A Review of Death Certificates Listing Lyme Disease as a Cause of Death in the United States

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Lyme disease was listed as an underlying or multiple cause of death on 114 death records during 1999–2003. Upon review, only 1 record was consistent with clinical manifestations of Lyme disease. This analysis indicates that Lyme disease is rare as a cause of death in the United States.

Lyme disease is a tickborne disease caused by *Borrelia burgdorferi*. In the United States, cases most commonly occur among persons aged 5–14 years and 45–54 years, and during the summer months in the northeastern, mid-Atlantic, and north-central states [1]. Clinically, early Lyme disease is characterized by fever, fatigue, headache, arthralgias, myalgias, and erythema migrans rash. Untreated, the infection may disseminate to cause various manifestations, including secondary skin lesions, cranial neuropathy, lymphocytic meningitis, radiculoneuritis, atrioventricular block, and oligoarthritis [2]. However, Lyme disease rarely has been reported as a cause of death in the United States [3–6].

The International Classification of Diseases (ICD) is the international standard for categorizing health and vital records, including death certificates. When the ICD was updated to version 10, which became effective in the United States in 1999, Lyme disease was given a unique code and thus could be captured as a cause of death on death certificates. During 1999–2003, the Morbidity and Mortality Weekly Report (MMWR) Summary of Notifiable Diseases listed 24 deaths (median per year, 5; range per year, 2–7) attributed to Lyme disease (available at http://www.cdc.gov/mmwr/mmwr_nd/index.html). To describe the epidemiology of deaths attributed to Lyme disease, we reviewed death records and death certificates in the United States during 1999–2003.

METHODS

Death records from 1999 to 2003 for which Lyme disease was coded as an underlying or multiple cause of death were requested from the National Center for Health Statistics (NCHS). The underlying cause of death is defined as "the disease or injury which initiated the chain of morbid events leading directly to death" [7]. A multiple cause of death is defined as "any other significant condition which contributed to the fatal outcome, but was not related to the disease or condition directly causing death" [7]. Part I of a death certificate contains the causal sequence from the underlying cause to the terminal event, and Part II contains any other significant medical conditions that contributed, but were not directly related, to the causal sequence. Death certificates were coded according to the ICD-10 in state vital records departments using a computerized algorithm updated annually by NCHS. All records with ICD-10 codes assigned to Lyme disease (ie, A69.2 and L90.4) were requested. Data obtained included month and year of death, age, sex, state of residence, state of death, and ICD-10 codes for underlying and multiple causes of death. Copies of corresponding death certificates were requested from states and reviewed. Analyses were conducted using Microsoft Excel and SAS software, version 9.1. Death record analysis was exempt from human subjects review at CDC, but approval was obtained from states when required. Plausibility of association with Lyme disease was based on well-established clinical manifestations of Lyme disease published in the peer-reviewed literature.

RESULTS

Approval to release death records during the study period was received from all states except Idaho, Iowa, Louisiana, Maine, and Tennessee. Among the 45 remaining states, Lyme disease was coded as an underlying or multiple cause of death for 119 records from 25 states. When requesting corresponding death certificates, one certificate could not be located by the state, one was never requested in error, two certificates did not contain a

