

Epidemiology of Extrapulmonary Tuberculosis in the United States, 1993–2006

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Background. Almost one-fifth of United States tuberculosis cases are extrapulmonary; unexplained slower annual case count decreases have occurred in extrapulmonary tuberculosis (EPTB), compared with annual case count decreases in pulmonary tuberculosis (PTB) cases. We describe the epidemiology of EPTB by means of US national tuberculosis surveillance data.

Methods. US tuberculosis cases reported from 1993 to 2006 were classified as either EPTB or PTB. EPTB encompassed lymphatic, pleural, bone and/or joint, genitourinary, meningeal, peritoneal, and unclassified EPTB cases. We excluded cases with concurrent extrapulmonary-pulmonary tuberculosis and cases of disseminated (miliary) tuberculosis. Demographic characteristics, drug susceptibility test results, and risk factors, including human immunodeficiency virus (HIV) status, were compared for EPTB and PTB cases.

Results. Among 253,299 cases, 73.6% were PTB and 18.7% were EPTB, including lymphatic (40.4%), pleural (19.8%), bone and/or joint (11.3%), genitourinary (6.5%), meningeal (5.4%), peritoneal (4.9%), and unclassified EPTB (11.8%) cases. Compared with PTB, EPTB was associated with female sex (odds ratio [OR], 1.7; 95% confidence interval [CI], 1.7–1.8) and foreign birth (OR, 1.5; CI, 1.5–1.6), almost equally associated with HIV status (OR, 1.1; CI, 1.1–1.1), and negatively associated with multidrug resistance (OR, 0.6; CI, 0.5–0.6) and several tuberculosis risk factors, especially homelessness (OR, 0.3; CI, 0.3–0.3) and excess alcohol use (OR, 0.3; CI, 0.3–0.3).

Slower annual decreases in EPTB case counts, compared with annual decreases in PTB case counts, from 1993 through 2006 have caused EPTB to increase from 15.7% of tuberculosis cases in 1993 to 21.0% in 2006.

Conclusions. EPTB epidemiology and risk factors differ from those of PTB, and the proportion of EPTB has increased from 1993 through 2006. Further study is needed to identify causes of the proportional increase in EPTB.

The decrease in tuberculosis case rates from 52.6 cases per 100,000 population in 1953 to 4.6 cases per 100,000 population in 2006 [1] demonstrates 53 years of improvement in United States tuberculosis control. This decrease was interrupted by a temporary tuberculosis resurgence from 1985 through 1992 [1, 2]. Factors con-

tributing to the resurgence included deterioration of tuberculosis public health infrastructure, the human immunodeficiency virus (HIV)/AIDS epidemic, increased immigration from countries endemic for tuberculosis, and tuberculosis transmission in congregate settings [1, 2].

Of 13,779 reported tuberculosis cases in 2006, 9678 (70.2%) were pulmonary tuberculosis (PTB), 2889 (21.0%) were extrapulmonary tuberculosis (EPTB), 954 (6.9%) were concurrent extrapulmonary-pulmonary tuberculosis, and 251 (1.8%) were disseminated (miliary) tuberculosis [1]. Although EPTB and PTB case counts have both decreased, EPTB has increased as a proportion of total tuberculosis cases from 3963 (7.6%) of 52,255 cases in 1962 [3] to 3940 (15.7%) of 25,107 cases in 1993 [1, 4] and to 2889 (21.0%) of 13,779 cases in 2006 [1], a trend seen in other industrialized coun-

Received 7 October 2008; accepted 12 May 2009; electronically published 30 September 2009.

The findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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Clinical Infectious Diseases 2009;49:1350–7

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1058-4838/2009/4909-0010\$15.00

DOI: 10.1086/605559

tries [2, 5–8]. Essential to achieving the national goal of tuberculosis elimination is understanding EPTB epidemiology and possible contributors to its proportional increase.

The last summary of EPTB in the United States that used the National Tuberculosis Surveillance System (NTSS) analyzed data from 1986, the year the tuberculosis resurgence began [1, 5]. Our analysis offers the first evaluation of EPTB in the HIV era [9] that uses NTSS data from 1993 through 2006. In addition, it is the first nationwide review of EPTB to capture drug susceptibility test results and additional tuberculosis risk factors, including HIV status [10]. This review is limited to reported public health surveillance system data and is not a clinical case review. Our goal is to describe EPTB epidemiology, compare the incidence and characteristics of EPTB with those of PTB, and suggest possible factors that are contributing to the increased proportion of EPTB-attributable tuberculosis cases.

