

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

Julia Olsen,¹ Gordon Brestrich,² Andreas Pilz,³ Kate Halsby,¹ Patrick Kelly,¹ Claudius Malerczyk,² Frederick Angulo,¹ James Stark¹

¹Medical Development and Scientific/Clinical Affairs, Pfizer Vaccines, Collegeville, Pennsylvania, USA; ²Pfizer Pharma GmbH, Berlin, Germany; ³Vaccines, Pfizer Corporation Austria, Vienna, Austria

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 under-ascertainment 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 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

METHODS

Steps when Adjusting Surveillance Data for Under-ascertainment:
1. Obtain data from a representative seroprevalence study with credible estimate of the prevalence of infection
2. 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:
Estimated number of incident cases from seroprevalence results = (seroprevalence x population size x 50% asymptomatic) / 10-year duration
3. Obtain number of reported cases from public health surveillance conducted in the same location and over the same time period as the seroprevalence study
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
5. 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
- Blood sample collected from 6,965 randomly selected adults
- Samples tested by ELISA and line blot
- 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 clinician-reported (EM) cases reported
- Online dashboard provides ability to filter and stratify data by several variables (state, year, age, case definition, case definition, etc.)

RESULTS

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 population-based incidence in the 9 states that reported LB cases of 31 reported LB cases per 100,000 population in 2021 (Figure 2)
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)
- When the estimated number of symptomatic LB infections were compared to the number of reported LB cases in children in 2005, the state-specific under-ascertainment multipliers ranged from 3–29, and resulted in an estimated 129,870 symptomatic LB infections in children in 2021 (Table 4)