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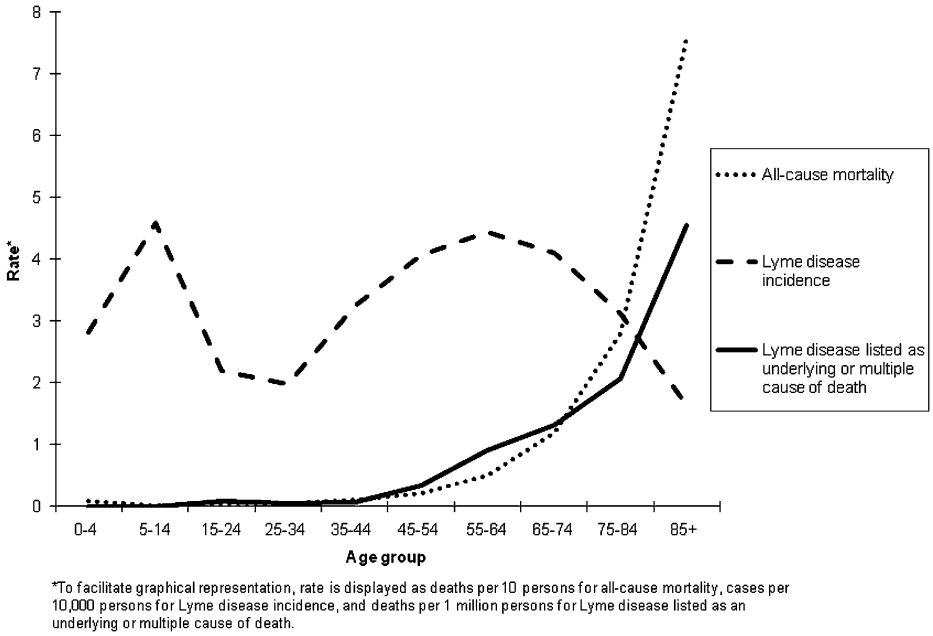

Figure 1. Relative age-group specific rates of all-cause mortality, Lyme disease incidence, and Lyme disease listed as a multiple or underlying cause of death-United States, 1999–2003

diagnosis or any wording of Lyme disease or *B. burgdorferi* infection, and one certificate was destroyed and the corresponding data deleted during our analysis due to expiration of the state's human subjects approval per state guidelines. Analyses were conducted on the remaining 114 death certificates.

The median age of decedents was 71 years (range: 19–99 years); 66 (58%) were male. The relative age-group specific rates of persons with Lyme disease listed as an underlying or multiple cause of death, all-cause mortality in the United States and incident cases of Lyme disease are shown in Figure 1. Deaths were evenly distributed throughout the study period (1999: n = 25; 2000: n = 23; 2001: n = 14; 2002: n = 25; 2003: n = 27) and across seasons. Deaths were reported among residents of Connecticut (19), Pennsylvania (18), New Jersey (13), New York (12), California (8), Massachusetts (5), Minnesota (5), Wisconsin (5), Virginia (4), Florida (3), Missouri (3), Texas (3), Maryland (2), Michigan (2), West Virginia (2), Alabama (1), Arkansas (1), Colorado (1), Iowa (1) (The death record and certificate for this decedent were from Kansas, but Iowa was listed as the state of residence.), Illinois (1), Indiana (1), North Carolina (1), North Dakota (1), South Carolina (1), and Washington (1).

Of 114 records, Lyme disease was coded as the underlying cause of death for 23 (20%) and as a multiple cause of death for 91 (80%) (Table 1). There were no significant differences between decedents with Lyme disease coded as an underlying versus multiple cause of death with respect to age, sex, or residence or death in a with respect to age, sex, or residence or death in a Healthy People 2010 highly endemic state as previously defined (Connecticut, Delaware, Maryland, Massachusetts, Minnesota, New Jersey, New York, Pennsylvania, Rhode Island, and Wisconsin) [1]. Four (17%) records for which Lyme disease was coded as the underlying cause of death had Lyme disease listed in Part II of the death certificate, but it was coded as the underlying cause because the listed causal pathway in Part I of the death certificate lacked an accepted cause of death (eg, "presumed natural disease"). Eleven (48%) death certificates with Lyme disease coded as the underlying cause of death were improperly completed, as evidenced by an implausible or ill-defined causal sequence of events (Table 1) [8]. Of the 12 certificates considered properly completed, the terminal events in the causal sequences were cardiopulmonary or cardiorespiratory arrest (3), respiratory arrest, failure, or anoxia (3), Lyme disease (2), coronary thrombosis (1), encephalopathy (1), seizure disorder (1), and stroke (1). Of these 12 certificates, 6 (50%) lacked enough information to evaluate the plausibility of the causal sequence, 2 (17%) listed other more plausible clinical explanations for the terminal event in Part II of the certificate (eg, atherosclerotic heart disease and chronic atrial fibrillation for the decedent with stroke), 2 (17%) contained disease processes in intervals substantially longer than that described in the scientific literature (eg, Lyme disease 5–10 years prior to seizure disorder onset), 1 (8%) listed a causal sequence not previously associated with Lyme disease (ie, coronary thrombosis and hypercoagulable state), and 1 (8%) listed a causal sequence possibly consistent with a prior case report (ie, "respiratory

