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Major Article

Differential declines in syphilis-related mortality in the United States, 2000-2014

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Background: After reaching an all time low in 2000, the rate of syphilis in the United States has been steadily increasing. Parallel benchmarking of the disease's mortality burden has not been undertaken.

Methods: Using ICD-10 classification, all syphilis-related deaths in the national Multiple Cause of Death dataset were examined for the period 2000-2014. Descriptive statistics and age-adjusted mortality rates were generated. Poisson regression was performed to analyze trends over time. A matched case-control analysis was conducted to assess the associations between syphilis-related deaths and comorbid conditions listed in the death records.

Results: A total of 1,829 deaths were attributed to syphilis; 32% (n = 593) identified syphilis as the underlying cause of death. Most decedents were men (60%) and either black (48%) or white (39%). Decedents aged ≥85 years had the highest average mortality rate (0.47 per 100,000 population; 95% confidence interval [CI], 0.42-0.52). For the sampled period, the average annual decline in mortality was –2.90% (95% CI, –3.93% to –1.87%). However, the average annual percent change varied across subgroups of interest.

Conclusions: Declines in U.S. syphilis mortality suggest early detection and improved treatment access likely helped attenuate disease progression; however, increases in the disease rate since 2000 may be offsetting the impact of these advancements.

Syphilis is an ulcerative, infectious disease caused by *Treponema pallidum*, a spirochete that enters the body via microtrauma to the mucosa and skin.[1] Transmission of syphilis occurs most commonly through sexual contact, but it can be transmitted from mother to child during pregnancy or through the birthing process. If left untreated, the infection can lead to cardiac complications, dementia, and ultimately, death.

The rate of syphilis in the United States steadily declined from 1941-2000, but recent increases in infection rates suggest a resurgence of the disease.[2] In 1999, the Centers for Disease Control and Prevention released a plan to eradicate syphilis from the U.S. general population[3]; however, in spite of this federal effort, syphilis rates increased from 11.2 cases per 100,000 population in 2000 to 18.0 cases per 100,000 population in 2013.[2]

Syphilis infection often goes undetected despite the availability of highly sensitive and specific diagnostic testing and curative antibiotic treatment.[1] Diagnosis of syphilis is based on antibody screening and confirmative testing, but because early disease can be asymptomatic, testing is often not performed unless there is a strong clinical suspicion for the disease. Routine screening is currently only recommended for patients who are either pregnant or known to be at high risk for the disease.[4,5] Once diagnosed, high-dose penicillin is the recommended treatment.[1,6]

Although there is a large amount of clinical and epidemiologic literature on the incidence and morbidity of syphilis, parallel data on the disease's mortality burden are sparse. To date, few studies have examined syphilis mortality since the recorded rate of cases reached an all time low in 2000; most of these studies focused on congenital syphilis.[7] The present analysis addresses this gap in the

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public health literature by examining all recorded syphilis-related deaths from 2000-2014, using the national Multiple Cause of Death (MCD) dataset.

METHODS

Syphilis-related deaths from 2000-2014 were identified for this analysis using MCD data derived from the National Vital Statistics System. MCD data are abstracted from standardized death certificates of all recorded deaths in the United States. Information collected on each certificate includes age, sex, race/ethnicity, and the underlying and associated causes of death as determined by the certifying physician or coroner. Cause of death is coded according to ICD-10.[8] For this analysis, death certificates identifying any of the following codes as an underlying or associated cause of death were classified as cases: A50 (congenital syphilis), A51 (early syphilis), A52 (late syphilis), and A53 (other or unspecified syphilis).

Syphilis mortality rates per 100,000 population were generated using bridged race population estimates provided by the National Center for Health Statistics.[9] Crude mortality rates and 95% confidence intervals (CIs) were estimated for sex, race-ethnicity, and age. Age-adjusted mortality rates (AAMRs) and rate ratios were calculated based on the 2000 U.S. standard population. Poisson regression analysis was conducted to model mortality trends over time for all decedents and subgroups of interest (eg, men, decedents with HIV diagnosis).

A matched case-control analysis was performed to examine the potential associations between syphilis and other medical conditions that were listed on the same death certificate. Each syphilis case was matched with 5 randomly selected controls that had no diagnosis of syphilis based on year of death, sex, race-ethnicity, and age category. Conditions selected for comparison were those that were commonly recorded on the death certificates (ie, at least 5 occurrences among all syphilis-related deaths), could exacerbate or mimic the signs and symptoms of syphilis, or are commonly associated with disease transmission (eg, drug or alcohol use). Decedents with multiple comorbid conditions were included in multiple disease categories. Matched odds ratios (MORs) and 95% CIs were generated for this comparison analysis.

All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC). Because MCD data are publically available, not individually identifiable, and contain no information that can be linked to live human subjects, the present analysis did not require formal institutional board review or approval.