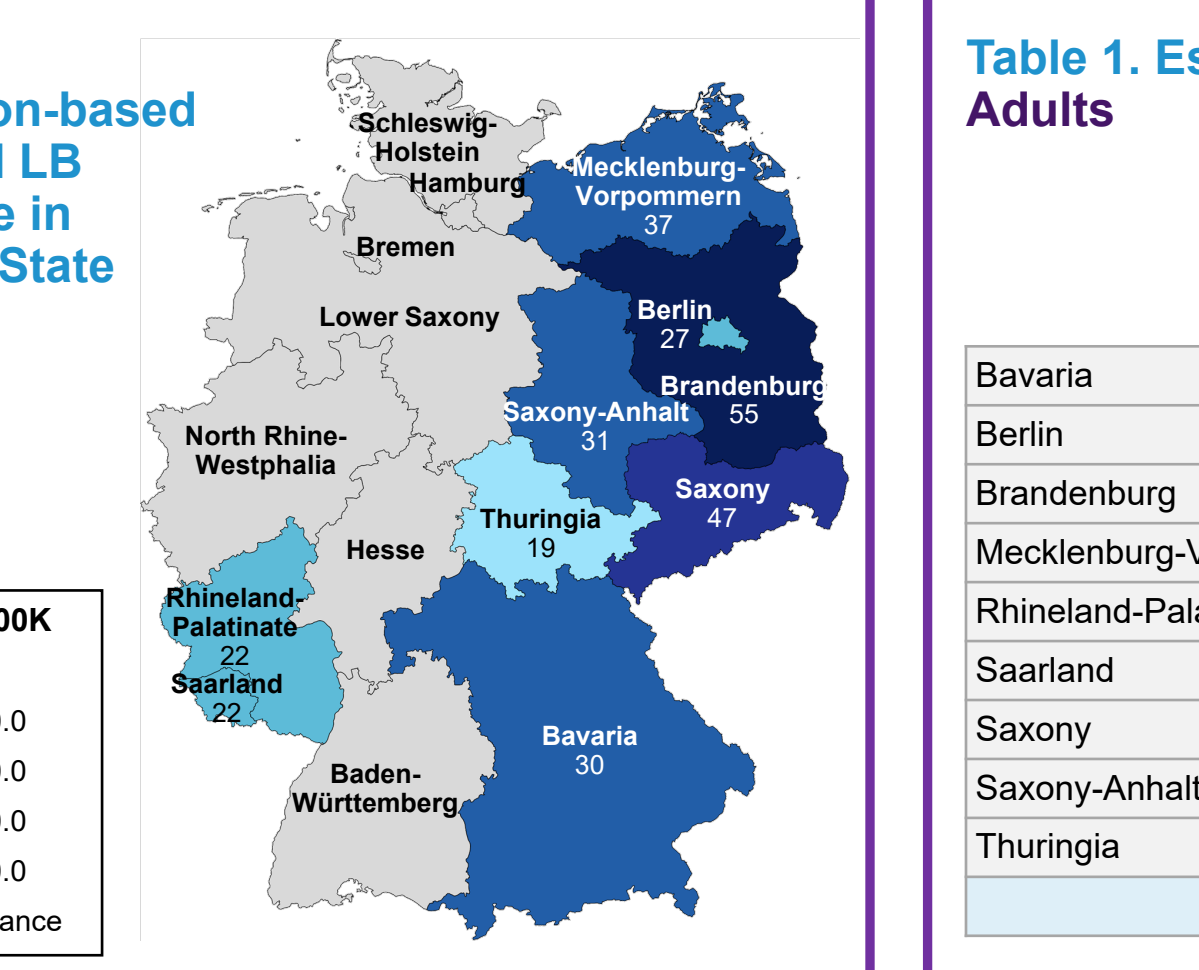
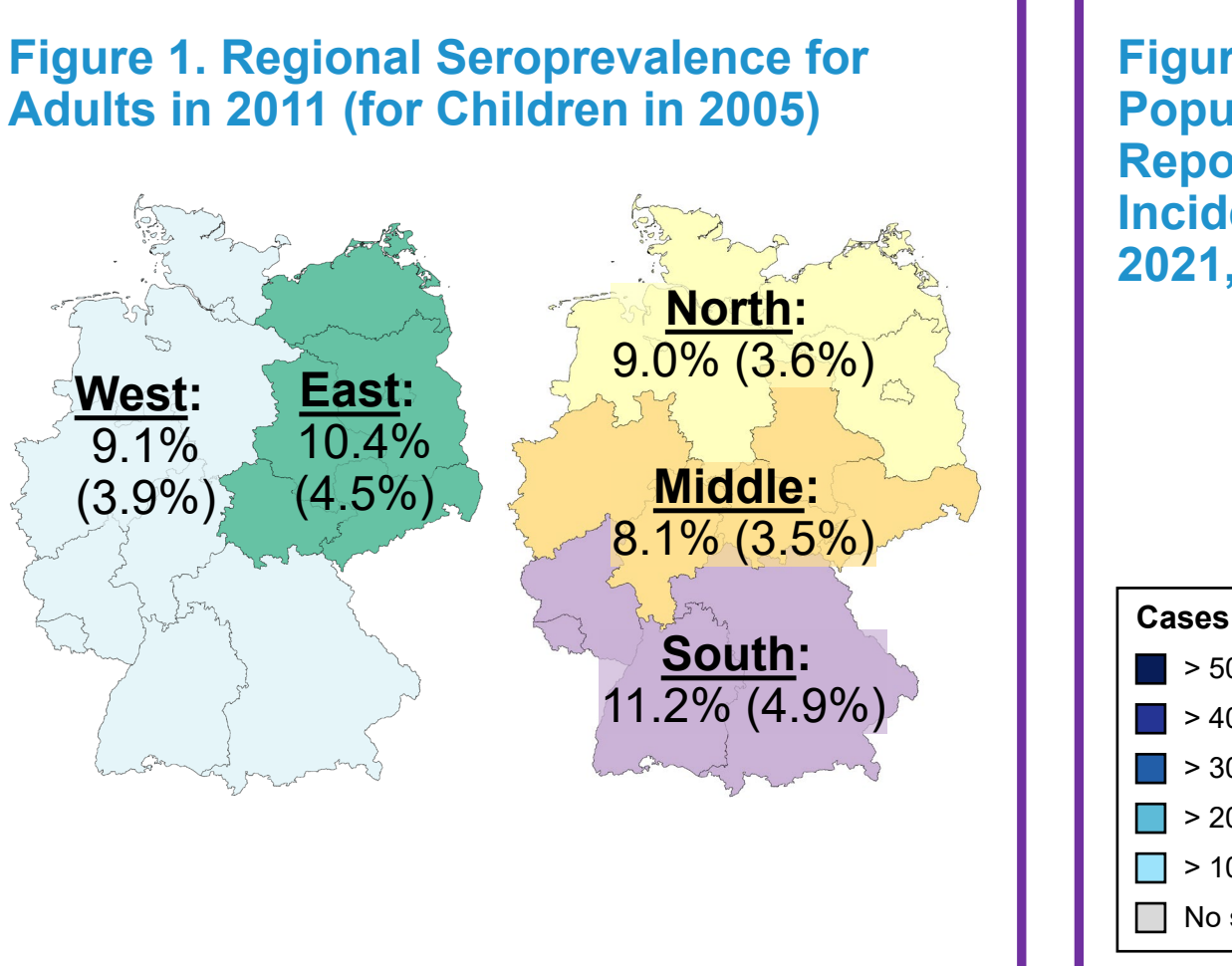


