

Lyme Borreliosis (LB) is a Significant Disease Burden in Germany: Estimated LB Incidence after Adjusting for Under-ascertainment by Public Health Surveillance, 2021

ABSTRACT

Background: Lyme borreliosis (LB), the most common tickborne disease in Europe, is endemic in Germany. Nine German states (with 42% of the German population) conduct LB surveillance with mandatory notification by clinicians and laboratories but an analysis of outpatient claims estimated that only one of every six LB cases in these states were reported. We estimated the LB incidence after adjusting for underascertainment of public health surveillance.

Methods: Nationally representative studies estimated the prevalence of antibodies against Borrelia burgdorferi sensu lato in adults and children in Germany. Published estimates of the asymptomatic proportion and the duration of antibody detection were used to estimate the number of LB cases from seroprevalence data in states that conduct LB surveillance. The number of estimated LB cases were compared to the number of surveillance-reported cases to derive under-ascertainment multipliers for adults and children. The derived multipliers were applied to the number of reported cases in 2021 to estimate the number and incidence of LB cases in the states that conducted surveillance in 2021. A sensitivity analysis evaluated the impact of different antibody durations.

Results: Using a 50% asymptomatic proportion and 10-year antibody duration, the estimated number (population-based incidence) of LB cases in states that conducted surveillance was 128,870 (408/100,000) in 2021. Since there were 11,051 reported cases in these states, these data indicate there were 12 LB cases in 2021 for every reported case in these states. Using 20-year or 5-year antibody duration, the estimated number (incidence) of LB cases in the states that conducted surveillance was 64,935–259,740 (204–816/100,000) in 2021, respectively.

Conclusion: Incidence of LB in states that conduct surveillance in Germany is higher than reported. Under-ascertainment of LB cases in states that conduct surveillance is even greater than that estimated in a claims data analysis of medically-attended LB cases. Enhancements of LB surveillance, including expanding nationwide, would facilitate further elucidation of the true LB disease burden in Germany. Disease prevention efforts, including availability of an efficacious vaccine are needed to address this important public health problem.

INTRODUCTION

Nine of 16 federal states in Germany, covering 42% of the total German population, conduct public health surveillance for Lyme borreliosis (LB) with mandatory notification by clinicians and laboratories of erythema migrans (EM), neuroborreliosis (NB), and Lyme arthritis (LA)

Surveillance systems may "under-ascertain" persons with LB because:

- A person with LB may not seek medical care
- May seek medical care but the clinician may not diagnosis LB
- May seek medical care but a diagnostic specimen may not be collected
- A diagnostic specimen may be collected but an appropriate test for LB may not be performed
- A clinician may not report the clinically-diagnosed or laboratory-diagnosed LB case
- A laboratory may not report the laboratory-confirmed LB case

We sought to estimate the number of LB cases in the 9 German states that conduct public health LB surveillance after adjusting the number of reported LB cases for under-ascertainment

- **Prior LB incidence estimates in Germany**
- Enkelmann (2018) reported that the annual population-based incidence of reported LB cases in the 9 states that conduct public health surveillance from 2013–2017 was 33 LB cases per 100,000 per year
- Huppertz (1999) conducted prospective population-based surveillance among clinicians in Wurtzburg in 1996–1997 and ascertained an incidence of 111 LB cases per 100,000 per year
- Akmatov (2021) compared number of reported LB cases in public health surveillance to estimated number of medically-attended LB cases in outpatient claims database and estimated an incidence of 429 LB cases per 100,000 in 2019
- Concluded that for every reported LB case, there were 6 LB cases recorded in the outpatient database
- Outpatient claims database-derived under-ascertainment multipliers estimate the under-ascertainment among medically-attended LB cases

Steps when Adjusting Surveillance Data for Under-ascertainment

- infection
- Convert prevalence to incidence using the formula: P≈I*t (where t is duration of antibody detection)
- Based on reviews of the literature, we assumed that 50% of seroconverted cases were symptomatic and the duration of antibody detection was 10 years and used the following formula to estimate the number of incident cases:

incident cases from

- 4. Compare estimated number of incident cases (from seroprevalence data) to the number of reported cases (from public health surveillance) to estimate under-ascertainment multiplier
- . Adjust most recent number of reported cases (from public health surveillance) by under-ascertainment multiplier to estimate most recent number of cases

Seroprevalence Data

- Wilking (2015): Nationwide cross-sectional study of German adults (DEGS) conducted from November 2008 – December 2011
- Participants selected using two-stage stratified random sampling design
- selected adults
- Dehnert (2012): Nationwide cross-sectional study of German children (KiGGS) conducted from May 2003 – May 2006
- Participants selected using two-stage stratified random sampling design
- Blood sample collected from 12,614 randomly selected children
- Samples tested by ELISA and line blot
- Both seroprevalence studies collected blood specimens over a 3-year period – we assumed that the results in each study represented the seroprevalence in the last full calendar year of the study (2011 for adults, 2015 for children)
- Both seroprevalence studies report regional multipliers based on two regional stratifications (East vs. West, and North vs. Middle vs. South)

Public Health Surveillance Data

- Robert Koch Institute aggregates (and de-duplicates) public health LB surveillance data from the nine states, with weekly data available by region
- Both laboratory-confirmed (LNB, LA) and clinicianreported (EM) cases reported
- Online dashboard provides ability to filter and stratify data by several variables (state, year, age, case definition, case definition, etc.)