Table 1. Direct Extraction of Part I of Death Certificates for which Lyme Disease Was Coded as the Underlying Cause of Death

State	Age	Immediate cause	Due to or as a consequence of	Due to or as a consequence of	Due to or as a consequence of	Lyme disease listed in Part II
CA	68	Dilated acute cardiomyopathy	Lyme disease			
CA	66	Probable cardiac arrythmia	Polymicrobial bacteremia from Lyme infection	New onset seizure disorder	Large left hemorrhagic stroke	
CT*	76	Stroke	Meningoencephalopathy	Lyme disease		
CT*	61	Cardiopulmonary arrest	Ventricular fibrillation	Lyme disease		
IN	60	Encephalopathy	Lyme disease			
MD*	92	Inanition				X
MN*	81	Pneumonia				X
MN*	69	Seizure disorder	Lymes disease [*sic*]			
MO	47	Lyme disease and ALS	Amyotrophic lateral sclerosis			
MO	57	Coronary thrombosis	Hypercoagulable state	Lyme disease		
NC	19	Anoxia	Respiratory failure	Cardiac failure	Lyme disease (CNS)	
ND	80	Respiratory failure	Probable aspiration	Severe cognitive deterioration	Central nervous system Lymes disease [*sic*]	
NJ*	63	Respiratory failure	Pneumonia	Lymes disease [*sic*]	Parkinsonism	
NJ*	76	Respiratory arrest	Endstage dementia	Lymes disease [*sic*]		
NJ*	59	Lyme disease	HTN, 1	Fracture ribs [*sic*]	Adrenal insuf.	
NY*	86	Respiratory arrest	Organic brain syndrome	Lyme borreliosis		
NY*	78	Lyme disease	Resp. failure			
NY*	87	Cardio-respiratory arrest	Inanition	End stage dementia and Lyme disease encephalopathy		
NY*	85	Complications of Lyme disease				
PA*	53	Presumed natural disease				X
PA*	72	Cardiorespiratory arrest	Lymes' disease [*sic*]			
SC	95	Lyme's disease [*sic*]				
WI*	73	Acute respiratory failure	Pneumonia			X

* Healthy People 2010 highly endemic states.

failure'' due to ''probable aspiration'' due to ''severe cognitive deterioration'' due to ''central nervous system Lymes disease'' [*sic*]) [3].

Among the 91 records for which Lyme disease was coded as a multiple cause of death, 45 different diseases were coded as the underlying cause of death, including infectious diseases (eg, tuberculosis), malignancies (eg, colon, prostate), diabetes mellitus, nervous system diseases (eg, motor neuron disease, Parkinson's disease), circulatory system diseases (eg, acute myocardial infarction, atherosclerotic heart disease), and chronic obstructive pulmonary disease.

DISCUSSION

In contrast to the 96,068 cases of Lyme disease reported to CDC during 1999–2003, Lyme disease was coded as an underlying cause of death on only 23 records. Decedents were predominately of an advanced age and age distribution that more closely approximates that of all-cause mortality than that of reported Lyme disease cases. Most terminal events on death certificates for which Lyme disease was the underlying cause of death were inconsistent with the well-characterized complications of Lyme disease and the rare published case reports of Lyme disease-associated mortality [3–6]. Additionally, the underlying causes of death when Lyme disease was listed as a multiple cause of death varied widely and also were inconsistent with the well-characterized complications of Lyme disease. While this analysis included data only through 2003, the number of deaths attributed to Lyme disease as reported in the MMWR Summary of Notifiable Diseases has remained consistent (available at http://www.cdc.gov/mmwr/PDF/wk/mm5754.pdf).