METHODS

Tuberculosis cases are reported to the NTSS at the Centers for Disease Control and Prevention from 50 states and the District of Columbia (Washington, DC) by means of a standard tuberculosis case definition for public health surveillance [1, 11, 12]. Cases are reported using the Report of Verified Case of Tuberculosis (RVCT), a standardized form that records tuberculosis case demographic, clinical, laboratory, risk factor, treatment, and outcome characteristics [12]. The RVCT was amended in 1993 to include variables such as HIV status, drug susceptibility test results, and known tuberculosis risk factors (alcoholism, incarceration, drug use, and homelessness) for the first time.

We analyzed tuberculosis cases reported from January 1, 1993, through December 31, 2006. Cases were categorized by major disease site, reported as either PTB or EPTB. The PTB group comprised cases with PTB listed as the only disease site. The EPTB group comprised any extrapulmonary disease site: pleural, lymphatic, bone and/or joint, genitourinary, meningeal, peritoneal, and unclassified EPTB disease sites listed as “other.” Lymphatic tuberculosis was subdivided into cervical, intrathoracic, and other and/or unknown lymphatic tuberculosis. For public health reporting purposes, intrathoracic lymphatic tuberculosis without a concurrent diagnosis of PTB is classified as EPTB. EPTB cases that included >1 EPTB disease site were classified according to their major site. Cases of disseminated tuberculosis and cases with concurrent extrapulmonary-pulmonary tuberculosis were excluded from our principal analyses, because they were not distinctly classifiable as either extrapulmonary or pulmonary. In order to determine possible ramifications of this definition of EPTB, we performed a separate analysis that compared disseminated and concurrent ex-

trapulmonary-pulmonary tuberculosis with EPTB only and with PTB only. In addition, we performed a separate analysis in which disseminated and concurrent extrapulmonary-pulmonary tuberculosis were added to our existing EPTB classification.

EPTB and PTB cases were compared using demographic, clinical, and risk factor variables, including HIV status. HIV status was classified as HIV-infected, HIV-negative, or missing or unknown HIV status. Missing or unknown HIV status included patients having indeterminate, unknown, or missing test results, as well as patients refusing or not offered testing.

Except California, all states and DC report HIV status yearly with these categorizations. California differs from other reporting jurisdictions, because it reports only positive HIV status and has not reported any HIV results since 2004. Therefore, we also performed a subgroup analysis to examine HIV data through 2004 for 50 states and DC, both including and excluding California patients.

Foreign-born patients were analyzed by region of birth on the basis of the 2006 World Health Organization classification system [13] but with a modification: patients reported in a US state or Washington, DC, but born in US-affiliated jurisdictions (American Samoa, Guam, Republic of Marshall Islands, Federated States of Micronesia, Commonwealth of Northern Mariana Islands, Republic of Palau, Puerto Rico, or US Virgin Islands) were classified as US born rather than foreign born. Classification of persons born in US-affiliated jurisdictions as US born is consistent with standard Centers for Disease Control and Prevention reporting methodology [1].

EPTB and PTB cases were examined for multidrug resistance (MDR), defined as resistance to at least isoniazid and rifampin [14, 15]. Analysis was performed using the Cochran-Mantel-Haenszel χ^2 test in SAS, version 9.1 (SAS Institute), with 2-tailed *P* values and 95% confidence intervals (CIs). This study was not classified as human subject research, because it used routinely collected surveillance data.

RESULTS

Reported tuberculosis cases. Among 253,299 total tuberculosis cases reported from 1993 through 2006 to the NTSS, 47,293 (19%) were EPTB, 186,540 (74%) were PTB, 4478 (2%) were disseminated tuberculosis, and 14,910 (6%) were concurrent extrapulmonary-pulmonary tuberculosis; 78 cases (<1%) had missing data for major disease site. The disease site constituting the largest proportion of EPTB cases was lymphatic tuberculosis, followed by pleural tuberculosis. More than 60% of lymphatic tuberculosis was cervical lymphatic tuberculosis (Figure 1).

