s. By 1993, almost two decades later, Asians now accounted for slightly more than half of the family-sponsored legal immigrants in California (Gould, 1996). In 2003, despite the shift in immigration status from refugee to family sponsorship, the CDC reported that Asians still had the highest TB case rate in the nation at 29.3 per 100,000 (this represents a decline from 45.0 per 100,000 case rate reported in 1993)(CDC, 2003a). The comparable TB case rate for US-born persons was 5.1 per 100,000 in 2003. The earlier TB control strategies that were developed to address the needs of U.S.-born individuals now need to respond to the differing regional and risk factors that characterize these groups of high-risk immigrants.

Chemotherapy for Tuberculosis

WHO, the CDC and local public health agencies have all agreed on the necessity for aggressive, mandated multi-drug therapy, preferably directly observed therapy (DOT), for active TB cases. While the treatment of infectious active TB has been and continues to be a public health priority, less emphasis and fewer resources have been allocated for preventive prophylaxis treatment for those with LTBI. For example, among the 262,602 SEA refugees who entered the U.S. from 1979 to 1980, 46,000 (about 18%)

were prescribed prophylaxis therapy (Powell et al., 1983). In addition, in 1984 to1988, more than 2,200 SEAs completed an intensive four-drug, six-month course of chemotherapy and 2,800 close family contacts were initiated on preventive therapy (Snider, Salinas, & Kelly, 1989). Yet, there has been no follow-up evaluation of the incidence of reactivation or drug efficacy on these cohorts. The data for both studies are no longer available (personal correspondence, Dr. E. Schneider, Medical Officer, CDC, June 15, 2004). The importance of evaluating the efficacy of both active and LTBI treatment outcome derives from the Working Group on TB, which estimates that, assuming an overall rate of effectiveness of preventive prophylaxis treatment of LTBI of 75% (allowing for nonadherence), at least 1,300 cases of tuberculosis could be prevented per year during the first five years of resettlement (*Ending Neglect: The Elimination of Tuberculosis in the United States.*, 2000). Currently for persons with indurations of 10 mm or more on a tuberculin skin test and either human immuno-deficiency virus (HIV) or evidence of old healed tuberculosis is present, the lifetime risk of reactivation TB is 20 percent or more (Horsburgh, 2004). The San Francisco Public Health Department's Tuberculosis Control Section guideline for patients with positive PPDs asserts that adequate LTBI prophylaxis treatment reduces the lifetime risk of reactivation TB to less than 1.6 percent (*Latent Tuberculosis Infection: A Guide for San Francisco Providers*, 2003).

Although Hippocrates addressed the issue of following doctors' orders, or completing any drug regimen orders, in his medical writings (Hayes, 1979), in the case of tuberculosis, nonadherence has a special significance. In chronic medical conditions, such as hypertension, a patient's decision not to adhere to medical therapy primarily

affects only the patient. As a communicable disease, TB differs in that the person who fails to adhere to the chemotherapy regimen not only spreads the disease to the community, but his/her treatment default fosters the development of drug-resistant M. bacterium strains. It has been estimated that each case of active TB infects two to three individuals before detection (Johnston & Wildrick, 1974; Sbarbaro, 1985). It was estimated that individuals with inactive TB who have never received adequate chemoprophylaxis treatment face an annual risk of reactivation at least one in 75 (CDC, 1971). In addition to this risk of reactivation has been the ominous development of drug-resistant strains of *M. tuberculosis* (MDRTB). The transmission of multi-drug resistant strains that progress to active disease is not only extremely costly in terms of the required intensive therapy and surveillance, but the MDRTB is incurable in nearly one-half of those infected (Earnest & Sbarbaro, 1996). Drug adherence in the treatment of TB is more than the practice of optimal medicine; it has become a mandated necessity.

Treating immigrants with reactivated TB as well as protecting those with LTBI with prophylaxis therapy will be essential if the global spread of TB is to be in contained in westernized countries (Brewer & Heymann, 2004; Li, Driver, Munsiff, Yip, & Fujiwara, 2003). Can this retrospective study on treatment outcomes identify the clinical, social and ecological factors that may have contributed to their drug adherence? Will positive treatment outcomes substantially reduce this reservoir of future cases of reactivated TB in this population? Has the DOT surveillance boosted adherence among the immigrants with reactivated TB? As the granddaughter of Asian immigrants and a healthcare provider in this immigrant-founded nation, I believe that the better we

understand what is effective in caring for the newest members in our communities, the sooner we will be able to loosen this Gordian knot between migration and tuberculosis.

The Disposition of the Thesis

Chapter 1:

- A brief introduction to the history and prevalence of TB infection among Asians who have migrated from tuberculosis-endemic countries to the United States.
- The prevalence and the significance of evaluating the treatment outcomes of the Asian immigrants with active TB and latent tuberculosis infections.

Chapter 2:

- A literature review of the studies conducted on the most widely studied group of Asian immigrants, the Southeast Asians.
- Introduction of the classic epidemiological triad of environment, host and agent associated with the study's health service outcome evaluation.

Chapter 3:

- The methodology of retrospective migrant studies and description of the five-year follow-up study that evaluated treatment outcomes of the Asian immigrants at Department of Public Health's TB Clinic at San Francisco General Hospital, from 1994 to 1998.
- Definitions of study terms and chemotherapy protocols.

Chapter 4:

- Descriptive findings that characterize the sample: active and latent tuberculosis cohorts.

- Analytic findings of the treatment outcomes using bivariate analyses followed by logistic regression analyses on the outcomes of care.

Chapter 5:

- Discussion of the study findings and limitations.
- Implications for treatment strategies for high-risk migrant populations.

Chapter 2: Literature Review and Theoretical Framework

"The largest number of cases occurs in the South-East Asia Region, which accounts for 33% of incident cases globally." (*Tuberculosis: Infection and Transmission*, 2004)."

This chapter on migration related tuberculosis among Asian immigrants will concentrate on the body of literature that centers on the Southeast Asians' migration to the United States. Prior to the migration of the SEAs, U.S. migrant studies on the early Asians and the arrivals of Chinese, Filipinos, Koreans and South Asians from India and Pakistan before 1970 were rare and, if reported, usually hidden in generic reports on Asian Pacific Islanders (APIs).[6] The studies on the SEAs provide a broad template to study Asian immigrants' exposure to TB and their post-migration patterns of reactivation. The proportion of LTBI and reactivated TB case rates has varied among the Asians according to their specific countries of origin.[7] Although the TB rates do vary by country and by their TB DNA fingerprints (Park, Bai, & Kim, 2000), the migrants from developing Asian countries share a common determinant. They left countries in which the majority of the population over the age of 20 has positive tuberculin skin tests (TST) (Gushulak, 1998; Murray, 1996; Plant et al., 2002; Wells, Zuber, Nolan, Binkin, & Goldberg, 1997; Zuber, Binkin et al., 1996) and arrived in developed westernized countries in which only a small minority in the native population still contends with the disease.

---

[6] The tuberculosis related studies have primarily been conducted on the SEAs. There are only two TB related studies on Filipinos (CDC,1993b; Yamada, Caballero, Matsunaga, Agustin, & Magana, 1999) and two qualitative studies on Chinese immigrants (Ho, 2003, 2004).

[7] The 2004 WHO Report on the all case prevalence of active TB per 100,000: India 156; China 246; Indonesia 569; Philippines 517; Vietnam 270; Laos 152; and Cambodia 1225.

Immigration Legislative Impact on TB Epidemiology in the United States

In 1965, the landmark Immigration and Nationality Act repealed the national origins quota system, which favored European migration, replacing it with a uniform limit of 20,000 immigrants per country for all countries outside the Western Hemisphere (Fix & Passel, 1994). For the first time since 1882, a limit was placed on immigration from the west European countries. By 1970, the foreign-born population in the United States dropped to a record low of 9.6 million, or 4.7% of the total population. This decline ended in 1975 beginning with the admission of 130,400 Southeast Asian refugees, 125,000 of whom were Vietnamese (Hing, 1993). The war-related waves of refugees and, later, immigrants from Latin America, gradually raised the total foreign-born population from 9.6 million in 1970 and 14.1 million in 1980, to 19.8 million in 1990 (region of birth: Europe 22%; Asia 25%; Latin America 42%; and Africa 2%). In less than three decades, from 1970 to 1997, the estimated percentage of the foreign-born population doubled from 4.7% to 9.7% of the total population. While Europeans were the majority of the newcomers in the past, today the U.S. is in transition from a population of whites and blacks to a diverse multi-ethnic nation. While new arrivals from Asia and Latin America were resettling in the U.S., the funding for TB control programs declined; multi-drug resistant TB strains were developing due to poor adherence (CDC, 1999); and HIV infection was spreading among the U.S.-born urban poor, resulting in the resurgence of TB, in 1992, as once again a threat to public health (*Ending Neglect: The Elimination of Tuberculosis in the United States*, 2000).

State tuberculosis control programs, which had received 96% of the 262,602 Indochinese refugees, reported an estimated prevalence of tuberculosis among the

refugees at the time of entry that initially peaked at 1,138 cases per 100, 000. The annual incidence after arrival in the United States for refugees who were screened for active tuberculosis prior to their overseas departure and were without evidence of disease was 407 per 100,000 (Powell, Brown & Farer, 1983). The CDC reported the annual prevalence among the newly arriving Southeast Asian refugees as high as 719 per 100,000 in 1979, the highest morbidity rate of any subpopulation in the United States (CDC, 1981). The rates varied by the countries of origin: the Cambodian refugees had the highest age-standardized prevalence of tuberculosis at 1,456 per 100,000; the Vietnamese had 1,109 per 100,000; the Laotians were the lowest at 419 per 100,000 (*Tuberculosis in the United States*, 1979).

Between 1985 and 1987, approximately 92 to 93% of the tuberculosis cases among Asians/Pacific Islanders (APIs) occurred among foreign-born Asians in the United States (CDC, 1987). As early as 1987, almost 50% of the active TB cases in California were reported among the foreign-born Asian refugees (Rieder, Cauthen, Kelly, Bloch, & Snider, 1989). The rising case rate among the Southeast Asians, who constituted 17% of the influx of 14 million migrants in the 1980s, did not noticeably affect the national case rate from 1981 through 1987. Instead the drop in the national case rate slowly declined from 6.7 % (1,706 cases) per year, from 27,373 cases in 1981 to only 1.1 % decline (22,517 cases) by 1987. Concerned that the influx of Southeast Asians would destabilize many communities, Congress passed the 1980 Refugee Act, which revoked the attorney general's parole authority and established a limit of 234,000 refugees for fiscal year 1980. The national prevalence in tuberculosis slowed accordingly as the total number of refugees admitted dropped to 70,000 in 1985. During this five year period from 1980 to

1985, the number of Southeast Asian refugees declined from 95,200 per year to 25,209 in 1985 (CDC, 1991; CDC, 1987). This restriction changed in the following year with the passage of the 1986 Immigration Reform and Control Act that granted amnesty to approximately three million undocumented residents (*History Online*, 2002). McKenna, McCray and Onorato's (1995) analysis of the influence of immigration on the epidemiology of TB referred to the Immigration Reform and Control Act of 1986 as a contributing factor to the escalating prevalence rate of 33.6 per 100,000 among the foreign-born from 1990 to 1993, compared to the U.S.-born population overall rate of 8.1 per 100,000.[8] In their study, 92.2% of the 16,643 persons diagnosed with tuberculosis came from five high prevalence countries: the Philippines (6,286 cases); Vietnam (4,941); South Korea (2,262); Cambodia (977); and Laos (878).

Classification of entrants.

The immigrants with these reported case rates were screened before their departure and by the U.S. Immigration Service when they entered the USA as legal permanent residents. Prior to being issued a permanent residence visa for entry into the United States, the CDC requires immigrants and refugees to undergo a medical examination by local designated physicians using the CDC guidelines, which includes a chest radiograph if they are over the age of 15. If the chest x-ray shows an abnormality consistent with active tuberculosis, sputum specimens are collected and examined for acid-fast bacilli (AFB). Applicants identified with active TB receive an intensive four-drug, six-month course of chemotherapy, which must be completed prior to their departure to assure that they do not enter the U.S. with active disease. These applicants

[8] The CDC (1990) had estimated the 1989 case rate among the foreign-born to be 124 per 100,000.

are classified as TB Class A (infectious). If the screened applicants have a chest x-ray compatible with TB and three negative sputums for AFB, they are permitted to enter the United States with a B1 (clinically active, non-infectious TB) notification status; if the chest x-ray is consistent with inactive TB, applicants enter the U.S. with a B2 notification status (clinically not active, noninfectious). Immigrants with abnormal chest X-rays not consistent with TB, or compatible with old healed TB have a TB Class B3 status (CDC, 1979, 1998a). Refugees and immigrants with B notifications are required to report to the local public health department for further evaluation (Sciortino, Mohle-Boetani, Royce, Will, & Chin, 1999; Snider et al., 1989).

The immigrants' most common countries of origin in 2002 were Mexico (24.8%), the Philippines (11.3%), Vietnam (8.6%), India (7.6%), China (4.5%), Haiti (3.4%), and South Korea (2.7%) (CDC, 2003b). Although, immigrants from Mexico comprise approximately 25% of all the recent arrivals with tuberculosis, only 1.7% entered with a B notification status. The proportion of immigrants with B notifications from the Philippines, Vietnam or China was more than fifty times greater than the proportion among the persons from Mexico (Sciortino et al., 1999).

The mandatory screening by the Immigration and Naturalization Service (INS) [9] and the state or local public health department notification of the arrival of refugees resulted in the Southeast Asian refugees, as a group, being cast in the public limelight as the most systematically screened group of all the foreign-born immigrants in recent public health history. This close attention and the continuing high proportion of LTBI

[9] On March 2003, the Immigration and Naturalization Service (INS) transitioned into the Department of Homeland Security (DHS) as the U.S. Citizenship and Immigration Services (USCIS).

and reactivated TB cases led to focusing this literature review on foreign-born Asians, specifically on the immigrants from the Southeast Asia region. [10]

Review Search Methodology

A MESH search for studies on pulmonary tuberculosis related to the Southeast Asian refugee population was conducted from June 2001 to December 2004 using the PubMed database (from 1966 to 2004) through the Internet site of the National Library of Medicine. The search for the terms pulmonary tuberculosis and immigrants in any fields retrieved 366 articles; further searching using AND/OR foreign-born immigrants produced 66 articles, AND/OR Asian immigrants returned 40 articles. Reference lists of articles on foreign-born and/or immigrant populations and tuberculosis were also included in the search. The retrieved articles were selected using the following inclusion criteria: the studies must specially focus on the identification and/or treatment of tuberculosis specifically among the Southeast Asian refugees who migrated from Vietnam, Laos and Cambodia after 1975; and the studies were restricted to Southeast Asian refugees who were admitted for permanent residency in the United States.

Studies were excluded using the following criteria: TB studies on non-immigrant aliens admitted for temporary purposes, i.e., students, visitors, government officials, information media on temporary visas; TB studies on illegal entrants who entered the United States without inspection or were inspected and admitted but subsequently violated the terms of that admission. Because of the substantial heterogeneity among Asian groups, studies of pulmonary tuberculosis that do not specify the country of origin

---

[10] In 2002, WHO reported that the Southeast Asian countries, with three million cases of active TB, continue to be the most TB burdened region in the world. The latest challenge to the global control of TB has been the pandemic link of human immunodeficiency virus (HIV) infection to the transmission of TB in developing countries and the urban centers in some industrialized countries (Corbett et al., 2003; *Tuberculosis*, 2002).

of the Asian immigrants were excluded. In the United Kingdom, "Asian" origin refers to persons from India, Pakistan, or Bangladesh or a person of Indian or Pakistani descent from East Africa. The same term "Asian" in Wang's (1989) Canadian study describes immigrants from Japan, Korea, the Philippines, India and Hong Kong (J. S. Wang et al., 1989). The risk of tuberculosis in a migrating population is extremely variable, for example, the pre-migration history of immigrants may have included exposure to such hardships as stays in refugee camps, multiple relocations and prolonged periods of deprivation. Therefore, comparative studies that aggregated immigrant groups without specifying their countries of origin into foreign-born versus U.S.-born populations categories are not included in this review (Wilcke et al., 1998; Wobeser et al., 2000). Also excluded are studies that primarily focused on extrapulmonary TB conditions among SEAs, drug therapy related issues, i.e., drug-resistance and toxicity and qualitative studies on the health beliefs of SEAs.

There were 25 articles that met the inclusion criteria. They included 17 studies on the SEAs' proportion of active TB cases, rate of LTBI reactivation and percentage of positive TST reactions in the United States; two pre-migration overseas screening reviews; and six international studies on the migration of SEAs to countries with low proportions of TB. Abbreviated descriptions of the selected studies for this review are listed in Appendix A. The Centers for Disease Control (CDC) reports that summarize state TB surveillance data on the proportion of tuberculosis and the drug-resistance to anti-tubercular chemotherapy among the Southeast Asians are listed in chart form in Appendix B. A chart summarizing the increasing percentage of tuberculosis cases among

the foreign-born population in the United States from 1990 to 2000 follows the CDC summary in the Appendix B.

Literature Review

The research on the epidemiology of tuberculosis among the SEA refugees began with descriptive studies in 1978 that later evolved into the clinical studies of the 1980s. These descriptive studies established not only the proportion of active and latent tuberculosis, but the co-morbidity with parasitic and hepatitis infections among these new arrivals. By 1983, the initial influx of SEA refugees had grown to a population of 550,000, and Powell, Brown and Farer (1983) and Nolan and Elarth (1988) had sufficient TB surveillance data to publish five-year longitudinal studies. Interspersed with these early descriptive studies were those that focused specifically on the high tuberculin-conversion rates from negative to positive TSTs reported in this high-risk population. While the significance of these conversion studies on reactivity was being disputed, the population of Vietnamese alone in the United States doubled to 1.12 million by 2000 (*The Asian Population*, 2002). Clearly the impact of this population could not be dismissed. Internationally, the migration of SEAs has had a similar effect on the proportion of TB cases in other countries with low TB case rates. Two of these countries, Australia and Denmark have recently published five, ten and 16 year longitudinal studies that focused on the post migration risk of reactivation TB among SEAs during their years of resettlement.

To clarify the progression of the research in this review, the 25 studies are divided by their study objectives into three groups: (1) the early descriptive and observational clinical studies, including the later descriptive overseas population studies on the

proportion of both active and latent TB; (2) the observational two-step tuberculin testing "booster" studies, and (3) the longitudinal studies in the United States, Australia and Denmark.

Early Descriptive and Observational Prevalence Studies

The nine descriptive and observational studies that consisted of health surveys or clinical findings and the two overseas screening studies comprise the majority of studies that focused almost exclusively on the SEAs' risk of tuberculosis. The domestic studies include: #1, Barrett-Connor, 1978; #2, Coleman and Root, 1981; #3, Catanzaro and Moser, 1982; #4, Goldenring, Davis and McChesney, 1982; #8, Barry, Craft, Coleman, Coulter and Horwitz, 1983; #6, Sutherland, Avant, Franz, Monzon, Stark, 1983; #9, Judson, Lince, Anders, Tapy, LeVan, Cohn and Kicera, 1984; #11, Fitzpatrick, Johnson, Shragg and Felice, 1987; and #17, Nelson, Bui and Samet, 1997. The overseas screening studies were conducted by #18, Sutter and Haefliger (1990) and # 19, Keane, O'Rourke, Bollini, Pampallona and Stein (1995).

The most striking feature and strength of these early studies has been the consistency in the high proportion of LTBI from Barrett-Connor's study in 1978 to almost twenty years later, in 1997, in Nelson, Bui and Samet's study on the infectious disease status of SEA refugees. In these nine studies, either tuberculosis or multiple parasitic infestations were identified as the predominant imported common infection among the SEAs. The SEAs were described as having the *highest case rate of positive tuberculin skin test (TST) sensitivity* [italics added] of any refugee group in the U.S. under the age of 35 years. The reports of positive TST reactions ranged among SEA teenagers from 34% (#4) to 52% (#10), and among adults from 38% (#9) to a high of 70.2% (#17).

These clinical findings support McKenna's (1995) report of 35% to 53% positive tuberculin-skin-test (TST) reactions in young foreign-born persons from Southeast Asia and Latin America. These young immigrants were described as potential sources of future cases of TB that would continue to be a public health threat unless major efforts are mounted to screen them for infection and provide treatment (McKenna et al., 1995).

Descriptive Overseas Studies

The descriptive overseas studies of tuberculosis morbidity among the Vietnamese in the SEA refugee camps by Sutter and Haeflilger (1990) (#18), and Keane, O'Rourke, Bollini, Pampallona, and Stein (1995) (#19) reported on the pre-migration proportion of active TB among emigrants prior to migration to their host countries. The proportion of TB among the 19,726 refugees screened in Thailand detention camps by chest radiography indicated a case rate of 580 per 100,000 with sputum smear-positive TB in one per 1,000 persons. In the second refugee camp in the Philippines (#18), 259 of the 741 (35%) Vietnamese refugees had positive TST tests; in both camps the male refugees had a higher proportion of positive TST than female refugees did. The Keane et al. (1995) study on the Orderly Departure Program that screened 39,581 prospective Vietnamese migrants reported a similar proportion of smear-positive TB cases, 641 per 100,000. Among the smear positive cases, 265 (82%) were cured with first-line drug treatment (isoniazid, rifampicin, ethambutol and pyrazinamide for two months), with the remainder continuing on for an additional four months, or a second-line drug regimen. Sutter and Haefliger's study reported that 85% of the TST positive refugees would have been eligible for prophylactic therapy; however, the follow-up treatment, a critical factor, was not discussed in the study. The authors in the second study (#19) suggested that the

higher proportion of active TB detected among the prospective migrants could be a result of the active case-finding, which contrasts with the passive screening in the Vietnamese national TB control program in which the rate of smear-positive TB from 1986 to 1992 was approximately 100 per 100,000. The authors speculated that the higher proportion of cases among the emigrants could be due to the greater percentage of elderly (20%) among the emigrants in contrast with the general population and that some of the emigrants came from disadvantaged groups, such as Amerasian children or former prisoners of political re-education camps.

These suppositions were offered since the aim of the study was to learn if the increased proportion of TB among the SEAs could be attributed to the high number of cases in their countries of birth or the inadequacy of pre-migration screening before entry and/or the poor living conditions in the host countries that reactivated latent TB infections. The authors concluded that the high proportion of active disease among the refugees, especially within the first five years of their arrival, appeared to point to inadequacies in the overseas screening programs. Other authors found support for the other two possible explanations for the high case rate and even included additional sources, such as the intense surveillance of this migrant population, which may have resulted in the over-diagnosis of TB among this cohort (Cantwell, Snider, Cauthen, & Onorato, 1994); recent transmission immediately prior to their migration; the stress of relocation; and the relapse of previously treated TB. The overseas screening studies, like the early descriptive studies in the United States, were limited by their research designs and were not able to address these key unanswered questions regarding the social or

environmental factors that may trigger the reactivation of disease among these immigrants.

The clinical studies on the health status of the SEA refugees also reported enteric parasitic infestation co-existing with the high proportion of LTBI ranged from 51% (#17) to as high as 82% (#6). The third common infection reported was the presence of asymptomatic chronic hepatitis B antigen (HBeAg) infections in 13% (#6) to 16% (#8) of the study participants. The co-morbidity and elevated risk of this triad of infectious conditions: tuberculosis, enteric parasitic infestations and chronic hepatitis B were documented. However, the association between the co-infections could not be further explored given the design limitations of descriptive studies. The interaction of HBeAg infections and potential drug toxicity in TB prophylaxis therapy has been noted in subsequent studies (McGlynn, Lustbader, Sharrar, Murphy, & London, 1986; Patel & Voigt, 2002). Despite demonstrating a high proportion of infectious diseases, the studies described a youthful population with a median age that ranged from 15 to 21 years old in the studies in the 1980s, increasing to a median age of 34 years in the 1997 study (#17). Sutherland, Avant, Franz, Monzon, and Stark, 1983, (#6) optimistically viewed this young population as generally very healthy with treatable infectious disease conditions rather than as a source of future reactivation cases of tuberculosis.

Methodology: sample selection and diagnostic tools.

The selection of the participants in the clinical studies and health survey was by referrals from local health departments and resettlement agencies or assignment by voluntary sponsoring agencies. The diagnostic data were collected during the medical examinations; the screenings included 5-TU PPD tuberculin skin test (Mantoux, or TST),

complete blood counts, stool examinations and HBsAg test. Menzies (1999) describes the TST as the first step in identification of latent TB. The TST used in these studies was seen as the main tool, a highly sensitive test for detecting latent or dormant infections (Menzies, Tannenbaum, & Fitzgerald, 1999). However, the Mantoux or TST is imperfect in terms of its sensitivity and specificity and can result in false-positive results in immuno-suppressed and elderly persons. Additionally, false-positives appear when the test reacts to indigenous nontuberculous bacteria that are endemic in countries where TB is common (Menzies, 2003). In fact, Parrish, Dick and Bishai (1998) cited Whipple, Bolin and Miller's (1996) study that cautions that no single technique has 100% sensitivity and the TST's lack of sensitivity may actually underestimate the proportion of LTBI. Despite the discovered inaccuracy of the TST, the test was the accepted screening tool the investigators had available to them at the time and none of the studies used the less reliable tine test technique for tuberculin testing.

Diagnostic chest radiographs.

Chest x-rays are recommended as part of the medical evaluation to rule out pulmonary TB (CDC, 2000), particularly in persons with positive TST reactions or latent TB infections (LTBI), as a diagnostic standard. In 1975, The CDC reported that the medical screening results of 59,309 Vietnamese over the age of 15 years indicated that 2,031 (3.4%) had suspicious chest x-rays. Of those with suspicious x-rays, 264 had positive sputums and 1,270 had both suspicious chest x-rays, positive TST reactions and negative sputums (CDC, 1975). In the early descriptive studies, there were four studies (#3), (#6), (#8), and (#17) that reported limited findings on LTBI subjects: in study (#3) 24% had cardiopulmonary abnormalities detected; study (#6) reported that less than 5%

of the LTBI had chest x-ray abnormalities. Study (#8) stratified the LTBI by age: 8% patients <35 years old and 28 % of the patients ≥35 years old had abnormal chest x-rays. Study (#17) reported that only three LTBI on two-drug chemotherapy had abnormal chest x-ray findings. Analytic studies that followed supported the importance of chest x-ray abnormality indicating fibronodular changes or a worsening status among LTBI as a predictive risk factor for disease reactivation.

Statistical analyses.

In three of the descriptive clinical studies (#4), (#9), and (#6) and the Keane et al. (#19) overseas screening study, the statistical analyses were limited to descriptive statistics. The other descriptive studies in this first group used chi-square test statistics or Fisher's Exact test in studies (#3), (#8), and (#17) and the Student's paired t test, one-way ANOVA test in study (#11), which provided a better analysis of the risk variables, as well as comparisons between the ethnic groups. As an example, Catanzaro and Moser's (1982) (#3) prospective observational chi-square analysis examined the dissimilarities between the separate SEA ethnic groups (Vietnamese, Laotian, Cambodian, Hmong, and Chinese/Vietnamese). Variability in the SEA population and each group's particular TB exposure and case history made identifying significance among confounding variables difficult. The categorical variables tested were: sex, age, ethnicity, and the pre-migration factors such as, specific refugee camp and length of stay in camp. Predictively, refugees who reported being in refugee camp six months to two years had a higher proportion of positive TST results than those whose stay in the camp was less than six months or longer than two years. The influence of these pre-migration variables was reduced when the effect of ethnicity was controlled for in the analysis. Among the tested categorical pre-

migration variables, the only variable that was statistically significant was the variance in the positive TST rates between the ethnic groups: Vietnamese (69%), Laotian (47%), Cambodians (57%), and Hmong (15%) ($p < .001$). Fitzpatrick, Johnson, Shragg and Felice's (1987) (#11) study on SEA teenagers did not include pre-migration variables. However, the authors did suggest that cultural differences among the SEAS were a potential source of variability. There were significant but unexplained time delays between the Cambodian and Vietnamese teenagers when they first arrived in the U.S. and their first clinic visit 10.7 ± 18 months and 4.6 months $\pm$ 7.5 months, respectively ($p < .05$). The delays in seeking treatment did not seem to be associated with the two ethnic groups' proportion of positive TST nor their treatment adherence. The authors of both studies suggested that inter-ethnic cultural differences such as their language, customs, lifestyle, education and social class differences could significantly influence their TB exposure and treatment adherence. They suggested that the exposure to crowded city conditions where TB is more common may explain the higher proportion of positive TSTs detected among the Vietnamese. Likewise, the increased proportion of parasitic infestations found among the Laotians and Hmong could be a result of their customary practice of walking barefoot in rural areas. The effect of these possible environmental exposures and social customs was not investigated in any of the descriptive studies.

Critique of Descriptive Prevalence Studies

The descriptive studies established clearly the high proportion of immigrants with LTBI and attempted to address some of the pre- and post-migration factors that may have influenced the prevalence rates. The question of reactivation of disease among those with previously acquired disease and those with LTBI cannot be answered without further

follow-ups on those with positive TSTs who were untreated, the individuals who were treated prophylactically and especially on those who developed active TB. The authors in these early descriptive studies supported Barrett-Connor's (1978) (#1) prescient observation that TB among the SEA refugees was not primarily imported active disease, but the subsequent breakdown of latent infections. This definitive and commonly accepted observation about the epidemiology of TB among the foreign-born immigrant population did not receive biological confirmation until almost two decades later when microbiological DNA fingerprinting studies could be conducted.

Observational Analytic Designs: Tuberculin Booster Reaction Studies

The early descriptive studies laid the groundwork for the small cluster of conversion studies in the 1980s. The alarming high proportion of positive TST reactions among the SEAs initiated the following five studies that explored what has been described as the "booster phenomenon" among these refugees: Morse, Hansen, Swalbach, Redmond and Grabau, (1982) (#5); Morse, Hansen, Grabau, Cauthen, Redmond and Hyde, (1985) (#10); Wenzel, (1991) (#14); Cauthen, Snider and Onorato, (1994) (#15); and Robertson, Burtt, Edmonds, Molina, Kiefe, and Ellner, (1996) (#16). The booster phenomenon was the result of the efforts to increase the sensitivity of TST by use of a two-step testing method. Using the two-step method, there was a large increase in the number of positive TST results, which, given the already high proportion of positive TST, was justifiably a source of great concern.

The booster effect occurred when the TST reaction of an individual, who initially tested negative, converts to positive upon a repeat TST one week to one month later. The presence of a "boosted" positive reaction does not indicate recent conversion, rather it

represents LTBI in an individual whose immune response to *M. tuberculosis* has waned, with the first TST being a reminder of the antigen and the second TST representing the true response. Using the American Thoracic Society criteria as the baseline: positive reactions were those > 10 mm or more; negative reactions as less than < 10 mm; conversion reaction was defined as an increase of 6 mm or more in the total induration.

Morse et al.'s study (1982) (#5) on the tuberculin booster rate among 664 SEA refugees reported that 307 (46%) had positive TSTs. However, of the 217 refugees with *negative* [italics added] TSTs, 94 (43%) of them converted to positive when retested after 60 days, which almost doubled the number of positive TST results. Although none of the converters had evidence of active TB disease, 90 (94%) of them were treated with isoniazid prophylactic therapy. The 1985 (#10) study reported a higher rate of conversion among 218 SEA refugees: 93 (43%) had positive TSTs, 118 (54%) had negative initial TST. Among the refugees with the negative TSTs, 61 (51.7%) had boosted positive responses on either the second or third TST. Wenzel's (1991) (#14) and Robertson et al.'s (1996) (#16) studies reported lower booster rates of 44% and 26% on the fifth or sixth day readings, respectively, among the initially negative TST participants.

Finding a causative explanation for this phenomenon became the focus of the initial and subsequent conversion studies. The investigations included the clinical testing procedures for the antigen, tester, reading criteria (#5); delayed reading intervals and/or two or three step testing (#10), (#14), (#16); possible social and environmental exposure factors, i.e., demographics, home country and length of time in camp (#5), (#10), (#14), (#15); and/or the biomedical factors such as prior history of Calmette-Guérin (BCG)

vaccination, previous TST status, immunologic recall factors and current health status (#5), (#15), (#16). It ruled out anergy with mumps and Candida skin testing (#10), (#14) and lymphocyte blastogenesis testing (#16). However, despite the wide range of methodical testing, none of these investigated factors in four of the five studies explained the high proportion of delayed boosted tuberculin reactions among SEAs.

