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Reported Neurologic Manifestations Among Persons With Syphilis by Stage of Infection—12 States, 2019–2022

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Abstract

National case-based surveillance data show that reported neurologic manifestations of syphilis increased during 2019–2022 among persons with early and late-stage syphilis. Neurologic manifestations occurred across demographic groups and among those with and without human immunodeficiency virus (HIV), highlighting the importance of evaluating for neurologic signs and symptoms in all persons with syphilis.

Keywords

neurosyphilis; syphilis; surveillance; *Treponema pallidum*

Clinical neurologic manifestations of syphilis can occur during any stage of infection and may result in increased morbidity and mortality if left untreated [1, 2]. Wide ranging in presentation—from meningeal and meningovascular involvement within months to years

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Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. This study used data that are routinely collected as a part of public health surveillance for the purpose of guiding public health disease control efforts and was therefore not subject to institutional review board approval for human subjects' protection.

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and parenchymatous involvement (eg, general paresis and tabes dorsalis) years to decades post-infection—these manifestations are considered rare [1, 3]. However, national syphilis rates have risen to a level not seen since the 1960s [4], raising concern that neurologic sequelae may be occurring with increasing frequency.

National syphilis surveillance is conducted through the National Notifiable Diseases Surveillance System (NNDS). Local jurisdictions send case-based data to the Centers for Disease Control and Prevention (CDC), applying a case definition by the Council of State and Territorial Epidemiologists to identify cases. The updated 2018 case definition allows for inclusion of neurologic manifestations for syphilis case notifications if persons have clinical signs/symptoms suggestive of neurosyphilis (without other known causes) and reactive serologic treponemal and nontreponemal test results (Supplementary Table 1). We describe the prevalence of neurologic manifestations of syphilis reported during 2019–2022 to better understand the burden of these potentially severe complications in the United States.

METHODS

We reviewed syphilis case reports among persons aged ≥ 15 years sent to CDC from 50 states and the District of Columbia during 2019–2022. We limited to jurisdictions with at least 70% annual completeness for the neurologic manifestations variable to limit bias introduced by missing data. We stratified by stage of infection; early syphilis included persons diagnosed within 12 months of infection (ie, assigned a surveillance stage of primary, secondary, or early non-primary non-secondary) and late syphilis included persons diagnosed more than 12 months after infection or with an unknown duration of infection (ie, assigned a surveillance stage of unknown duration or late).

Persons with reported neurologic manifestations included those with a neurologic manifestation classification of “verified”, “likely” or “possible.” All classifications require a reactive serologic treponemal and non-treponemal test and the presence of clinical signs/symptoms consistent with neurosyphilis without other known cause. Additionally, a “verified” classification requires a reactive cerebrospinal fluid (CSF) Venereal Disease Research Laboratory (VDRL) test. When CSF VDRL is unavailable, uninterpretable, or non-reactive, a “likely” classification requires an elevated CSF protein or white blood cell (WBC) count without other known causes (Supplementary Table 1).

Among stratified groups, we determined prevalence and prevalence ratios (PR) of neurologic manifestations by year, stage of infection and selected characteristics of persons from whom case reports were collected, including age at diagnosis, race/Hispanic ethnicity, sex, sex of sex partner(s), and human immunodeficiency virus (HIV) status. All case reports within each stratum were included in the denominator regardless of whether the presence or absence of neurologic manifestations was known. Analyses were performed using RStudio.

RESULTS

A total of 171 855 syphilis case reports for persons aged ≥ 15 years were sent to CDC during 2019–2022 from the 12 jurisdictions with complete reporting for neurologic manifestations

(Supplementary Figure 1); case counts increased annually, ranging from 33 975 in 2019 to 54 640 in 2022. Case reports included in this analysis accounted for 27% of all syphilis reports sent to CDC during 2019–2022. About 92% had a neurologic manifestation response value that was not missing or unknown.

Neurologic manifestations were infrequently reported but increased in prevalence among both persons with early and late syphilis (Table 1). In 2019, 0.6% (141/22 855) of early syphilis was reported with neurologic manifestations, increasing to 1.0% (313/32 603) in 2022. In 2019, 1.3% (146/11 120) of late syphilis was reported with neurologic manifestations, increasing to 1.8% (391/22 037) in 2022.