Demographic and risk factor characteristics of EPTB cases. The mean age of patients with EPTB was 44 years (Table 1).

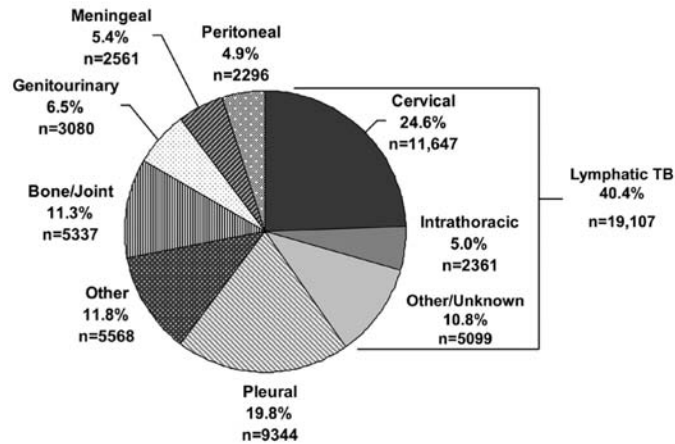


Figure 1. Extrapulmonary tuberculosis sites of disease, United States, 1993–2006 ($N = 47,293$).

The mean ages of patients with lymphatic tuberculosis (38 years) and of patients with meningeal tuberculosis (42 years) were younger than the mean ages of patients who had bone and/or joint (50 years), genitourinary (52 years), or pleural (49 years) tuberculosis. Although 27% of all reported EPTB patients were >60 years old, as much as 35% of bone and/or joint and 34% of genitourinary tuberculosis cases occurred among patients >60 years old. Children <15 years old accounted for 6% of all tuberculosis patients but accounted for as much as 12% of meningeal cases and 13% of lymphatic cases. Among 2,526 children <15 years old with lymphatic tuberculosis, there were nearly equal proportions of cervical (42%) and intrathoracic (41%) tuberculosis cases; among patients ≥ 15 years old ($n = 16,581$), there was a far larger proportion of cervical (64%) than of intrathoracic (8%) tuberculosis.

Slightly more than half of the EPTB patients were male (Table 1). Except for lymphatic tuberculosis, in which 58% of the patients were female, and peritoneal tuberculosis, in which 50% of the patients were female, all other extrapulmonary disease sites were slightly more common in males. The largest male proportion occurred among pleural cases (67%).

Most EPTB cases (81%) occurred in nonwhite racial and/or ethnic groups (Table 1), with blacks constituting the largest racial and/or ethnic group, followed by Asians. Blacks also represented the largest racial and/or ethnic group proportionally among all EPTB disease sites except genitourinary tuberculosis (30% white) and lymphatic tuberculosis (33% Asian).

Among EPTB cases, proportions of foreign-born and US-born patients were similar (Table 1), and this was true of all EPTB disease sites except lymphatic tuberculosis (61% foreign-born), pleural tuberculosis (61% US-born), and meningeal tuberculosis (61% US-born). Notably, 93% of children <1 year old with meningeal disease were US born (39 of 42 children).

Among EPTB patients reported through 2004 ($n = 41,465$),

10% were HIV-infected (Table 1). The EPTB disease sites with the highest proportion of HIV infection were meningeal tuberculosis and lymphatic tuberculosis, with 20% of meningeal tuberculosis patients and 11% of lymphatic tuberculosis patients having HIV.

Among cases in which isoniazid and rifampin drug susceptibility testing was performed ($n = 31,633$), 1.0% had MDR tuberculosis (Table 1). The proportion of MDR cases varied little between EPTB disease sites.

On average, most EPTB diagnoses (72%) were confirmed by *Mycobacterium tuberculosis* cultures, but this proportion decreased over time, from 76% in 1993 ($n = 2,979$) to 67% in 2006 ($n = 1,939$). The proportion of EPTB patients diagnosed using positive tissue stains was constant at 2% in 1993 ($n = 68$) and 2006 ($n = 50$).

Comparison of EPTB and PTB cases. Table 1 displays patient characteristics of EPTB, compared with those of PTB. The mean age of EPTB patients was slightly younger than that of PTB patients. The odds of EPTB, compared with PTB, were ≥ 1.5 times as high for females, Asians, the foreign-born, and healthcare workers.