An exception in this group of boosted reaction studies was Cauthen, Snider and Onorato's study (1994) (#15) in the Philippines. In their study, nontuberculous mycobacterial antigens in addition to delayed sequential TST tests were administered to 2,469 SEA refugees at the Bataan Refugee Processing Center. Among the refugees, 35.5% had $\geq$ 10 mm positive TST reactions and 30.9% of those with negative TSTs converted to positive reactions on subsequent testing. Using logistic regression analysis it was possible to differentiate the associated factors for persons with positive TSTs compared to with those with boosted reactions. Among persons with initial positive TSTs, 74% had a larger reaction to tuberculin than to the accompanying nontuberculous mycobacterium (NTM) test. The opposite was true for the boosters: 19% had a larger reaction to tuberculin, 27% had equal reactions to both the tuberculin and NTM skin tests, and 55% had larger reactions to the NTM skin test compared to the initial tuberculin test. The degree of boosting measured by increases in the mm induration was significantly associated with reactivity to the NTM antigens ($p < 0.0001$).

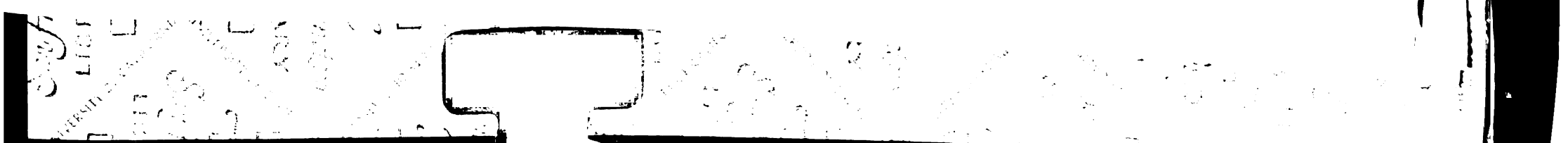
Multiple linear regression analysis showed an increase in boosting of 0.27 mm (95% CI, 0.14 to 0.39 mm) for each millimeter increase in NTM reactivity. The association between boosting and the greater reactivity to NTM indicated that among the study participants with boosted reactions, the response was attributed to their previous

environmental exposure to NTM in Southeast Asia, or to prior BCG vaccination. Cauthen, Snider and Onorato's study tested Morse et al.'s (1985) hypothesis that the boosting phenomenon among the refugees was cross-reactivity response to NTM since there were no accompanying new cases of active TB or transmission reports to close contacts among the test converters. Their analysis suggested that the proportion of boosting among the SEAs was not associated with the future risk of disease reactivation and the practice of sequential TST testing compared to the one-step method was not useful in detecting persons at high risk for developing tuberculosis. This observation has influenced the current CDC guidelines that required prophylactic isoniazid treatment for those under 35 years, which has prevented the diversion of resources in an overburdened public health system, especially since a substantial proportion of the converters would fall otherwise within the treatment guidelines.

Critique of the Two-Step Booster Studies

The findings of the two-step booster studies did not identify those at risk for reactivation, however the studies did identify those who would be *less likely* [italics added] to be at risk. The TST negative SEAs, despite their false-positive reactions, were less likely to be candidates for reactivation compared to the SEAs who tested positive on their first initial TST. This clarified the understanding that preventive treatment efforts should continue to be concentrated on those who have initial positive TST reactions, not the substantial percentage of the SEAs who have and will present with boosted positive reactions. [11]

[11] Two-step testing has been used as a diagnostic tool to differentiate between a hypersensitivity to the TST and a newly acquired infection. Two-step testing has been suggested for newly employed health care workers (HCW) who have an initial negative TST reaction. If the second TST performed one to two weeks later results in a positive test, the result is considered to be a booster reaction in which the subject's



Analytic Longitudinal, Case-Control, and Retrospective Studies

The question of who is most likely to reactivate still remains. To address this, the third group of domestic studies shared the common objective of defining the epidemiology of reactivation in this refugee cohort. This objective linked Powell, Brown and Farer's (1984) (#7) two-year pivotal study that established the singular disease presence of TB among the SEAs with Nolan and Elarth's (1988) (#12) five-year longitudinal study. Using the same sample population, Nolan, Teklu, and Wu (1989) (#13) tested Powell et al.'s hypothesis that TB had been over diagnosed in this SEA cohort with the use of sputum cultures in a case-control and prospective study.

Powell, Brown and Farer's (1983) (#7) longitudinal study was the first attempt to evaluate the refugees' impact on the national TB case rate, the caseload burden placed on the public health infrastructure, and the numbers of refugees enrolled in the recommended prophylactic treatment programs. The authors collected state surveillance data on 96% of the 262,602 refugees who entered the U.S. during the two-year period from 1979 to the end of 1980. During this two-year period, although 3,895 SEAs were added to the TB case registries during the two-year time period, only 2,850 (73.2%) were included by the states in the official U.S. TB morbidity count. This 5.3% increase in cases was sufficient to offset the national TB morbidity trend that had been steadily declining by 5% per year. The study reported an estimated proportion of active TB among the refugees at the time of arrival of 1,238 per 100,000 with the annual number of

---

immune system memory recalls a prior TB infection after being boosted by a second TST. The HCW would be classified as previously infected either in his/her childhood with TB, or exposed to NTM. If the second TST is negative, the HCW is classified as uninfected. Later, in subsequent TSTs a positive reaction would indicate a new *M. tuberculosis* infection (*Booster Phenomenon*, 2003). Cauthen, Snider and Onorato cited the Thompson, Glassroth, Snider, and Farer (1979) study on sequential testing of hospital workers that attributed their boosted TST reactions to prior sensitivity to NTM. Garber, San Gabriel, Lambert and Saiman (2003) reported a positive TST proportion of 57% (n = 196) among laboratory health care workers, but the TST conversion rate was only 1%. (Garber, San Gabriel, Lambert, & Saiman, 2003)

new cases of TB among the SEAs estimated at 407 per 100,000 after their arrival. The proportion of TB was age-related, with a higher proportion among refugees from 0-14 years old, than among the refugees 15 years and older. The Vietnamese had the highest rates (1,410 per 100,000 for refugees for 0-14 years, and 503 per 100,000 for those 15 years and older) followed by the Cambodians (1,309 per 100,000 and 499 per 100,000). The lowest rates were reported among the Laotians (607 per 100,000 and 250 per 100,000). The annual proportion of TB cases for the refugees who entered in 1979 was 719 per 100,000; this later dropped to 231 per 100,000 in 1980. The detection of active TB correlated with the overseas certification status, with 37.4% of those certified as Class A. These constituted only 2.3% of the refugees but 57.2% of the registered TB cases among the SEAs during 1979 to 1980. Twelve point seven percent were certified as Class B, which was also 2.3% of the refugees but 19.6% of the cases. For the first time, there was bacteriological confirmation of TB that was reported for 26% of the refugees, excluding the refugees certified as Class A, who would be expected to have negative cultures: 31% had positive sputum tests, 53% had negative results, and 20% either had no bacteriological test or the results were unknown to the health department. The disproportionate state TB caseloads reflected the uneven resettlement pattern of the refugees, with California accounting for more than 30% of the registered cases.

Although 3,895 cases were registered, 26.8% of SEA cases were not included in the TB registries. The authors suggested that the undercount occurred as a result of local differences in case criteria and the presumption that the excluded cases were already included in the overseas count. This discrepancy and other inadequacies in the national TB screening and control strategies were highlighted in the study. Refugees prior to

1980 under the age of 15 years were not routinely required to have an overseas chest x-ray examination. Because the number of new cases of TB among these unscreened and uncertified young refugees actually exceeded the estimated case rates, the overseas screening procedures were changed to include chest x-rays on all refugees two years of age and older (CDC, 1990). The sharp decrease (68%) in cases from 1979 to 1981 was credited to both the improvements in the overseas screening procedures that resulted in fewer refugees arriving with active disease and secondly, the implementation of the prophylaxis treatment to more than 46,000 refugees (approximately 18% of the total) upon arrival. There is no published follow-up study on the outcomes of the 46,000 refugees who received this chemoprophylaxis therapy.

The unexpected low rate of positive bacteriological confirmation in the TB cases caused the authors to hypothesize that the heightened suspicion triggered by the sharp rise in case reports may have resulted in an over-diagnosis of TB by physicians in the U.S. The overdiagnosis of TB also implies that some of the refugees were overtreated, given full multi-drug TB therapy when only prophylactic treatment was required, some may not have needed treatment, and some may have been misdiagnosed (i.e., lung cancer, paragonimiasis), resulting in local health resources potentially being unnecessarily drained. The authors concluded that, despite, the probability that the reported high rate of active TB may have been inflated due to overdiagnosis, the number of TB cases among the SEAs had been the highest recorded for an immigrant group since the turn of the century in the United States.

United States five-year surveillance study.

Powell et al.'s (1983) concern with overdiagnosis influenced Nolan and Elarth's (1988) (#12) subsequent morbidity estimates in their five-year surveillance study on SEAs. To estimate the annual proportion and the 5-year cumulative rates of TB in this cohort, the authors used an average rather than the total number of the proportion of culture-positive cases and all reported cases that were detected during the arrival screening process at specified cut-off dates in 1985 and 1986. This resulted in a downward adjustment in the study's TB rates.

The study utilized the public health data collected on 9,328 SEA refugees who entered King County, Washington, in 1980 and 1981 through December 1986. Upon arrival, TB was diagnosed in 78 (0.8%) of the 9,328 refugees with 46.1% of the cases being culture-positive for *M. tuberculosis*. Among the 9,328 refugees screened, 3,300 (35.7%) had significant positive TST reactions with 185 having abnormal, stable chest x-rays consistent with inactive TB. In the five years of surveillance, 25 cases of TB were diagnosed in this latter group of refugees who were classified as being free of current disease. The five-year adjusted cumulative proportion of TB among the refugees was 268 cases per 100,000 while the comparative cumulative proportion of TB in the general population in King County was 39 per 100,000. Similar to Powell et al.'s (1983) findings, the highest proportion was among the Vietnamese (317 per 100,000) and Kampucheans (Cambodians) (306 per 100,000) and the lowest proportion was among the Laotians (184 per 100,000). Notably, the refugees with positive TSTs and abnormal chest x-rays were six times more likely to develop TB than were the refugees with positive TSTs and normal chest x-rays. In contrast, the proportion of active TB among

the TST negative refugees was 50 per 100,000, which was only slightly higher than the 39 per 100,000 in the general population in King County (the authors did not indicate if this difference was statistically significant).

The findings described a pattern of an initially high rate of active TB that rapidly declined from the estimated 30.6 cases per 10,000 at the time immigration to five cases per 10,000 by the fourth and fifth year of resettlement.. The high proportion of TB detected among the refugees, which was predicted to be a major health problem, did not occur in children in the sample, nor were there any deaths and no evidence of close-contact transmission during the study's five-year timeframe.

Nolan and Elarth's (1988) study did reveal that a significant predictive risk factor for reactivation among the refugees was the presence of positive TSTs and fibrotic lesions on their chest x-rays. The five-year cumulative risk for these refugees was over ten times that of the general refugee population and six times that of other TST positive refugees. The authors reported that this extensive morbidity occurred despite the administration of isoniazid preventive therapy. This led the authors to question the efficacy of prophylactic therapy, especially, since they had observed that refugees' compliance with the isoniazid treatment was not optimal. The authors concluded that, given the risk factors in this cohort, it would be useful to know if this recommended intervention contributed to the decline of TB in these refugees. [12]

[12] The efficacy of the prophylactic therapy in preventing the reactivation of TB was addressed in a Canadian trial (Grzybowski, Ashley, & Pinkus, 1976) that evaluated the outcomes of 1,571 treated patients and 834 control patients. The observation period in the trial varied: 83% were observed for five years, 61% for eight years and 32% for ten years. The participants who took INH alone for six months or more had a reactivation rate of 1.2 per 1,000 persons per year; participants who took INH plus PAS for more than six months had a reactivation rate of 0.38 per 1,000 persons per year, a reactivation rate that was 90% less than the controls (the reactivation rate of the controls was 3.9 per 1,000 persons per year). Hann (1994) and Schwartzman (2002) cite a 1982 randomized controlled trail with Eastern European patients with fibrotic

Case-control study

Using the same study sample, Nolan, Teklu and Wu (1989) (#13) conducted a prospective cohort study and a case-control study to evaluate the usefulness of sputum smears and cultures as a diagnostic tool on the refugees who were classified as TB suspects at the time of visa application process. The TB treatment policy at that time was to treat immigrants diagnosed with TB based on compatible symptoms (changes on serial chest x-rays, and with or without positive sputum cultures) with multiple chemotherapeutic agents. The participants in both studies were selected from the Seattle-King County Department of Public Health clinic and case registries. The aim of the study (#13) was to address the difficulties of using symptom assessments and chest x-ray comparisons to determine treatment strategies on this second group of relatively asymptomatic immigrants. For the cohort study, 249 participants met the inclusion criteria: no symptoms of current TB disease and had at least one overseas and one current chest x-ray available for comparison indicating abnormal but stable pulmonary status. Any patients who were classified as tuberculosis suspects were excluded from the cohort study. The results of the short two-year prospective portion of the study were: among the 249 participants, 13 (5.2%) had one or more positive cultures for *M. tuberculosis*; none had a positive smear (53.8% or seven of the 13 positive cultures were drug-resistant). Immigrants in the prospective cohort who were younger than 50 years old and whose countries of origin were Cambodia and Laos had a fivefold to tenfold increased risk of having positive cultures.

---

lesion that demonstrated that six months of daily isoniazid reduced the reactivation rate by 65% and one year of treatment by 75%, compared to the untreated controls (Hann, 1994; Schwartzman, 2002).

In the case-control section of the study, 37 patients were selected based on being asymptomatic with stable abnormal chest x-rays and at least one positive sputum culture, and 48 controls were randomly selected based on the same inclusion criteria, except they had at least two negative sputum cultures. Twenty-four of the 37 cases were SEAs with the remaining immigrant cases from the Philippines, China, Korea and one case from Ethiopia. Compared to the controls, the cases were found to be associated with the following three risk factors: the cases were more likely to have positive TSTs and report a cough, and less likely to report a prior history of antituberculosis treatment. Another critical factor was noted during retrospective blinded readings of the radiographic films, which showed that the case subjects had cavitary lung lesions more frequently than the controls did (RR 5.4, 95% CI 0.9-27.5). The detected radiographic differences suggested that the cases who were diagnosed as having stable nonprogressive TB may have had more advanced disease than originally assumed.

Since it was reported that nearly 50% of the TB cases in Asian immigrants occurred within the first two years of their arrival in the United States (CDC, 1987a), Nolan, Teklu, and Wu (1989) (#13) speculated that it was possible that the refugees described in this study who had positive sputum cultures, yet appeared to be asymptomatic, may not be clinically recognized. To detect the 13 patients in the prospective cohort study with positive cultures, 519 sputum specimens were processed; the total cost of processing specimens on the study patients was estimated to be between $25,950 and $38,925 and the cost per case would have ranged from $1,996 to $2,994. The practice of indiscriminate sputum culturing of all immigrants would have been prohibitively expensive. Therefore, the authors suggested using the profiles of the cases

(positive TST reactions, the presence of cavitary lesion on chest x-ray, and/or report of cough in the symptom review) as a means of identifying the immigrants who should submit sputum specimens.

After these three studies were published, perhaps because of the expense and the lengthy time commitment, there were no further longitudinal studies in the U.S. that focused on the TB outcomes on the SEA refugees. The epidemiological profile that characterized the SEAs' reactivation pattern was merged, despite the continuing high case rates among Asian immigrants, with the present studies on foreign-born populations in the United States. In Denmark, epidemiological investigations continued to use the less costly retrospective historic cohort research designs to track the SEAs who had arrived in 1979, as did the Australian studies on the SEA refugees who migrated in the 1980s.

International Longitudinal Studies

In contrast to the U.S. emphasis on active case finding, Denmark approached the high proportion of active TB among the SEAs using a strategy of passive diagnosis without preventive prophylactic therapy. Denmark and Poland are the only European countries that rely on a passive diagnostic TB control strategy. Wilcke, Poulsen, Askgaard, Enevoldsen, Rønne, and Kok-Jensen's (1998) (#25) sixteen-year study evaluated the screening of the 1,936 SEA refugees who entered Denmark from 1979 to 1982. The general Danish TB surveillance screening at the time of entry consisted of chest x-ray examination, if pulmonary symptoms had persisted for more than six weeks, and sputum or gastric lavage specimens if the chest x-rays were compatible with TB. Refugees with positive TSTs who had recent exposure to smear positive TB subjects

were followed by chest x-rays every six months for three years. A four-drug antituberculosis regimen was prescribed for those detected with active TB and preventive prophylactic chemotherapy was only prescribed for tuberculin converters below the age of seven years. All TB patients in Denmark were identified under the Danish notification system under their civil registration number. The proportion of TB in this cohort was calculated in 1996 by tracing their national civil registration numbers in the national TB register data. During the first year of arrival, a total of 36 of the 1,936 (1.86%) refugees with TB were identified; the diagnosis was based on positive cultures in 76% of the cases. In the subsequent ten years, the annual proportion of TB averaged 0.07% (the comparative proportion of TB in the Danish population from 1978-1995 was approximately 0.007 %-0.004 %, respectively). There were no TB cases reported on the cohort in the following 11 to 16 years after their arrival. The pattern of high case rate of TB during the first years of arrival that declines in the subsequent years reported in Denmark was similar to the reports on the SEAs in U.S. and Canada in the 1970s.

The low specificity of chest x-rays as a diagnostic tool that was reported in the Nolan et al. (#12) (#13) studies was also noted in the Danish study, with the chest x-rays detecting only 40-50% of the TB cases among the immigrants during their first year of arrival. [13] In the study, the x-ray screening of immigrants with a TB case rate of more than 0.05% at entry was considered acceptable, but the authors suggested that routine follow-up is unnecessary if there is reliable access to the refugees with symptoms. The Danish passive control policy that did not require preventive chemotherapy was

[13] McAdams (1995) and Heldal (2000) differ with these findings and consider the chest x-ray as the mainstay in the radiologic evaluation of suspected or proven pulmonary TB, especially among those who appear to be clinically asymptomatic (Heldal et al., 2000; McAdams, Erasmus, & Winter, 1995).

supported by the low proportion of reactivation among the SEA immigrants during the sixteen years of surveillance. Several factors possibly contributed to the Danish passive TB policy's positive outcomes, namely, the relatively small size of the SEA Danish cohort, 1,936 refugees as compared to 262,602 refugees surveyed in the Powell et al. U.S. study, the centralized Danish TB registration system that combined active case treatment with contact-investigations, and the availability of easy and free access to diagnosis that may not be replicable in other public health surveillance systems.

Australian studies.

Shorter retrospective TB studies on SEA refugees took place in Australia. MacIntyre, and Epi, and Plant (1998) (#20) and MacIntyre and Plant (1999) (#21) conducted two closely related retrospective studies on the SEA refugee population in Victoria, Australia. These were followed by a series of three studies (2000) (#22), (2001) (#23) and (2001) (#24) by Mark, Bai, Simpson, Sullivan and Stewart on the SEAs in Sidney, Australia.

The first MacIntyre et al. (1998) study on 1,101 SEA refugees reported the initial proportion of TB cases among the SEAs as 363 per 100,000 and the annual five-year rate as 109 per 100,000 among the refugees who entered the State of Victoria from July 1989 to January 1990. The intent of the study was to identify refugees with positive TST reactions and institute isoniazid prophylactic therapy to reduce future cases of reactivation. The criterion for case definition was a TST reaction of 15 mm post-BCG or 10 mm with past BCG, or chest x-ray evidence of inactive TB. At the time of the 1989 study, isoniazid treatment was recommended for refugees with TST 20 mm or more, or 15 mm or more in the presence of BCG. Over the duration of the five-year study, six

supported by the low proportion of reactivation among the SEA immigrants during the sixteen years of surveillance. Several factors possibly contributed to the Danish passive TB policy's positive outcomes, namely, the relatively small size of the SEA Danish cohort, 1,936 refugees as compared to 262,602 refugees surveyed in the Powell et al. U.S. study, the centralized Danish TB registration system that combined active case treatment with contact-investigations, and the availability of easy and free access to diagnosis that may not be replicable in other public health surveillance systems.

Australian studies.

Shorter retrospective TB studies on SEA refugees took place in Australia. MacIntyre, and Epi, and Plant (1998) (#20) and MacIntyre and Plant (1999) (#21) conducted two closely related retrospective studies on the SEA refugee population in Victoria, Australia. These were followed by a series of three studies (2000) (#22), (2001) (#23) and (2001) (#24) by Mark, Bai, Simpson, Sullivan and Stewart on the SEAs in Sidney, Australia.

The first MacIntyre et al. (1998) study on 1,101 SEA refugees reported the initial proportion of TB cases among the SEAs as 363 per 100,000 and the annual five-year rate as 109 per 100,000 among the refugees who entered the State of Victoria from July 1989 to January 1990. The intent of the study was to identify refugees with positive TST reactions and institute isoniazid prophylactic therapy to reduce future cases of reactivation. The criterion for case definition was a TST reaction of 15 mm post-BCG or 10 mm with past BCG, or chest x-ray evidence of inactive TB. At the time of the 1989 study, isoniazid treatment was recommended for refugees with TST 20 mm or more, or 15 mm or more in the presence of BCG. Over the duration of the five-year study, six

cases occurred (109 per 100,000 per year) among the 1,101 refugees screened in 1989; four of the six cases were culture positive, one was culture negative but positive on pleural histology and the sixth case was culture negative but had radiographic changes that resolved with treatment. The authors estimated that five of the six cases were potentially preventable, which would have reduced the proportion of cases to 18 per 100,000 per year over the five-year period. The authors argued that increasing the sensitivity of the definition for infection would have increased the number of refugees eligible for prophylactic therapy. In the study, 162 of the 1,101 refugees were eligible for prophylactic therapy; 75 of the 162 eligible refugees were started on INH. If more sensitive guidelines (positive TST reactions of 10 mm or more as a cutoff point) were used an additional 295 refugees would have been eligible for preventive treatment, potentially preventing 24 new cases of TB.

MacIntyre and Plant's (1999) second study followed the same 1,101 SEA cohort and reiterated the same TB case findings. In the second study (#21), additional data were presented on the pre- and post-migration screening on this cohort. There were 27 culture-positive TB cases diagnosed in the refugee camps indicating a proportion of 2,452 per 100,000 prior to their migration to Australia. The post-migration TST results reported on 85% (928/1,101 refugees) revealed that 60% (561/938) had TST reactions of 10mm or more and 22% (124/561) of the refugees with positive TSTs received preventive chemotherapy. Although in both studies follow-up screening was strongly recommended to prevent the reactivation of TB among the refugees, screening all refugees was considered unnecessary and funding for the program ceased in Australia by 1992.

The last three longitudinal Australian studies by Marks et al. (#22), (#23) and (#24) followed the high proportion of reactivated LTBI found in a larger cohort of 24,653 refugees aged 12 years and over who migrated to Sydney from 1984 to 1994. The majority of the refugees (83.9%) were from Vietnam, Cambodia, and Laos with 11.7% from El Salvador and Chile and the remaining 4.4% from other countries. The 2000 and 2001 studies (#22) and (#23) reported the proportion of reactivation among the 15,489 refugees who had clear chest x-rays with positive TST results > 10 mm and had not received antituberculosis chemotherapy or isoniazid preventive therapy at the time of their arrival screening from 1984 to 1994. Cases of TB were identified by record linkage analysis of the immigration database of screened refugees using their birthdates, a manual check by surname, sex, country of origin and arrival date with the database of notified cases of TB. In the second study (2001) (#23), by June 1998, there were 290 notified cases of TB [14] and of these, 189 (65%) were confirmed by case review. [15] Although the highest proportion was in the 40-49 year olds, the median age of the study cohort was 22.1 years old. The follow-up interval to diagnosis averaged 10.3 years and resulted in the overall case rate of 74.9 per 100,000 person years. In contrast, the Australian general population case rate of TB was 5.4 per 100,000 and predominately reported among older-aged males.

---

[14] The first study (#22) reported 151 notified cases of TB; 122 (81%) were bacteriologically confirmed cases. As the study continued, the number of cases increased to 290.

[15] The accepted case criteria for active TB diagnosis included: positive *M. tuberculosis* culture, positive direct AFB smear, histopathological report of caseating granulomas, or radiological report of pulmonary infiltrate regression after antituberculosis chemotherapy and positive TST, with the clinical features of extrapulmonary TB and treatment response.

In the first study (2000) (#22), those with TST reactions of >15 mm were associated with an annual proportion of 213 (95% CI, 150 to 300) per 100,000 person years in the first three years of arrival and 122 (95% CI, 90 to 165) per 100,000 person years in the subsequent ten years. Only the increasing size of the TST reaction had a significant linear effect (p. <0.0001) on the cohort's risk of TB. The presence of a BCG scar did not affect the relationship between the TST reaction size and the risk of reactivation.

The authors discounted the post-migration screening and active case finding that took place on arrival and at six and 18-month intervals as an effective public health strategy. This observation was the focus of Mark et al.'s third study (2001) (#24) in which 65 cases were detected during the 18-month post arrival period. Of the 189 confirmed cases of TB detected in the cohort, 55 cases (29.1%) occurred within one year of arrival and 124 cases (65.6%) within five years of arrival. In the first year, the proportion of cases was 223.8 per 100,000 person years; in the subsequent five years, the proportion dropped to 102.1 per 100,000 person years. The majority of cases (66.6%) were identified by their symptomatic presentation at primary clinics and occurred after the 18 months of screening. The routine post-migration screening identified 56 cases (29.6%) and contact investigations revealed the remaining seven cases (3.7%). During the 18-month post-migration screening only 43 cases were identified, which meant that 572 persons in the cohort were screened to detect one case. The authors estimated that even if the specificity of the screening protocols were improved by focusing on the refugees with positive TST results and abnormal chest x-rays, only 16% of reactivated cases would have been detected. Mark et al. concluded that even if the frequency and

duration of the post migration screenings were increased, the strategy of active case finding has not proven to be cost effective for the control of TB in refugee populations. Similar to the Danish study (#25), the authors suggested that a more effective strategy would be strengthening passive case finding by increasing the awareness of the high proportion of TB reactivation among primary care physicians serving the refugee and migrant communities and improving access to diagnostic services.

Summation of Studies

The research design of the case-control and longitudinal studies provided a better means to examine the question of the reactivation of TB within this specific population of refugees. Most noticeably, the studies' findings were supported by the larger sample size: 262,602 subjects (#7), 1,936 subjects (#25), 1,101 subjects (#20), (#21), and 24,610 subjects in (#22), (#23), (#24). The latter studies incorporated gradual improvements and better-defined measures of validity. They used more extensive statistical analyses of the data, multivariate (#13), (#22), (#23), (#24), univariate (#20), (#21), and survival analysis (#25). Most importantly, the design frameworks afforded the opportunity to study the proportion of reactivation over time in this population.

Powell et al. (1983) (#7) estimated that approximately 1.5% of 262, 602 SEA refugee who entered in 1979 had active TB, resulting in 3,895 new cases being added to the U.S. TB registries by the end of 1980. However, Powell et al. noted that only 31% of the 3,895 TB cases identified had supporting bacteriological confirmation. This discrepancy in case confirmation suggested that the estimated high proportion of TB cases could be a result of over-diagnosis of TB by U.S. physicians. In the subsequent studies, the identified TB cases were confirmed either by positive cultures, pleural

histology or chest x-ray changes that resolved with treatment, thus reducing the possibility of over-diagnosis and over-reporting the proportion of reactivation. Nolan and Elarth's (1988) five-year prospective study identified 25 (.268%) confirmed cases in the cohort of 9,328 refugees with a drop in the proportion to 0.05% at the end of five years.

The pattern of reactivation found in the U.S. with the majority of cases occurring within the first to third year of arrival then sharply declining in the following resettlement years was verified by the international longitudinal studies. The smaller Danish (1998) 16-year study detected 22/1936 cases (1.14%) in the first year with an overall annual average of reactivation of 0.07% in the following ten years and none thereafter. In the Australian studies, MacIntyre et al. 's (1998-1999) five-year study reported six cases (.544%) in 1,101 subjects; Mark et al.'s (2000-2001) ten-year studies identified 189 (.766%) confirmed cases of TB in 24,652 subjects. The sharp decline after the first five years led Mark et al. (2001) (#24) to question the effectiveness of Australia's current strategy of active case-finding, which detected only 29.6% of the cases in the ten-year follow-up study and required the costly follow-up screening of several hundred individuals for each case detected. The authors suggested a passive case-finding stratagem similar to the Danish policy as an alternative that would not only be less costly but, importantly, more likely to identify cases of reactivation in this refugee cohort.

Although the estimated proportion of reactivation in these studies was lower than was indicated by the high proportion of positive TST reactions among the refugees, the studies in the review and the CDC consistently report initial rates that were 14 to 70 times higher than the general population (Powell, Brown and Farer, 1983). The current TB rate among foreign-born Asian Pacific Islanders in the United States of 41.3 per 100,000 is

eight times higher than the U.S.-born population (CDC, 2003b). In Denmark and Australia, the proportion is 10 to 18 times higher among the SEA refugees than the native population. In the U.S., Talbot, Moore, McCray, and Binkin (2000) concluded that the current U.S. policy of interrupting the transmission of TB through treatment and contact investigations has been clearly ineffective in reducing the proportion of reactivation cases of TB among foreign-born persons.

The early descriptive and observational studies in the review contributed evidence that identified risk factors for this cohort. These included the overall young median age of SEA refugees (from 15 to 22 years old) on arrival in the 1980s, the high proportion of positive TST reactions and association with chest x-ray abnormalities among the refugees, and the ethnic differences in the TB rates between the Vietnamese, Cambodians and Laotians. Perhaps more significantly, the early studies provided the impetus for needed refinements in the nation's pre and post-migration screening protocols. Powell, Brown and Farer's (1981) early observation that migrants infected prior to migration are at greater risk at the time of entry than later was validated in their 1983 study that documented a 68% decrease in cases from 1979 to 1980 among the refugees. They attributed this decrease in the proportion of cases to changes in the immigration screening protocols. A TB screening protocol was specifically developed for SEA refugees over the age of nine that CDC circulated in 1990 (CDC, 1990).

The social benefit of a centralized public health system with ready access to diagnostic and chemoprophylaxis services was credited in the Australian and Danish longitudinal studies with reducing the proportion of reactivation among the refugees. However, in the U.S. the mixed use of private physicians and local public health

departments by the SEA refugees and the inter-state mobility of the refugee communities limit the feasibility of replicating similar longitudinal studies here.

Gushulak (1998) pointed out that although the descriptive studies on refugee populations in this literature review substantiate the incidence and prevalence of LTBI, controlled studies on their health outcomes have been limited. It is my hope to add to the body of literature that explores this latter aspect, the treatment outcomes, in the long migratory trajectories undertaken by so many Asian immigrants to reach San Francisco.

Theoretical Framework

In addition to clinical trials, epidemiologic methods have been used to determine the most effective treatment in a given situation, particularly to describe the impact that health interventions have on disease patterns and on the environment. In the case of infectious disease, the intrinsic characteristics of TB, its pathogenicity, infectivity, virulence, and immunogencity have been well-studied and documented throughout the world.

Within epidemiology, the prevention of disease is an essential component of designing health care for specific populations. Prevention activities can be categorized as primary, secondary, or tertiary based on the progression of the disease process from no disease to clinical disease, with its associated disability and possibility of death. Primary prevention is concerned with eliminating risk factors for a disease. Secondary prevention focuses on early detection and treatment of disease (subclinical and clinical). Tertiary prevention attempts to eliminate or moderate disability associated with advanced disease. This retrospective study examines the secondary prevention of LTBI and reactivated disease in the Asian immigrant population in San Francisco using the classic

epidemiological framework of the triad of environment, host and agent (Combs, O'Brien, & Geiter, 1990) to assess the treatment outcomes.

The primary objective of the outcomes assessment has been to evaluate retrospectively the quality and effectiveness of health care services in the routine, uncontrolled delivery of health care. The descriptive data is instructive based on the epidemiological premise that disease is not randomly distributed in populations. Disease occurs in specific individuals and groups of individuals in specific geographic areas, during specific periods of time. In the case of migration-related TB, factors such as, the prevalence rates in country of origin, the age at immigration, demographics, clinical status and the therapeutic services available influence the outcome assessment.