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METHODS

. Obtain data from a <u>representative</u> seroprevalence study with credible estimate of the prevalence of

- Estimated number of = (seroprevalence x population size x 50% asymptomatic) / seroprevalence results 10-year duration

Obtain number of reported cases from public health surveillance conducted in the same location and over the same time period as the seroprevalence study

- Blood sample collected from 6,965 randomly
- Samples tested by ELISA and line blot

Seroprevalence Data

• Seroprevalence results in adults in 2011 ranged from 9.1% in the West to 10.4% in the East, and from 8.1% in the Middle to 11.2% in the South, while results in children in 2005 ranged from 3.9% in the West to 4.5% in the East, and 3.5% in the Middle to 4.9% in the South (Figure 1)

Public Health Surveillance Data

• There were 11,051 reported LB cases in 2021, for a populationbased incidence in the 9 states that reported LB cases of 31 reported LB cases per **100,000 population** in 2021 (Figure 2)



Table 3. Under-ascertainment Multipliers & Estimated Number of LB Cases in 2021, by State – Adults

	Total number of reported	Estimated number of of incident cases in 2011		l number Under- nt cases ascertainment 011 multipliers		Total number	Estimated number of LB cases in 2021		er of LB 21		Total number of reported	Estimated number of incident cases in 2005		Under- ascertainment multipliers		Total Estimat		ited number of LB ases in 2021					Total number of reported cases in 2021			Estimated total number of LB cases in 2021			Population-based LB incidence
	cases in 2011 or avg of 1 st	East vs. West	North vs. Middle vs.	East vs West	North vs. Middle vs	reported cases in	East vs. West	North vs. Middle vs	. Average		cases in 2005 or avg of 1 st	East vs. West	North vs. Middle vs.	East vs. West	North vs. Middle vs.	reported cases in	East vs. West	North vs. Middle vs.	Average			Children (0-17)	Adults (18+)	Total	East vs. West	North vs. Middle vs. South	Average	(0-79)	(LB cases per 100,000 in 2021)
	3 years		South		South	2021		South			3 years		South		South	2021		South		Ba	Bavaria	620	3,269	3,889	43,656	53,858	48,757	12,268,594	397
Bavaria	3,731	44,151	54,340	12	15	3,269	38,680	47,607	43,144	Bavaria	564	4,526	5,686	8	10	620	4,975	6,251	5,613	B	Berlin	76	918	994	21,998	18,894	20,446	3,442,846	594
Berlin	648	13,983	12,101	22	19	918	19,819	17,151	18,485	Berlin	40	1,147	917	29	23	76	2,179	1,743	1,961	В	Brandenburg	137	1,258	1,395	9,499	8,186	8,843	2,322,407	381
Brandenburg	1,448	10,322	8,933	7	6	1,258	8,968	7,761	8,364	Brandenburg	218	846	677	4	3	137	532	425	478	Μ	Vecklenburg-	50	E 4 0	004	4 4 2 0	2 5 2 2	2.024	4 477 050	250
Mecklenburg- Vorpommern	1,144	6,793	5,879	6	5	542	3,218	2,785	3,002	Mecklenburg- Vorpommern	36	562	450	16	12	59	921	737	829	Va	Vorpommern Rhineland-Palatinate	09 151	54Z	860	4,139 6 731	3,522	7 518	3 804 965	108
Rhineland-Palatinate	1,681	14,142	17,406	8	10	709	5,964	7,340	6,652	Rhineland-Palatinate	287	1,460	1,835	5	6	151	768	964	866			40	160	205	2,020	2 742	2 201	0,004,000	274
Saarland	200	3.597	4.427	18	22	162	2.913	3.585	3.249	Saarland	118	344	432	3	4	43	126	158	142	5	Saariand	43	162	205	3,039	3,743	3,391	905,903	374
Saxonv	1.432	16.841	13.116	12	9	1.782	20.957	16.322	18.640	Saxonv	155	1.328	1.033	9	7	129	1.105	860	983	Sa	Saxony	129	1,782	1,911	22,062	17,182	19,622	3,694,954	531
Saxony-Anhalt	514	9.849	7.671	19	15	626	11.996	9.343	10.669	Saxony-Anhalt	56	772	600	14	11	40	551	429	490	Sa	Saxony-Anhalt	40	626	666	12,547	9,772	11,159	1,989,373	561
Thuringia	485	9.181	7.151	19	15	349	6.607	5.146	5.876	Thuringia	75	736	572	10	8	49	481	374	427	Tł	Thuringia	49	349	398	7,087	5,519	6,303	1,941,067	325
TOTAL	11,283	128,859	131,024			9,615	119,122	117,040	118,081	TOTAL	1,549	11,721	12,202	-		1,304	11,637	11,940	11,789		TOTAL	1,304	9,615	10,919	130,758	128,980	129,870	31,847,467	408