Of 253,221 total tuberculosis cases with reported major sites of disease, more patients were US born (57%) than foreign born (43%). US-born predominance held true for PTB patients but not EPTB patients, of whom a slightly higher proportion were born outside the United States (Table 1). Among total foreign-born PTB cases, 44% of patients were from the Americas, followed by the Western Pacific (35%), Southeast Asia (7%), Africa (5%), Europe (5%), and the Eastern Mediterranean (3%). Among foreign-born EPTB cases, there was an increase in the proportion of patients born in Southeast Asia (15%), Africa (7%), and the Eastern Mediterranean (6%), compared with the proportion born in the Americas (35%), the Western Pacific (30%), and Europe (4%).

Table 1. Characteristics of Patients with Extrapulmonary Tuberculosis (EPTB), Compared with Patients with Pulmonary Tuberculosis (PTB), United States, 1993–2006 (N = 233,833)

Characteristic ^a	EPTB (n = 47,293)	PTB (n = 186,540)	OR (95% CI) ^b
Age, years			
Median	41	45	
Mean (range)	44 (0–105)	47 (0–112)	
Sex			
Female	22,660 (47.9)	64,979 (34.8)	1.7 (1.7–1.8)
Male	24,624 (52.1)	121,543 (65.2)	Reference
Race			
Asian ^c	11,644 (24.6)	33,611 (18.0)	1.8 (1.8–1.9)
Hispanic	11,009 (23.3)	43,597 (23.4)	1.3 (1.3–1.4)
Black ^c	14,462 (30.6)	58,473 (31.3)	1.3 (1.3–1.3)
Native American ^c	618 (1.3)	2297 (1.2)	1.4 (1.3–1.6)
White ^c	8827 (18.7)	46,720 (25.0)	Reference
Origin of birth			
US	22,822 (48.3)	109,438 (58.7)	Reference
Foreign	24,139 (51.0)	76,107 (40.8)	1.5 (1.5–1.6)
Occupation^d			
Any	18,124	64,514	
Health care workers	1860/18,124 (10.3)	4154/64,514 (6.4)	1.7 (1.6–1.8)
Non–healthcare workers	16,264/18,124 (89.7)	60,360/64,514 (93.6)	Reference
HIV status^e			
Any	41,465	166,997	
HIV-infected	4179/41,465 (10.1)	16,413/166,997 (9.8)	1.1 (1.1–1.1)
HIV-negative	12,709/41,465 (30.6)	55,109/166,997 (33.0)	Reference
HIV status unknown or missing ^f	24,577/41,465 (59.3)	95,475/166,997 (57.2)	1.1 (1.1–1.1)
Drug susceptibility testing^g			
Any result	31,633	144,529	
MDR	299/31,633 (.9)	2365/144,529 (1.6)	0.6 (0.5–0.6)
Not MDR ^h	31,077/31,633 (98.2)	141,199/144,529 (97.7)	Reference

NOTE. Data are number or no. (%) or proportion (%) of patients, unless otherwise indicated. CI, confidence interval; HIV, human immunodeficiency virus; MDR, multidrug resistance; OR, odds ratio.

^a Totals equal 47,293 extrapulmonary tuberculosis patients and 186,540 pulmonary tuberculosis patients except where noted and except when there are cases for which the given characteristic is missing or unknown.

^b Unadjusted ORs of EPTB vs PTB for the risk group, relative to the odds in the reference group. All *P* values are statistically significant at *P* < .001.

^c Includes non-Hispanic patients only.

^d Includes only employed patients.

^e Includes data only through 2004, including California patients. There was no notable difference when California patients were excluded.

^f Includes patients with HIV status listed as indeterminate, refused testing, test done but results unknown, test not offered, unknown, blank.

^g Includes patients with positive *Mycobacterium tuberculosis* culture results and drug susceptibility testing for isoniazid and rifampin.

^h Excludes 257 patients with unknown MDR status.

Children (<15 years old) were only slightly more likely to have EPTB than patients ≥15 years old (odds ratio [OR], 1.2; *P* < .001). HIV-infected patients had similar odds of EPTB compared with HIV-negative patients (Table 1).