Table 1. Estimated Number of Incident Cases in 2011, by State – Adults. Table with columns: State, Seroprevalence in 2011 (East vs. West, North vs. Middle vs. South), Adult (18-79) population in 2011, and Estimated number of incident cases in 2011 (East vs. West, North vs. Middle vs. South). Total: 26,480,999, 128,859, 131,024.

Table 2. Estimated Number of Incident Cases in 2005, by State – Children. Table with columns: State, Seroprevalence in 2005 (East vs. West, North vs. Middle vs. South), Children (0-17) population in 2005, and Estimated number of incident cases in 2005 (East vs. West, North vs. Middle vs. South). Total: 5,641,776, 11,721, 12,202.

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

Table 3 data table showing under-ascertainment multipliers and estimated number of LB cases in 2021 by state for adults. Columns: Total number of reported cases in 2011 or avg of 1st 3 years, Estimated number of incident cases in 2011 (East vs. West, North vs. Middle vs. South), Under-ascertainment multipliers (East vs. West, North vs. Middle vs. South), Total number of reported cases in 2021, and Estimated number of LB cases in 2021 (East vs. West, North vs. Middle vs. South, Average).

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

Table 4 data table showing under-ascertainment multipliers and estimated number of LB cases in 2021 by state for children. Columns: Total number of reported cases in 2005 or avg of 1st 3 years, Estimated number of incident cases in 2005 (East vs. West, North vs. Middle vs. South), Under-ascertainment multipliers (East vs. West, North vs. Middle vs. South), Total number of reported cases in 2021, and Estimated number of LB cases in 2021 (East vs. West, North vs. Middle vs. South, Average).

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

Table 5 data table showing estimated total number and population-based incidence of LB cases in 2021 by state for all ages. Columns: Total number of reported cases in 2021 (Children 0-17, Adults 18+, Total), Estimated total number of LB cases in 2021 (East vs. West, North vs. Middle vs. South, Average), Population in 2020 (0-79), and Population-based LB incidence (LB cases per 100,000 in 2021).

DISCUSSION

Strengths of Study:
- National, representative seroprevalence data is available in Germany for both adults and children
- Only 9 states conduct LB surveillance
- Germany has surveillance system in 9 states that captures both clinician-reported and laboratory-confirmed LB cases
Limitations of Study:
- Seroprevalence studies do not provide seroprevalence by state
- 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:
- 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
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
- For every reported LB case in these 9 states, there were an estimated 12 LB cases
- The seroprevalence-derived under-ascertainment multiplier is for all LB cases (i.e., symptomatic LB cases 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)
- 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
- Compared with 31 reported LB cases per 100,000 population in the 9 states in 2021