Mortality data are a fundamental component of disease surveillance. While standard forms and procedures are developed

and recommended for nationwide use, improper completion of death certificates is not unique to our analysis [9]. Common errors include listing underlying or multiple causes of death in the wrong section, listing nonspecific processes, and listing inappropriate events in the causal sequence [9]. Sparse dedicated resources at the state level may limit follow-up of improperly or inaccurately completed death certificates, thereby decreasing the public health utility of this data source.

Without approval from every state to receive death record data, some relevant death records may have been excluded. However, these 5 states accounted for ~1% of Lyme disease cases reported during 1999–2003, and this analysis captured 23 of 24 reported underlying deaths due to Lyme disease. In contrast, deaths attributed to Lyme disease likely are overestimated in this report because 9 certificates (8%) had uncertain terms listed such as "Lyme disease?," "Lyme disease—past history," or "possible chronic Lyme disease." Most importantly, we did not conduct medical chart reviews. Therefore, we were unable to confirm or deny the diagnosis of Lyme disease or the causal sequence leading to death.

Despite these limitations, our review of death records and death certificates supports the finding that Lyme disease is rare as a cause of death. Therefore, we strongly encourage health care providers to thoroughly document and report any death suspected to be caused by Lyme disease. Additionally, health care providers should be reminded to carefully and accurately complete death certificates as this data is a vital source of health information. Lastly, prompt diagnosis and treatment of persons infected with *Borrelia burgdorferi* are critical to the prevention of more serious illness and potential long-term complications.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention, US Department of Health and Human Services.

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References

1. Bacon RM, Kugeler KJ, Mead PS. Surveillance for Lyme disease–United States, 1992–2006. MMWR Surveill Summ **2008**; 57:1–9.
2. Steere AC, Coburn C, Glickstein L. The emergence of Lyme disease. J Clin Invest **2004**; 113:1093–101.
3. Waniek C, Prohovnik I, Kaufman MA, Dwork AJ. Rapidly progressive frontal-type dementia associated with Lyme disease. J Neuropsychiatry Clin Neurosci **1995.** Summer; 7:345–7.
4. Marcus LC, Steere AC, Duray PH, Anderson AE, Mahoney EB. Fatal pancarditis in a patient with coexistent Lyme disease and babesiosis. Demonstration of spirochetes in the myocardium. Ann Intern Med **1985**; 103:374–6.
5. Kirsch M, Ruben FL, Steere AC, Duray PH, Norden CW, Winkelstein A. Fatal adult respiratory distress syndrome in a patient with Lyme disease. JAMA **1988**; 259:2737–9.
6. Tavora F, Burke A, Ling L, Franks TJ, Virmani R. Postmortem confirmation of Lyme carditis with polymerase chain reaction. Cardiovasc Pathol **2008**; 17:103–7.
7. WHO. International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10). Geneva: WHO, **1992**.
8. Physician's Handbook on Medical Certification of Death. Hyattsville, MD: National Center for Health Statistics, **2004**.
9. Sehdev AES, Hutchins GM. Problems with proper completion and accuracy of the cause-of-death statement. Arch Intern Med **2001**; 161:277–84.

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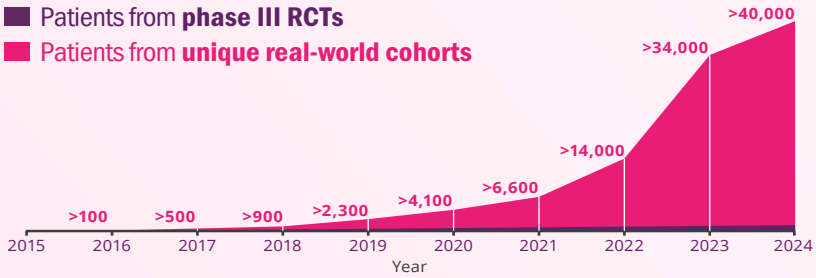