Patients having MDR tuberculosis had lower odds of EPTB than of PTB (Table 1). In addition, patients with each tuberculosis risk factor we evaluated (incarceration, homelessness, injection and/or noninjection drug use, and excess alcohol use)

had significantly lower odds of EPTB, compared with those not reporting the risk factor (*P* < .001). Odds of having a previous tuberculosis episode were also lower for EPTB patients, compared with PTB patients (*P* < .001).

To determine whether our EPTB case definition, which excluded cases with concurrent extrapulmonary-pulmonary tuberculosis and disseminated tuberculosis, affected odds related to HIV infection and younger age, we compared disseminated

Table 2. Data on Patients with Concurrent Extrapulmonary-Pulmonary Tuberculosis,^a Compared with Patients with Pulmonary Tuberculosis (PTB) Only and Patients with Extrapulmonary Tuberculosis (EPTB) Only, by HIV Status and Age Group

Characteristic	Concurrent	PTB only	OR (95% CI), concurrent vs PTB	EPTB only	OR (95% CI), concurrent vs EPTB
HIV status^b					
Any	16,907	166,997		41,465	
HIV-infection	4747/16,907 (28.1)	16,413/166,997 (9.8)	3.3 (3.2–3.5)	4179/41,465 (10.1)	3.0 (2.8–3.2)
HIV-negative	4824/16,907 (28.5)	55,109/166,997 (33.0)	Reference	12,709/41,465 (30.7)	Reference
Age group^c					
Any	19,388	186,540		47,293	
<15 years	1121/19,388 (5.8)	11,356/186,540 (6.1)	0.9 (0.9–1.0)	3513/47,293 (7.4)	0.8 (0.7–0.8)
≥15 years	18,267/19,388 (94.2)	175,184/186,540 (93.9)	Reference	43,780/47,293 (92.6)	Reference

NOTE. Data are number or proportion (%) of patients, unless otherwise indicated. CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio.

^a Includes cases of concurrent extrapulmonary-pulmonary tuberculosis as well as cases of disseminated (miliary) tuberculosis.

^b Includes patients diagnosed through 2004. Not shown are patients for whom HIV status data were missing or unknown.

^c Includes patients diagnosed through 2006.

tuberculosis and concurrent extrapulmonary-pulmonary tuberculosis cases with PTB-only cases and then repeated the analysis with EPTB-only cases (Table 2). Patients with HIV infection had greater odds of having concurrent extrapulmonary-pulmonary tuberculosis or disseminated tuberculosis than of having EPTB or PTB alone. Children <15 years of age had slightly lower odds of concurrent extrapulmonary-pulmonary tuberculosis or disseminated tuberculosis when compared with EPTB but similar odds when compared with PTB.

A separate analysis in which the categories of disseminated and concurrent extrapulmonary-pulmonary tuberculosis were added to EPTB and then compared with PTB did not change the association for any variable except HIV. HIV-infected patients had an OR of 1.1 ($P < .001$) for EPTB with our original EPTB definition, and this changed to 1.7 ($P < .001$) when the definition was revised to include disseminated and concurrent extrapulmonary-pulmonary tuberculosis.

Trends in EPTB, compared with trends in PTB. Both EPTB and PTB case counts decreased over time, but EPTB counts decreased more slowly; case counts of PTB decreased an average of 5.1% annually, compared with a 2.3% annual decrease for EPTB cases (Figure 2). As a result of the slower decrease in the number of EPTB cases, EPTB increased from 15.7% of all tuberculosis cases in 1993 to 21.0% in 2006.

The increasing percentage of EPTB during the study period was seen among both US-born patients (EPTB increased from 14.4% to 17.9% of all tuberculosis cases) and foreign-born patients (from 18.6% to 23.3% of all tuberculosis cases). Among EPTB patients, the percentage who were foreign born rose from 35.4% in 1993 to 63.1% in 2006, and the percentage who were US born decreased from 64.6% in 1993 to 36.9% in 2006.