The efficacy of the multi-drug chemotherapy for primary or reactivated TB and the protective duration of prophylaxis therapy have been well established in numerous studies (Douglas & McLeod, 1999; R. F. Johnston & Wildrick, 1974; "Long-term follow-up of a clinical trial of six-month and four-month regimens of chemotherapy in the treatment of pulmonary tuberculosis," Singapore Tuberculosis Service/British Medical Research Council, 1986, 1991; Migliori, Ambrosetti, Besozzi, Casali, & Raviglione, 1999). As a result of controlled clinical trials, the antituberculosis drug regimens have been based on three fundamental principles: the regimens for treatment of TB must contain multiple drugs to which organisms are susceptible, (2) the drugs must be taken regularly, and (3) the drug therapy must continue for a sufficient period of time (Perez-Stable & Hopewell, 1989; Schluger, Harkin, & Rom, 1996). The American Thoracic Society and CDC (1994) reiterated Johnson's 1974 statement unequivocally, "The major

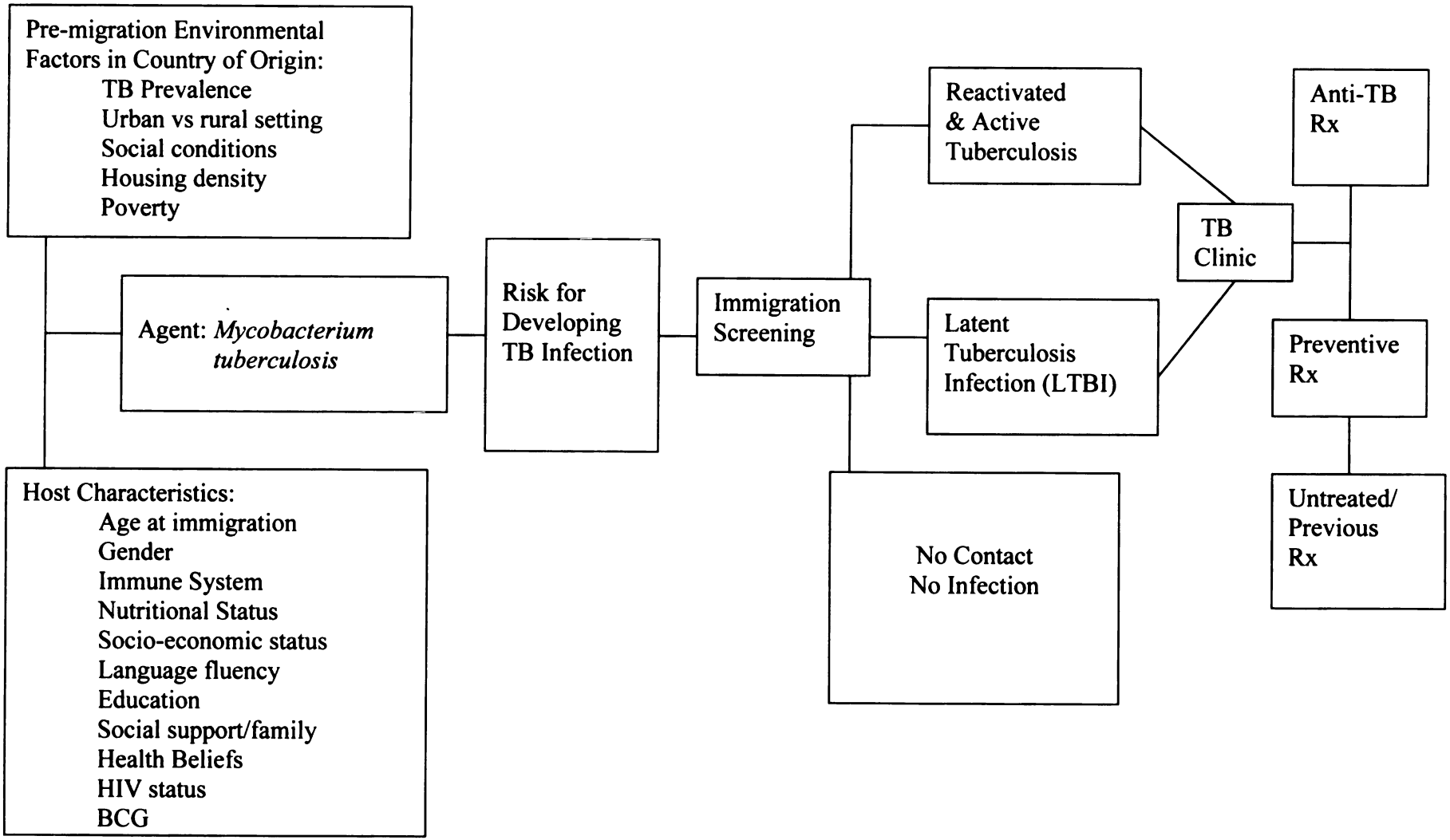
determinant of the outcome of treatment is patient adherence to the drug regimen." (1994, p.1359).

Ensuring that patients complete the full duration of the recommended chemotherapy raises a number of complex questions. Asymptomatic LTBI patients may see little reason for prophylaxis treatment. Symptomatic patients who experience early symptomatic improvement may require close monitoring to ensure treatment completion. The sheer length of treatment regimens that may extend over one to two years and the required close medical supervision of side effects that may range from pruritus to fatal hepatotoxicity have already taxed the resources and infrastructures of many overburdened local and state public health agencies.

Studies on adherence rates for antituberculosis treatment vary widely from a high of 91.1% (el-Sadr, Medard, Berthaud, & Barthaud, 1996) to the dismal adherence failure rate of 89% in Brudney's 1991 study. (Brudney & Dobkin, 1991). The epidemiological factors that influence the foreign-born immigrants' drug adherence are not as well known as the factors that compromise adherence in the high-risk, under-served, marginalized populations in the U.S.

The theoretical model on the treatment outcomes examines the data on the host characteristics of the immigrants, the reported environmental variables and the bacteriological status of the agent, *M. tuberculosis* (See Figure 2).

Figure 2. Epidemiological Model for Migration-related Tuberculosis



Research Questions

The research questions in this retrospective study focus on analyzing the differential impact of TB on the immigrants from China, the Philippines and Southeast Asia region, as well as identifying the demographic, clinical and social factors, such as English fluency, that are potential predicators of the immigrants' treatment adherence.

Questions for the Asian Immigrant Cohort with Active Tuberculosis

Research question 1: Are there significant differences in the treatment adherence of the Asian immigrants who received chemotherapy for active tuberculosis associated with their countries of origin?

Ho_1: There are no significant differences in the treatment adherence of the Asian immigrants who received chemotherapy for active tuberculosis at SFGH TB clinic who had clinic records opened from January 1, 1994, to December 31, 1998 associated with their countries of origin.

Research question 2: What are the differences that characterize the Asian immigrants who received curative chemotherapy for active tuberculosis at SFGH TB clinic who had clinic records opened from January 1, 1994, to December 31, 1998 associated with their countries of origin?

Ho_2: There are no differences in the host characteristics of the Asian immigrants who received curative chemotherapy for active tuberculosis associated with their countries of origin.

Research question 3: Has the length of stay in the United States influenced the treatment adherence in the immigrants who received chemotherapy for active tuberculosis?

Ho_3: The immigrants' length of stay in the United States has made no difference in the drug adherence of immigrants who received chemotherapy for active tuberculosis.

Questions for the Asian Immigrant Cohort with LTBI

Research question 1: Are there significant differences associated with the treatment adherence between the Asian immigrants with LTBI associated with their countries of origin?

Ho_1: The country of origin makes no difference in the treatment adherence of the Asian immigrants with LTBI who received preventive prophylaxis therapy at SFGH TB clinic who had clinic records opened from January 1, 1994, to December 31, 1998.

Research question 2: What were the host characteristics of the Asian immigrants with LTBI who received preventive prophylaxis therapy associated with their drug adherence?

Ho_2: There are no differences in the host characteristics of the Asian immigrants with LTBI who received preventive prophylaxis therapy associated with their drug adherence.

Research question 3: How has the length of stay in the United States influenced the treatment adherence rates among the immigrants with LTBI who received preventative prophylaxis therapy?

Ho_3: The length of stay in the United States of immigrants treated for LTBI has made no difference in their drug adherence.

Chapter 3: Methodology

This chapter introduces this dissertation's historical cohort study and the methodology used to evaluate the treatment outcomes of Asian immigrants who were screened for the presence of reactivated or active and latent TB infection (LTBI) at the San Francisco General Hospital TB Clinic from 1994-1998. Descriptions of the setting for the study, the sample selection criteria, data collection methods, the data analysis, and the potential biases are detailed. Definitions of terms associated with the cohort study can be found in Appendix C.

The previous cross-sectional studies of the characteristics of new immigrants have provided useful information on the burden of disease in this population. Longitudinal studies have provided further information on the success of treatment and the likelihood of activation of disease. But studies of SEAs and foreign-born immigrants have combined persons who come from distinctly different regions with different patterns of risk. This study uses a longitudinal or cohort design to evaluate in more detail subgroups of Asian immigrants who present with active or latent TB.

In a cohort or follow-up study, a clearly defined group of persons is studied over a specified period of time to determine the incidence of death, disease, or injury that occurs within the group (Jekel, Katz, & Elmore, 2001). Cohort studies may be classified as either prospective or retrospective, depending on the temporal relationship between the initiation of the study and the occurrence of disease. Ideally, a prospective cohort study that followed a high-risk immigrant group until death, with autopsy confirmation of TB disease, would yield the most substantial findings on TB reactivation. However, the advantages of a prospective study would be outweighed by the high cost and time

considerations in conducting lifetime studies. In the United States, with only Powell, Brown and Farer's (1983) (#7) two-year and Nolan and Elarth's (1988) (#12) five year studies available, the long-term treatment outcomes for the foreign-born Asian immigrants who arrived in the 1990s remain largely unknown. It would be of value to continue the long-term follow-up evaluation of this subgroup of high-risk immigrants now that more than a decade has passed since Nolan and Elarth's longitudinal study. This is especially important for these immigrant groups since the CDC (2000) acknowledged, that although more than half (55.5%) of the active TB cases among immigrants occur during their first five years in the United States,[16] the current screening procedure for immigrants does not and cannot detect or prevent many of these reported cases of TB that occur among immigrants (*Ending Neglect: The Elimination of Tuberculosis in the United States*, 2000).

Historical Cohort Design

A feasible alternative to prospective studies has been the use of a historic cohort design. In a historic cohort study, the investigator assembles a cohort as he or she would with a prospective cohort, and follows them forward in time, but the cohort is identified at a point or period in the past. The feature that distinguishes historic cohort design from a prospective cohort design is whether the outcome of interest has occurred at the time the study has been initiated. In a prospective cohort study, a group of individuals is identified and measured on a number of characteristics, and then followed forward in real time for the development of one or more outcomes. In contrast, a historic cohort study would investigate the occurrence of reactivated TB cases among exposed persons and

[16] In 1985, the CDC reported that active TB developed in 40.3% of all foreign-born Asian Pacific Islanders with known dates of arrival within the first year of residency (CDC, 1987a).

follow them forward for their treatment outcomes (Jekel et al., 2001; Mausner & Kramer, 1985). [17] In this dissertation study, the groups that will be studied using retrospective cohort methods, in two separate analyses, are those found with active TB at entry into care at the TB clinic, and those who are found with LTBI at entry into care at the TB clinic. The drug adherence or nonadherence to the chemotherapy regimens for each group is the outcome of interest. Comparisons by the immigrants' countries of origin within each group have been separately conducted to analyze the effect of environmental and host risk factors on treatment completion or default rates. The clinic data on the two immigrant cohorts were collected without prior knowledge of the treatment outcomes to avoid selection bias.

The retrospective cohort design is particularly advantageous in the understanding of the pathology of *M. tuberculosis* with its long latency period. The term latency or dormancy describes a state from which the bacilli reemerge or reactivate when the host's resident innate immunity and acquired immunity deteriorates (Orme, 2001). The existence of this latent or quiescent state of TB has been very difficult to study directly in human populations primarily because individuals with a latent TB infection (LTBI) appear asymptomatic, without any clinical signs or symptoms of manifest disease. In past studies, the reactivation of LTBI has been described simply as the development of a prior or endogenous infection that develops into active disease (Menzies, Tannenbaum, & FitzGerald, 1999).

In the past ten years, molecular subtyping studies that use the international standardized method of restriction fragment-length polymorphism (RFLP) DNA

---

[17] TB was the subject of one of the earliest retrospective cohort studies conducted by Frost in 1933 on the spread of TB in families (Doll, 2001).

fingerprinting have been used to differentiate between active cases of TB as a result of a recent infection versus reactivation of a remotely acquired LTBI. Recently, the time interval or the latency associated with persons with LTBI was estimated by Lillebaek's et al. (2003) study to be 36 years (95% C.I., 25-54 years) based on the half-life of IS6110 DNA patterns. The estimated rate of change in the DNA pattern in Lillebaek et al.'s 57 cases was 1.94% per year (95% CI, 1.29%-2.82%).

The lengthy intervals for LTBI differ from the half-life of TB strains involved in active disease that have been estimated to be as short as three years. The authors suggested that the rate of change was high during the early active disease phase of TB and low during its latency phase. This pattern of a high rate of disease change within the first five years of arrival followed by a low rate of change in the subsequent years was evident in the international longitudinal studies on the Southeast Asian (SEA) refugees. To capture this high rate of disease change in the dissertation study, the follow-up time for each treatment cohort was a minimum of five-years.

Migration-Related Tuberculosis among Asian Immigrants in San Francisco: Treatment Outcomes, 1994-1998

Study background.

California has 15 official ports of entry for immigrants; however, nearly 70% of all legal immigrants enter through just two ports, Los Angeles or San Francisco. California also receives nearly one-half the illegal immigrants entering the U.S. (Brown, 1997).[18] In 1994, 43,941 legal immigrant residents entered San Francisco with the

[18] An "illegal" or undocumented immigrant is an individual who enters or lives in the U.S. without official authorization. In 1993, the INS estimated that approximately 3.8 million undocumented immigrants live in the U.S. (*San Francisco Profile of Immigrants & Refugees*, 1997).

majority of the entrants from Asian countries. During the study time period from 1994 to 1998, Asian Pacific Islanders constituted 30% to 32% of the city's ethnic population and in 1993, the highest per capita rate of legal permanent residents (17.6 per 1,000 county residents) of all the Californian counties (*Race/Ethnic Population Estimates: Components of Change for California Counties, April 1990 to April 2000.*, 2033). One-third of the Chinese coming to California during 1987 to 1993 preferred to resettle in San Francisco, along with 27% of Hong Kong immigrants, 8% of the Filipinos and 6% of the Vietnamese. These influxes are illustrated in Figure 3.

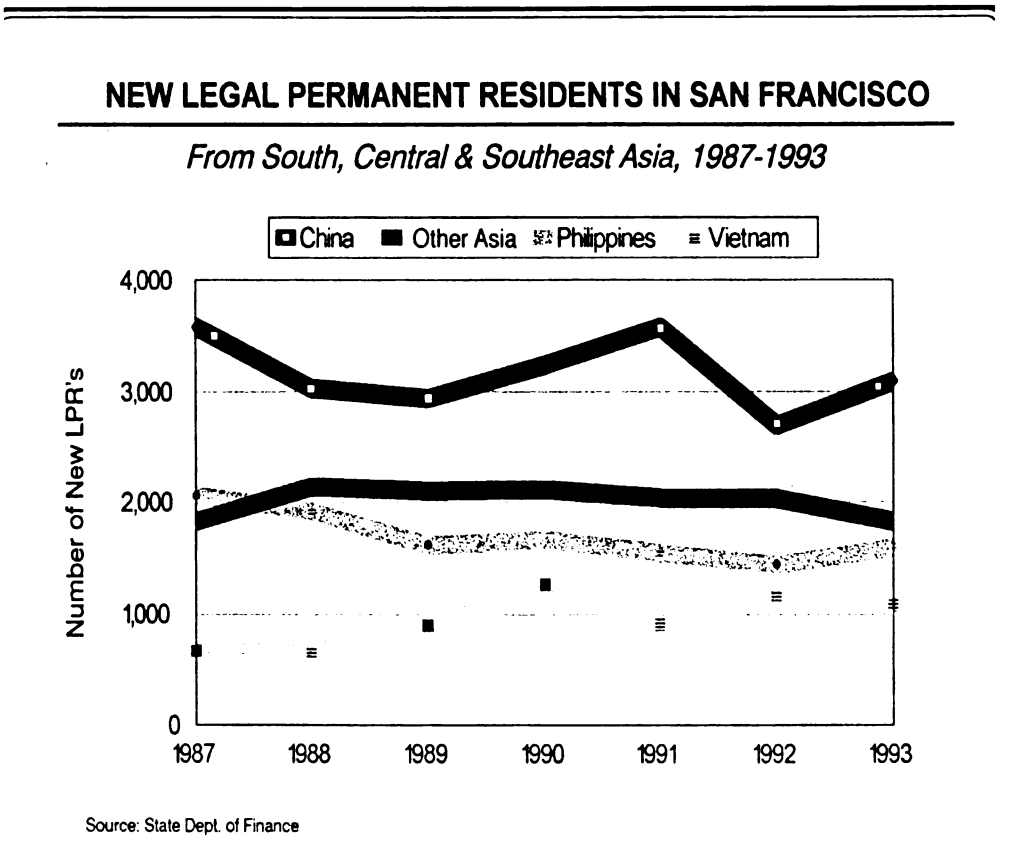


Figure 3. Source: San Francisco Profile of Immigrants & Refugees, Newcomer Information Clearhouse, International Institute of the East Bay for the San Francisco Foundation, March 1997, p. 50.

Historically, San Francisco ranked among the top ten cities with populations greater than 250,000 that reported disproportionately high TB from 1985 through 1990 (CDC, 1992). In 1995, San Francisco had the third highest TB case rate for a metropolitan area with a population over 500,000 at 23 per 100, 000 (McCray, Weinbaum, Braden, & Onorato, 1997). The latest annual city report, published in 2003, reported 162 cases for a decline in the case rate to 20.4 per 100,000. This lower case rate in 2003 was still four times the national rate and twice California's state case rate. During the time period of this study from January 1994 to December 1998, approximately 22,779 new clinical records were opened on patients at the TB clinic (an average of 4,556 records per year) (Ginsdale, 2004). The Asian immigrant clientele at the SF TB control clinic constituted approximately 34.4% of these newly opened medical records.

All of the subjects' selected Asian countries of origin in the study are considered to be high-risk TB endemic countries with an estimated prevalence of TB infection over 35% (*Ending Neglect: The Elimination of Tuberculosis in the United States*, 2000).[19] These countries also represent the primary countries of origin for Asian immigrants resettling in California.

[19] To define high-risk countries, the estimated global median proportion of LTBI was 36%. Therefore any country with a proportion over 35% would be classified at high risk for tuberculosis. There were 53 countries with a proportion over 35%; the top ten countries at high-risk are: Cambodia .64, Somalia .54, Haiti .54, Djibouti .52, Indonesia .49, Macao .48, Philippines .47, Bangladesh .46, Nepal .45, and Mongolia .45. Mexico had a proportion of .17 and was included due to the high volume of immigrants (*Ending Neglect: The Elimination of Tuberculosis in the United State.*, 2000). In San Francisco, the majority of TB cases have come from the high prevalence countries, but not limited to, China, Philippines, Southeast Asia, India, Mexico, Central and South America (*Latent Tuberculosis Infection: A Guide for San Francisco Providers*, 2003).

Study setting.

The setting for the study is the San Francisco City and County Tuberculosis Control Section's TB clinic, which is housed at San Francisco General Hospital. The TB clinic's educational, prevention, diagnosis, and treatment services for active and latent TB infection are available to all the residents of San Francisco. The clinic serves individuals who have been referred for further follow-up from the local district health centers, the U.S. Immigration Board, private physicians, schools and jails; it does not provide drop-in TB screening services. All suspected and confirmed cases of TB in San Francisco must be reported to the TB control section. In 1993, medical charts at the TB clinic were converted into computerized electronic records. The conversion of the clinic records to an electronic dataset made it feasible to select and downloaded the files for analysis in this study.

Sample population.

The study sample population was drawn from foreign-born Asian immigrants and refugees who had presented at the City and County of San Francisco TB Clinic at San Francisco General Hospital during the period from January 1994 to December 1998 and were eligible for preventive and/or antituberculosis chemotherapy. Individuals were included in the study if they were of Asian ancestry, were born in the People's Republic of China, the Philippines, Vietnam, Cambodia, India or the Republic of Korea and had a clinic record opened from January 1, 1994, to December 31, 1998.

The electronic medical records for 7,824 clinic clients were initially downloaded using the following search criteria: date the clinic record opened/greater than 12/31/1993 and date clinic record opened/less than 1/1/1999; and by place of birth, China, Republic

of Philippines, Vietnam, Laos, India, Korea, or Cambodia. From this initial sample of 7,824, records of 22 subjects who were not of Asian descent did not meet the inclusion criteria and were removed from the study. This reduced the sample to 7,802 subjects.

The next step taken was to identify the cohort being treated for active or reactivated TB disease. To identify this cohort the search criteria were run using variable major site (site of TB disease), RVCT registration date, and RVCT casecode number. This search initially identified 426 subjects (5.46% of 7,802) for the active TB cohort. A total of thirty subjects were excluded from the active TB cohort. This included: 18 subjects whose charts were opened for follow-up visits with no further treatment prescribed; six subjects without RVCT registration dates, one subject classified as TB2 with normal chest x-ray finding, smear negative, and treated only with isoniazid; and five subjects (1.2%) from India due to the small number of subjects from this country of origin. The final sample for the active TB cohort had a total of 396 subjects from China, Republic of Philippines and Southeast Asia; 334 subjects had pulmonary TB and 62 subjects had extrapulmonary TB. All 396 active TB subjects had RVCT registration dates.

After the cohort of active TB subjects were separated from the initial sample, five drug variables (which would indicate that isoniazid, Rifamate, rifampin, pyrazinamide, ethambutol, streptomycin, Cycloserine, and/or Ofloxacin had been prescribed) were used as a search criteria to select the LTBI subjects who were initiated on drug treatment. This resulted in identifying 4,658 subjects with LTBI who had been initiated on preventive prophylaxis therapy. The 2,719 subjects who did not receive drug therapy were removed from the study. In the cohort of 4,658 subjects with LTBI, the following were excluded:

63 (1.4%) subjects from India; 39 (.8%) subjects from Korea; five subjects who were not prescribed drug prophylaxis; and ten subjects previously treated. Six smear and culture negative TB4 subjects were added. The final sample for the cohort with LTBI who were initiated on preventive prophylaxis treatment comprised 4,547 subjects.

Study data.

Data items extracted from the electronic record included demographic data on the immigrant's country of origin, subject's self-reported ethnicity, race, age, date of arrival, primary language, and English fluency. Data on the outcome variables were obtained from the final TB evaluation and closure status recorded on the electronic record. The clinical data downloaded included the subjects' drug treatment start dates, restart and end dates, PPD reactions, chest x-ray readings and drug susceptibility results. The dataset for the active TB cohort included the items obtained from the CDC's Report of Verified Case of Tuberculosis (RVCT).[20] Table 1 lists the outcome, the hypothesized predictor variables, covariates and demographic variables that were extracted from the electronic medical record.

[20] The Report of a Verified Case of TB (RVCT) surveillance form was approved in 1992 for reporting cases to the CDC. The RVCT form included the results of human immunodeficiency virus (HIV) testing, occupation, history of substance abuse, homelessness, and residence in a correctional and long-term facility (1994).

Table 1: Selected Variables

Variable	Indicators
Outcome variables	
Final LTBI treatment evaluation	1. TB2 reactor 2. TB4 Old TB 3. Completed 2 months Rifampin & PZA 4. Completed 4 months INH & Rifampin 5. Completed 4 months Rifampin 6. Completed 6 months Rifampin 7. Completed 6 months of INH 8. Completed 12 months or more INH 9. Completed 4 months multi-drug rx 10. Completed less than 6 months INH 12. Completed less than 4 months of multi-drug rx 13. Incomplete rx-patient self-stopped 14. Incomplete rx – lost to follow-up 15. Excluded Treatment discontinued by physician. 17. Expired 18. Moved/referred 19. Returned/Left U.S.
Final active TB multi-drug treatment evaluation	1. Less than 2 months 2. Completed 2-5 months rx 3. Completed 6-9 months rx 4. Completed 9 months rx 5. Completed over 9 months rx 6. Moved/referred 7. Returned/Left U.S. 8. Expired 9. Incomplete rx – lost to follow-up 10. Incomplete rx – patient self-stopped
Main predictor variables	
Country of Origin	1. China 2.Republic of Philippines 3. Vietnam 4. Laos 5. India* 6. Korea* 7. Cambodia
Age	Date of birth
Age at immigration	Age at immigration
Age at diagnosis	Age at diagnosis

Years in U.S.	Years of residency in U.S. 1. 0 to 5 years 2. 5 years and over
Treatment relapse	Time interval from drug start date to drug restart date
Covariate variables	
PPD reading	0. Negative 0-9mm 1. Positive ≥10mm 99. Unknown.
Xray readings (dated serial readings, with condition and cavitation reports)	Normal/Abnormal/Unknown
Past TB treatment	No/Yes/Unknown
Converter	No/Yes/Unknown
BCG history	No/Yes/Unknown
Drug susceptibility	Susceptible/Resistant/Not Done
Drugs, including start, restart and end dates Separate variables for dosages	1. Amikacan 2. Augmentin 3. Capreomycin 4. Ciprofloxacin 5. Clofazimine 6. Cycloserine 7. Ethambutol 8. Ethionamide 9. Imipenum 10. Isoniazid 11. Kanamycin 12.Levofloxacin 13. Ofloxacin 14. Pyrazinamide 15. Rifabutine 16. Rifamate 17. Rifampin 18.Streptomycin 19.Para-Amino Salicylic Acid 20. Vitamin B6
RCVT covariate variables	
Major site of disease	1. Bone and/or joint 2.Genitourinary 3. Intrathoracic 4.Lymphatic-cervical 5. Meningeal 6.Other Lymphatic 7. Peritoneal 8.Pleural 9. Pulmonary
RVCT sputum smear	Negative/Positive/Not Done/Unknown
RVCT sputum culture	Negative/Positive/Not Done/Unknown
Homelessness within past year?	No/Yes/Unknown
HIV status	1. Negative 2. Positive 3. Indeterminate 4. Refused test 5. Test done results unknown

	6. Test not done 7. Unknown
Correctional facility at time of diagnosis?	No/Yes/Unknown
Long-term facility at time of diagnosis?	No/Yes/Unknown
IV drug use in past year?	No/Yes/Unknown
Non IV drug use	No/Yes/Unknown
Excess alcohol use	No/Yes/Unknown
DOT therapy	1. Self-administered 2. Both DOT and self-administered 3. Totally DOT supervised
Descriptive variables	
Age	Date of birth
Gender	Male/Female
Ethnicity	1.Asian 2.Black* 3.White* 4.Indian* 5.Korean 6.Burmese 7.Chinese 8.Laotian 9. Tibetan 10.Filipino 11.Hispanic* 12.Cambodian 13.Malaysian 14.Vietnamese 15.Asian/Pacific Islander
Language	1.Thai 2.Hindi 3.French 4.Korean 5.Burmese 6.English 7.Laotian 8.Spanish 9.Tagalog 10.Tibetan 11.Mandarin 12.Cambodian 13.Cantonese 14.Vietnamese
Speak English	No/Yes/Unknown
B-waiver	Date
Alien status	Immigrant/Refugee/Citizen
Occupation	Work type: 1. Unemployed 2. Student 3. Service trades 4. Healthcare services 5. Social/Educational services 6. Managerial/Business 7. Self-employed 8. Homemaker/Caregiver 9. Retired 10. Other

* removed

Outcome variables.

In this study, the outcome variables adherence [21] or treatment completion of the prescribed chemotherapy and nonadherence (to some or all of the prescribed therapy) were defined by the clinical evaluation of his or her course of treatment. In the active TB cohort, evidence of treatment adherence, treatment default or nonadherence, or exclusion was assigned according to the final evaluation in the electronic clinical record. The subjects' drug adherence was not validated by periodic analyses of urine metabolites, or by pill counts, nor linked to an incentive program.

Interruptions in the course of treatment and treatment failures were identified by intervals of three months or more between the date the first drug was started and the date the drug was restarted. At the TB clinic, treatment relapse was defined as a case that was adequately treated in the past or case whose treatment was interrupted for more than three months. Treatment failure was defined as a case that during the course of treatment, after three months of treatment or at the end of treatment showed a worsening of radiographic findings, a return of symptoms, and/or a conversion back to a positive bacteriological state from a negative state. Charts were manually reviewed on ten cases with treatment lapses over three months but less than one year from the date their clinic record was opened; 11 cases with restart dates over one year from the initial drug start dates for retreatment; and the 19 cases with RVCT registration dates after 1998. At the TB clinic, clients are not routinely classified as relapse or treatment failure cases. The clinic

[21] The term adherence is used in this study in accordance with the CDC (1994) recommendations. The CDC stated that patients and healthcare providers share the responsibility for treatment outcomes; therefore, the CDC does not use the word compliance, which connotes a more passive role for the patient. Adherence, the term preferred by the CDC and used in this dissertation study, better describes the desired partnership and shared responsibility between patient and healthcare provider. For additional background on the historical construct of noncompliance, see Lerner's (1997) paper (Lerner, 1997).

currently has molecular epidemiological analyses available to distinguish between cases of re-infection and relapse. The present RVCT form does not classify the outcomes of treatment failures.

Subjects with LTBI were considered to be adherent or nonadherent to the prescribed preventive prophylaxis therapy based on their final clinical evaluation. Treatment relapses were identified by intervals of more than three months between the first drug start date and the drug restart date. In this cohort, 157 of the 4,547 subjects with LTBI had treatment relapses of more than three months in the course of their chemotherapy. Nine charts were manually reviewed to obtain the subjects' final LTBI treatment outcomes; one chart in this group could not be located.

Main predictor, covariate and demographic variables.

The immigrant's country of origin has been the primary factor associated with the high frequency of LTBI and TB reactivation found in these populations (CDC, 1998b; LoBue & Moser, 2004; Wobeser et al., 2000). This etiologic factor, the subject's country of origin, has also been hypothesized to be one of the main predictor variables influencing their treatment adherence or nonadherence. The use of the immigrants' birth outside the United States as a predictor factor implies, but does not identify specific etiologic conditions or health conditions experienced by these immigrants.

In studies comparing the outcomes of foreign-born and native populations, being classified as an immigrant or foreign-born status alone, not specific countries of origin, have been used a predictive factor in treatment outcomes (Cayla et al., 2004; Helbling et al., 2002). However, as all the subjects in this study are foreign-born immigrants, their

migration from specific Asian countries has been analyzed as a predictor factor in their treatment outcomes.

Age at the time of immigration and the age at onset of disease are the second critical predictive factors related to the immigrants' treatment adherence. Disease patterns have been directly correlated with age for many years with disease rates typically being the highest in the young and the very old in the early stages of an epidemic (Fos & Fine, 2000). Prior to the beginning of this dissertation study, Zuber, McKenna, Binkin, Onorato, and Castro's (1997) analysis of 55,387 verified tuberculosis cases among foreign-born reported from 1986 to 1994 found that almost 45% of the cases were diagnosed among persons younger than 35 years, and 63% were younger than 35 years of age at the time of arrival (Zuber et al., 1997). This coincides with the findings in a retrospective study on active adult TB in Wuhan, China in which the median age of admission among the clients was 35 years (Chamla, Nie, & Duan, 2004). This pattern is expected to change as the average age of the patients at risk gradually increases, resulting in the late reactivation of latent tuberculosis infections among older adult men (Bates & Stead, 1993; CDC, 1996a; D. Enarson & Murray, 1996; Stead & Bates, 1996). In a treatment study conducted in Vietnam from 1990 to 1996, subjects whose age was over 45 years had significantly increased chance of treatment failure. The variables sex, age, presence of cavities, and previous TB treatment in this study did not affect the chance of cure ("Outcome of second-line tuberculosis treatment in migrants from Vietnam. International Organization for Migration (IOM) Tuberculosis Working Group," 1998). This was supported in Morisky et al.'s study (2003) in which younger age (OR = 1.15,

95% CI 1.03-1.29) was associated with the completion of care (Morisky, Ebin, Malotte, Coly, & Kominski, 2003).