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REFERENCES

1. Maggiolo F et al. BMC Infect Dis 2022; 22(1): 782.
2. Taramasso L et al. AIDS Patient Care STDS 2021; 35(9): 342–353.
3. Ciccullo A et al. JAIDS 2021; 88(3): 234–237.
4. ViiV Healthcare. Data on File. REF-223795. 2024.
5. Cahn P et al. AIDS 2022; 36(1): 39–48.
6. Rolle C et al. Open Forum Infect Dis 2023; 10(3): ofad101.
7. Cordova E et al. Poster presented at 12th IAS Conference on HIV Science. 23–26 July 2023. Brisbane, Australia. TUPEB02.
8. De Wit S et al. Slides presented at HIV Glasgow. 23–26 October 2022. Virtual and Glasgow, UK. M041.
9. Llibre J et al. Clin Infect Dis 2023; 76(4): 720–729.
10. ViiV Healthcare. Data on File. REF-220949. 2024.
11. Rolle C et al. Poster presented IDWeek. 11–15 October 2023. Virtual and Boston, USA. 1603.
12. Slim J et al. Abstract presented IDWeek. 11–15 October 2023. Virtual and Boston, USA. 1593.
13. DOVATO. Summary of Product Characteristics. June 2023.

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ABBREVIATIONS

3TC, lamivudine; **CD4,** cluster of differentiation 4; **DTG,** dolutegravir; **FDA,** United States Food and Drug Administration; **FTC,** emtricitabine; **HIV,** human immunodeficiency virus; **ITT-E,** intention-to-treat exposed; **NRTI,** nucleoside/nucleotide reverse transcriptase inhibitor; **RCT,** randomised controlled trial; **RNA,** ribonucleic acid; **TAF,** tenofovir alafenamide fumarate; **TDF,** tenofovir disoproxil fumarate; **XTC,** emtricitabine.

FOOTNOTES

*Data extracted from a systematic literature review of DTG+3TC real-world evidence. Overlap between cohorts cannot be fully excluded.

**The reported rate reflects the sum-total of resistance cases calculated from GEMINI I and II (n=1/716, through 144 weeks), STAT (n=0/131, through 52 weeks), and D2ARLING (n=0/106, through 24 weeks).[5–7]

†GEMINI I and II are two identical 148-week, phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority, controlled clinical trials testing the efficacy of DTG/3TC in treatment-naïve patients. Participants with screening HIV-1 RNA ≤500,000 copies/mL were randomised 1:1 to once-daily DTG/3TC (n=716, pooled) or DTG + TDF/FTC (n=717, pooled). The primary endpoint of each GEMINI study was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).[13]

‡STAT is a phase IIIb, open-label, 48-week, single-arm pilot study evaluating the feasibility, efficacy, and safety of DTG/3TC in 131 newly diagnosed HIV-1 infected adults as a first line regimen. The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 24.[6]

§D2ARLING is a randomised, open-label, phase IV study designed to assess the efficacy and safety of DTG/3TC in treatment-naïve people with HIV with no available baseline HIV-1 resistance testing. Participants were randomised in a 1:1 ratio to receive DTG/3TC (n=106) or DTG + TDF/XTC (n=108). The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48.[7] Results at week 24 of the study.

||The reported rate reflects the sum-total of resistance cases calculated from TANGO (n=0/369, through 196 weeks) and SALSA (n=0/246, through 48 weeks).[8,9]

¶TANGO is a randomised, open-label, trial testing the efficacy of DOVATO in virologically suppressed patients. Participants were randomised in a 1:1 ratio to receive DOVATO (n=369) or continue with TAF-containing regimens (n=372) for up to 200 weeks. At Week 148, 298 of those on TAF-based regimens switched to DOVATO. The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL (virologic non-response) as per the FDA Snapshot category at Week 48 (adjusted for randomisation stratification factor).[8,13]

#SALSA is a phase III, randomised, open-label, non-inferiority clinical trial evaluating the efficacy and safety of switching to DTG/3TC compared with continuing current antiretroviral regimens in virologically suppressed adults with HIV. Eligible participants were randomised 1:1 to switch to once-daily DTG/3TC (n=246) or continue current antiretroviral regimens (n=247). The primary endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).[9]

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