Strengths of Study:

- National, representative seroprevalence data is available in Germany for both adults and children
- Germany has surveillance system in 9 states that captures both clinician-reported and laboratory-confirmed LB cases

CONCLUSION

There were an estimated 129,870 LB cases in the 9 states that conduct surveillance in 2021 • Compared with 10,919 reported LB cases in the 9 states in 2021

RESULTS

Under-ascertainment

- Using seroprevalence data, there were an estimated 128,859–131,024 symptomatic LB infections in adults in 2011 (Table 1) and 11,721–12,202 symptomatic LB infections in children in 2005 (Table 2)
- When the estimated number of symptomatic LB infections were compared to the number of reported LB cases in adults in 2011, the state-specific under-ascertainment multipliers ranged from 5-22, and resulted in an estimated 118,081 symptomatic LB infections in adults in 2021 (Table 3)

- population in 2021

Table 1. Estimated N	Number	of Incident Ca	ses in 201	1, by St	ate –	Table 2. Estimated N	lumber	of Incident Ca	ses in 200	5, by St	ate –	
Addito	Seropre	evalence in 2011	Adult (18-79)	Estima incider	ated number of at cases in 2011		Seropre	evalence in 2005	Children (0-17)	Estimated numbe incident cases in 2		
	East vs. West	North vs. Middle vs. South	population in 2011	East vs. West	North vs. Middle vs. South		East vs. West	North vs. Middle vs. South	population in 2005	East vs. West	North vs. vs. So	
Bavaria	9.1%	11.2%	9,703,505	44,151	54,340	Bavaria	3.9%	4.9%	2,320,986	4,526	5,68	
Berlin	10.4%	9.0%	2,689,013	13,983	12,101	Berlin	4.5%	3.6%	509,591	1,147	91	
Brandenburg	10.4%	9.0%	1,985,034	10,322	8,933	Brandenburg	4.5%	3.6%	375,950	846	67	
Mecklenburg-Vorpommern	10.4%	9.0%	1,306,373	6,793	5,879	Mecklenburg-Vorpommern	4.5%	3.6%	249,769	562	450	
Rhineland-Palatinate	9.1%	11.2%	3,108,241	14,142	17,406	Rhineland-Palatinate	3.9%	4.9%	748,960	1,460	1,83	
Saarland	9.1%	11.2%	790,451	3,597	4,427	Saarland	3.9%	4.9%	176,165	344	432	
Saxony	10.4%	8.1%	3,238,640	16,841	13,116	Saxony	4.5%	3.5%	590,319	1,328	1,03	
Saxony-Anhalt	10.4%	8.1%	1,894,122	9,849	7,671	Saxony-Anhalt	4.5%	3.5%	343,064	772	600	
Thuringia	10.4%	8.1%	1,765,620	9,181	7,151	Thuringia	4.5%	3.5%	326,972	736	572	
		TOTAL	26,480,999	128,859	131,024			TOTAL	5,641,776	11,721	12,2	

Table 4. Under-ascertainment Multipliers & Estimated Number of LB Cases in 2021, by State – Children

DISCUSSION

Limitations of Study:

- Seroprevalence studies do not provide seroprevalence by state
- Only 9 states conduct LB surveillance
- Under-ascertainment multipliers from 2011 in adults (2005 in children) were applied to 2021 incident data; do not know if factors influencing under-ascertainment (i.e., seeking care) are the same from 2011 in adults (or 2005 in children) to 2021

This Under-ascertainment Multiplier Approach Relies on Several Assumptions:

For every reported LB case in these 9 states, there were an estimated 12 LB cases When adjusted for under-ascertainment, the estimated incidence of LB in the 9 states that conduct surveillance was 408 LB cases per 100,000 population in 2021 • The seroprevalence-derived under-ascertainment multiplier is for all LB cases (i.e., symptomatic LB cases • Compared with 31 reported LB cases per 100,000 population in the 9 states that are medically-attended and not medically-attended), and therefore higher than the outpatient claims database-derived under-ascertainment multiplier of 6-8 (which only includes medically-attended LB cases in 2021

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• When the estimated number of symptomatic LB infections were compared to the number of reported LB cases in children in 2021, the state-specific under-ascertainment multipliers ranged from 3–29, and resulted in an estimated 11,789 symptomatic LB infections in children in 2021 (Table 4)

• Taken together, there were an estimated 129,870 symptomatic LB infections in all ages in 2021 (Table 5) • In the nine states that conduct LB surveillance, for every reported LB case in surveillance in 2021, there were an estimated 12 symptomatic LB infections

• The incidence, adjusted for under-ascertainment, was 408 symptomatic LB infections per 100,000

Table 5. Estimated Total Number and Population-based Incidence of LB Cases in 2021, by State – All ages

• Genospecies distribution in Germany is relatively similar to the genospecies distribution in the asymptomatic and duration of antibody detection study populations

• Percent of seroconverted cases that are asymptomatic is 50%; if a higher percent are asymptomatic, the estimated number of cases would be lower

• Duration of antibody detection is 10 years; if duration is shorter, the estimated number of cases would be higher