The covariates downloaded from the electronic record have been cited in studies as factors in the adherence and nonadherence to treatment completion. Perhaps, the most controversial covariate has been the effect of directly observed therapy (DOT) versus self-administered therapy (SAT) on adherence (Burman et al., 1997; el-Sadr et al., 1996; Jasmer et al., 2004; Mac, Doordan, & Carr, 1999; Pang, Harrison, Brearley, Jegathesan, & Clayton, 1998; Tandon, Gupta, Tandon, & Gupta, 2002; Zwarenstein, Schoeman, Vundule, Lombard, & Tatley, 1998). The lifestyle covariates, injection drug use and excessive use of alcohol, were predictive factors for nonadherence to chemotherapy regimens (Jaiswal et al., 2003; Lorvick et al., 1999). In Pablos-Mendez's study (1997) subjects who were homeless required longer treatment regimens (Gutierrez et al., 1998; Moss et al., 2000; Pablos-Mendez, Knirsch, Barr, Lerner, & Frieden, 1997). Poor adherence to preventive therapy among patients released from short-term correctional facilities (Bandyopadhyay, Murray, & Metersky, 2002) and high rates of adherence in persons incarcerated in the prisons in Barcelona, Spain were reported (Marco et al., 1998). Coinfection with HIV status greatly increased the risk of TB reactivation among those with HIV-related immunosuppressed status (CDC, 1993c; Greenberg et al., 1994; Rocha, Pereira, Ferreira, & Barros, 2003; Wood, Maartens, & Lombard, 2000). Drug susceptibility results were obtained to follow subjects with drug resistant strains, particularly multidrug resistant TB (MDRTB), who are reported to have significantly higher treatment failure rates than those with drug-susceptible strains (Espinal et al., 2000; Pablos-Mendez et al., 1997). Drug therapy start, restart and end dates were used to

evaluate the duration of treatments and potential retreatment cases. In addition to characterizing the two sample populations, the demographic variables male gender and non-European ethnicity have been associated with higher default rates in adherence studies (Balasubramanian et al., 2004; Jordan, Lewitt, & Reichman, 1991; Santha et al., 2002).

The cohort of subjects who were prescribed antituberculosis chemotherapy for active TB was followed for relapse and retreatment rates for a minimum of five years subsequent to the dates their clinic records were opened from January 1, 1994, to December 31, 1998, or if their RVCT registration date was after 1998.

The subjects who received preventive prophylaxis treatment were followed for five years after their treatment end date for incidence of prophylaxis failure.

Data analysis.

Descriptive statistics were calculated separately on the two cohorts' demographic and clinical variables; means and standard deviations were reported for the continuous data. To calculate the completion of therapy rates, the numerator included individuals in the cohort who completed therapy based on his or her final clinical evaluation. The denominator included individuals who completed therapy, or were lost to follow-up or self-stopped therapy before completion. Excluded from the completion of therapy were individuals who died, moved or were ineligible because the physician discontinued treatment. Odds ratios were analyzed and compared in a univariate analysis using chi-square tests. For variables with more than two categories, such as countries of origin, the category with the lowest rate of association was chosen as the reference category. Logistic regression was performed to analyze the effect of explanatory variables in

determining the association with treatment adherence of the cohort with LTBI, the primary outcome of interest. The association between independent and dependent variables in all tests was considered significant at alpha = .05. Statistical analyses of the data were performed using the Statistical Package for the Social Sciences software (Version 11.0; SPSS: Chicago, IL).

The study was reviewed by the Committee on Human Research at the University of California San Francisco and was granted approval, number H7085-25667-01, on September 8, 2004. All specific patient identifiers (i.e., names, clinic record numbers) were removed to protect patient confidentiality prior to the data being imported into SPSS for analysis.

Potential for Selection Bias

In epidemiological studies, bias has been defined as any systematic error in the manner that the subjects are selected or the way that information is collected or interpreted that results in an incorrect estimate of the association between exposure and the risk of disease. The subsequent differences identified may be partly or entirely due to differences between the subjects rather than to the effect of the interventions. In California, many of the newly arriving immigrants have favored particular cities for resettlement. For example, the most popular destination for Filipinos is San Diego, then Daly City, and San Francisco as a fifth choice; Vietnamese tend to migrate to Westminster and Garden Grove in Southern California; for Chinese newcomers, the first choice is San Francisco followed by Monterey Park (Gould, 1996). The ethnic composition of the Asian clientele at SFGH TB clinic reflects these resettlement

preferences. This bias in resettlement preferences can potentially affect the external validity or generalizability of the study findings.

Information Bias

The information gathered on persons with active TB was derived from the state-mandated Report of Verified Case of Tuberculosis (RVCT). In comparison, public health departments are not required to report outcome data on their LTBI clientele. Therefore, less data was available on the LTBI cohort's demographic and covariate variables for analysis.

Hennekens (1987) noted that in virtually every cohort study, only a proportion of those who eligible to participate actually agree to do so and participate in the study. Those that agree to participate may differ from nonparticipants in levels of motivation and attitudes towards health and perhaps, in characteristic risk factors (Hennekens & Buring, 1987). In this retrospective cohort study, 2,881 individuals who either declined preventive prophylaxis, were not prescribed chemotherapy or had prior adequate treatment were removed from the study. Therefore, the study data represents persons who were adherent in attending the clinic at least for their participation in their drug regimen to be recorded and not the individuals who did not return to the clinic.

A second source of bias in cohort studies concerns the potential number of study participants who are lost to follow-up due to interstate relocations or dropout from the study for unknown reasons. Persons lost to follow-up in the chemotherapy regimens may differ from those who completed treatment with respect to both their exposure and their outcomes. There remains the possibility that these persons may have completed their

chemotherapy elsewhere, or that they may have developed reactivated TB, but in a different county or out of the country.

Chapter 4: Results

This chapter presents a description of the study sample and the outcomes of the Asian immigrants who received anti-tuberculosis chemotherapy and preventive prophylaxis therapy at the tuberculosis control clinic at San Francisco General Hospital (SFGH) from 1994 to 1998.

The immigrants were selected for this study using the electronic clinic database of the TB control unit at SFGH from January 1, 1994, to December 31, 1998. The initial downloaded sample had 7,824 persons of Asian ancestry whose countries of origin included the People's Republic of China, Republic of Philippines, India, Korea and the Southeast Asian countries of Vietnam, Laos, and Cambodia. The entire electronic dataset was reviewed for the inclusion and exclusion criteria. Twenty-two non-Asians were removed from the dataset reducing the initial sample to 7,802 clients. To identify the clients with active and reactivated TB, the search criteria used the variables major diagnostic site, Report of Verified Case of Tuberculosis (RVCT) registration date and RVCT casecode number yielding 426 cases. From this initial sample of active TB, 30 clients were eliminated: 18 clients who had returned for follow-up visits without medication prescribed, six cases without RVCT registration dates, one TB2 client with normal radiographic findings on isoniazid monotherapy, and five clients from India due the small number of clients from this country of origin. The final sample consisted of 396 clients with active tuberculosis.

Treatment Outcomes of Active Pulmonary TB Sample

The 396 clients with active and reactivated TB with (RVCT) registration dates consisted of 334 cases with pulmonary TB and 62 clients with extrapulmonary TB.

Among the pulmonary TB cases, 248 (74.3 %) of 334 cases were culture positive by the isolation of *Mycobacterium tuberculosis*. The treatment outcome was a remarkable100 percent completion rate for the 300 cases who were prescribed anti-tuberculosis chemotherapy. In this sample, 34 (10.2%) cases were excluded: 17 expired, nine moved and were referred, and eight persons left the country. These 34 cases were excluded from the completion rate. Figure 4 illustrates the treatment outcomes for both the pulmonary and extrapulmonary clients in the active TB cohort. The 62 cases of extrapulmonary TB are described following the results of pulmonary cases.

The varying duration of chemotherapy regimens for the pulmonary TB clients in Table 3 was based on the national and clinic guidelines for antituberculosis multi-drug therapy. At the time of this study, the recommended anti-tuberculosis treatment length was a six-month course of treatment. Of the 300 clients who completed chemotherapy, the majority, 201 (60.2%), completed a six-month course of multi-drug chemotherapy, 47 (14.1%) completed nine months and 51 (15.3%) completed over nine months. Treatment length, or duration, can be extended beyond the recommended six months based on clinical medical judgment. The reasons for extending a client's treatment can include radiologic changes, delayed sputum conversions, co-infections, and pre-existing co-morbid conditions.

The comparative demographics for this pulmonary TB cohort are described by country of origin in Table 3.

Figure 4. Treatment Outcomes of Active Tuberculosis Subjects

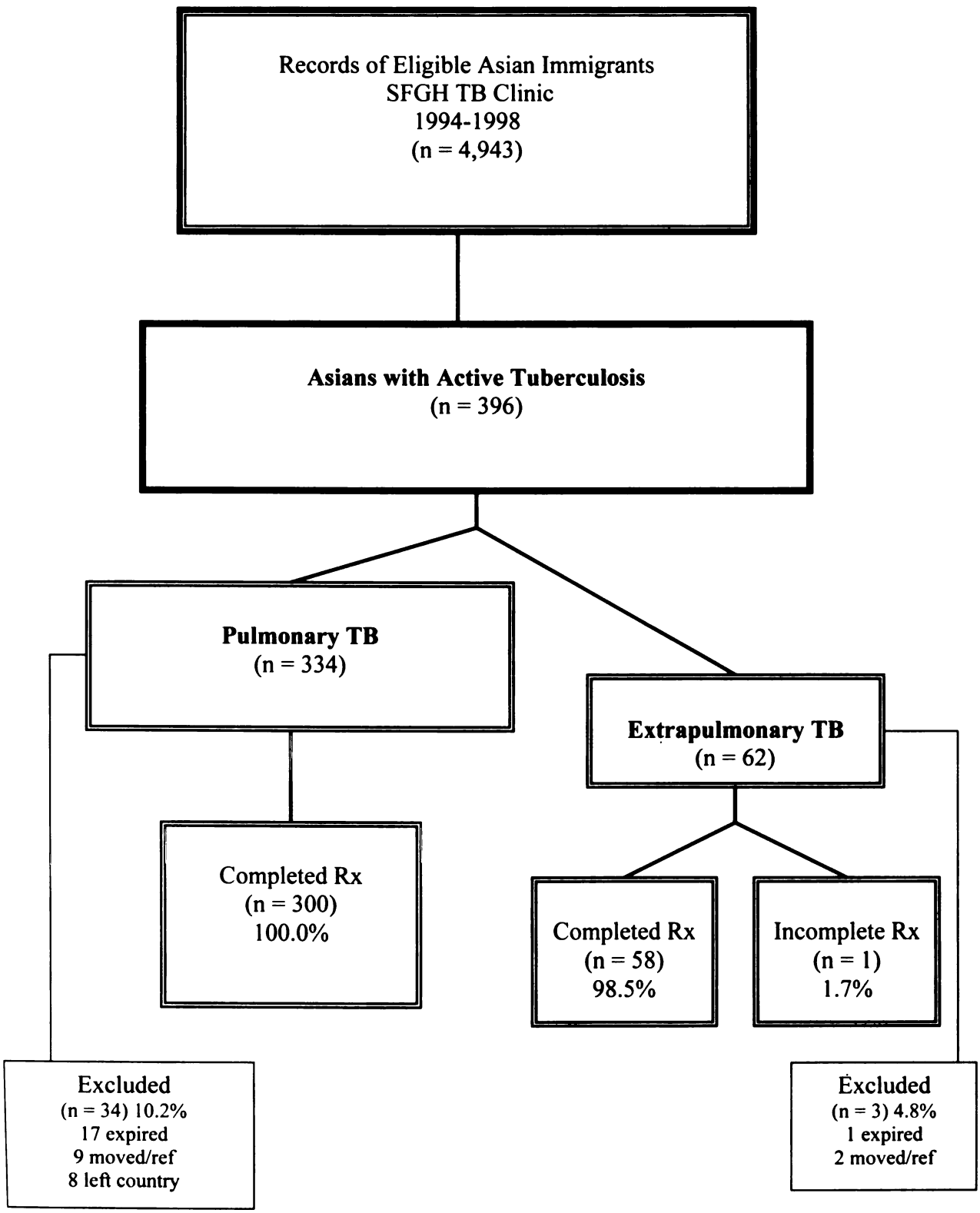


Table 2. Pulmonary Tuberculosis Treatment Outcomes by Country of Origin*

CHEMOTHERAPY	CHINA n =114	PHILIPPINES n =145	SOUTHEAST ASIA n = 41	TOTAL n =300
COMPLETED 6-9 MONTHS	74	99	28	201 (60.2)
COMPLETED 9 MONTHS	21	23	3	47 (14.1)
COMPLETED OVER 9 MONTHS	19	22	10	51 (15.3)
COMPLETED 4 MONTHS INH & RIFAMPIN OR 4 DRUG CHEMOTHERAPY		1		1 (.3)

* Analysis does not include 34 people who were excluded for the following reasons: 17 expired, 9 moved and referred, and 8 left the country.

Table 3. Demographics: Active Pulmonary Tuberculosis

	CHINA n=127 38.%	PHILIPPINES n= 162 48.5.%	SOUTHEAST ASIA n=45 13.5%	TOTAL* n = 334 100%	P VALUE
GENDER					
Male	92 (72.4)	119 (73.5)	22 (48.9)	233 (69.8)	.005
Female	35 (27.6)	43 (26.5)	23 (51.1)	101 (30.2)	
AGE					
Mean	57.0242	52.5634	45.6085	53.3225	.002
Median	61.9849	54.1040	45.2129	56.0986	
SD	18.40082	19.25519	17.99040	19.07054	
AGE AT IMMIGRATION					
Mean	47.6956	46.1799	39.6895	45.8809	.043
Median	48.9637	49.0349	39.9589	47.6057	
SD	16.69783	19.95027	17.26752	18.53767	
U.S. RESIDENCY					
0 to 5 Years in U.S.	62 (48.8)	102 (63.0)	26 (57.8)	190 (56.9)	.047
> 5 Years	65 (51.2)	59 (36.4)	19 (46.2)	143 (42.8)	
YEARS IN U.S. TO CLINIC DATE					
Mean	9.3286	6.4153	5.9191	7.4593	.032
Median	5.1800	2.1684	2.6831	3.2033	
SD	12.62048	8.81073	6.43916	10.27335	

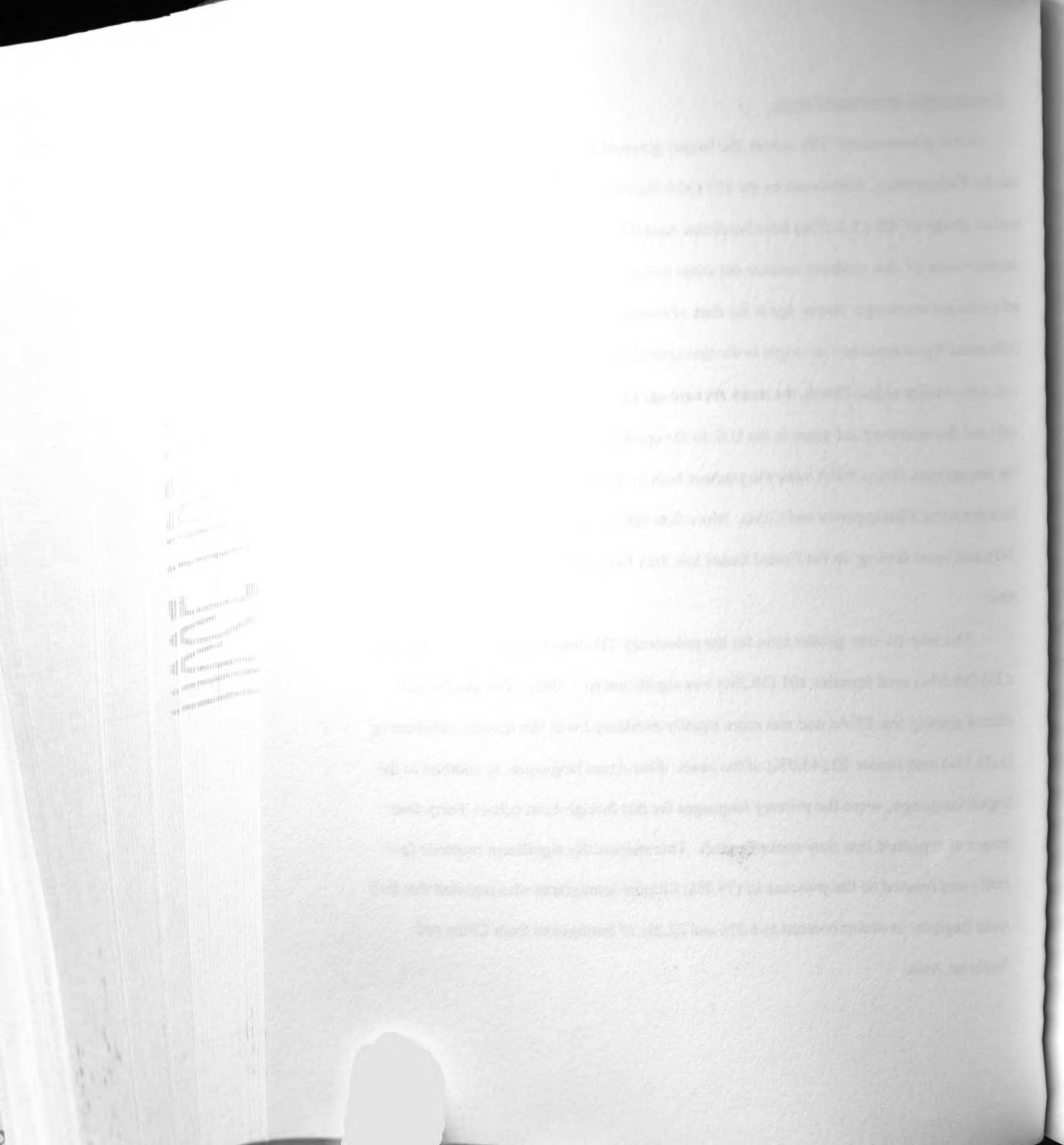
	CHINA n=127 38.%	PHILIPPINES n= 162 48.5.%	SOUTHEAST ASIA n=45 13.5%	TOTAL* n = 334 100%	P VALUE
ETHNICITY					
Asian		1 (.6)		1 (.3)	
Chinese	127 (100.0)		25 (55.6)	152 (45.5)	
Laotian			2 (4.4)	2 (.6)	
Filipino		161 (99.4)		161 (48.2)	
Cambodian			1 (2.2)	1 (.3)	
Vietnamese			17 (37.8)	17 (5.1)	
PRIMARY LANGUAGE					
English	4 (3.1)	78 (48.1)	3 (6.7)	85 (25.4)	
Laotian			1 (2.2)	1 (.3)	
Tagalog		78 (48.1)		78 (23.4)	
Mandarin	11 (8.7)			11 (3.3)	
Cantonese	103 (81.1)		15 ((33.3)	118 (35.3)	
Vietnamese			24 (53.3)	24 (7.2)	
SPEAK ENGLISH					
No	96 (75.6)	9 (5.6)	26 (57.8)	131 (39.2)	<.0005
Yes	8 (6.3)	129 (79.6)	10 (22.2)	147 (44.0)	
HIV STATUS					
Negative	59 (46.5)	80 (49.4)	28 (62.2)	167 (50.0)	
Positive		3 (1.9)		3 (.9)	

- Numbers do not add to 334 or to 100% because of missing data.

Demographic characteristics.

In the pulmonary TB cohort, the largest group of 162 (48.5%) immigrants came from the Philippines, followed by the 127 (38.0 %) immigrants from China and the smallest group of 45 (13.5%) from Southeast Asia (SEA). In Table 3, the age-related characteristics of the cohort indicate the mean average age of 53.32 (SD = 19.1) years and a younger average mean age at the time of immigration of 47.61 (SD = 18.5) years. Differences by countries of origin in the immigrant's three age-related characteristics were statistically significant, the mean average age (p = .002), age of immigration (p = .043) and the number of years in the U.S. to the opening of their clinic record (p = .032). The immigrants from SEA were the younger both in age and when they migrated than those from the Philippines and China. More than half of the cohort, 190 (56.9%) (p = .047), had been living in the United States less than five years before presenting at the clinic.

The two to one gender ratio for the pulmonary TB cohort on the whole with males at 233 (69.8%) and females 101 (30.2%) was significant (p = .005). The gender ratio differed among the SEAs and was more equally distributed with the females constituting 23 (51.1%) and males 22 (48.9%) of the cases. Five Asian languages, in addition to the English language, were the primary languages for this foreign-born cohort. Forty-four percent of reported that they spoke English. This statistically significant response (p = .0005) was related to the presence of (79.6%) Filipino immigrants who reported that they spoke English, in sharp contrast to 6.3% and 22.2% of immigrants from China and Southeast Asia.



Only 3% of the Chinese reported English as their primary language with the majority (89.8%) identifying either Cantonese or Mandarin as their first language. Among the SEAs, 53.3% preferred Vietnamese and 33.3% Cantonese indicating the ethnic diversity within the group. The SEAs represented four ethnic groups, Chinese (55.6%), Vietnamese (37.8%), Laotian (4.4%) and one Cambodian (2.2%). With the exception of the yes/no speak English factor, these interethnic and language differences within the groups were not further explored.

Health-related characteristics and immigration status

The health-related variables indicated that 202 (60.5%) of the pulmonary cohort had positive first PPD readings, 83 (24.9%) positive sputum smears, and 248 (74.3%) positive sputum cultures; 295 (88.3%) with a history of TB were classified as TB4, defined as previously acquired TB or old TB. Only 20 (6%) of the cohort reported a history of BCG vaccination. The HIV status was evaluated in 322 (96.4%) of clients with three (.9%) clients from the Philippines, who tested seropositive and 16.7% who refused the test. The remaining high-risk behavior covariates also had similar low response rates: no reports of intravenous drug use, two (.6%) nonintravenous drug use, one (.3%) from correctional facility at time of disease, two (.6%) from long-term facility at the time of disease, six (1.6%) used alcohol in past year, and seven (2.1%) reported being homeless. The two immigration-related variables B-waiver notifications (95.2% missing) and report of alien status (immigrant or refugee) (77.2% missing), were eliminated from the analysis due to the high proportion of missing data.

In Table 4, the majority of clients, 84 (55.1%), used self-administered therapy (SAT) for their multi-drug antituberculosis regimens and 50 (15.0%) used a combination

of directly observed therapy (DOT) and SAT. Only 74 (22.2%) of the clients were assigned total DOT supervision. The use of DOT or self-administration as a factor in treatment adherence could not be analyzed since the clients using the three levels of observation all completed their chemotherapy regimens.

The presence of drug resistant TB strains can increase the treatment duration, thus potentially reducing adherence (Bloch et al., 1999). The drug susceptibility results on Table 5 indicated that 40 (12%) and ten (3.0%) of the pulmonary TB cases were isoniazid and rifampin drug-resistant, respectively. Even among this subset of clients with isoniazid and rifampin resistant TB, 17 (34%) completed six to nine months of chemotherapy, 29 (58%) were treated for nine months or more, and two clients expired while on treatment, and two moved and were referred.

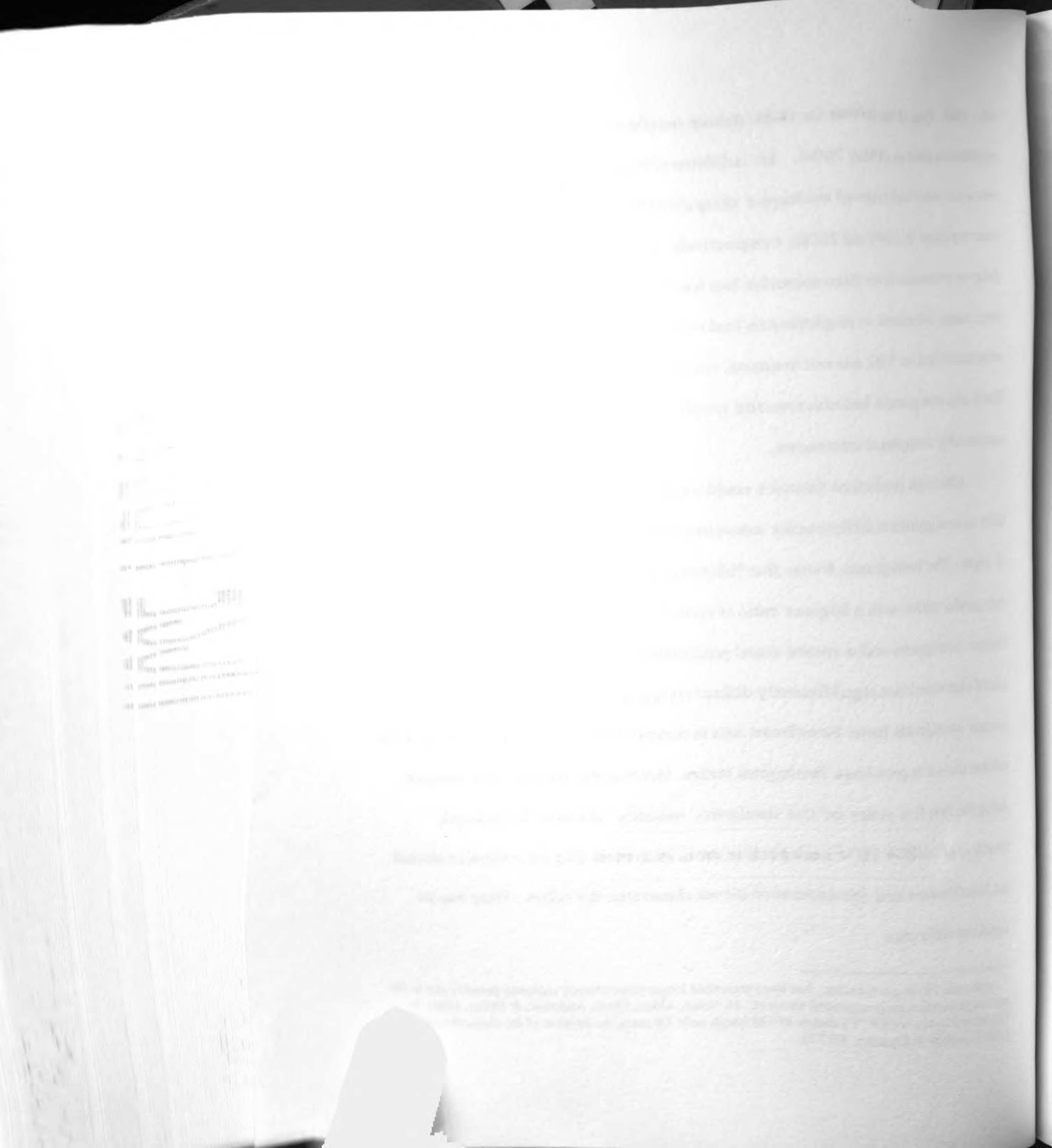
Retreatment and Relapse Cases

Although the cohort of active pulmonary TB did achieve 100% treatment adherence, the cases were reviewed for incidences of retreatment and treatment relapse. A variable was created to estimate the time intervals between the clinic open dates and the RVCT registration dates and calculate the intervals between the drug start dates and drug restart dates. These dates were available in the electronic dataset because when a clinic record is opened on a client, all subsequent return visits to the clinic will trigger a reopening of his or her record. All of the clinic charts of cases with RVCT registration dates after 1998 and extended intervals were manually reviewed. In the chart review, 12 cases had received a full course of isoniazid prophylaxis therapy during the study time frame from January 1, 1994, to December 31, 1998. Their electronic records were reopened when they returned with reactivated TB resulting in RVCT registration dates

fter 1998. One of the clients in this group completed chemotherapy with a RVCT egistration date as of May 2004. In addition to these 12 retreatment cases, there were two cases who had received multiple drug chemotherapy during 1996 to 1998 and then were retreated in 1999 and 2000, respectively. Treatment relapse, defined as an interval delay in treatment over three months but less than one year, occurred in nine cases. In three cases, isoniazid as prophylaxis had not been prescribed due to their older age, three were classified as TB2 and not treated, one expired on treatment, one left the United States and one person had reactivated lymph node TB.[22] All of the reviewed cases successfully completed treatment.

Although predictive factors could not be identified with the 100% adherence rate, there were significant differences associated with the immigrants from the three countries of origin. The immigrants from the Philippines, China and Southeast Asia differed in their gender ratios with a higher ratio of males to females among the Filipinos and Chinese immigrants and a more equal gender distribution among the SEAs. Two age-related characteristics significantly differed among the Asian immigrants, particularly the younger immigrants from Southeast Asia in contrast to those from China. Similar to the patterns shown in previous immigrant studies, 56.9 % of the TB cases were detected during the first five years of the immigrants' residency. However, the high-risk covariates of positive HIV seropositive status, intravenous drug use, excessive alcohol use, homelessness and incarceration did not characterize this cohort. There was no significant difference

[22] Lymph node TB, in particular, has been prescribed longer chemotherapy regimens possibly due to the poor drug penetration in lymphoid tissue (C. M. Nolan, Aitken, Elarth, Anderson, & Miller, 1986). In Campbell and Dyson's (1977) study of 108 lymph node TB cases, the duration of the chemotherapy was 18 months (Campbell & Dyson, 1977).



($p = .173$) in the use of self-administration or DOT observation among the immigrants by their countries of origin.

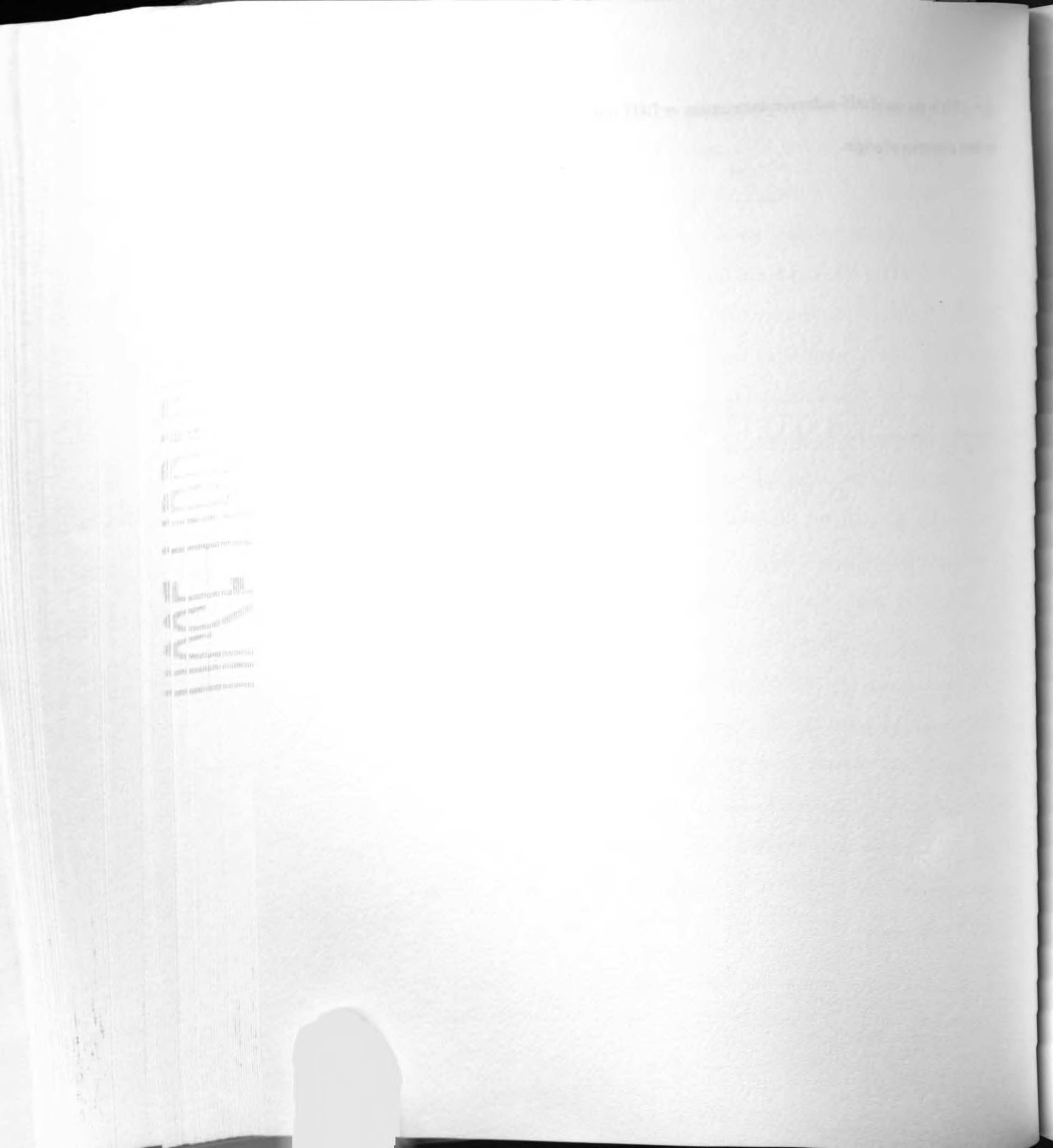


Table 4. Asian Immigrants at SFGH TB Clinic: Self Administration and Directly Observed Therapy 1994-1998*

	PULMONARY TB (n=334)	EXTRAPULMONARY TB (n=62)
SELF ADMINISTERED	184 (55.1)	45 (72.6)
BOTH DOT & SELF	50 (15.0)	10 (16.1)
DOT TOTALLY	74 (22.2)	1 (1.6)
TOTAL	308 (92.2)	56 (90.3)

* Numbers do not add to sample totals or to 100 percent due to missing values.