DISCUSSION

To our knowledge, this is the first use of national surveillance data to describe EPTB in the United States since standardized collection of drug susceptibility test results and tuberculosis risk factors, including HIV status, began in 1993. Consistent with other studies, our study found an increased association between EPTB and female sex, nonwhite race and/or ethnicity, and foreign birth [5, 16–21] and a disproportionately slower decrease in EPTB case counts, compared with the decrease in PTB case counts. Compared with PTB, EPTB was negatively associated with MDR and selected tuberculosis risk factors (alcoholism, incarceration, drug use, and homelessness). Unlike

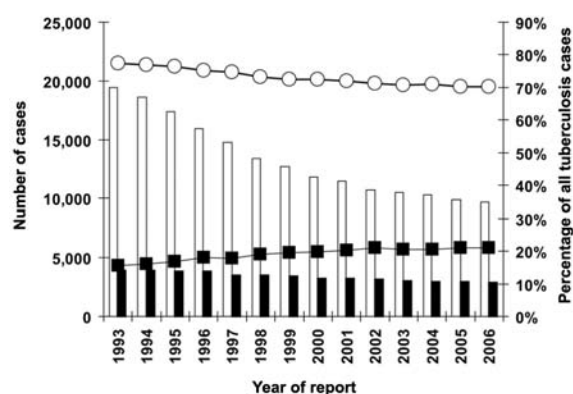


Figure 2. Trends in extrapulmonary tuberculosis (EPTB) and pulmonary tuberculosis (PTB), United States 1993–2006. The denominator is the total number of EPTB and PTB cases per year, excluding disseminated cases and concurrent extrapulmonary-pulmonary tuberculosis cases. *Black bars*, number of EPTB cases; *white bars*, number of PTB cases; *white circles*, percentage of all cases that is PTB; *black squares*, percentage of all cases that is EPTB.

previous studies, our study did not find strong associations between EPTB and age or HIV status, compared with PTB [5, 17, 19, 21], possibly because of definitional differences in EPTB between studies. Among EPTB disease sites, we found variations by age group, sex, HIV status, and foreign birth.

The disproportionately slower decrease in EPTB compared with the decrease in PTB is not new; it was also described between 1963 and 1986, before the HIV-driven tuberculosis increase [5, 22]. Understanding the reasons for the slower EPTB decrease is important to the goal of tuberculosis elimination in the United States. Although not usually contagious, EPTB may eventually disseminate to the lungs and become contagious, thereby posing a significant and latent threat to public health [2]. Improved recognition of EPTB risk factors may facilitate earlier diagnosis, thus preventing progression to the contagious state and sparing individual patients significant morbidity and/or mortality.

The increasing proportion of EPTB-attributable tuberculosis since 1993 is probably not a consequence of overdiagnosis: the decreased proportion of culture-confirmed EPTB since 1993 could indicate more erroneously diagnosed EPTB cases, but declining US tuberculosis cases overall have probably decreased physician suspicion of tuberculosis and thereby resulted in more missed cases. We are unable to determine whether the introduction of molecular-based diagnostic methods is associated with increased diagnoses of EPTB over time, because the RVCT did not undergo revision to capture information about molecular-based diagnostic methods before 2009.

We suggest 3 possible reasons for the slower decrease of EPTB relative to PTB. First, public health measures effectively focus on reducing contagious PTB cases but may be less effective against EPTB. Second, shifting US and tuberculosis demographics may favor populations with proportionally higher EPTB than others. Third, factors perpetuating EPTB may be poorly recognized, compared with those perpetuating PTB.

In this analysis, we find a higher prevalence of EPTB, compared with the prevalence of PTB, among specific populations, which confirms earlier observations [5, 7, 8, 16, 20, 23–27]. Since the early to mid-1990s, the proportion of all legal residents, refugees, and asylees who are from Southeast Asia has increased [28], as has the proportion of total tuberculosis patients who are foreign born or from nonwhite racial and/or ethnic groups [1, 12]. These demographic shifts to favor populations with a higher prevalence of EPTB may contribute to the consistency of EPTB in the US population.

Population shifts only partly explain the slow decrease of US EPTB, because other developed countries that differ in their demographic compositions also observe this trend [24, 27, 29, 30]. Furthermore, traditional tuberculosis risk factors (homelessness, incarceration, excess alcohol use, and drug use) do

not describe the prevalence of EPTB in this study. Detection of EPTB may therefore require more information about disease site-specific risk factors in populations not traditionally at risk for tuberculosis as well as greater clinical suspicion for EPTB.