RESULTS

A total of 1,829 cases of syphilis-related deaths were identified for the period 2000-2014. Among these cases, 593 (32%) had syphilis listed as the underlying cause of death. In comparison analyses, differences in syphilis mortality by sex, race-ethnicity, age, and year were observed (Table 1). Men experienced a higher number of syphilis-related deaths (n = 1,095) than women (n = 734). Men also experienced a higher AAMR (0.05 per 100,000 population; 95% CI, 0.05-0.06) than women (0.03 per 100,000 population; 95% CI, 0.02-0.03). The age-adjusted rate ratio for men when using women as the referent group was 1.97 (95% CI, 1.82-2.14). Among race-ethnicity groups, blacks experienced the highest frequency of syphilis-related deaths and the highest AAMR (n = 873; 0.21 per 100,000 population; 95% CI, 0.19-0.22). American Indians had the second highest AAMR (0.07 per 100,000 population; 95% CI, 0.03-0.11) followed by Hispanics (0.05 per 100,000 population; 95% CI, 0.04-0.06). Decedents aged 75-84 years and ≥85 years exhibited the highest frequency of syphilis-related deaths and AAMRs (n = 436; 0.22 per 100,000 population; 95% CI, 0.20-0.24 and n = 364; 0.47 per 100,000 population; 95% CI, 0.42-0.52, respectively).

Table 1
Syphilis-related mortality frequency, age-adjusted mortality rates, and age-adjusted rate ratios per 100,000 population in the United States, 2000-2014

Characteristic	Frequency (N = 1,829), n (%)*	Age-adjusted mortality rate (95% CI)	Age-adjusted rate ratio (95% CI)
Sex			
Female	734 (40.1)	0.03 (0.02-0.03)	†
Male	1,095 (59.9)	0.05 (0.05-0.06)	1.97 (1.82-2.14)
Race-ethnicity			
White	716 (39.1)	0.02 (0.02-0.02)	†
Hispanic	185 (10.1)	0.05 (0.04-0.06)	2.65 (2.45-2.87)
Black	873 (47.7)	0.21 (0.19-0.22)	10.71 (9.5-11.54)
Asian	39 (2.1)	0.02 (0.02-0.03)	1.22 (1.11-1.35)
American Indian	16 (1.0)	0.07 (0.03-0.11)	3.67 (3.39-3.96)

Characteristic	Frequency n (%)	Age-specific mortality rate (95% CI)	Age-adjusted rate ratio (95% CI)
Age (y)			
0	38 (2.1)	0.06 (0.04-0.08)	—
1-4	3 (0.2)	0.00 (0.00-0.00)	—
5-14	5 (0.3)	0.00 (0.00-0.00)	—
15-24	11 (0.6)	0.00 (0.00-0.00)	—
25-34	33 (1.8)	0.01 (0.00-0.01)	—
35-44	97 (5.3)	0.02 (0.01-0.02)	—
45-54	213 (11.6)	0.03 (0.03-0.04)	—
55-64	291 (15.9)	0.06 (0.05-0.07)	—
65-74	338 (18.5)	0.11 (0.10-0.12)	—
75-84	436 (23.8)	0.22 (0.20-0.24)	—
≥85	364 (19.9)	0.47 (0.42-0.52)	—

CI, confidence interval.
*Numbers may not add up to 100% because of rounding.
†Referent group.

Overall, the age-adjusted time trends indicated a –2.90% (95% CI, –3.93% to –1.87%) average annual decline in mortality during 2000-2014. However, time trends examined by subgroup exhibited differential patterns of change (Fig 1). Women exhibited an increased average annual rate of decline when compared with men (–4.75%; 95% CI, –6.35% to –3.13% and –1.78%; 95% CI, –3.12% to –0.42%, respectively). When classified by race, only black decedents exhibited a statistically significant average decline in mortality (–5.19%; 95% CI, –6.63% to –3.72%). Those aged 25-44 years showed the greatest average annual decline at –5.65% (95% CI, –9.39% to –1.75%) for the 15-year time period. Although not statically significant, an increase in annual mortality rates was identified in decedents aged 0-14, 15-24, and 45-64 years. Only those decedents diagnosed with late or other or unspecified syphilis showed a significant decline in average annual mortality (–3.05%; 95% CI, –4.29% to –1.08% and –2.62%; 95% CI, –4.62% to –0.58%, respectively). Those who had no recorded diagnosis of HIV exhibited a significant average decline in mortality (–2.90%; 95% CI, –3.97% to –1.82%); however, those with a recorded HIV diagnosis showed no significant change in mortality during the study period.

Several comorbid conditions were found to be significantly associated with a syphilis diagnosis on the death certificates (Table 2). Codiagnoses with the highest MOR included HIV (MOR, 30.35; 95% CI, 19.22-47.91), mental health disorders (MOR, 5.94; 95% CI, 3.86-9.57), chronic hepatitis (MOR, 4.58; 95% CI, 3.04-6.89), and drugs (MOR, 4.04; 95% CI, 3.08-5.30).

DISCUSSION

In contrast with increases in disease rates since 2000, overall syphilis-related mortality has been on the decline.[1,2,10-13] These opposing trends likely can be attributed, in part, to earlier disease detection coupled with wider access to treatment and better