[illegible]

[illegible]	[illegible]	
	[illegible]	[illegible]
	[illegible]	[illegible]
	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]

[illegible]

Table 5. Asian Immigrants on Anti-tuberculosis Chemotherapy: Drug Susceptibility Reports, 1994-1998*

	PULMONARY DISEASE n = 334	EXTRAPULMONARY DISEASE n=62
	ISONIAZID	
RESISTANT	40 (12.0)	0
SUSCEPTIBLE	217 (65.0)	43 (69.4)
	RIFAMPIN	
RESISTANT	10 (3.0)	0
SUSCEPTIBLE	247 (74.0)	43 (69.4)

* Numbers do not add to sample totals or to 100 percent due to missing values.

Treatment Outcomes of Extrapulmonary TB Sample

In the active TB cohort, 58 of the 62 extrapulmonary TB clients completed the prescribed chemotherapy regimen resulting in a 98.5% treatment adherence rate. One (1.7%) subject in the cohort failed to complete treatment. This client was 87 years old, the second oldest person in the extrapulmonary cohort, and refused to continue chemotherapy. Three clients were excluded, one subject expired and two moved and were referred for further treatment.

Extrapulmonary TB, with the exception of renal TB, has been particularly common in immigrant groups with rates up to 150 times higher than the native populations (Davies & Grange, 2001). The different diagnostic sites described in Table 6 have been associated with differences by age, race/ethnicity, sex, immigrant status and the person's country of origin (Rieder, Snider, & Cauthen, 1990; Schneider, Lasch, & Brade, 1994). In cases associated with HIV co-infection, the person's immune response fails to contain *M. tuberculosis*, thus enabling the dissemination of TB to single or multiple nonpulmonary sites ("Diagnostic Standards and Classification of Tuberculosis in Adults and Children.," 2000; Sandman, Schluger, Davidow, & Bonk, 1999; Wohl et al., 2001). Table 6 describes the major diagnostic sites for the extrapulmonary TB cohort. Seventy-one percent of the extrapulmonary clients were micro tissue positive. Compared to the active pulmonary TB cohort, there was less emphasis placed in this study on persons with extrapulmonary TB. Extrapulmonary TB, like pulmonary TB, can be debilitating and deadly, but since it is not air-borne, it is considered less infectious and less a threat to public health.

Demographic characteristics.

Cases in this cohort differed from those in the pulmonary TB cohort with a higher female to male ratio, 44 (71%) female and 18 (29.0%) male, although this difference was not statistically significant. The average mean age of 45.5 year (SD = 20.3) was lower than that of the pulmonary cohort, particularly the mean average age of the SEA, 37.7 years (SD = 16.49). The average mean age ($p = .047$) and the average mean age at immigration was 35.67 years, (SD 17.01), ($p = .025$). Differences by country of origin were significant. At the time of treatment, the cohort was almost equally divided in their length of residency in the U.S. with 29 (46.8%) less than five years and 33 (53%) who had resided in the U.S. five years or more. This cohort spoke four Asian languages and English. The majority of clients, 19 (79.2%), who spoke English were from the Philippines, similar to the finding in the pulmonary TB cohort.

Health-related and social characteristics.

The health-related characteristics of this cohort included 43 (69.4%) positive PPD readings and only five (8.1%) with a history of BCG. None of the 60 (96.8%) extrapulmonary TB clients evaluated reported a seropositive HIV status. Only one subject (1.6%) was in a long-term care facility at the time of diagnosis, 58 (93.5%) of the extrapulmonary clients denied being homeless, intravenous drug use, nonintravenous drug use, excessive alcohol use, and presence in a correctional facility. None of the extrapulmonary TB clients had B-waiver notifications, only one (1.6%) subject reported refugee status, and five (8.1%) reported a history of BCG vaccination. The majority (72.6%) of the extrapulmonary cases self-administered their drug regimens, ten (16.1%)

had combined DOT and self-administration and one case was assigned full DOT observation.

Table 6. Extrapulmonary Tuberculosis Major Sites*
(n=62)

enitourinary	5 (8.1)
ıtrathoracic	1 (1.6)
ymphatic-Cervical	30 (48.4)
Meningeal	1 (1.6)
Other Lymphatic	4 (6.5)
Peritoneal	1 (1.6)
Pleural	7 (11.3)
Bone and/or Joint	6 (9.7)
Other	6 (9.7)

* Numbers do not add to total sample or to 100 percent due to missing values.

Treatment Outcomes for Cohort with LTBI

Of the 4,547 clients with LTBI, 3,576 (82.6%) completed preventive prophylaxis therapy and 755 (17.4%) were nonadherent. In this cohort, 216 (4.8%) clients were excluded for the following reasons: 139 (3.1%) moved and were referred, six (.1%) died, 66 (1.5%) had their treatment discontinued by the physician and one subject's treatment outcome was unknown. Figure 5 illustrates the outcomes of Asian immigrants treated for LTBI. In Table 7, the adherence and nonadherence treatment outcomes are differentiated by the immigrants' countries of origin.

Demographic Characteristics.

In Table 8, which describes the cohort's demographics, China was the country of origin for 2,257 (49.6%) of the clients with LTBI, the second largest group, 1,549 (34.1%) was from the Philippines, and the smallest group, 741 (16.3%), came from Southeast Asia. The mean average age of the cohort was 31.23 years (SD = 19.5). The age at immigration was younger at 27.13 years (SD = 18.7), with the majority, 3,314 (72.9%), residing in the U.S. less than five years. The two age and residency measures, the mean average age ($p < .0005$), mean average age at immigration ($p < .0005$), years in U.S. to presenting at the clinic ($p < .0005$), and U.S. residency under or over five years (called new/old immigrant) ($p < .0005$) significantly differed among the immigrants by their countries of origin. This difference by country of origin indicates that Chinese (79.6%) were more likely to have resided in the country for less than five years as compared to 67.7% of the Filipinos, or SEAs (68.3%) ($p < .0005$).

Figure 5.

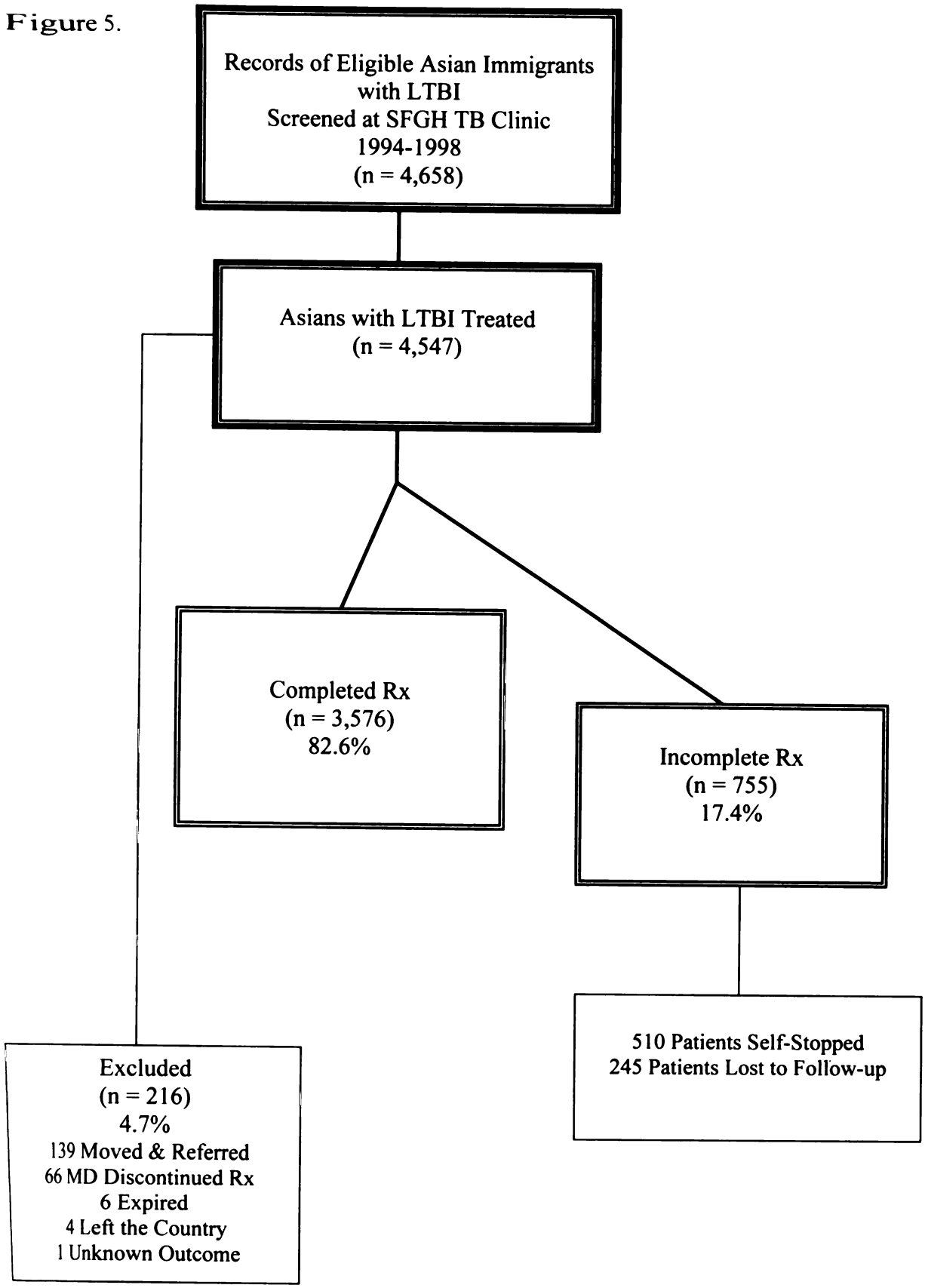

Records of Eligible Asian Immigrants
with LTBI
Screened at SFGH TB Clinic
1994-1998
(n = 4,658)
Asians with LTBI Treated
(n = 4,547)
Completed Rx
(n = 3,576)
82.6%
Incomplete Rx
(n = 755)
17.4%
510 Patients Self-Stopped
245 Patients Lost to Follow-up
Excluded
(n = 216)
4.7%
139 Moved & Referred
66 MD Discontinued Rx
6 Expired
4 Left the Country
1 Unknown Outcome

Table 7. Latent Tuberculosis Infection Treatment Outcomes by Country of Origin*

COMPLETED CHEMOTHERAPY	CHINA n = 1,926 53.9%	PHILIPPINES n = 1,066 29.8%	SOUTHEAST ASIA n = 584 16.3%	TOTAL 3,576 (82.6%)
INH or RIFAMPIN 6 MONTHS OR MORE	1,613	725	489	2,827 (62.2)
INH 12 MONTHS	65	75	22	162 (3.6)
INH & RIFAMPIN OR 4 MONTHS MULTI-DRUG RX	247	265	71	583 (12.8)
RIFAMPIN & PZA 2 MONTHS	1	1	2	4 (.1)
INCOMPLETE CHEMOTHERAPY	CHINA n = 250 33.1%	PHILIPPINES n = 378 50.1%	SOUTHEAST ASIA n =127 16.8%	TOTAL 755 (17.4%)
PATIENT SELF-STOP	180	245	85	510 (11.2)
LOST TO FOLLOW-UP	70	133	42	245 (5.4)
TOTAL	2176 50.2%	1444 33.3%	711 16.4%	4331 100%

* Analysis does not include 216 people who were excluded for the following reasons: 139 moved & referred, 66 MD discontinued Rx, 6 expired, 4 left the country, and 1 with unknown treatment outcome.

Table 8. Subjects with LTBI: Sample Demographics and by Country of Origin

	CHINA (n = 2,257) 49.6%	PHILIPPINES (n = 1,549) 34.1%	SOUTHEAST ASIA (n = 741) 16.3%	TOTAL (n = 4,547) 100.0%	P VALUE
GENDER					
Male	1,025 (45.4)	749 (48.4)	379 (51.1)	2,153 (47.3)	.016
Female	1,232 (54.6)	800 (51.6)	362 (48.9)	2,394 (52.7)	
AGE					
Mean	28.0676	37.0946	28.6151	31.2331	<.0005
Median	19.6413	33.9740	24.6571	25.2238	
SD	18.85730	21.12867	15.00791	19.57074	
AGE AT IMMIGRATION					
Mean	25.0628	31.6600	24.0234	27.1335	<.0005
Median	17.4018	26.2259	20.9158	20.1068	
SD	17.53788	20.82023	15.47871	18.70222	
YEARS IN US TO CLINIC OPEN DATE					
Mean	2.9809	5.2837	4.6660	4.0382	<.0005
Median	.1520	.9336	.7885	.3176	
SD	5.85006	8.04382	6.23577	6.81667	
US RESIDENCY					
0 to 5 Years	1779 (78.8)	1034 (66.8)	501 (67.6)	3314 (72.9)	<.0005
> 5 Years	455 (20.2)	493 (31.6)	232 (31.3)	1180 (26.0)	

	CHINA (n = 2,257) 49.6%	PHILIPPINES (n = 1,549) 34.1%	SOUTHEAST ASIA (n = 741) 16.3%	TOTAL (n = 4,547) 100.0%	P VALUE
ETHNICITY					
Asian	56 (2.5)	20 (1.3)	17 (2.3)	93 (2.0)	
Tibetan	1 (.0)			1 (.0)	
Chinese	2,187 (96.9)	3 (.2)	148 (20.0)	2,338 (51.4)	
Laotian			16 (2.2)	16 (.4)	
Filipino	2 (.1)	1,525 (98.5)	1 (.1)	1,528 (3.6)	
Cambodian			9 (1.2)	9 (.2)	
Vietnamese	2 (.1)		549 (74.1)	551 (12.1)	
LANGUAGE					
Korean	1 (.0)			1 (.0)	
English	155 (6.9)	763 (49.3)	123 (16.6)	1,041 (22.9)	
Laotian			9 (1.2)	9 (.2)	
Tagalog	1 (.0)	779 (50.3)	1 (.1)	781 (17.2)	
Mandarin	128 (5.7)	1 (.1)		129 (2.8)	
Cambodian	1 (.0)		4 (.5)	5 (.1)	
Cantonese	1,845 (81.7)		169 (22.8)	2,014 (44.3)	
Vietnamese	1 (.0)		426 (57.5)	427 (9.4)	
SPEAK ENGLISH					
No	1,735 (76.9)	116 (7.5)	436 (58.8)	2,287 (50.3)	
Yes	429 (19.0)	1417 (91.5)	288 (38.9)	2,134 (46.9)	<.0005
		HEALTH STATUS INDICATORS			
PPD READING					
Positive	2,028 (89.9)	1,254 (81.0)	648 (67.4)	3,930 (86.4)	
Negative	141 (6.2)	229 (14.8)	72 (9.7)	442 (9.7)	
X-RAY READING					
Normal	1,773 (78.6)	971 (62.7)	603 (81.4)	3,347 (73.6)	
Abnormal	467 (20.7)	553 (35.7)	125 (16.9)	1,145 (25.2)	

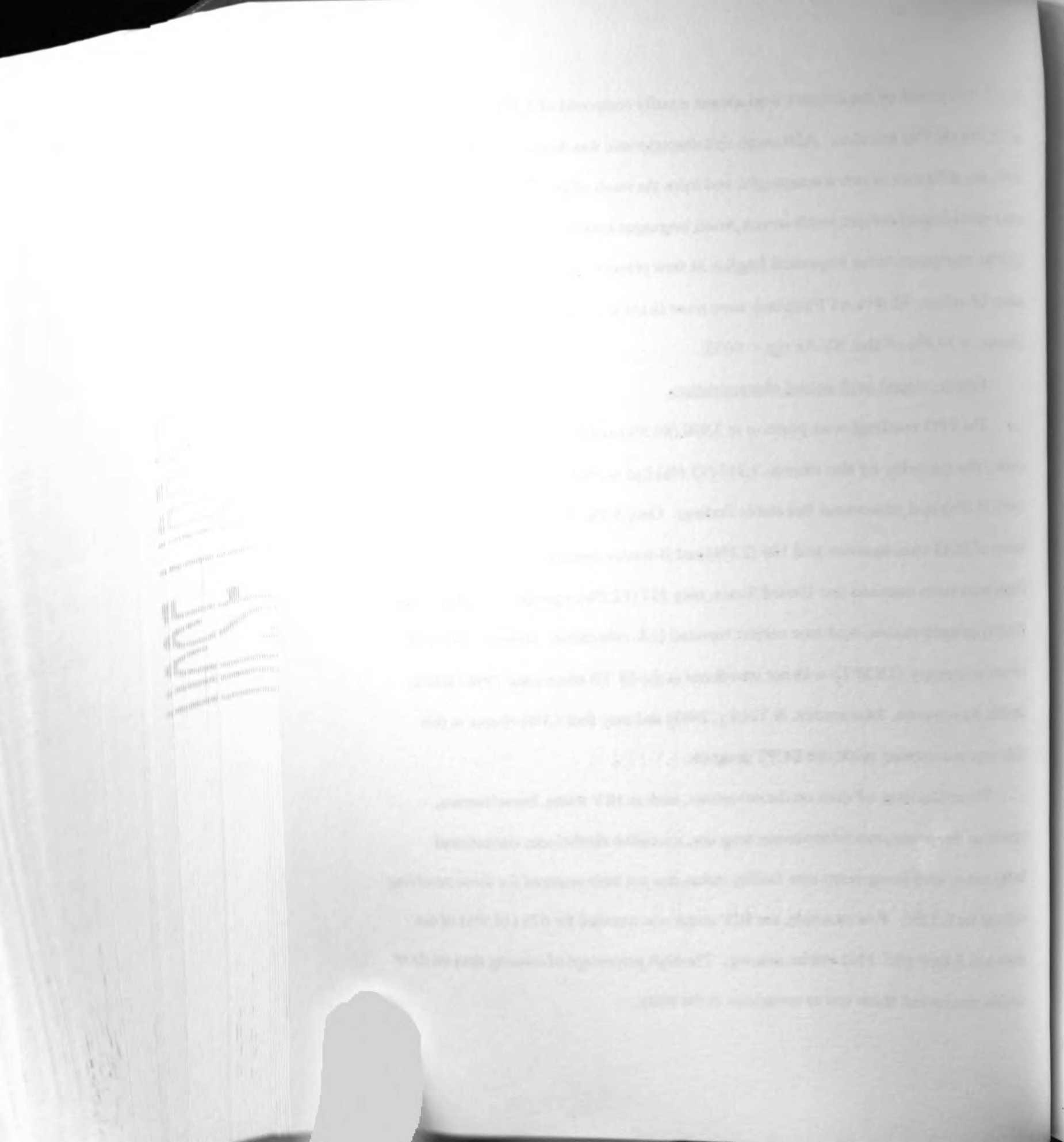
* Numbers do not add to total sample or to 100 percent due to missing values.

The gender of the cohort was almost equally composed of 2,153 (49.6%) males and 2,394 (52.7%) females. Although this characteristic was found to be significant ($p = .016$), the difference is not meaningful and more the result of the large sample size. It was a multi-lingual cohort with seven Asian languages spoken, in addition to 1,041 (22.9%) immigrants who reported English as their primary language. Similar to the active TB cohort, 92.4% of Filipinos were more likely to speak English than 19.8% of the Chinese, or 39.8% of the SEAs ($p < .0005$).

Health-related and social characteristics.

The PPD reading was positive in 3,930 (89.9%) and negative in 442 (9.7%) of the cohort. The majority of the clients, 3,347 (73.6%) had normal chest x-ray readings and 1,145 (25.2%) had abnormal but stable findings. Only 5.3% of the cohort reported a history of BCG vaccination and 106 (2.3%) had B-wavier notifications. Although all the clients were born outside the United States, only 557 (12.2%) reported immigrant status, 21 (.5%) refugee status, and one subject reported U.S. citizenship. Directly observed preventive therapy (DOPT) was not introduced at the SF TB clinic until 1996 (White, Gournis, Kawamura, Menendez, & Tulsky, 2003) and only four (.1%) clients in this study were monitored with the DOPT program.

The collection of data on the covariates, such as HIV status, homelessness, intravenous drug use, nonintravenous drug use, excessive alcohol use, correctional facility status, and long-term care facility status, has not been required for those receiving treatment for LTBI. For example, the HIV status was reported for 678 (14.9%) of the cohort with 3,869 (85.1%) entries missing. The high percentage of missing data on these variables precluded their use as covariates in the study.



Bivariate and Logistic Regression Analyses

The results of a bivariate analysis for predictors of treatment completion were country of origin, gender, age, age at immigration, years in U.S., the dichotomous variable new/old immigrant status, and the report of speaking English are described in Table 9. Gender and age at immigration did not significantly predict treatment completion among the Asian immigrants with LTBI. Identified significant predictors for treatment completion were country of origin ($p < .0005$), age ($p = .003$), years in the U.S. ($p < .0005$), new/old immigrant status ($p < .0005$), and speaking English ($p < .0005$). Cramer's V calculations ranged from 17% for the country of origin, 18% for the new versus old immigrant status and 21% for speak English variable's relationship to treatment completion. Cramer's V test, a measure of association for nominal data, indicated a low to moderate relationship. The Eta squared calculations of the continuous variables demonstrated that the variable years in U.S to clinic open date explained only 3.3% in the variance in treatment outcomes.

Country of origin as a predictive factor indicated that the immigrants from China (88.5%) were more likely to complete treatment than were the Filipino immigrants (73.8%), or SEA immigrants (82.1%). Younger mean age of 30.5 years, $F(1,4327) = 8.652$, $p = .003$, and a shorter average mean stay in the U.S. of 3.41 years, $F(1,4279), = 141.471$, $p < .0005$, were predictive of treatment completion. Immigrants who were in the U.S. less than five years were 2.7 times more likely to complete treatment than those who were here more than five years (OR 2.7, 95% CI 2.26 –3.1). In the analysis of the English speaking variable, immigrants who did not speak English were 3.3 times more

ikely to complete treatment than immigrants who did speak English (OR 3.3, 95%CI 2.8-3.9).

A logistic regression analysis was performed to examine the significant predictive variables for treatment completion using the variables country of origin, speaking English and years in the U.S. in the bivariate analysis (see Table10). This analysis indicated that controlling for years in the U.S., immigrants from China were 1.3 times more likely to complete treatment for LTBI than immigrants from the Philippines, and immigrants from SEA were no more or less likely than the Filipinos to complete prophylaxis therapy (AOR 1.3, 95% CI 1.06-1.67, p = .014). Immigrants who spoke English were 41.7% as likely to finish treatment compared to immigrants who were non-English speakers. The immigrants' time in the U.S. remains statistically significant: for every additional year in the U.S., a decreasing proportion of the immigrants are likely to complete treatment over time. In the first year, 96.4% of the immigrants are likely to adhere and for every decade only 68.4% are likely to be treatment adherent.

Table 9. Bivariate Analysis of Predicators for Treatment Completion by Asian Immigrants with Latent Tuberculosis Infection in San Francisco, 1994-1998

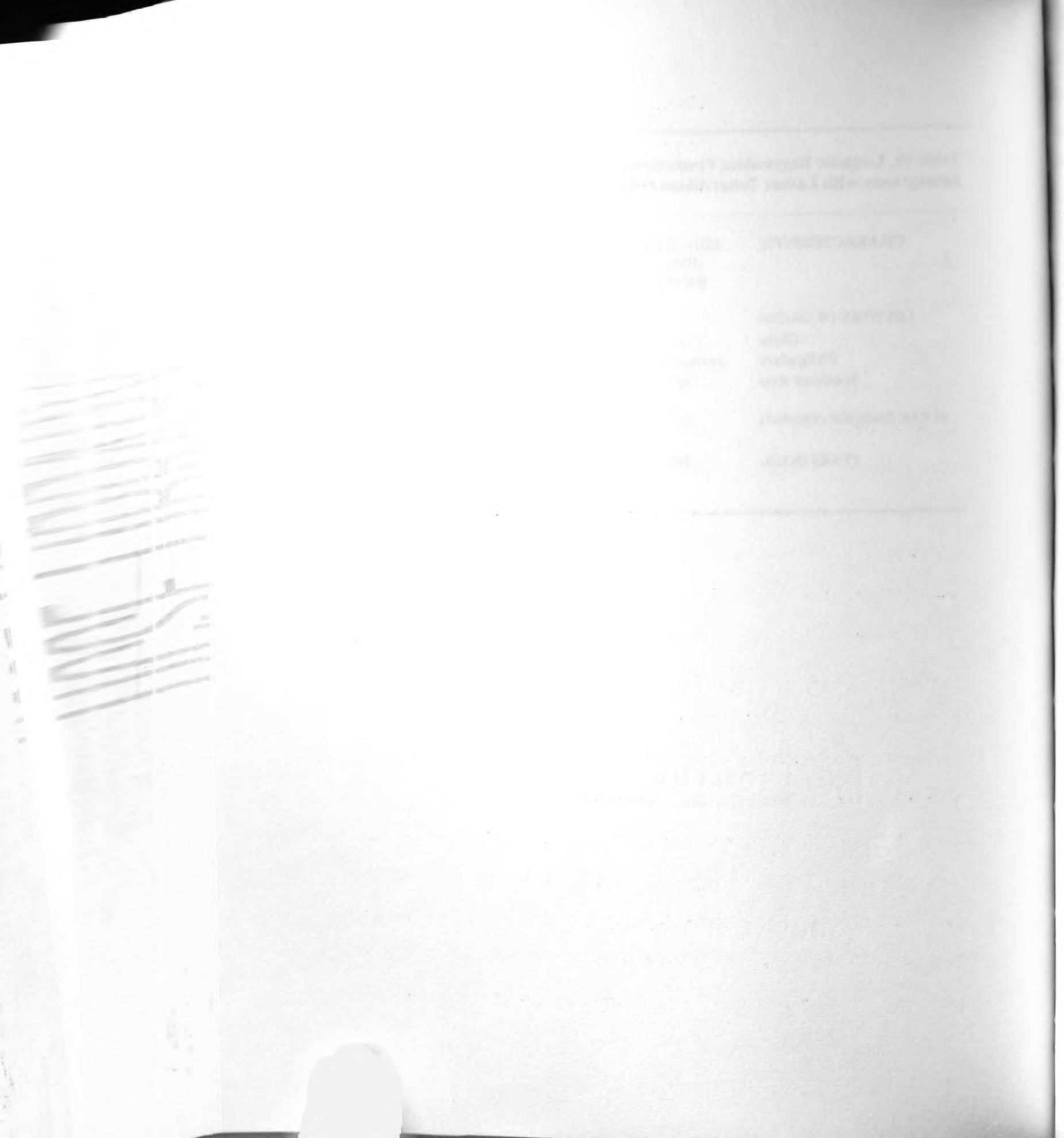
	TOTAL (n=4,331)	COMPLETE RX n=3,576 (82.6%)	INCOMPLETE RX (n= 755) (17.4%)	P VALUE	MEASURES OF EXPLAINED VARIANCE
GENDER					
Male	n = 2,056	1,691 (82.2)	365 (17.8)	.597 ns	0.008 [a]
Female	n = 2,275	1,885 (82.9)	390 (17.1)		
AGE	n = 4,329	N=3,574	N=755		
Mean		30.4797	32.7733	.003	0.002 [b]
(SD)		(19.53109)	(19.16337)		
Median		23.6290	27.8631		
AGE AT IMMIGRATION	n = 4,289	N=3548	N=741		
Mean		27.0662	25.8599	.108 ns	0.001 [b]
(SD)		(18.59638)	(18.60773)		
Median		19.8987	19.9754		
YEARS IN U.S.	n = 4,281	N=3,540 (82.7)	N=741 (17.3)		
Mean		3.4053	6.5963	<.0005	0.033 [b]
(SD)		(6.34931)	(7.88863)		
Median		.1492	3.5181		
NEW/OLD IMMIGRANT					
< 5 years	n = 3,176	2,755 (86.7)	421 (13.3)	<.0005	0.182 [a]
> 5 years	n = 1,105	785 (71.0)	320 (29.0)		
SPEAK ENGLISH					
No	n =2,201	1,990 (90.4)	211 (9.6)	<.0005	0.217 [a]
Yes	n =2,008	1,484 (73.9)	524 (26.1)		
COUNTRY OF ORIGIN					
China	n = 2,176	1,926 (88.5)	250 (11.5)	<.0005	0.173 [a]
Philippines	n = 1,444	1,066 (73.8)	378 (26.2)		
Southeast Asia	n = 711	584 (82.1)	127 (17.9)		

[a] Cramer's V

[b] Eta Squared

Table 10. Logistic Regression: Predictors of Treatment Completion of Asian Immigrants with Latent Tuberculosis Infection in San Francisco, 1994-1998

CHARACTERISTIC	ADJUSTED ODDS RATIO	95% CONFIDENCE INTERVAL	P VALUE
COUNTRY OF ORIGIN			<.0005
China	1.333	1.061-1.675	.014
Philippines	(reference)		
Southeast Asia	.995	.775-1.279	.972 ns
SPEAK ENGLISH (YES/NO)	.417	.333-.524	<.0005
YEARS IN U.S.	.964	.953-.974	<.0005



Chapter 5: Discussion

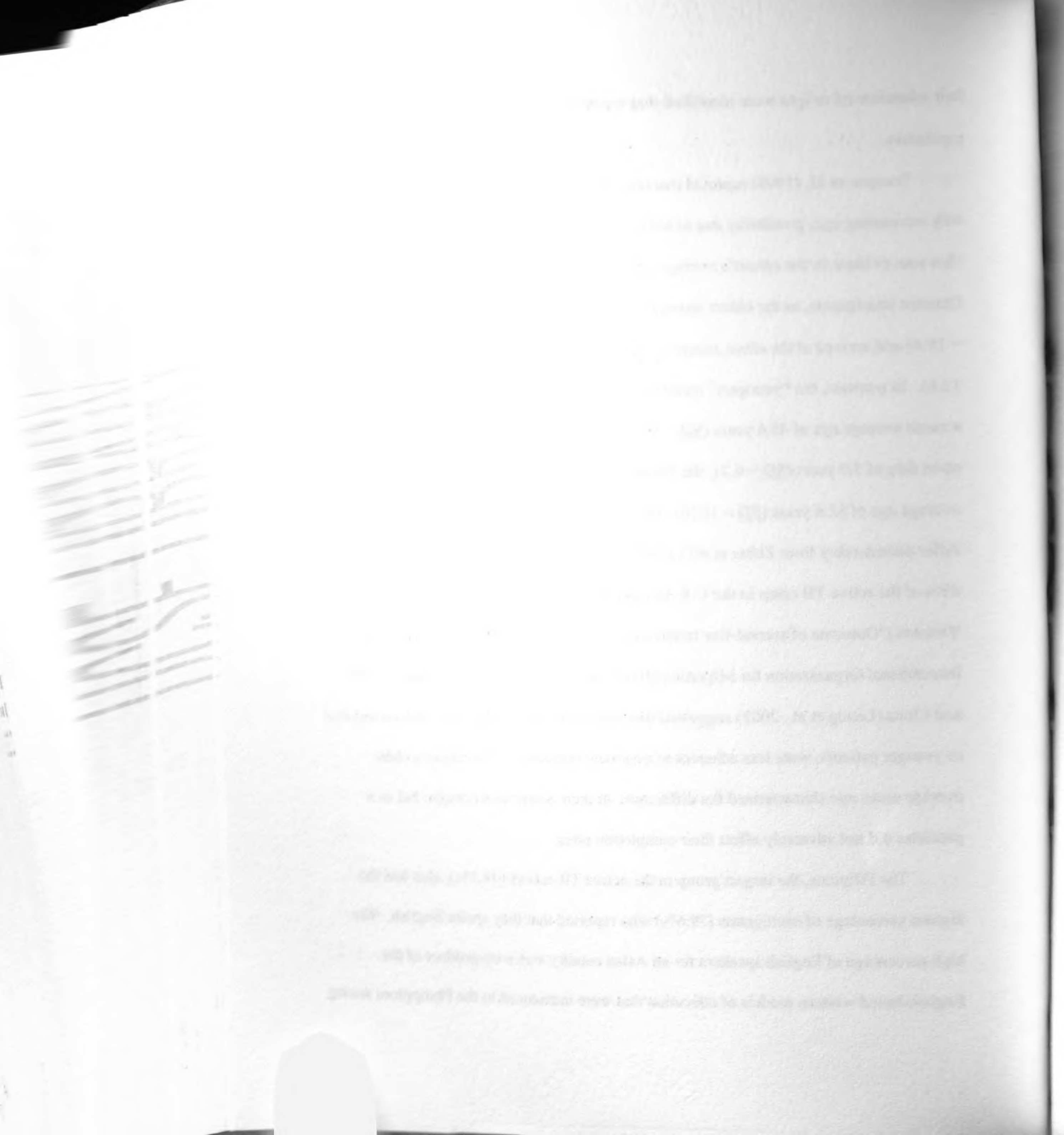
The 100% treatment adherence rate of the Asian immigrants with active pulmonary TB in this historic cohort study surpassed today's international and national TB control goals. The cohort met the World Health Organization's 2005 projected goal of a 70% case detection rate and 85% treatment success rate for active TB (WHO, 2004). In the United States, since 1992, the CDC's goal has been a 90% treatment completion for active TB cases. Bloch et al.'s national surveillance study reported that this goal was met in 1993 with 91.2% treatment adherence (Bloch et al., 1999). However, CDC's latest data available for 2001 reported lower completion rates, within one year of therapy, of 81.4% among U.S.-born cases and 80.4% for foreign-born cases (CDC, 2005). Although 15% of cases in this study received chemotherapy that extended to12 months and more, the treatment outcomes of the 396 Asian immigrants with active TB clearly exceeded these goals. The study's first null hypothesis for this cohort was supported by the 100% treatment adherence findings. There were no significant differences in the treatment adherence of the Asian immigrants who received chemotherapy for active tuberculosis associated with their countries of origin.