Prevalence of neurologic manifestations increased by age group. For early syphilis, prevalence among persons aged 65+ years was seven times that of persons aged 15–24 years (PR 7.5; 95% confidence interval [CI]: 5.2–10.8). For late syphilis, this increased to over 20 times that of persons aged 15–24 years (PR 22.6; 95% CI: 16.8–30.6).

Regarding race/ethnicity, prevalence of neurologic manifestations was higher among non-Hispanic White and non-Hispanic multiracial persons compared to non-Hispanic Black persons for early and late syphilis (Table 1).

There were inconsistent findings by sex and sex of sex partner(s). Though neurologic manifestations were reported more frequently among females (1.1%) compared to males (0.7%) with early syphilis, this was not observed among persons with late syphilis. Among persons with late syphilis, neurologic manifestations were reported more frequently among men who reported having sex with women only (MSW) (2.1%) and men with unknown sex partner(s) (2.0%) compared to men who reported having sex with men or men and women (MSM) (1.5%); this was not observed among persons with early syphilis.

Neurologic manifestations were four times as prevalent among persons with secondary syphilis (PR 4.2; 95% CI: 3.3–5.3) and five times as prevalent among persons with unknown duration or late syphilis (PR 5.2; 95% CI: 4.1–6.5) compared to primary syphilis. Persons with HIV had a higher prevalence of neurologic manifestations compared to those without HIV for early (PR 1.2; 95% CI: 1.0–1.4) and late syphilis (PR 1.5; 95% CI: 1.3–1.8).

DISCUSSION

Although the number of syphilis case reports with neurologic manifestations increased over time, the annual prevalence of neurologic manifestations remained low and relatively stable during a period of substantial increases in syphilis; this suggests that observed increases in neurologic manifestations largely reflects the concurrent increase in syphilis. This is concerning given the increased morbidity and mortality associated with neurologic involvement and the higher lifetime medical cost compared to uncomplicated syphilitic infections [5].

We found a higher prevalence of reported neurologic manifestations among older adults. Although prolonged infection may contribute to this finding among those with late syphilis, there are also diagnostic challenges pertinent to older adults with any stage of infection.

Non-specific neurologic signs/symptoms (eg, altered mental status) may occur more often with increasing age for a variety of reasons. Older adults may be at increased risk for false-positive syphilis laboratory results due to age-related increases in autoantibodies (including VDRL or rapid plasma reagin test results) [6]. These factors complicate the interpretation of clinical signs/symptoms and syphilis testing that may be included as part of diagnostic evaluation.

Differences in screening practices may contribute to observed differences by sex and sex of sex partner(s). Among non-pregnant adults, annual syphilis screening is recommended for sexually active MSM, transgender and gender diverse persons compared to risk-based screening for women and MSW [3]. This may lead to more asymptomatic infections being identified among MSM, transgender and gender diverse persons. Social determinants also influence disease prevalence, with intersectional structural inequities related to race, gender, sexuality, and class contributing to observed disparities by sex, sex of partner(s), and race/ethnicity [7,8]. Further exploration is needed to better understand and contextualize our findings.

We found a higher prevalence of neurosyphilis among persons with HIV compared to those without HIV. Published literature shows variability in the prevalence of neurologic manifestations by reported HIV status [9–11]. This may be due to differences in applied definitions or in *Treponema pallidum* strain types [12]. Our findings may be limited by ascertainment bias from enhanced follow-up and, consequently, increased detection of neurosyphilis among people with HIV. The proportion of missing data for HIV status may also limit interpretability (Supplementary Table 3). Furthermore, CSF WBC and CSF protein may be elevated in people with HIV in the absence of syphilitic infection, limiting the specificity of surveillance criteria [1]. Future analyses could consider incorporating measures of disease severity, anti-retroviral therapy use, and timing of HIV diagnosis for a more comprehensive understanding of neurologic involvement by HIV status.

We provide estimates of prevalence using passive national case-based surveillance data, which is subject to limitations. Our findings likely represent a minimum burden of neurologic manifestations: late syphilis, considered non-infectious, may not be prioritized in non-pregnant persons for investigation by health departments; neurologic signs/symptoms may not be reported by patients; and neurologic screening and evaluation practices may vary among providers. Furthermore, the syphilis case definition does not capture neurologic involvement in asymptomatic persons with syphilis or symptomatic neurosyphilis in persons with reactive treponemal and non-reactive non-treponemal test results. Reported neurologic manifestations were mostly classified as “possible” in our data (Supplementary Table 2), meaning that CSF laboratory data were not available or did not meet surveillance criteria. Clinical details beyond the reported presence or absence of neurologic manifestations were not available, limiting further assessment of validity and patterns of classification. Recent changes in reporting guidance also prevent us from describing ocular and otic manifestations, both of which can overlap with central nervous system involvement. Our sample represents a minority of national syphilis case notifications limiting generalizability. Efforts are ongoing to improve the completeness and quality of syphilis case notification data submitted to CDC.