As one example of a potential disease site-specific risk factor, we found meningeal tuberculosis more frequently in US-born patients. Some studies have suggested a possible explanation for the higher proportion of meningeal tuberculosis in US-born patients by saying that the BCG vaccine, which foreign-born patients from countries endemic for tuberculosis commonly receive, may confer some protective immunity against meningeal or disseminated tuberculosis [31]. Our finding that most infants with meningeal tuberculosis were US born may reflect a protective effect of BCG vaccination among foreign-born infants. However, the NTSS does not collect BCG vaccination data, so comparison of tuberculosis meningitis in BCG-vaccinated persons versus in unvaccinated persons was not possible.

One surprising finding in this analysis is the similar odds of HIV infection among EPTB and PTB cases. Previous studies associate EPTB more than PTB with immunosuppression or innate immune function abnormalities [32–34]. Accordingly, HIV infection has been suggested as a contributor to the increasing EPTB proportion relative to PTB [17, 19, 35]. Our lack of association between HIV and EPTB is likely attributable to differences in the definition of EPTB. At least one other study with results similar to ours also excluded concurrent extrapulmonary-pulmonary tuberculosis from its EPTB definition [27]. Studies reporting a positive association between EPTB and HIV define EPTB to include any extrapulmonary disease, including concurrent extrapulmonary-pulmonary tuberculosis as well as disseminated tuberculosis [17, 19, 21]. In contrast, we restricted analysis to EPTB-only and PTB-only cases. On the basis of our separate analysis investigating associations between HIV and disseminated and concurrent extrapulmonary-pulmonary tuberculosis, we conclude that HIV is a risk factor for disseminated tuberculosis and concurrent extrapulmonary-pulmonary tuberculosis, compared with either EPTB or PTB.

Also surprising in this analysis is our finding that MDR tuberculosis occurs less often among EPTB cases than among PTB cases. We anticipated the opposite, because greater difficulties in sampling from EPTB sites, compared with difficulties in sampling from PTB sites, may lead more frequently to treatment without culture confirmation. Perhaps the negative association between MDR and EPTB is explained by our finding of lower odds of previous tuberculosis episodes among EPTB cases, compared with previous tuberculosis episodes among PTB cases, because this would afford fewer chances for resistance to develop.

Although we would have liked to better identify the risk factors that have prevented EPTB cases from declining at the same rate as PTB cases, our analysis is limited to variables collected in this public health surveillance dataset. Data on many clinical comorbidities, behavioral factors, and social factors that catalyze progression from latent tuberculosis infection to tuberculosis disease are not collected.

Another limitation is that slightly more than half of HIV-status data in the national surveillance system is missing or unknown. However, the impact on comparisons of EPTB and PTB is expected to be small, because the percentage of missing or unknown HIV status data is similar for EPTB (59.3%) and PTB (57.2%) cases.

We do not know why some groups consistently develop proportionally more EPTB, compared with others. Some authors have identified a higher frequency of EPTB, compared with the frequency of PTB, among patients on particular immunosuppressive therapies [36] or have advocated increased suspicion of EPTB in rheumatologic patients [37]. Others have investigated possible differences between EPTB and PTB in genetic or immune-mediated predispositions [38, 39]. Another possibility is that there are geographic differences in circulating *M. tuberculosis* strains [40] or variations in *Mycobacterium* receptor affinity for certain target organs that influence tuberculosis disease site development.

Because >20% of tuberculosis in the United States is EPTB, it is necessary to identify whether certain comorbidities, patient characteristics, immunologic and genetic susceptibilities, or differences by population and region in endemic tuberculosis strains impact EPTB development. Improved understanding of EPTB risk factors in the US population is important to the goal of tuberculosis elimination and would enable clinicians to apply a higher index of suspicion to populations at risk for EPTB.

Acknowledgments

We gratefully acknowledge the staff from local and state health departments throughout the United States who have collected and reported data about tuberculosis cases for more than 50 years. We also thank Steve Kammerer for his assistance with statistical analysis, Thomas Navin for assistance with data interpretation, and Maryam Haddad and Allison Taylor for editing assistance.

Potential conflicts of interest. All authors: no conflicts.

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