There were substantial differences identified between the Asian groups associated with their countries of origin, thus the second null hypothesis was rejected. For the first time in migration-related studies on Asians, the dominant group in the sample was from the Philippines (48.5%) followed by immigrants from mainland China (38.0%). Unlike the earlier studies that focused on the TB prevalence among the Southeast Asians, the SEA immigrants comprised only 13.5% of this cohort. Although predictive factors could not be tested for their effect on treatment adherence, significant differences related to

their countries of origin were identified that would aid in characterizing this treatment population.

Tocque et al. (1998) reported that the TB in developing countries was associated with increasing age, possibility due to today's increased longevity (Tocque et al., 1998). This was evident in the cohort's average mean age of 53.3 years (SD = 19.1). The Chinese immigrants, as the oldest immigrants, had a mean average age of 57.0 years (SD = 18.4) and arrived at the clinic almost a decade after their migration, (9.3 yrs, SD = 12.6). In contrast, the "youngest" members of the cohort were from Southeast Asia with a mean average age of 45.6 years (SD = 18.0) and the shortest time interval to their clinic open date of 5.9 years (SD = 6.4); the Filipino immigrants were in between with a mean average age of 52.6 years (SD = 19.3). The older average ages in this 1994-1998 cohort differ considerably from Zuber et al.'s (1997) reported age range of less than 35 years in 45% of the active TB cases in the U.S. foreign-born population. The outcome studies in Vietnam ("Outcome of second-line tuberculosis treatment in migrants from Vietnam. International Organization for Migration (IOM) Tuberculosis Working Group," 1998) and China (Leung et al., 2002) suggested that patients over 45 years old, when compared to younger patients, were less adherent to treatment regimens. The cohort's older average mean age characterized the differences in their countries of origin, but as a predictor did not adversely affect their completion rates.

The Filipinos, the largest group in the active TB cohort (48.5%), also had the highest percentage of immigrants (79.6%) who reported that they spoke English. The high percentage of English speakers for an Asian country was a by-product of the English-based western models of education that were introduced in the Philippines during



the United States military and political involvement from 1898 to 1946. Pilipino (based on Tagalog) and English are the official languages in the schools, government and private institutions in the Philippines (Rodell, 2002). In contrast to the English speaking Filipinos, the majority of the immigrants from China (75.6%), and to a lesser extent, the SEAs (57.8%), reported that they did not speak English. This ability to speak English that distinguished the Filipino immigrants from the Chinese and SEAs non-English speakers was a more pronounced factor in the LTBI treatment cohort.

The low reported incidence of HIV (.9%) and the absence of high-risk lifestyle factors in this active TB cohort corresponds to similar observations in TB studies comparing U.S.-born and foreign-born risk factors. TB studies in the 1990s reported the low prevalence of HIV in most foreign-born persons with the exception of persons from Haiti (Chin et al., 1998; El Sahly et al., 2001; Granich et al., 1998). The cohort's rare response to the adult HIV-risk factors such as substance abuse, homelessness and incarceration points out the need to examine the risk factors for nonadherence in the foreign-born population (Pablos-Mendez et al., 1997; Tornieporth et al., 1997). Contributing factors that have been associated with nonadherence in overseas outcome studies, such as previous treatment history, incidence of smoking, past adherence, number of return visits and social support systems have yet to be explored in the foreign-born Asian population.

The 100% adherence rate suggests that there was no difference in the use of directly observed therapy (DOT) or self-administered therapy (SAT) observation in the active TB cohort or that the treated immigrants were assigned to the appropriate level of treatment observation. DOT officially became the standard of treatment for active TB in

1993 (CDC, 1993a). By 1994, only 38% of the TB cases in California were under DOT supervision for at least part of their therapy. It took another four years before DOT coverage had increased to 65% in California (*Report on Tuberculosis in California, 2000*, 2001). Perhaps, the low percent of DOT supervision, only 22.2%, noted in this cohort was the result of gradual introduction of the DOT program throughout the state. Instead of DOT monitoring, the majority of the Asian immigrants (55.1%) self-administered their medications (SAT) and 15% were supervised using a combination of DOT and SAT. Mac, Doordan and Carr's (1999) evaluation of the use of DOT program from 1994 to 1997 in a sample of 50 Vietnamese TB patients reported that the cases with DOT coverage had a 16% higher completion and an 8% lower relapse rate than the non DOT patients (Mac et al., 1999). In this study, the three approaches to drug monitoring did not appear to be related to the length of treatment, which varied from six to as long as 45 months, nor could the effectiveness of each approach be compared given the optimal outcome.

It was difficult to estimate the actual number of retreatment cases in the study sample. The 14 (4%) retreatment cases identified in the study had received prior isoniazid prophylaxis from 1994 to 1998 before their chemotherapy for active TB. These retreatment cases only represent a subset of clients who had received prior prophylaxis therapy at the SF TB clinic. The electronic clinic record contained numerous staff reports of patients' anecdotal accounts of previous TB treatments that were not included in these retreatment cases. It is highly probable that the 14 retreatment cases identified in the cohort underestimates the number of individuals in the reactivated TB cohort who had received varying courses of treatment prior to their migration and before their arrival at

the clinic. In Nolan and Elarth's (1988) five-year surveillance study, 15 of 22 of the refugees identified with reactivated TB had been prescribed earlier isoniazid prophylaxis; ten of the 15 refugees had completed a full treatment course of treatment (Nolan & Elarth, 1988).

These issues of retreatment, relapse and treatment default were addressed by the CDC (1998) report that noted U.S. health providers were rarely able to obtain this information from the past medical records on their foreign-born clients (CDC, 1998b). Without the medical records, it is difficult to evaluate whether the person treated for TB had received previous inadequate or incomplete treatment in his or her home country. At the SF TB control clinic, if clients report that they have been treated in the U.S. then copies of their records are requested from the other agency or practitioner. Frequently, a client arrives at the TB clinic without his or her previous medical record from the birth country. A client would be considered likely to have been adequately treated in the past if he or she can reliably report a history of rifampin treatment after 1972, with at least two months of intermuscular injections out of six months of medications, and orange colored urine for at least the first two months of treatment (Dewan, 2005). Clients who were classified as having previous adequate chemotherapy according to their clinic record were removed from the study sample. In the remaining sample, 17.9% of the clients reported past treatment regimens, but the treatment history was missing on 74.9% of sample. The past treatment history of immigrants and the over-the-counter use of antituberculosis medications has been closely associated with the higher rate of drug resistance found in the foreign-born populations (Nolan et al., 1986; Tornieporth et al., 1997; Zuber, Knowles, Binkin, Tipple, & Davidson, 1996). There were 40 (12%)

isoniazid-resistant cases and ten (3%) rifampin-resistant cases detected in the study cohort, but there was insufficient data available to evaluate the cases for acquired drug-resistance and the potential impact on the treatment length.

Extrapulmonary TB Cohort

Compared to the pulmonary cohort, the Asians in the extrapulmonary TB cohort were younger with a mean age at 45.5 years (SD = 20.3) and had a higher female to male ratio, although this gender distribution difference was not significant ($p = .375$). The clients with lymphatic-cervical TB were at risk for nonadherence as a result of the longer treatment durations prescribed for lymph node TB, one of the frequent extrapulmonary diagnoses (Campbell & Dyson, 1977). The treatment duration for the 30 (48.4%) extrapulmonary clients treated for lymphatic-cervical TB varied in length with 16 (53.3%) having completed six to nine months of chemotherapy, seven (23.3%) nine months, and four (13.3%) over nine months. Even with these varying treatment durations the extrapulmonary TB cohort achieved a 98.5% adherence rate. It is interesting that the one client in the cohort who did not complete treatment did not fit the profile characteristic of the extrapulmonary patient. The one nonadherent client was older (87 years old), male, monitored with a combination of SAT and DOT supervision and was being treated for lymphatic-cervical TB.

Treatment Outcomes of Immigrants with LTBI

The 82.6% completion rate of those with LTBI was equally impressive. The treatment outcomes for the Asians treated for LTBI were analyzed separately from the cohort with active disease. The treatment for active disease is mandatory and involuntary in-hospital confinement can be legally enforced if the patient defaults from treatment

(Coker, 2000; Etkind, Boutotte, Ford, Singleton, & Nardell, 1991). In contrast, the treatment for LTBI is recommended for those under the age of 35 years and at risk, but unlike the treatment for active disease, the treatment is optional. Individuals with LTBI often do not feel sick, nor are they infectious. The treatment of latent (TB2) or inactive TB (TB4) is not routinely required for entry or resettlement in the U.S. (Gushulak, 1998). The absence of symptoms, optional treatment status, and the long duration of LTBI treatment presented different adherence problems.

The high proportion of reactivated TB rates among the foreign-born populations with LTBI led to a renewed interest in their treatment outcomes. For example, the state of Oregon initially set a 75% completion rate as a goal for LTBI treatment; it had a completion rate of only 47% in 1998 that gradually increased to 64% by 2002.[23] The 64% completion rate was similar to the CDC's estimate that only 60% of patients who started treatment for LTBI finish at least six months (2000; LoBue & Moser, 2003). At the San Francisco TB Control clinic, an analysis of the 2001-2003 data on the clientele treated for LTBI indicated an overall completion rate of 72%: among the foreign-born clients the rate was 74-80%, and among the U.S. born approximately 60-65% (Ginsdale, 2004). This makes the achievement of the 82.6% completion rate of this subset of 3,572 Asian clients at the SF TB Control clinic all the more remarkable. Only four clients (.1%) in the cohort were monitored through the directly observed preventive therapy (DOPT) program, therefore the reported 82.6% completion rate was achieved almost exclusively through self-administered (SAT) courses of therapy.

The higher completion rates among the immigrants with LTBI were associated with country of origin, years in the U.S. and, unexpectedly, the factor not speaking English,

---

[23] (*National Tuberculosis Program Objectives Oregon Status 1998-2002*, 2005)

thus rejecting the cohort's first null hypothesis. In this cohort, the majority of the 2,257 immigrants were from China comprising 49.6% of the sample, followed by 1,549 Filipinos (34.1%) and 741 (16.3%) Southeast Asians. Individuals from China, the largest immigrant group, who were in the United States less than five years and did not speak English were 1.3 times more likely to complete treatment than were immigrants from the Philippines or Southeast Asia. In contrast, the Filipino immigrants who spoke English and had resided in the United States for more than five years were less likely to complete treatment. The Southeast Asians were neither more nor less likely than the Filipino immigrants to be treatment adherent.

Significant differences were demonstrated among the immigrants by their countries of origin in a bivariate analysis: gender, chronological age, age at immigration, years to clinic arrival, new versus old immigrant status and the self-reported ability to speak English. With regard to age and immigration-related factors, the cohort's mean age of 31.23 years (SD = 19.5) ($p < .0005$) reflected the CDC and clinic recommendation to treat individuals with positive tuberculin skin tests under the age of 35 years. Filipinos with LTBI were chronologically the oldest migrants with a mean average age of 37.1 years (SD = 21.2); and were the oldest when they migrated at 31.7 years (SD = 20.8). As a consequence of the CDC's treatment emphasis on new immigrants, the majority, 3,314 (72.9%) ($p < .0005$), in this treatment cohort were recent immigrants, having resided in the U.S. less than five years. The Chinese had the shortest U.S. residency (mean 2.98 years, SD = 5.9) prior to being seen at the clinic compared to the Filipinos (mean 5.28 years, SD = 8.0) or SEAs (mean 4.66 years, SD = 6.8). The most noticeable difference among the Asian groups was the contrast between the large percentage of Chinese

(75.6%) who did not speak English and the majority of Filipinos (91.5%) who did speak English. In the logistic regression analysis, this factor, speaking English, country of origin and years in the U.S. were the three factors that predicted treatment completion in the LTBI treatment cohort.

As a factor, the immigrant's country of origin is assumed to designate the environmental factors of a specific geographic area that contribute to the population's resistance and susceptibility to tuberculosis (Davies & Grange, 2001). However, the term country of origin as a predictive factor for treatment adherence also has been used to imply a broad array of socioeconomic, cultural and immigration-related factors that are not clearly defined. For example, it is difficult to separate the issues of immigration from a developing country of origin per se from the issues of poverty. In this cohort of TB exposed immigrants, identifying their differences by specifying their home countries does not inform the reader of the varying incidence of TB, deprivation indices and cultural attitudes related to treatment that may be influencing their treatment adherence in the United States. Nor could the incomplete entries for occupation and past employment in the electronic record provide a socioeconomic picture of the immigrants' past and current status. In the study, there were two immigration related factors available to link the immigrants to their countries of origin that may have played a role in their treatment adherence: the B-wavier notification from the U.S. admission immigration screening process and the alien status report.

For legal entrants screened for immigration, the State TB Registry reports to the local public health departments verified TB cases among immigrants and refugees with Class A (infectious active TB), B1 (active, but not infectious) or B2 (inactive TB) status.

The TB registry collects the overseas information on sex, date of birth, nationality, date of entry to U.S., primary site of TB and the results of sputum smear examinations. This information is used to notify local public health departments of the arrival of class B1 and B2 individuals (Zuber, Binkin et al., 1996) and alert the departments that the individuals with B1 and B2 status need prompt and active follow-up. In DeRiemer et al.'s (1995) study on active and preventable cases of TB, the researchers detected 51 (6.9%) cases in the 745 immigrants and refugees identified with B-waiver notifications. The authors reported that the predictive factors for the B1 immigrants and refugees with active TB were the medical examination in the country of origin (OR, 3.5; 95% CI, 2.0-6.2) and being from mainland China (OR, 4.4; 95% CI, 1.9-9.9) (DeRiemer, Chin, Schecter, & Reingold, 1998).

In this large cohort of Asian immigrants treated for LTBI, only 2.3% of the 4,547 clients had a B-waiver notification date and just 12.2% reported their alien status as immigrant. It was not evident in the electronic record if the TB registry data was coordinated with the clinic database. Without the B-waivers and alien status self reports, it may be still be reasonable to assume that a greater percentage of the cohort had legal permanent residency (LPR) status or temporary worker, student or visitor status compared to those without visas or undocumented status. This assumption about immigrants' legal status was based on the greater difficulty of entering the U.S. from overseas versus by land. To avoid discouraging or excluding undocumented immigrants from seeking treatment, the SF TB control unit does not restrict or charge for its healthcare services to any foreign-born individual who is at-risk for developing TB (Chin et al., 1998; DeRiemer et al., 1998). If a higher percentage of the TB clinic's foreign-

born Asians have permanent or temporary legal immigration status, does this factor reduce their fears of deportation when seeking treatment for TB? Once enrolled in the clinic services, does the immigrant's anxiety as a newcomer or the desire to "fit-in" motivate his or her treatment adherence? Did the Chinese immigrants, who are the most adherent group in the study, complete treatment because as legal permanent residents they did not fear detection and possible deportation; or as newcomers did they feel "obligated" to accept U.S. treatment recommendations? These questions underlie the use of country of origin and the implicit role that the immigration process possibly plays in an immigrant's adherence.

Some of the problems associated with TB treatment among the foreign-born have been attributed to linguistic and cultural barriers. This issue is clearly raised when interpreting the culturally related predictive factor, no English. The yes/no response to the study variable, speak English, does not measure language proficiency or indicate if the English was the speaker's first or second language (Stevens, 1999). In this study, not speaking English could be interpreted as an indication of less acculturation and less assimilation into American mainstream society. It could be speculated that the non-English speakers would be less adherent in the LTBI treatment cohort due to unfamiliarity with living in a predominantly English-speaking country. The results of the treatment study suggest the opposite findings. The English-speaking Filipino immigrant was 42% less likely to complete treatment compared with the non-English speaking Chinese immigrant. This observation is counter-intuitive; most health education programs that serve culturally diverse populations would assume that those who speak English and were more familiar with American culture would more readily understand

the reasons for treatment and be willing to cooperate with treatment. Yet, the analysis of the predictor factor for adherence singled out the non-English speaking newly arrived Chinese immigrant as more likely to complete treatment than the English-speaking Filipino immigrant. From a health services perspective this suggests that, in addition to the urgency of reaching out to the newly arriving immigrants, cultural assumptions regarding which patients are at risk need to be evaluated. To identify the characteristics of the foreign-born patients who are most likely to be nonadherent, health care providers need to be aware that the English-speaking Filipino immigrant who appears to be more acculturated may actually be the client who requires DOPT observation to complete treatment.

The third significant predictive factor for treatment adherence was the length of time that an immigrant had lived in the U.S. The high rate reactivation of TB in the first five years after migration has been well established in past studies. This study adds to these findings in that not only are new immigrants more likely to reactivate; they are also more likely to be treatment adherent during this vulnerable time period. Conversely, the longer the English-speaking Filipino immigrants remains in U.S. the likelihood that they complete treatment decreases with each year. After a decade has passed, the treatment adherence of these immigrants will decline to 68.4%, which is only slightly higher than the 60% reported for the U.S.-born population.

Limitations of the Study Findings and Generalizability

There is little known about the characteristics of foreign-born populations that influence their adherence and nonadherence. However, the findings in this study are limited to San Francisco's Asian immigrant population; the study observations are not

representative of the clinic's foreign-born population or the Asian immigrant populations in other American cities. The second study limitation is that the recommended length of prophylaxis treatment was six months at the time of the study; but now the standard length of treatment has increased to nine months. The added months in treatment length could have reduced the high LTBI adherence rates reported in study. Lastly, the completion rates in the study were based on the final clinic evaluation and the actual rates may have been lower if there were other measures to confirm or monitor adherence, such as urine metabolite testing, or the increased use of DOT supervision with the active TB cohort, or DOPT with the clients with LTBI.

Conclusion

This historic cohort study on TB treatment outcomes offers promising insights in defining the factors that characterize and influence the reactivation of TB in Asian immigrants after they have resettled in their new homes. The findings in this study suggest that a surprisingly counter-intuitive approach be taken to identify the Asian client at risk for nonadherence. The outcomes suggest that the immigrant who speaks English and appears more acculturated was more likely be nonadherent than the immigrant who is non-English speaking and recently arrived in the United States. The second finding supports targeting the newly arriving immigrants not only because of the associated high proportion of reactivation during this period, but because these newest arrivals are more likely to complete the suggested TB treatment. This recommendation suggests the active involvement of the medical and a culturally competent healthcare staff. The electronic dataset used in this study did not reflect details of the TB clinic staff's monthly client interventions or the availability of the clinic's multi-lingual services. The influential role

representative of the clinic's foreign-born population or the Asian immigrant populations in other American cities. The second study limitation is that the recommended length of prophylaxis treatment was six months at the time of the study; but now the standard length of treatment has increased to nine months. The added months in treatment length could have reduced the high LTBI adherence rates reported in study. Lastly, the completion rates in the study were based on the final clinic evaluation and the actual rates may have been lower if there were other measures to confirm or monitor adherence, such as urine metabolite testing, or the increased use of DOT supervision with the active TB cohort, or DOPT with the clients with LTBI.

Conclusion

This historic cohort study on TB treatment outcomes offers promising insights in defining the factors that characterize and influence the reactivation of TB in Asian immigrants after they have resettled in their new homes. The findings in this study suggest that a surprisingly counter-intuitive approach be taken to identify the Asian client at risk for nonadherence. The outcomes suggest that the immigrant who speaks English and appears more acculturated was more likely be nonadherent than the immigrant who is non-English speaking and recently arrived in the United States. The second finding supports targeting the newly arriving immigrants not only because of the associated high proportion of reactivation during this period, but because these newest arrivals are more likely to complete the suggested TB treatment. This recommendation suggests the active involvement of the medical and a culturally competent healthcare staff. The electronic dataset used in this study did not reflect details of the TB clinic staff's monthly client interventions or the availability of the clinic's multi-lingual services. The influential role

representative of the clinic's foreign-born population or the Asian immigrant populations in other American cities. The second study limitation is that the recommended length of prophylaxis treatment was six months at the time of the study; but now the standard length of treatment has increased to nine months. The added months in treatment length could have reduced the high LTBI adherence rates reported in study. Lastly, the completion rates in the study were based on the final clinic evaluation and the actual rates may have been lower if there were other measures to confirm or monitor adherence, such as urine metabolite testing, or the increased use of DOT supervision with the active TB cohort, or DOPT with the clients with LTBI.

Conclusion

This historic cohort study on TB treatment outcomes offers promising insights in defining the factors that characterize and influence the reactivation of TB in Asian immigrants after they have resettled in their new homes. The findings in this study suggest that a surprisingly counter-intuitive approach be taken to identify the Asian client at risk for nonadherence. The outcomes suggest that the immigrant who speaks English and appears more acculturated was more likely be nonadherent than the immigrant who is non-English speaking and recently arrived in the United States. The second finding supports targeting the newly arriving immigrants not only because of the associated high proportion of reactivation during this period, but because these newest arrivals are more likely to complete the suggested TB treatment. This recommendation suggests the active involvement of the medical and a culturally competent healthcare staff. The electronic dataset used in this study did not reflect details of the TB clinic staff's monthly client interventions or the availability of the clinic's multi-lingual services. The influential role

#4 1982 Pediatric screening of Southeast Asian immigrants.	Goldenring, Davis & McChesney	Clinical Pediatrics	Descriptive population health screening survey of SEA children and young adults	Sample: 623 SEAs; 94% Vietnamese, 4% Laotian and 2% Cambodian Santa Clara County, California	Age-dependence prevalence of + TST results: 13% in infants rising to 34% in young adults; parasitism detected in average of 58.8% of subjects screened. Prevalence of anemia especially high (35.7%) in infants and young children.
#5 1982 High rate of tuberculin conversion in Indochinese refugees.	Morse, Hansen, Swalbach, Redmond, & Grabau	JAMA	Descriptive clinical study	Total: 664 screened; 307 (46%) with + PPD Monroe County, New York	All initial 227 nonreactors were retested at 60 days; 94 (43%) converted from a negative to positive test. Notably, none of the 94 converters had clinical evidence of disease or chest x-ray changes suggestive of current tuberculosis.
#6 1983 Indochinese refugee health assessment	Sutherland, Avant, Franz, Monzon, & Stark.	The Journal of Family Practice	Descriptive clinical retrospective review of health findings of refugee patients	Sample: 426 refugee patients treated from 1975 to mid-1981 Rochester, Minnesota	Refugees: 54% with + TST results; 82% with intestinal parasites; & 13% with hepatitis B antigen. More comprehensive report on psychosomatic or psychiatric disorders, contraceptive usage and frequency of hematologic genetic disorders.

#7 1983 Tuberculosis among Indochinese refugees in the United States.	Powell, Brown, & Farer	JAMA	Observational cross-sectional CDC survey on SEAs	State TB surveillance data on 262,602 Indochinese refugees entered the U.S from 1979 to 1980	The estimated 1979 incidence rates for TB ranged from 719/100,000 to 231/100,000. In 1980, the annual incidence rate declined to 480/100,000. The SEAs' age and sex-specific incidence rates were 30 to 200 times higher than comparable U.S.-born groups. From 1979 to 1980, approximately 18% of the 46,000 of the refugees were given chemoprophylaxis therapy. The decreased incidence in 1980 was seen as the result of efforts to reduce transmission upon arrival and improvements in the overseas screening procedures. The low rate of 34% positive bacteriologic findings even among incident cases suggested as a result of over-diagnosis by U.S. physicians.
#8 1983 Clinical findings of Southeast Asian refugees: Child development and public health concerns.	Barry, Craft, Coleman, Coulter, & Horwitz	JAMA	Descriptive clinical survey of health status of SEA refugees	Sample: 142 SEA refugees from September 1979 to November 1980	Refugees: 39% with + TST results, with one active case of TB; 59% with intestinal parasitism and 16% with hepatitis B antigenemia.
#9 1984 Health status of Southeast Asian refugees	Judson, Lince, Anders, Tapy, Le Van, Cohn, & Kicera	Western Journal of Medicine	Descriptive clinical report on health screening.	Sample: 991 SEA refugees: Vietnamese 58%, Cambodian 26%, Laotian 12% and Hmong 5%; screened from July 1981 to June 1982. Nashville, Tennessee	Refugees: 38% with + TST results with 3% with CXRs consistent with past or current TB; highest rate of TST positivity among 40 to 59 year olds (68%) followed by 20 to 39 year olds (50%). Intestinal parasitic infections in 71%, hepatitis B antigen, 15%. Infection rates varied among the Vietnamese, Cambodians, and Laotians.

#10 1985 Tuberculin conversions in Indochinese: an assessment of boosting and anergy.	Morse, Hansen, Grabau, Cauthen, Redmond, & Hyde	American Review of Respiratory Disease	Observational follow-up study on tuberculin conversion rates	Sample: 225 Asian refugees from November 1981 to October 1982 Monroe Country, New York	Out of the 218 SEA refugees 52% with initial tuberculin tests that were negative converted to positive reactions on subsequent testing. Conversion rates could not be explained in terms of antigen, technique, previous BCG, country of origin, TB exposure, recent illnesses, or immunizations. Authors suggest boosting of sensitivity plays a major role, but not anergy, as measured by mumps and candida tests.
#11 1987 Health care needs of Indochinese refugee teenagers.	Fitzpatrick, Johnson, Shragg & Felice	Pediatrics	Descriptive clinical report on the health status of Indochinese refugee teenagers	Sample: 80 Indochinese refugee teenagers. San Diego, California	Among the Cambodian and Vietnamese teenagers: 52% with + TST results; intestinal parasites detected in 24/69 (35%); and hepatitis B antigen in 10/74 (14%). The LTBI was seen as the most common health problem among SEA teenagers.
#12 1988 Tuberculosis in a cohort of Southeast Asian refugees: a five-year surveillance study.	Nolan & Elarth	American Review of Respiratory Diseases	Observational retrospective cohort study	Sample: 9,328 SEA refugees screened from January 1980 to December 1981 with a 5-year follow-up study on 25 cases with TB, who were classified free of TB at the time of immigration Seattle-King County, Washington	Active TB diagnosed in 78/9,328 (0.8%) refugees; 3,300/9,328 (35.7%) had significant TST reactions. The 5-year cumulative incidence of TB for this cohort was 26.8 cases per 100,000 population. Among the 25 TB cases: 10/25 (40%) developed pulmonary TB with other 12 cases involving cervical lymph nodes, lymphatic tuberculosis or extrapulmonary sites. The remaining 3 TB cases with negative TSTs: one case had pulmonary TB and lung cancer concurrently; and 2 cases had extrapulmonary TB.

#13 1989 The use of sputum cultures in the evaluation of immigrants classified as tuberculosis suspects.	Nolan, Teklu, & Wu	American Review of Respiratory Disease	Observational prospective 2-year cohort study to evaluate use of sputum smears and cultures to screen new immigrants with suspected TB. Secondly, a retrospective case-control study to identify risk factors to selectively guide the use of sputum examinations in new immigrants	Cohort study on 249 asymptomatic Asian immigrants w/stable abnl CXRs from July 1984 to June 1986. Case-control sample: 37 cases selected from case registries from 1981 to 1986; 48 control subjects were randomly selected with at least two negative sputum smears and cultures Seattle-King County, Washington	Cohort study: 13/249 (5.2%) had one or more positive cultures for TB; none had positive smears. The incidence rate of Cambodian and Laotian immigrants was from 3-10x greater than immigrants from other Asian countries. Case-control study: 24/37 (65%) were refugees from Vietnam, Kampuchea, and Laos; 6/37 (16%) were Filipino, 5 (13%) were Chinese either from Taiwan or Hong Kong; 3 were Korean; 1 was Ethiopian. Results: Cases were twice as likely to be under 50 yrs of age; have TB tests > 10 mm; report a cough and 5x less likely to report having received prior treatment for TB.
#14 1991 An alternative to 'two-step' tuberculin skin testing for Southeast Asian refugees.	Wenzel	Nurse Practitioner	Descriptive clinical evaluation of SEAs antigenic response to tuberculin skin test	Sample 101 SEA refugees in 1988 Maricopa County, Arizona	Initial reading: 49/101 (48.5%) had + TSTs; 22/52 (22%) nonreactors at second reading had + TST three to five days later. The remaining 28 refugees with - TSTs had two-step testing; with 2/28 (3.8%) with + TSTs. Authors recommended a single TST read at 5-7 days might be a cost effective alternative to two-step TST testing.
#15 1994 Boosting of tuberculin sensitivity among Southeast Asian refugees.	Cauthen, Snider, & Onorato	American Journal of Respiratory Critical Care Medicine	Descriptive clinical evaluation of SEAs' tuberculin sensitivity to boosting	Sample: 2,469 SEA refugees Refugee Processing Center in Bataan, Philippines	Initial test 35.5% refugees had + TST; 30.9% of the nonreactors exhibited boosting on subsequent tuberculin test. Authors suggested that the boosting was associated with reactivity to nontuberculous mycobacterial antigens and the history of BCG vaccination.