Our analysis showed that neurologic manifestations were reported among persons with early and late syphilis, across every age group, sex, race/ethnicity, and HIV status. Healthcare providers should evaluate all patients with syphilis for evidence of neurologic signs/symptoms, with collection of CSF for analysis if clinical evidence of neurologic involvement is observed [3]. Early detection and treatment is crucial to prevent potential long-term neurologic sequelae of syphilis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Data statement.

Data are not publicly available.

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Table 1.

Prevalence of Reported Neurologic Manifestations by Year, Stage of Infection and Selected Characteristics of Persons From Whom Syphilis Case Reports Were Collected— 12 States^a, 2019–2022

Characteristic (no. cases)	All Stages				Early Syphilis				Late Syphilis						
	Total Syphilis Case Reports	Syphilis Case Reports With Neurologic Manifestations	Prevalence (Row %)	PR	95% CI	Total Syphilis Case Reports	Syphilis Case Reports With Neurologic Manifestations	Prevalence (Row %)	PR	95% CI	Total Syphilis Case Reports	Syphilis Case Reports With Neurologic Manifestations	Prevalence (Row %)	PR	95% CI
All reported cases of syphilis	171 855	1972	1.2	...	...	109 945	869	0.8	...	...	61 910	1103	1.8	...	...
Reporting Year															
2019	33 975	287	0.8	Ref	Ref	22 855	141	0.6	Ref	Ref	11 120	146	1.3	Ref	Ref
2020	35 857	394	1.1	1.3	1.1– 1.5	24 838	157	0.6	1.0	0.8– 1.3	11 019	237	2.2	1.6	1.3– 2.0
2021	47 383	587	1.2	1.5	1.3– 1.7	29 649	258	0.9	1.4	1.1– 1.7	17 734	329	1.9	1.4	1.2– 1.7
2022	54 640	704	1.3	1.5	1.3– 1.8	32 603	313	1.0	1.6	1.3– 1.9	22 037	391	1.8	1.4	1.1– 1.6
Age at Diagnosis in years															
15–24	29 510	127	0.4	Ref	Ref	19 093	76	0.4	Ref	Ref	10 417	51	0.5	Ref	Ref
25–34	66 985	413	0.6	1.4	1.2– 1.7	43 569	238	0.6	1.4	1.1– 1.8	23 416	175	0.8	1.5	1.1– 2.1
35–44	40 769	448	1.1	2.6	2.1– 3.1	26 229	244	0.9	2.3	1.8– 3.0	14 540	204	1.4	2.9	2.1– 3.9
45–54	20 229	377	1.9	4.3	3.5– 5.3	12 927	154	1.2	3.0	2.3– 3.9	7302	223	3.0	6.2	4.6– 8.4
55–64	10 839	339	3.1	7.3	5.9– 8.9	6616	112	1.7	4.2	3.2– 5.7	4223	227	5.4	11.0	8.1– 14.8
65+	3523	268	7.6	17.7	14.4– 21.8	1511	45	3.0	7.5	5.2– 10.8	2012	223	11.1	22.6	16.8– 30.6
Race/ Ethnicity ^b															
American Indian/Alaska Native	4716	51	1.1	1.4	1.0– 1.9	2593	20	0.8	1.7	1.1– 2.6	2123	31	1.5	1.1	0.8– 1.6