#16 1996 Delayed tuberculin reactivity in persons of Indochinese origin: implications for preventive therapy.	Robertson, Burtt, Edmonds, Molina, Kiefe, & Ellner	Annals of Internal Medicine	Observational cross-sectional study on the variant delayed reaction to tuberculin testing	Sample: 121 adult Vietnamese refugees North Carolina	Variant delayed reaction defined as reactivity of < 10 mm at standard reading of 48 to 72 hours, when reassessed at 6 days, increases in size to 10 mm or greater. Results: after 72 hours, 35/121 (29%) had + TSTs; 54/121 (45%) were - TST; and 32/121 (26%) had variant reactivity. Those with variant reactions with subsequent booster testing 65% had positive reactions when retested.
#17 1997 Screening in special populations: a "case study" of recent Vietnamese immigrants.	Nelson, Bui, & Sarnet	The American Journal of Medicine.	Descriptive program evaluation of health screening protocols	Sample: 99 Vietnamese immigrants who had resided in U.S. less than six months between October, 1994 to June, 1995 Boston, Massachusetts	Data collected on smoking status, alcohol use, depression and infectious health conditions. Immigrants: + TSTs in 66/94 (70.2 %) with chemotherapy recommended for 37/94 (39%); 41/80 (51%) with enteric parasites; and, 13/96 (14%) diagnosed as chronic hepatitis B carriers. Last screening study published on SEAs health status.
Overseas Screening Programs for Asian Immigrants					
#18 1990 Tuberculosis morbidity and infection in Vietnamese in South Asian refugee camps.	Sutter & Haefliger	American Review of Respiratory Disease	Descriptive population study of Vietnamese in two refugee camps	Sample: 19,726 in Suan Phlu & 741 Vietnamese refugees screened from April 1985 to October 1986 Suan Phlu Camp, Bangkok, Thailand & Palawan, Philippines	In Suan Phlu the prevalence of pulmonary TB was 5.8/1000 and prevalence of sputum smear positive TB was 1/1000. In Palawan 35% of refugees had positive skin tests. The estimated annual risk of infection was 2.2% with male refugees risk of infection being twice as high as the female refugees. Using the CDC criteria 85% of the +TST refugees would have been candidates for prophylaxis treatment.

#19 1995 Prevalence of tuberculosis in Vietnamese migrants: the experience of the Orderly Departure Program.	Keane, O'Rourke, Bollini, Pampallona, & Siem	The Southeast Asian Journal of Tropical Medicine and Public Health	Descriptive population study of Vietnamese migrants and refugees prior to their departure to U.S.A.	Sample: 322 Vietnamese who were AFB smear positive from November 1992 to June 1993 Ho-Chi-Minh City, Vietnam	Among the 39,581 prospective Vietnamese migrants and refugees screened prior to departure, 322 were smear positive (641/100,000) and started chemotherapy. Of these patients, 265 (82.3%) were cured and 24 (7.5%) patients continued treatment with first line drugs; 16 (4.9%) patients did not complete treatment.
International Studies on SEAs in Low-Incidence Countries					
#20 1998 Tuberculosis in South-East Asian refugees after resettlement-can prevention be improved by better policy and practice?	MacIntyre, App, & Plant	Preventive Medicine	Observational retrospective cohort study	Sample: 1,101 refugees from Laos, Cambodia & Vietnam from July 1989 to January 1990 Western Australia	Incidence of active TB was 363/100,000 in the first year then dropped to 109/100,000 in the first 5 years after resettlement. Increased the sensitivity of the definition of TB to TST>15mm post BCG or 10mm without BCG, or CXR evidence of inactive TB, New definition would have added 229 refugees to the 162 as candidates eligible for prophylaxis therapy, possibly preventing 24 new cases of TB.
#21 1999 Longitudinal incidence of tuberculosis in South-East Asian refugees after resettlement.	MacIntyre & Plant	The International Journal of Tuberculosis and Lung Disease	Observational retrospective cohort study.	Sample: 1101 refugees from Laos, Cambodia & Vietnam from July 1989 to January 1990; with cases matched with refugee database for 1989 to 1994 Western Australia	Refugees: 561/938 (60%) with TST >10mm or more; 124/561 (22%) received INH prophylaxis therapy. Normal CXRs on 761 (89.2%), 492 (65%) with nl CXRs had + TSTs. Abnormal CXRs on 92 (10.8%) with 82/92 (90%) also had + TST. No cases of TB occurred in refugees with TST < 10mm. Posed that the stress of migration increased the susceptibility to disease by affecting the refugees' immunity. Other possible explanation is the presence of chronic malnutrition, hepatitis B, psychosomatic problems and intestinal parasitaemia.

#22a 2000 Incidence of tuberculosis among a cohort of tuberculin-positive refugees in Australia.	Marks, Bai, Simpson, Sullivan, & Stewart	American Journal of Respiratory Critical Care Medicine	Observational historical cohort study from 1984 to 1994; mean duration of follow-up to June 1998 or time of diagnosis of TB was 10.3 yrs	Sample: 15,486 refugees; 86% originated from SEA: Vietnam, 67.5%; Cambodia, 10.5%; and Laos, 7.8% New South Wales, Australia	Refugee profile: 58% male, median age 27 yrs, 53.3% with +TST and 63% with BCG scars. Crude annual incidence of TB was 76.2 (95% CI), 63.5 to 91.3 per 100,000 PY; incidence greatest in first three years, 112 (95% CI. 85-148) per 100,000 PY, over next 10 years incidence averaged 66 (95% CI, 52 to 84) per 100,000 PY. Notably, among persons with TST > 15 mm, the annual incidence rate was 213 (95% CI, 150 to 300) in the first 3 years and in the next ten years averaged 122 (95% CI, 90 to 165) per 100,000 PY. There was a significant linear relationship for the increased risk of TB corresponding to the increasing size of the TST reaction. First study to examine the incidence of LTBI reactivation among SEAs in Australia whose native TB rate was 5.4/100,000.
#23b 2001 The incidence of tuberculosis in a cohort of South-East Asian refugees arriving in Australia 1984-94.	Marks, Bai, Stewart, Simpson, & Sullivan	Respirology	Observational historic cohort study from 1984 to 1994	Same study sample New South Wales, Australia	Overall incidence rate in the cohort increased to 74.9 per 100,000 PY; 47% of the cases were among females with the highest rate among 40-49 year olds. The epidemiological profile of equal gender distribution and the predominately young age of the cohort (20 to 29 years old, median age 22.1 years) resemble the earlier stage of the evolution of the TB epidemic.

#24c 2001 Effectiveness of postmigration screening in controlling tuberculosis among refugees: a historical cohort study, 1984-1998.	Marks, Bai, Stewart, Simpson, & Sullivan	American Journal of Public Health	Observational historic cohort study from 1984 to 1994 to assess effectiveness of postmigration screening.	Same study sample	In June 1998, there were 290 cases of active TB in study cohort after an average follow up interval of 10.3 years. In the first year there were 55 cases (29.1%) and 124 cases (65.6%) within the first 5 years after arrival. Routine screening identified only 43 cases; 572 persons were screened per each detected case. Short-term screening only detected less than one-third cases that occurred in cohort; concluded active case finding approach was not cost-effective TB control strategy for SEA population.
#25 1998 Tuberculosis in a cohort of Vietnamese refugees after arrival in Denmark 1979-1982.	Wilcke, Poulsen, Askgaard, Enevoldsen, Rønne, & Kok-Jensen	International Journal of Tuberculosis and Lung Disease	Observational historic cohort study; 16 year follow-up	Sample: 1,983 Vietnamese refugees who arrived from 1979 to 1982 Denmark	Notifications for TB from a high of 1.14% in the first year after arrival to 0.07% in the following 10 yrs. 1,936 (98%) of refugees identified in the 16 yrs of follow-up; 36 (1.86%) refugees developed TB. Patients were identified by civil registration numbers; TB can be controlled among high-prevalence immigrants through limited passive diagnostic program without preventive chemotherapy.

Appendix B

Center for Disease Control and Prevention Reports: Prevalence Studies				
Study	**Year**	**Author**	**Prevalence**	**Findings**
Health status of Indochinese refugees	1979	CDC MMWR (Vol 28/No. 33, 1979)	1979 Data from San Francisco, Los Angeles, and Washington state indicate 1%-2% of refugees have active TB.	Overseas screening and notification procedures described. Recommendations for follow-up on Class A refugees and chemoprophylaxis treatment for Class B tuberculosis patients.
Health screening of resettled Indochinese refugees-Washington, D.C., Utah.	1980	CDC MMWR (Vol 1/No. 1, 1980)	1980 Indochinese children 10/45 (22%) tested positive for TB; in SEA refugees in Utah 152/356 (43%) had positive PPDs.	Noted that the rates of hepatitis B antigenemia, tuberculin reactions, and intestinal parasitism were consistent with findings in 1979. More than 100,000 Indochinese refugees have been admitted in 1980 yet little population-based data has been published on health conditions other than tuberculosis and intestinal parasitism.
Tuberculosis – United States 1984	1985	CDC MMWR, (Vol 34/No.6, 1985)	1985 Provisional overall incidence rate was 9.2 cases/100,000	Noted: 1978 to 1981 large influx of SEA refugees decreasing the average annual decline to only 3.2%. 1984 the downward trend resumed due to fewer indigenous TB cases; decline in number of refugees; and more states using new national case reporting system.
Topics in Minority Health: Tuberculosis in Minorities – United States	1987	CDC MMWR, (Vol.36/No.6, 1987)	1985 22,701 cases of known race, 11,524 (52%) were whites, 10,646 (48%) were nonwhites	TB among minorities peaks in 25 to 34-age range – greater potential of infecting their children. Childhood TB cases should be viewed as sentinel health events.
Topics in Minority Health: Tuberculosis among Asian/Pacific Islanders – United States, 1985	1987	CDC MMWR, (Vol 36/No. 20.21,22,1987)	1985 22,201 TB cases; overall incidence rate was 9.5 cases/100,000.	2,530 cases (11.4%) were API patients. Case rate was 49.6/100,000; 8.7 times higher than 1985 rate of 5.7/100,000 for white U.S. population.

Extrapulmonary TB in the United States	1989	Rieder, Snider, Cauthen	3,942 cases with extrapulmonary TB sites	63% of pulmonary & extrapulmonary cases among racial/ethnic minorities and the foreign-born. FB patients more likely than U.S.-born to develop extrapulmonary TB.
Tuberculosis among Foreign-born Persons Entering the United States	1990	CDC MMWR, December 28, 1990, Vol.39/No.RR-18	1989 overall TB rate 9.5/100,000; foreign-born persons case rate 124/100,000	1986-1989, 22%(20,316) cases occurred among FB population. Majority of FB persons who develop TB do so within first 5 years after entering US. Recommendations for health screening and follow-up requirements for aliens.
Prevention and Control of TB in U.S. Communities At-Risk Minority Populations	1992	CDC MMWR, (Vol 41/No. RR-5)	1990, 25,701 cases with an overall case rate of 10.3/100,000	1990, almost 70% of all TB cases and 86% of those among children ages <15 occurred among racial/ethnic minorities. Compared to case rate of 4.2/100,000 among non-Hispanic whites the case rate among APIs was 9.9 times higher. From 1986 to 1990 the percentage of total cases among FB increased from 21.6% to 24.4%.
Tuberculosis Morbidity – United States, 1995	1996	CDC MMWR, (Vol. 45/No.18)	1995, 22,813 cases with an overall case rate of 8.7/100,000.	FB TB cases account for 35.7% of total reported cases; 63.3% increase since 1986. Six countries of origin for 63.6% of cases: Haiti, India, Mexico, People's Republic of China, Philippines, and Vietnam. Among the 4,804 FB persons reported in 1995, 1,441 (30%) had TB diagnosed with 1 year; 2,567 (53.4%) were diagnosed within 5 years after entering the United States.
Tuberculosis Morbidity – United States, 1996	1997	CDC MMWR, (Vol 46/No. 30).	1996, 21,337 cases reported with case rate of 8.0/100,000	Fourth consecutive year of decline in TB cases. U.S.-born case rate decreased to 5.6/100,000 in 1996. TB cases among FB accounted for 36.6% with a decrease of 2.9%; the first decrease among FB persons since 1986. Of the 5,225 foreign-born persons, 1,439 (27.5%) were diagnosed with TB within 1 year and 1,431 (27.4%), 1-5 years after entering the United States.

Progress Toward the Elimination of Tuberculosis in the United States.	1999	CDC MMWR, (Vol.48/No.33)	In 1998, a total of 18,361 TB cases reported; with a case rate of 6.8/100,000.	Number of U.S.-born cases decreased 44%; foreign-born cases increased by 4%; the proportion of foreign-born cases rose from 27% in 1992 to 42% in 1998.
Tuberculosis Morbidity among U.S.-born and Foreign-born Populations – United States	2002	CDC MMWR (Vol. 51/No. 5).	In 2000, a total of 16.377 TB cases reported; with a case rate of 5.8/100,000	Among U.S.-born 8,714 cases - (3.5/100,000); 7,554 cases of foreign-born persons (25.8/100,000) representing 46% of all cases.
Trends in Tuberculosis Morbidity – United States, 1992-2002	2003	CDC MMWR, (Vol.52/No.11)	During 2002, a total of 15,078 TB cases reported; with a case rate of 5.2/100,000	In 2002.the ratio of foreign-born to U.S.-born rates doubled, from 4.2 in 1992 to 8.4. U.S.-born non-Hispanic blacks are 46.7% of TB in U.S.-born persons and ~25% of all cases. **TB cases among the foreign-born are now the majority of TB cases (51%) in the United States.**

Appendix C

Definition of Terms & Treatment Protocols

LTBI Latent tuberculosis infection

TB1 Tuberculosis exposure without evidence of infection
History of exposure
Negative reaction to tuberculin skin test

TB2 Tuberculosis infection – no disease
Positive reaction to tuberculin skin test
Negative bacteriologic studies (if done)
No clinical, bacteriological or radiographic evidence of current disease.

TB3 Tuberculosis disease – clinically active
Mycobacterium tuberculosis cultured (if done)
Clinical, bacteriological or radiographic evidence of current disease

TB4 Tuberculosis: not clinically active
History of episode(s) of tuberculosis, or
Abnormal but stable radiographic findings
Positive reaction to tuberculin skin test
Negative bacteriologic studies (if done), and
No clinical or radiologic evidence of current disease

TB5 Tuberculosis disease suspected
Diagnosis pending

Case definition: (MMWR May 2, 1997)

A clinically verified case of TB is a case that meets *all* of the following criteria:

- A positive TST; and
- Other signs and symptoms compatible with TB (an abnormal or unstable, i.e., worsening or improving) x-ray, or clinical evidence of current disease; and
- Treatment with two or more anti-TB meds; and
- Completed diagnostic evaluation.

- Lab criteria: isolation of MTB from clinical specimen, or NAA test or acid-fast bacilli in a clinical specimen when a culture has not or cannot be obtained.

A case should not be counted twice within any consecutive 12-month period. However, cases in which the patients had previously had verified disease should be reported again if the patients were discharged from treatment. Cases lost to FU for > 12 months and the disease can be verified again should be reported again.

Anti-Tuberculosis Treatment Guidelines

The accepted anti-tuberculosis guidelines endorsed by American Thoracic Society in 1993 and published in 1994; and followed by the SFGH TB Clinic during the study time period:

1. A six-month regimen of isoniazid (INH), rifampin, pyrazinamide (pza) for two months followed by INH & rifampin for four months is the preferred treatment for patients with fully susceptible organisms: if there is less than 4% primary resistance to INH in the community and the patient has no previous treatment.
2. Alternatively, a nine-month regimen of INH and rifampin is acceptable if the person cannot or should not take pza. If INH resistance is demonstrated, rifampin and emb should be continued for a minimum of 12 months.
3. Extrapulmonary TB should be managed according to the principles and the drug regimens outlined for pulmonary TB. Six to nine month short course regimens are effective. The exception is the treatment for children who have miliary TB, bone/joint TB or TB meningitis who should receive a minimum of 12 months of therapy.
4. A four-month regimen of INH, rifampin is acceptable therapy for adults who have active TB and who are sputum and culture negative, if there is little possibility of drug resistance. Because of the risk of inducing INH resistance when INH is used as monotherapy in a person with current tuberculosis, the recommended regimens for treatment of disease should be used until diagnosis is clarified. If the evaluation confirms previous but not current tuberculosis, multi-drug therapy may be stopped after four months.

5. Persons who had been adequately treated in the past should be excluded from preventive therapy.
6. For latent TB Infections: Preventive therapy with INH given for six to 12 months is effective in decreasing the risk of future TB in adults and children with tuberculosis infection demonstrated by positive TB skin test reactions.
7. For children and adults with HIV infection, close contacts of infectious cases, and those with fibrotic lesions on chest radiographs, a reaction of >5 is considered positive. For other at-risk adults and children, including infants and children younger than four years of age a reaction of >10 mm is positive.
8. Persons with positive skin tests and any of the following risk factors should be considered for preventive therapy regardless of age:
    - Persons with HIV infection
    - Persons at risk for HIV infection with unknown HIV status
    - Close contacts of sputum positive persons with newly diagnosed infectious TB
    - Newly infected persons (recent skin test converters)
    - Persons with medical conditions reported to increase the risk of TB: i.e. diabetes mellitus, adrenocorticosteroid therapy and other immunosuppressive therapy, end stage renal disease, intravenous drug use, hematologic and reticuloendothelial malignancies, and clinical conditions associated with rapid weight loss or chronic undernutrition.
9. TB skin test positive adults with abnormal chest films that show fibrotic lesions likely representing old healed tuberculosis and adults with silicosis should usually receive four months of multidrug chemotherapy or 12 months of INH preventive therapy.
10. In the absence of any of the above risk factors, persons younger than 35 years of age with positive skin test in the following high incidence groups should be considered for preventive therapy:
    - Foreign-born persons from high-prevalence countries
    - Medically underserved low-income persons from high-prevalence populations (especially blacks, Hispanics and Native Americans) and residents of long-

term care (i.e., correctional institutions, nursing homes, and mental institutions). The Tuberculosis Control Section of the San Francisco Department of Public Health follows this guideline to define high-risk persons who should have a TB test.

11. For adults and children with HIV infection, 12 months of preventive therapy is recommended; persons without HIV infection should receive at least six months of preventive therapy; nine months of therapy is recommended for children.
12. In patients who have positive tuberculin skin test and either silicosis or a chest radiograph demonstrating old fibrotic lesions with no evidence of active disease, acceptable regimens include: four months of INH and rifampin or 12 months of INH, providing that infection with drug resistant organisms is unlikely. Persons who are presumed to be infected with INH-resistant organisms should be treated with rifampin rather than INH.

Bibliography

2003 Yearbook of Immigration Statistics. (2003). Washington, D.C.: U.S. Department of Homeland Security: Office of Immigration Statistics.

The Asian Population. (2002). Washington, DC: U.S. Department of Commerce: Economics and Statistics Administration: U.S. Census Bureau.

American Thoracic Society (1994). Treatment of tuberculosis and tuberculosis infection in adults and children. *American Journal of Respiratory and Critical Care Medicine, 149*, 1359-1374.

American Thoracic Society. (2000). Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). *American Journal of Respiratory and Critical Care Medicine, 161*(4 Pt 2), S221-247.

Balasubramanian, R., Garg, R., Santha, T., Gopi, P. G., Subramani, R., Chandrasekaran, V., Thomas, A., Rajeswari, R., Anandakrishnan, S., Perumal, M., Niruparani, C., Sudha, G., Jaggarajamma, K., Frieden, T. R., & Narayanan, P. R. (2004). Gender disparities in tuberculosis: report from a rural DOTS programme in south India. *International Journal of Tuberculosis and Lung Disease, 8*(3), 323-332.

Bandyopadhyay, T., Murray, H., & Metersky, M. L. (2002). Cost-effectiveness of tuberculosis prophylaxis after release from short-term correctional facilities. *Chest, 121*(6), 1771-1775.

Barrett-Connor, E. (1978). Latent and chronic infections imported from Southeast Asia. *JAMA, 239*, 1901-1906.

Barry, M., Craft, J., Coleman, D., Coulter, H. O., & Horwitz, R. (1983). Clinical findings in Southeast Asian refugees: Child development and public health concerns. *JAMA, 249*(23), 3200-3203.

Bates, J. H., & Stead, W. (1993). The history of tuberculosis as a global epidemic. *Medical Clinics of North America, 77*(6), 1205-1217.

Bennett, J., Pitman, R., Jarman, B., Innes, J., Best, N., Alves, B., Cook, A., Hart, D., & Coker, R. (2001). A study of the variation in tuberculosis incidence and possible influential variables in Manchester, Liverpool, Birmingham and Cardiff in 1991-1995. *International Journal of Tuberculosis and Lung Disease, 5*(2), 158-163.

Bloch, A. B., Cauthen, G. M., Simone, P. M., Kelly, G. D., Dansbury, K. G., & Castro, K. G. (1999). Completion of tuberculosis therapy for patients reported in the United States in 1993. *International Journal of Tuberculosis and Lung Disease, 3*(4), 273-280.

Booster Phenomenon (2003). Department of Public Health. Retrieved December 10, 2003, from the World Wide Web: http://www.state.ma.us/dph/cdc/tb/tbboos.html

Borgdorff, M. W., Behr, M. A., Nagelkerke, N. J., Hopewell, P. C., & Small, P. M. (2000). Transmission of tuberculosis in San Francisco and its association with immigration and ethnicity. *International Journal of Tuberculosis and Lung Disease, 4*(4), 287-294.

Borgdorff, M. W., Veen, J., Kalisvaart, N. A., Broekmans, J. F., & Nagelkerke, N. J. (2000). Defaulting from tuberculosis treatment in The Netherlands: rates, risk

factors and trend in the period 1993-1997. *European Respiratory Journal, 16*(2), 209-213.

Brewer, T. F., & Heymann, S. J. (2004). To control and beyond: moving towards eliminating the global tuberculosis threat. *Journal of Epidemiology and Community Health, 58*(10), 822-825.

Brown, C. (1997). *Legal Immigration to California 1984-1994: A Summary.* Sacramento, CA: Department of Finance: Demographic Research Unit.

Brudney, K., & Dobkin, J. (1991). Resurgent tuberculosis in New York City. Human immunodeficiency virus, homelessness, and the decline of tuberculosis control programs. *American Review of Respiratory Disease, 144*(4), 745-749.

Burman, W. J., Cohn, D. L., Rietmeijer, C. A., Judson, F. N., Sbarbaro, J. A., & Reves, R. R. (1997). Noncompliance with directly observed therapy for tuberculosis. Epidemiology and effect on the outcome of treatment. *Chest, 111*(5), 1168-1173.

Camie, J., Christensen, A., Eyeson-Annan, M., Gill, J., Konstantinos, A., Krause, V., Hurwitz, M., & Misrachi, A. (2001). Tuberculosis notifications in Australia, 1998. *Communicable Disease Intelligence, 25*(1), 1-8.

Campbell, I. A., & Dyson, A. J. (1977). Lymph node tuberculosis: a comparison of various methods of treatment. *Tubercle, 58*(4), 171-179.

Cantwell, M. F., Snider, D. E., Jr., Cauthen, G. M., & Onorato, I. M. (1994). Epidemiology of tuberculosis in the United States, 1985 through 1992. *JAMA, 272*(7), 535-539.

Catanzaro, A., & Moser, R. J. (1982). Health status of refugees from Vietnam, Laos, and Cambodia. *JAMA, 247*(9), 1303-1308.

Cauthen, G., Snider, D., & Onorato, I. (1994). Boosting of tuberculin sensitivity among Southeast Asian refugees. *American Journal of Respiratory Critical Care Medicine, 149*, 1597-1600.

Cayla, J. A., Caminero, J. A., Rey, R., Lara, N., Valles, X., & Galdos-Tanguis, H. (2004). Current status of treatment completion and fatality among tuberculosis patients in Spain. *International Journal of Tuberculosis and Lung Disease, 8*(4), 458-464.

CDC. (1971). Preventive treatment of tuberculosis. A joint statement of the American Thoracic Society, National Tuberculosis and Respiratory Disease Association, and the Center for Disease Control. *American Review of Respiratory Disease, 104*(3), 460-463.

CDC. (1975). Update on Vietnamese refugee health status. *MMWR Morbidity and Mortality Weekly Report, 28*, 267-268.

CDC. (1979). Health status of Indochinese refugees. *MMWR Morbidity and Mortality Weekly Report, 28*(33), 385-398.

CDC. (1980a). Health screening of resettled Indochinese refugees-Washington, D.C., Utah. *MMWR Morbidity and Mortality Weekly Report, 1*, 4-11.

CDC. (1980b). *Tuberculosis in the United States*. Atlanta, GA: U.S. Department of Health and Human Services.

CDC. (1981). Tuberculosis among Indochinese refugees--an update. *MMWR Morbidity and Mortality Weekly Report, 30*(48), 603-606.

CDC. (1985). Tuberculosis - United States, 1984. *MMWR Morbidity and Mortality Weekly Report, 34*(6), 86-87.

CDC. (1987). Topics in minority health tuberculosis among Asian/Pacific Islanders - United States, 1985. *MMWR, 36*(21), 331-334.

CDC. (1990). Tuberculosis among foreign-born persons entering the United States. Recommendations of the Advisory Committee for Elimination of Tuberculosis. *MMWR Recommendations Reports, 39*(RR-18), 1-21.

CDC. (1992). Prevention and control of tuberculosis in U.S. communities with at-risk minority populations. *MMWR Morbidity and Mortality Weekly Report, 41*(RR5), 1-11.

CDC. (1993a). Initial therapy for tuberculosis in the era of multidrug resistance. Recommendations of the Advisory Council for the Elimination of Tuberculosis. *MMWR Recommendations Reports, 42*(RR-7), 1-8.

CDC. (1993b). Tuberculosis in Philippine National World War II Veterans immigrating to Hawaii, 1992-1993. *MMWR Morbidity and Mortality Weekly Report, 42*(34), 656-657, 663.

CDC. (1993c). Tuberculosis Morbidity - United States, 1992. *MMWR CDC Surveillance Summaries, 42*(36), 696-704.

CDC. (1994). Expanded Tuberculosis Surveillance and Tuberculosis Morbidity-United States, 1993. *MMWR: Morbidity and Mortality Weekly Report, 43*(20), 361-365.

CDC. (1996a). Characteristics of foreign-born Hispanic patients with tuberculosis--eight U.S. counties bordering Mexico, 1995. *MMWR Morbidity and Mortality Weekly Report, 45*(47), 1032-1036.

CDC. (1996b). Tuberculosis Mortality. *MMWR Morbidity and Mortality Weekly Report, 45*(18), 365-370.

CDC. (1997). Tuberculosis Morbidity-United States, 1996. *MMWR Morbidity and Mortality Weekly Report, 46*(30), 695-700.

CDC. (1998a). Recommendations for prevention and control of tuberculosis among foreign-born persons. Report of the Working Group on Tuberculosis among Foreign-Born Persons. *MMWR Morbidity and Mortality Weekly Report, 47*(RR 16), 1-26.

CDC. (1998b). Report of the Working Group on Tuberculosis among Foreign-Born Persons: Recommendations for prevention and control of tuberculosis among foreign-born persons. *MMWR Recommendations Reports, 47*(RR-16), 1-29.

CDC. (1999). Progress towards the elimination of tuberculosis-United States, 1998. *MMWR Morbidity and Mortality Weekly Report, 48*(33), 732-736.

CDC. (2000). *Core Curriculum on Tuberculosis*. Atlanta, Georgia: U.S. Department of Health & Human Services: Center for Disease Control and Prevention: National Center for HIV, STD, and TB Prevention.

CDC. (2002). Tuberculosis morbidity among U.S.-born and foreign-born populations--United States, 2000. *MMWR Morbidity and Mortality Weekly Report, 51*(5), 101-104.

CDC. (2003a). *Reported Tuberculosis in the United States, 2003*. Atlanta, GA: U.S. Department of Health and Human Services.

CDC. (2003b). Trends in tuberculosis morbidity - United States, 1992-2002. *MMWR Morbidity and Mortality Weekly Report, 52*(11), 217-224.

CDC. (2005). Trends in Tuberculosis-United States, 2004. *MMWR CDC Surveillance Summaries, 54*(10), 245-249.

DC. (1997). Tuberculosis Morbidity-United States, 1996. *MMWR Morbidity and Mortality Weekly Report, 46*(30), 695-700.

DC. (1998a). Recommendations for prevention and control of tuberculosis among foreign-born persons. Report of the Working Group on Tuberculosis among Foreign-Born Persons. *MMWR Morbidity and Mortality Weekly Report, 47*(RR-16), 1-26.

CDC. (1998b). Report of the Working Group on Tuberculosis among Foreign-Born Persons: Recommendations for prevention and control of tuberculosis among foreign-born persons. *MMWR Recommendations Report, 47*(RR-16), 1-26.

CDC. (1999). Progress towards the elimination of tuberculosis--United States, 1998. *MMWR Morbidity and Mortality Weekly Report, 48*(11), 241-245.

CDC. (2000). *Core Curriculum on Tuberculosis.* Atlanta, Georgia: U.S. Department of Health & Human Services: Center for Disease Control and Prevention: National Center for HIV, STD, and TB Prevention.

CDC. (2002). Tuberculosis morbidity among U.S.-born and foreign-born persons--National Notifiable Diseases Surveillance System, United States, 2000. *MMWR Morbidity and Mortality Weekly Report, 51*(10), 101-104.

CDC. (2003a). *Re[illegible]uberculosis in the United States, 2002.* Atlanta, GA: U.S. Departme[illegible]h and Human Services.

[illegible] (2003b). Tu[illegible]erculosis morbidity--United States, 1992-2002. *MMWR* [illegible]C. [illegible] Weekly Report, 52*(11), 217-224.

[illegible]ne, 163, [illegible]uberculosis--United States, 2004. *MMWR CDC Surveillance* [illegible]240.

Chamla, D. D., Nie, S., & Duan, Q. (2004). Retrospective descriptive study of adult tuberculosis in Wuhan, China. *International Journal of Tuberculosis and Lung Disease, 8*(6), 730-736.

Chin, D. P., DeRiemer, K., Small, P. M., de Leon, A. P., Steinhart, R., Schecter, G. F., Daley, C. L., Moss, A. R., Paz, E. A., Jasmer, R. M., Agasino, C. B., & Hopewell, P. C. (1998). Differences in contributing factors to tuberculosis incidence in U.S. -born and foreign-born persons. *American Journal of Respiratory and Critical Care Medicine, 158*(6), 1797-1803.

Codecasa, L. R., Porretta, A. D., Gori, A., Franzetti, F., Degli Esposti, A., Lizioli, A., Carreri, V., Di Proietto, M. C., Perozziello, F., & Besozzi, G. (1999). Tuberculosis among immigrants from developing countries in the province of Milan, 1993-1996. *International Journal of Tuberculosis and Lung Disease, 3*(7), 589-595.

Coker, R. (2000). *From Chaos to Coercion* (1st ed.). New York: St. Martin's Press.

Coleman, D., & Root, R. K. (1981). Pulmonary infections in Southeast Asian refugees. *Clinics in Chest Medicine, 2*(1), 133-143.

Combs, D. L., O'Brien, R. J., & Geiter, L. J. (1990). USPHS Tuberculosis Short-Course Chemotherapy Trial 21: effectiveness, toxicity, and acceptability. The report of final results. *Annals of Internal Medicine, 112*(6), 397-406.

Corbett, E., Watt, C., Walker, N., Maher, D., Williams, B., Raviglione, M., & Dye, C. (2003). The growing burden of tuberculosis. *Archives of Internal Medicine, 163*, 1009-1021.

Davies, P. D., & Grange, J. M. (2001). Factors affecting susceptibility and resistance to tuberculosis. *Thorax, 56*(Suppl 2), ii23-29.

De Bruyn, G., Adams, G. J., Teeter, L. D., Soini, H., Musser, J. M., & Graviss, E. A. (2001). The contribution of ethnicity to Mycobacterium tuberculosis strain clustering. *International Journal of Tuberculosis and Lung Disease, 5*(7), 633-641.

DeRiemer, K., Chin, D. P., Schecter, G. F., & Reingold, A. L. (1998). Tuberculosis among immigrants and refugees. *Archives of Internal Medicine, 158*(7), 753-760.

Dewan, P. (2005). Evaluating client's past treatment history-correspondence. In S. Arai (Ed.). San Francisco, CA.

Diagnostic Standards and Classification of Tuberculosis in Adults and Children. (2000). *American Journal of Respiratory and Critical Care Medicine, 161*, 1376-1395.

Doll, R. (2001). Cohort studies: history of the method. II. Retrospective cohort studies. *Soz-Praventivmed, 46*, 152-160.

Douglas, J. G., & McLeod, M. J. (1999). Pharmacokinetic factors in the modern drug treatment of tuberculosis. *Clinical Pharmacokineics, 37*(2), 127-146.

Earnest, M., & Sbarbaro, J. A. (1996). Tuberculosis: adherence to regimens and directly observed therapy. In W. N. Rom & S. Garay (Eds.), *Tuberculosis* (First ed., pp. 927-934). Boston: Little, Brown and Company.

El Sahly, H. M., Adams, G. J., Soini, H., Teeter, L., Musser, J. M., & Graviss, E. A. (2001). Epidemiologic differences between United States- and foreign-born tuberculosis patients in Houston, Texas. *Journal of Infectious Diseases, 183*(3), 461-468.

el-Sadr, W., Medard, F., Berthaud, V., & Barthaud, V. (1996). Directly observed therapy for tuberculosis: the Harlem Hospital experience, 1993. *American Journal of Public Health, 86*(8 Pt 1), 1146-1149.

Enarson, D., & Murray, J. F. (1996). Global epidemiology of tuberculosis. In W. N. Rom & S. Garey (Eds.), *Tuberculosis* (pp. 57-75). Boston: Little, Brown and Company.

Enarson, D. A. (1984). Active tuberculosis in Indochinese refugees in British Columbia. *CMAJ, 131*(1), 39-42.

Enarson, D. A., Sjogren, I., & Grzybowski, S. (1980). Incidence of tuberculosis among Scandinavian immigrants in Canada. *European Journal of Respiratory Diseases, 61*(3), 139-142.

Ending Neglect: The Elimination of Tuberculosis in the United States. (2000). Washington, D.C.: National Academy Press.

Espinal, M. A., Kim, S. J., Suarez, P. G., Kam, K. M., Khomenko, A. G., Migliori, G. B., Baez, J., Kochi, A., Dye, C., & Raviglione, M. C. (2000). Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries. *JAMA, 283*(19), 2537-2545.

Etkind, S., Boutotte, J., Ford, J., Singleton, L., & Nardell, E. A. (1991). Treating hard-to-treat tuberculosis patients in Massachusetts. *Seminars in Respiratory Infections, 6*(4), 273-282.

Fitzpatrick, S., Johnson, J., Shragg, P., & Felice, M. E. (1987). Health care needs of Indochinese refugee teenagers. *Pediatrics, 79*(1), 118-124.

Fix, M., Passel, J., Enchautegui, M., & Zimmermann, W. (1994). *Immigration and immigrants: setting the record straight.* Washington, D.C.: Urban Institute.

Fos, P. J., & Fine, D. J. (2000). *Designing Health Care for Populations* (First ed.). San Francisco: Jossey-Bass.

Garber, E., San Gabriel, P., Lambert, L., & Saiman, L. (2003). A survey of latent tuberculosis infection among laboratory healthcare workers in New York City. *Infection Control in Hospital Epidemiology, 24*(11), 801-806.

Geng, E., Kreiswirth, B., Driver, C., Li, J., Burzynski, J., DellaLatta, P., LaPaz, A., & Schluger, N. W. (2002). Changes in the transmission of tuberculosis in New York City from 1990 to 1999. *New England Journal of Medicine, 346*(19), 1453-1458.

Ginsdale, J. (2004). Clinic population, 1994-1998-correspondance. with S. Arai (Ed.). Epidemiologist -San Francisco TB Control.

Goldenring, J. M., Davis, J., & McChesney, M. (1982). Pediatric screening of Southeast Asian immigrants. *Clinical Pediatrics., 21*(10), 613-616.

Gordis, L. (2000). *Epidemiology* (Second ed.). Philadelphia: W.B. Saunders Company.

Gould, R. S. (1996). *Refugee Immigration to California, 1990-1994: A Summary in Tables.* Sacramento, CA: Department of Finance.

Granich, R. M., Zuber, P. L., McMillan, M., Cobb, J. D., Burr, J., Sfakianaki, E. D., Fussell, M., & Binkin, N. J. (1998). Tuberculosis among foreign-born residents of southern Florida, 1995. *Public Health Reports, 113*(6), 552-556.

Greenberg, B. L., Weisfuse, I. B., Makki, H., Adler, J., el-Sadr, W., Clarke, L., Gainey, S., Alford, T., McFarlane, K., & Thomas, P. A. (1994). HIV-1 seroprevalence in chest clinic and hospital tuberculosis patients in New York City, 1989-1991. *AIDS, 8*(7), 957-962.

Grzybowski, S., Ashley, M. J., & Pinkus, G. (1976). Chemoprophylaxis in inactive tuberculosis: long-term evaluation of a Canadian trial. *CMAJ, 114*, 607-611.

Gushulak, B. D. (1998). Tuberculosis control in refugees - policy and practices. *International Journal of Tuberculosis and Lung Disease, 2*(9), 587-593.

Gutierrez, M. C., Vincent, V., Aubert, D., Bizet, J., Gaillot, O., Lebrun, L., Le Pendeven, C., Le Pennec, M. P., Mathieu, D., Offredo, C., Pangon, B., & Pierre-Audigier, C. (1998). Molecular fingerprinting of Mycobacterium tuberculosis and risk factors for tuberculosis transmission in Paris, France, and surrounding area. *Journal of Clinical Microbiology, 36*(2), 486-492.

Hann, R. (1994). Tuberculosis. In N. Zane & D. Takeuchi & K. Young (Eds.), *Confronting Critical Health Issues of Asian and Pacific Islander Americans* (1st ed.). Thousand Oaks, CA: Sage.

Hayes, R. B. (1979). Introduction. In R. B. Hayes (Ed.), *Compliance in Health Care* (pp. pp. 1-6). Baltimore: John Hopkins University Press.

Heath, T. C., Roberts, C., Winks, M., & Capon, A. G. (1998). The epidemiology of tuberculosis in New South Wales 1975-1995: the effects of immigration in a low prevalence population. *International Journal of Tuberculosis and Lung Disease, 2*(8), 647-654.

Helbling, P., Medinger, C., Altpeter, E., Raeber, P. A., Beeli, D., & Zellweger, J. P. (2002). Outcome of treatment of pulmonary tuberculosis in Switzerland in 1996. *Swiss Medical Weekly, 132*(35-36), 517-522.

Heldal, E., Docker, H., Caugant, D. A., Tverdal, A., van Rie, A., Warren, R., Richardson, M., Victor, T. C., Gie, R. P., Enarson, D. A., Beyers, N., van Helden, P. D.,

Hopewell, P. C., McAdams, H. P., Erasmus, J., & Winter, J. A. (2000). Pulmonary tuberculosis in Norwegian patients. The role of reactivation, re-infection and primary infection assessed by previous mass screening data and restriction fragment length polymorphism analysis. *International Journal of Tuberculosis and Lung Disease, 4*(4), 300-307.

Hennekens, C. H., & Buring, J. E. (1987). *Epidemiology in Medicine* (First Edition ed.). Boston: Little, Brown and Company.

Hing, B. O. (1993). *Making and remaking Asian America through immigration policy, 1850-1990.* Stanford, CA: Stanford University Press.

Ho, M. J. (2003). Migratory journeys and tuberculosis risk. *Medical Anthropology Quarterly, 17*(4), 442-458.

Ho, M. J. (2004). Health-seeking patterns among Chinese immigrant patients enrolled in the directly observed therapy program in New York City. *International Journal of Tuberculosis and Lung Disease, 8*(11), 1355-1359.

Hopewell, P. C. (1998). Using conventional and molecular epidemiological analyses to target tuberculosis control interventions in a low incidence area. *Novartis Foundation Symposium, 217*, 42-54; discussion 54-46.

Horsburgh, C. R., Jr. (2004). Priorities for the treatment of latent tuberculosis infection in the United States. *New England Journal of Medicine, 350*(20), 2060-2067.

Jaiswal, A., Singh, V., Ogden, J. A., Porter, J. D., Sharma, P. P., Sarin, R., Arora, V. K., & Jain, R. C. (2003). Adherence to tuberculosis treatment: lessons from the urban setting of Delhi, India. *Tropical Medicine and International Health, 8*(7), 625-633.

Jasmer, R. M., Nahid, P., & Hopewell, P. C. (2002). Clinical practice. Latent tuberculosis infection. *New England Journal of Medicine, 347*(23), 1860-1866.

Jasmer, R. M., Seaman, C. B., Gonzalez, L. C., Kawamura, L. M., Osmond, D. H., & Daley, C. L. (2004). Tuberculosis treatment outcomes: directly observed therapy compared with self-administered therapy. *American Journal of Respiratory and Critical Care Medicine, 170*(5), 561-566.

Jekel, J. F., Katz, D. L., & Elmore, J. G. (2001). *Epidemiology, Biostatistics, and Preventive Medicine* (Second Edition ed.). Philadelphia, PA: W.B. Saunders Company.

Johnston, R. F., & Wildrick, K. H. (1974). The impact of chemotherapy on the care of patients with tuberculosis. *American Review of Respiratory Disease, 109*(6), 636-664.

Johnston, R. N. (1974). Current patterns of tuberculous infection--tuberculous disease in Dundee 1959-1971. *Health Bull (Edinb), 32*(4), 163-166.

Jordan, T. J., Lewitt, E. M., & Reichman, L. B. (1991). Isoniazid preventive therapy for tuberculosis: Decision analysis considering ethnicity and gender. *American Review of Respiratory Disease, 144*, 1357-1360.

Judson, F. N., Lince, D. M., Anders, B., Tapy, J., Le Van, D., Cohn, D. L., & Kicera, T. (1984). Health status of Southeast Asian refugees. *Western Journal of Medicine, 141*, 183-188.

Keane, V. P., O'Rourke, T. F., Bollini, P., Pampallona, S., & Siem, H. (1995). Prevalence of tuberculosis in Vietnamese migrants: the experience of the Orderly Departure

Program. *Southeast Asian Journal of Tropical Medicine and Public Health, 26*(4), 642-647.

Kraut, A. (1995). *Silent travelers: Germs, genes, and the "immigrant menace".* Baltimore: John Hopkins University Press.

Kumar, D., Watson, J. M., Charlett, A., Nicholas, S., & Darbyshire, J. H. (1997). Tuberculosis in England and Wales in 1993: results of a national survey. Public Health Laboratory Service/British Thoracic Society/Department of Health Collaborative Group. *Thorax, 52*(12), 1060-1067.

Landmarks in Immigration History (2002, August 28, 2002). Gilder Lehrman Institute of American History. Retrieved August 27, 2002, 2002, from the World Wide Web: htt://www.gliah.uh.edu/historyonline/immigration_chron.cfm

Lange, P., Mortensen, J., & Viskum, K. (1986). Tuberculosis in a developed country. *Acta Medica Scandinavica, 219*(5), 481-487.

Latent Tuberculosis Infection: A Guide for San Francisco Providers. (2003). San Francisco, CA: San Francisco Department of Public Health: Tuberculosis Control Section.

Leonhardt, K. K., Gentile, F., Gilbert, B. P., & Aiken, M. (1994). A cluster of tuberculosis among crack house contacts in San Mateo County, California. *American Journal of Public Health, 84*(11), 1834-1836.

Lerner, B. H. (1997). From careless consumptives to recalcitrant patients: the historical construction of noncompliance. *Social Science and Medicine, 45*(9), 1423-1431.

Leung, C. C., Yew, W. W., Chan, C. K., Chau, C. H., Tam, C. M., Lam, C. W., Tam, W. O., Lau, K. S., & Liu, W. T. (2002). Tuberculosis in older people: a retrospective

and comparative study from Hong Kong. *Journal of American Geriatric Society, 50*(7), 1219-1226.

Li, J. H., Driver, C. R., Munsiff, S. S., Yip, R., & Fujiwara, P. I. (2003). Differential decline in tuberculosis incidence among US- and non-US-born persons in New York City. *International Journal of Tuberculosis and Lung Disease, 7*(5), 451-457.

LoBue, P. A., & Moser, K. S. (2003). Use of isoniazid for latent tuberculosis infection in a public health clinic. *American Journal of Respiratory and Critical Care Medicine, 168*(4), 443-447.

LoBue, P. A., & Moser, K. S. (2004). Screening of immigrants and refugees for pulmonary tuberculosis in San Diego County, California. *Chest, 126*(6), 1777-1782.

Long-term follow-up of a clinical trial of six-month and four-month regimens of chemotherapy in the treatment of pulmonary tuberculosis. Singapore Tuberculosis Service/British Medical Research Council. (1986). *American Review of Respiratory Disease, 133*(5), 779-783.

Lorvick, J., Thompson, S., Edlin, B. R., Kral, A. H., Lifson, A. R., & Watters, J. K. (1999). Incentives and accessibility: a pilot study to promote adherence to TB prophylaxis in a high-risk community. *Journal of Urban Health, 76*(4), 461-467.

Mac, J. T., Doordan, A., & Carr, C. A. (1999). Evaluation of the effectiveness of a directly observed therapy program with Vietnamese tuberculosis patients. *Public Health Nursing, 16*(6), 426-431.

MacIntyre, C., Epi, M., & Plant, A. J. (1998). Tuberculosis in South-East Asian refugees after resettlement: Can prevention be improved by better policy and practice? *Preventive Medicine, 27*, 815-820.

MacIntyre, C. R., & Plant, A. J. (1999). Longitudinal incidence of tuberculosis in South-East Asian refugees after re-settlement. *International Journal of Tuberculosis and Lung Disease, 3*(4), 287-293.

Marco, A., Cayla, J. A., Serra, M., Pedro, R., Sanrama, C., Guerrero, R., & Ribot, N. (1998). Predictors of adherence to tuberculosis treatment in a supervised therapy programme for prisoners before and after release. Study Group of Adherence to Tuberculosis Treatment of Prisoners. *European Respiratory Journal, 12*(4), 967-971.

Marks, G. B., Bai, J., Simpson, S., Stewart, G., & Sullivan, E. (2001). The incidence of tuberculosis in a cohort of South-East Asian refugees arriving in Australia 1984-194. *Respirology, 6*, 71-74.

Marks, G. B., Bai, J., Simpson, S., Sullivan, E., & Stewart, G. (2000). Incidence of tuberculosis among a cohort of tuberculin positive refugees in Australia: Reappraising the estimates of risk. *American Journal of Respiratory Critical Care Medicine, 162*, 1851-1854.

Marks, G. B., Stewart, G., Simpson, S., & Sullivan, E. A. (2001). Effectiveness of postmigration screening in controlling tuberculosis among refugees: A historical cohort study, 1984-1998. *American Journal of Public Health., 2001*(11), 17971799.

Mausner, J. S., & Kramer, S. (1985). *Mausner & Bahn: Epidemiology- An Introductory Text* (First Edition ed.). Philadelphia: W.B. Saunders Company.

McAdams, H. P., Erasmus, J., & Winter, J. A. (1995). Radiologic manifestations of pulmonary tuberculosis. *Radiology Clinics of North America, 33*(4), 655-678.

McConkey, S. J., Williams, M., Weiss, D., Adams, H., Cave, M. D., Yang, Z., Lindner, T., & Bailey, T. C. (2002). Prospective use of molecular typing of Mycobacterium tuberculosis by use of restriction fragment-length polymorphism in a public tuberculosis-control program. *Clinical Infectious Diseases, 34*(5), 612-619.

McCray, E., Weinbaum, C. M., Braden, C. R., & Onorato, I. M. (1997). The epidemiology of tuberculosis in the United States. *Clinical Chest Medicine, 18*(1), 99-113.

McGlynn, K. A., Lustbader, E. D., Sharrar, R. G., Murphy, E., & London, W. T. (1986). Isoniazid prophylaxis in Hepatitis B carriers. *American Review of Respiratory Disease, 134*, 666-668.

McKenna, M. T., McCray, E., & Onorato, I. (1995). The epidemiology of tuberculosis among foreign-born persons in the United States, 1986 to 1993. *New England Journal of Medicine, 332*(16), 1071-1076.

Menzies, D. (2003). Screening immigrants to Canada for tuberculosis: Chest radiography or tuberculin skin testing? *CMAJ, 169*(10), 1035-1036.

Menzies, D., Tannenbaum, T., & Fitzgerald, J. M. (1999). Tuberculosis: 10. Prevention. *Canadian Medical Association Journal, 161*, 717-724.

Menzies, D., Tannenbaum, T. N., & FitzGerald, J. M. (1999). Tuberculosis: 10. Prevention. *CMAJ, 161*(6), 717-724.

Migliori, G. B., Ambrosetti, M., Besozzi, G., Casali, L., & Raviglione, M. C. (1999). Prospective multicentre study on the evaluation of antituberculosis treatment results in Italy: comparison of the culture- versus the smear-based methods. National AIPO Tuberculosis Study Group. *European Respiratory Journal, 13*(4), 900-903.

Minh, V., Prendergast, T. J., & Engle, P. (1982). Tuberculosis in refugees from Southeast Asia (Editorial). *Chest, 82*(2), 133-135.

Morisky, D. E., Ebin, V. J., Malotte, C. K., Coly, A., & Kominski, G. (2003). Assessment of tuberculosis treatment completion in an ethnically diverse population using two data sources. Implications for treatment interventions. *Evaluations in the Health Professions, 26*(1), 43-58.

Morse, D. L., E., H. R., Grabau, J. C., Cauthen, G., Redmond, S. R., & Hyde, R. W. (1985). Tuberculin conversions in Indochinese refugees. *American Review of Respiratory Disease, 132*, 516-519.

Morse, D. L., Hansen, R. E., Swalbach, W. G., Redmond, S. R., & Grabau, J. C. (1982). High rate of tuberculin conversion in Indochinese refugees. *JAMA, 248*(22), 2983-2986.

Mortality Statistics: 1906. (1908). Washington, D.C.: Department of Commerce and Labor: Bureau of the Census.

Moss, A. R., Hahn, J. A., Tulsky, J. P., Daley, C. L., Small, P. M., & Hopewell, P. C. (2000). Tuberculosis in the homeless. A prospective study. *American Journal of Respiratory and Critical Care Medicine, 162*(2 Pt 1), 460-464.

Murray, C. (1996). Results of directly observed short-course chemotherapy in 112,842 Chinese patients with smear-positive tuberculosis. China Tuberculosis Control Collaboration. *Lancet, 347*(8998), 358-362.

National Tuberculosis Program Objectives Oregon Status 1998-2002 (2005). [electronic]. Oregon Tuberculosis Control. Retrieved April 4, 2005, 2005, from the World Wide Web: http://egov.oregon.gov/DHS/ph/tb/tbobj.sthml

Nelson, K. R., Bui, H., & Samet, J. H. (1997). Screening in special populations: a "case study" of recent Vietnamese immigrants. *American Journal of Medicine, 102*(5), 435-440.

Nolan, C. M., Aitken, M. L., Elarth, A. M., Anderson, K. M., & Miller, W. T. (1986). Active tuberculosis after isoniazid chemoprophylaxis of Southeast Asian refugees. *American Review of Respiratory Disease, 133*(3), 431-436.

Nolan, C. M., & Elarth, A. M. (1988). Tuberculosis in a cohort of Southeast Asian refugees. *American Review of Respiratory Disease, 137*, 805-809.

Nolan, C. M., Teklu, B., & Wu, R. (1989). The use of sputum cultures in the evaluation of immigrants classified as tuberculosis suspects. *American Review of Respiratory Disease, 140*(996-1000.).

Ott, K. (1996). *Fevered Lives: Tuberculosis in American Culture since 1870* (1st ed.). Cambridge, Massachusetts: Harvard University Press.

Outcome of second-line tuberculosis treatment in migrants from Vietnam. International Organization for Migration (IOM) Tuberculosis Working Group. (1998). *Tropical Medicine and International Health, 3*(12), 975-980.

Pablos-Mendez, A., Knirsch, C. A., Barr, R. G., Lerner, B. H., & Frieden, T. R. (1997). Nonadherence in tuberculosis treatment: predictors and consequences in New York City. *American Journal of Medicine, 102*(2), 164-170.

Pang, S. C., Harrison, R. H., Brearley, J., Jegathesan, V., & Clayton, A. S. (1998). Preventive therapy for tuberculosis in Western Australia. *International Journal of Tuberculosis and Lung Disease, 2*(12), 984-988.

Park, Y. K., Bai, G. H., & Kim, S. J. (2000). Restriction fragment length polymorphism analysis of Mycobacterium tuberculosis isolated from countries in the western pacific region. *Journal of Clinical Microbiology, 38*(1), 191-197.

Patel, P. A., & Voigt, M. D. (2002). Prevalence and interaction of hepatitis B and latent tuberculosis in Vietnamese immigrants to the United States. *American Journal of Gastroenterology, 97*(5), 1198-1203.

Pedersen, J. T., & Revsbech, P. A. (1999). [Tuberculosis and migration]. *Ugeskr Laeger, 161*(23), 3440-3443.

Perez-Stable, E. J., & Hopewell, P. C. (1989). Current tuberculosis treatment regimens. Choosing the right one for your patient. *Clinical Chest Medicine, 10*(3), 323-339.

Plant, A. J., Watkins, R. E., Gushulak, B., O'Rourke, T., Jones, W., Streeton, J., & Sang, D. (2002). Predictors of tuberculin reactivity among prospective Vietnamese migrants: the effect of smoking. *Epidemiology and Infection, 128*(1), 37-45.

Powell, K. E., Brown, E. D., & Farer, L. S. (1983). Tuberculosis among Indochinese refugees in the United States. *JAMA, 249*, 1455-1460.

Race/Ethnic Population Estimates: Components of Change for California Counties, April 1990 to April 2000. (2033). Sacramento, CA: State of California, Department of Finance.

Ravessoud, M., & Zellweger, J. P. (1992). [Clinical presentation of tuberculosis among immigrants seen at the antituberculosis outpatient clinic in Lausanne]. *Schweiz Med Wochenschr, 122*(27-28), 1037-1043.

Raviglione, M. C., Snider, D. E., Jr., & Kochi, A. (1995). Global epidemiology of tuberculosis. Morbidity and mortality of a worldwide epidemic. *JAMA, 273*(3), 220-226.

Report from the British Thoracic and Tuberculosis Association: Tuberculosis among immigrants related to length of residence in England and Wales. (1975).

Report on Tuberculosis in California, 2000. (2001). Berkeley, CA: California Department of Health Services: Division of Communicable Disease Control, Tuberculosis Control Branch.

Rieder, H. L., Cauthen, G., Kelly, G. D., Bloch, A. B., & Snider, D. (1989). Tuberculosis in the United States. *JAMA, 262 3*(385-89.).

Rieder, H. L., Snider, D., & Cauthen, G. (1990). Extrapulmonary tuberculosis in the United States. *American Review of Respiratory Disease, 141*, 347-351.

Robertson, J. M., Burtt, D. S., Edmonds, K. L., Molina, P. L., Kiefe, C. I., & Ellner, J. J. (1996). Delayed tuberculin reactivity in persons of Indochinese origin: implications for preventive therapy. *Annals of Internal Medicine, 124*(9), 779-784.

Rocha, M., Pereira, S., Ferreira, L., & Barros, H. (2003). The role of adherence in tuberculosis HIV-positive patients treated in ambulatory regimen. *European Respiratory Journal, 21*(5), 785-788.

Rodell, P. A. (2002). *Culture and Customs of Philippines* (1st ed.). Westport, CT: Greenwood Press.

San Francisco Profile of Immigrants & Refugees. (1997). Oakland, CA: Newcomer Information Clearinghouse International Institute of the East Bay.

Sandman, L., Schluger, N. W., Davidow, A. L., & Bonk, S. (1999). Risk factors for rifampin-monoresistant tuberculosis: A case-control study. *American Journal of Respiratory and Critical Care Medicine, 159*(2), 468-472.

Santha, T., Garg, R., Frieden, T. R., Chandrasekaran, V., Subramani, R., Gopi, P. G., Selvakumar, N., Ganapathy, S., Charles, N., Rajamma, J., & Narayanan, P. R. (2002). Risk factors associated with default, failure and death among tuberculosis patients treated in a DOTS programme in Tiruvallur District, South India, 2000. *International Journal of Tuberculosis and Lung Disease, 6*(9), 780-788.

Sbarbaro, J. A. (1985). Strategies to improve compliance with therapy. *American Journal of Medicine, 79*(6A), 34-37.

Schluger, N., Harkin, T., & Rom, W. N. (1996). Principles of Therapy of Tuberculosis in the Modern Era. In W. N. Rom & S. Garay (Eds.), *Tuberculosis* (1st ed., pp. 751-761). Boston: Little, Brown and Company.

Schneider, C., Lasch, C., & Brade, V. (1994). [Have the incidence and resistance of tuberculosis increased? Epidemiologic follow-up based on diseases confirmed by culture]. *Pneumologie, 48*(11), 803-808.

Schwartzman, K. (2002). Latent tuberculosis infection: old problem, new priorities. *CMAJ, 166*(6), 759-761.

Sciortino, S., Mohle-Boetani, J., Royce, S. E., Will, D., & Chin, D. P. (1999). B notifications and the detection of tuberculosis among foreign-born recent arrivals in California. *International Journal of Tuberculosis and Lung Disease, 3*(9), 778-785.

Shah, N. (2001). *Contagious Divides*. Berkeley, CA: University of California.

Singapore Tuberculosis Service. (1991). Assessment of a daily combined preparation of isoniazid, rifampin, and pyrazinamide in a controlled trial of three 6-month regimens for smear-positive pulmonary tuberculosis. Singapore Tuberculosis Service/British Medical Research Council. *American Review of Respiratory Disease, 143*(4 Pt 1), 707-712.

Small, P. M., Hopewell, P. C., Singh, S. P., Paz, A., Parsonnet, J., Ruston, D. C., Schecter, G. F., Daley, C. L., & Schoolnik, G. K. (1994). The epidemiology of tuberculosis in San Francisco. A population-based study using conventional and molecular methods. *New England Journal of Medicine, 330*(24), 1703-1709.

Snider, D. E., Jr., Salinas, L., & Kelly, G. D. (1989). Tuberculosis: an increasing problem among minorities in the United States. *Public Health Reports, 104*(6), 646-653.

Stead, W. W., & Bates, J. H. (1996). Geographic and evolutionary epidemiology of tuberculosis. In W. N. Rom & S. Garey (Eds.), *Tuberculosis* (1st ed., pp. 77-84). Boston: Little, Brown and Company.

Stevens, G. (1999). A century of U.S. censuses and the language characteristics of immigrants. *Demography, 36*(3), 387-397.

Sutherland, J. E., Avant, R. F., Franz, W. B., Monzon, C. M., & Stark, N. M. (1983). Indochinese refugee health assessment and treatment. *Journal of Family Practice, 16*(1), 61-67.

Sutter, R. W., & Haefliger, E. (1990). Tuberculosis morbidity and infection in Vietnamese in Southeast Asian refugee camps. *American Review of Respiratory Disease, 141*, 1483-1486.

Talbot, E. A., Moore, M., McCray, E., & Binkin, N. J. (2000). Tuberculosis among foreign-born persons in the United States, 1993-1998. *JAMA, 284*(22), 2894-2900.

Tandon, M., Gupta, M., Tandon, S., & Gupta, K. B. (2002). DOTS versus self administered therapy (SAT) for patients of pulmonary tuberculosis: a randomised trial at a tertiary care hospital. *Indian Journal Medical Sciences, 56*(1), 19-21.

Tocque, K., Bellis, M. A., Tam, C. M., Chan, S. L., Syed, Q., Remmington, T., & Davies, P. D. (1998). Long-term trends in tuberculosis. Comparison of age-cohort data between Hong Kong and England and Wales. *American Journal of Respiratory and Critical Care Medicine, 158*(2), 484-488.

Tornieporth, N. G., Ptachewich, Y., Poltoratskaia, N., Ravi, B. S., Katapadi, M., Berger, J. J., Dahdouh, M., Segal-Maurer, S., Glatt, A., Adamis, R., Lerner, C., Armstrong, D., Weiner, M., D'Amato, R., Kiehn, T., Lavie, S., Stoeckle, M. Y., & Riley, L. W. (1997). Tuberculosis among foreign-born persons in New York City, 1992-1994: implications for tuberculosis control. *International Journal of Tuberculosis and Lung Disease, 1*(6), 528-535.

uberculosis in the United States. (1979). Atlanta, GA: U.S. Department of Health and Human Services: Public Health Service: Center for Disease Control.

uberculosis: Infection and Transmission. (Fact Sheet Number 104)(2004). WHO: World Health Organization.

uberculosis. (No. 104)(2002). Geneva: World Health Organization.

erver, S., Bwire, R., & Borgdorff, M. W. (2001). Screening for pulmonary tuberculosis among immigrants: estimated effect on severity of disease and duration of infectiousness. *International Journal of Tuberculosis and Lung Disease, 5*(5), 419-425.

os, A. M., Meima, A., Verver, S., Looman, C., Bos, V., Borgdorff, M. W., & Habbema, J. (2004). High incidence of pulmonary tuberculosis persists a decade after immigration, the Netherlands. *Emerging Infectious Diseases, 10*(4), 736-739.

ang, J. S., Allen, E. A., Chao, C. W., Enarson, D., & Grzybowski, S. (1989). Tuberculosis in British Columbia among immigrants from five Asian countries, 1982-85. *Tubercle, 70*(3), 179-186.

ang, J. S., Allen, E. A., Enarson, D. A., & Grzybowski, S. (1991). Tuberculosis in recent Asian immigrants to British Columbia, Canada: 1982-1985. *Tubercle, 72*(4), 277-283.

ells, C. D., Zuber, P. L., Nolan, C. M., Binkin, N. J., & Goldberg, S. V. (1997). Tuberculosis prevention among foreign-born persons in Seattle--King County, Washington. *American Journal of Respiratory and Critical Care Medicine, 156*(2 Pt 1), 573-577.

Wenzel, M. (1991). An alternative to 'two-step' tuberculin skin testing for Southeast Asian refugees. *Nurse Practitioner, 16*(8), 25-28.

White, M. C., Gournis, E., Kawamura, M., Menendez, E., & Tulsky, J. P. (2003). Effect of directly observed preventive therapy for latent tuberculosis infection in San Francisco. *International Journal of Tuberculosis and Lung Disease, 7*(1), 30-35.

WHO. (2004). *Progress Report on Global Plan to Stop TB* (WHO/HTM/STB/2004.29): World Health Organization.

WHO Report 2002 Global Tuberculosis Control: Surveillance, Planning, Financing. (2002). Geneva: World Health Organization (WHO).

Wilcke, J. T., Poulsen, S., Askgaard, D. S., Enevoldsen, H. K., Ronne, T., & Kok-Jensen, A. (1998). Tuberculosis in a cohort of Vietnamese refugees after arrival in Denmark 1979-1982. *International Journal of Tuberculosis and Lung Disease, 2*(3), 219-224.

Wilson, L. G. (1992). The rise and fall of tuberculosis in Minnesota: The role of infection. *Bulletin of the History of Medicine, 66*(1), 16-53.

Wobeser, W. L., Yuan, L., Naus, M., Corey, P., Edelson, J., Heywood, N., & Holness, D. L. (2000). Expanding the epidemiologic profile: risk factors for active tuberculosis in people immigrating to Ontario. *CMAJ, 163*(7), 823-828.

Wohl, A. R., Lu, S., Rollins, J. N., Simon, P. A., Grosser, S., & Kerndt, P. R. (2001). Comparison of AIDS progression and survival in persons with pulmonary versus extrapulmonary tuberculosis in Los Angeles. *Aids Patient Care and STDS, 15*(9), 463-471.

Wood, R., Maartens, G., & Lombard, C. J. (2000). Risk factors for developing tuberculosis in HIV-1-infected adults from communities with a low or very high incidence of tuberculosis. *Journal of Acquired Immune Deficiency Syndrome, 23*(1), 75-80.

Yamada, S., Caballero, J., Matsunaga, D. S., Agustin, G., & Magana, M. (1999). Attitudes regarding tuberculosis in immigrants from the Philippines to the United States. *Family Medicine, 31*(7), 477-482.

Zuber, P. L., Binkin, N. J., Ignacio, A. C., Marshall, K. L., Tribble, S. P., Tipple, M. A., & Vogt, R. L. (1996). Tuberculosis screening for immigrants and refugees. Diagnostic outcomes in the state of Hawaii. *American Journal of Respiratory and Critical Care Medicine, 154*(1), 151-155.

Zuber, P. L., Knowles, L. S., Binkin, N. J., Tipple, M. A., & Davidson, P. T. (1996). Tuberculosis among foreign-born persons in Los Angeles County, 1992-1994. *Tuber Lung Dis, 77*(6), 524-530.

Zuber, P. L., McKenna, M. T., Binkin, N. J., Onorato, I. M., & Castro, K. G. (1997). Long-term risk of tuberculosis among foreign-born persons in the United States. *JAMA, 278*(4), 304-307.

Zwarenstein, M., Schoeman, J. H., Vundule, C., Lombard, C. J., & Tatley, M. (1998). Randomised controlled trial of self-supervised and directly observed treatment of tuberculosis. *Lancet, 352*(9137), 1340-1343.