Characteristic (no. cases)	All Stages					Early Syphilis					Late Syphilis				
	Total Syphilis Case Reports	Syphilis Case Reports With Neurologic Manifestations	Prevalence (Row %)	PR	95% CI	Total Syphilis Case Reports	Syphilis Case Reports With Neurologic Manifestations	Prevalence (Row %)	PR	95% CI	Total Syphilis Case Reports	Syphilis Case Reports With Neurologic Manifestations	Prevalence (Row %)	PR	95% CI
Asian	2566	24	0.9	1.2	0.8– 1.8	1602	5	0.3	0.7	0.3– 1.6	964	19	2.0	1.5	0.9– 2.3
Black/ African American	73 269	567	0.8	Ref	Ref	46 850	215	0.5	Ref	Ref	26 419	352	1.3	Ref	Ref
Hispanic/ Latino	29 263	211	0.7	0.9	0.8– 1.1	17 926	99	0.6	1.2	0.9– 1.5	11 337	112	1.0	0.7	0.6– 0.9
Native Hawaiian/ Pacific Islander	727	12	1.6	2.1	1.2– 3.8	423	6	1.4	3.1	1.4– 6.9	304	6	2.0	1.5	0.7– 3.3
Multiracial	8914	113	1.3	1.6	1.3– 2.0	6591	70	1.1	2.3	1.8– 3.0	2323	43	1.8	1.4	1.0– 1.9
White	44 718	896	2.0	2.6	2.3– 2.9	30 122	431	1.4	3.1	2.6– 3.7	14 596	465	3.2	2.4	2.1– 2.7
Other race	2830	32	1.1	1.5	1.0– 2.1	1676	9	0.5	1.2	0.6– 2.3	1154	23	2.0	1.5	1.0– 2.3
Current Sex															
Male	131 033	1401	1.1	Ref	Ref	88 707	629	0.7	Ref	Ref	42 326	772	1.8	Ref	Ref
Female	40 773	568	1.4	1.3	1.2– 1.4	21 210	238	1.1	1.6	1.4– 1.8	19 563	330	1.7	0.9	0.8– 1.0
Sex/Sex of sex partner(s)															
MSM	64 112	568	0.9	Ref	Ref	49 736	358	0.7	Ref	Ref	14 376	210	1.5	Ref	Ref
MSW	26 489	303	1.1	1.3	1.1– 1.5	18 064	125	0.7	1.0	0.8– 1.2	8425	178	2.1	1.4	1.2– 1.8
Men with unknown sex partner(s)	40 432	530	1.3	1.5	1.3– 1.7	20 907	146	0.7	1.0	0.8– 1.2	19 525	384	2.0	1.3	1.1– 1.6
Women	40 773	568	1.4	1.6	1.4– 1.8	21 210	238	1.1	1.6	1.3– 1.8	19 563	330	1.7	1.2	1.0– 1.4
Syphilis stage															
Primary	22 141	76	0.3	Ref	Ref	22 141	76	0.3	Ref	Ref					
Secondary	34 247	488	1.4	4.2	3.3– 5.3	34 247	488	1.4	4.2	3.3– 5.3					

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Characteristic (no. cases)	All Stages					Early Syphilis					Late Syphilis				
	Total Syphilis Case Reports	Syphilis Case Reports With Neurologic Manifestations	Prevalence (Row %)	PR	95% CI	Total Syphilis Case Reports	Syphilis Case Reports With Neurologic Manifestations	Prevalence (Row %)	PR	95% CI	Total Syphilis Case Reports	Syphilis Case Reports With Neurologic Manifestations	Prevalence (Row %)	PR	95% CI
Early Non- Primary Non- Secondary	53 557	305	0.6	1.7	1.3– 2.1	53 557	305	0.6	1.7	1.3– 2.1					
Unknown duration/late	61 910	1103	1.8	5.2	4.1– 6.5						61 910	1103	1.8	NA	NA
HIV status															
Positive	51 088	615	1.2	1.2	1.1– 1.4	38 062	340	0.9	1.2	1.0– 1.4	13 026	275	2.1	1.5	1.3– 1.8
Negative	83 471	811	1.0	Ref	Ref	53 012	390	0.7	Ref	Ref	30 459	421	1.4	Ref	Ref

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; MSM, men who reported sex with men or men and women in the past 12 m; MSW, men who reported sex with women only in the past 12 m; PR, prevalence ratio; Ref, reference.

^a Jurisdictions were included if at least 70% of their annual acquired syphilis case reports for persons ≥15 years old included neurologic manifestation values that were not missing or unknown.

^b Persons with Hispanic or Latino (Hispanic) ethnicity were categorized as Hispanic and might be of any race; persons with non-Hispanic ethnicity were categorized into single race groups or as multiracial (more than one race category selected).

See Supplementary Table 3 for missingness of race/ethnicity, sex/sex of sex partner(s) and HIV status.