International Journal of Infectious Diseases 149 (2024) 107242

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Incidence of symptomatic Lyme borreliosis in nine European countries

Frederick J. Angulo[1,*], Emily Colby[1], Anne-Mette Lebech[2], Per-Eric Lindgren[3,4], Anna Moniuszko-Malinowska[5], Franc Strle[6], Julia Olsen[1,#], Gordon Brestrich[7], Andrew Vyse[8], Madiha Shafquat[9], L. Hannah Gould[9], Patrick H. Kelly[1], Andreas Pilz[10], Kate Halsby[8], Jennifer C. Moïsi[11], James H. Stark[12]

[1] *Vaccines and Antivirals Medical Affairs, Pfizer US Commercial Division, Collegeville, PA, USA*
[2] *Department of Infectious Diseases, University Hospital Copenhagen-Rigshospitalet, Copenhagen, Denmark*
[3] *Division of Inflammation and Infection, Linköping University, Linköping, Sweden*
[4] *Department of Laboratory Medicine, Division of Clinical Microbiology, Ryhov County Hospital, Jönköping, Sweden*
[5] *Department of Infectious Diseases and Neuroinfections, Medical University of Bialystok, Bialystok, Poland*
[6] *Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia*
[7] *Vaccines and Antivirals Medical Affairs, Pfizer Pharma GmbH, Berlin, Germany*
[8] *Vaccines and Antivirals Medical Affairs, Tadworth, Surrey, UK*
[9] *Vaccines and Antivirals Medical Affairs, Pfizer US Commercial Division, New York, NY, USA*
[10] *Vaccines and Antivirals Medical Affairs, Pfizer Corporation Austria, Vienna, Austria*
[11] *Vaccines and Antivirals Medical Affairs, Paris, France*
[12] *Pfizer US Commercial Division, Vaccines and Antivirals Medical Affairs, Cambridge, MA, USA*

ARTICLE INFO

Article history:
Received 17 June 2024
Revised 6 September 2024
Accepted 10 September 2024

Keywords:
Lyme disease
Epidemiology
Disease burden
Surveillance
Seroprevalence
Tickborne diseases

ABSTRACT

Objectives: To better understand the Lyme borreliosis (LB) burden in Europe, we aimed to estimate the incidence of symptomatic *Borrelia burgdorferi* sensu lato (Bbsl) infections after adjusting public health LB surveillance data for under-detection of symptomatic Bbsl infections.

Methods: Data from seroprevalence studies and estimates of the symptomatic proportion and duration of antibody detection in Bbsl-infected individuals, derived from reviews of the published literature, were used to adjust public health LB surveillance data to estimate the incidence of symptomatic Bbsl infection in nine European countries from 2018 to 2022.

Results: The prevalence of anti-Bbsl antibodies ranged from 2.3% in Romania to 9.4% in Germany. Under-detection multipliers varied across surveillance systems; using 10-year duration of antibody detection, multipliers were 2.4-10.5 in countries reporting all LB cases and 54.6-722.2 in countries reporting only Lyme neuroborreliosis cases. The incidence of symptomatic Bbsl infection adjusted for under-detection was highest in Finland, Germany, Norway, Poland, and Switzerland, intermediate in the Czech Republic and Denmark, and lowest in Ireland and Romania.

Conclusion: Adjustment of LB surveillance for under-detection found a high incidence of symptomatic Bbsl infection in several European countries. Differences in LB surveillance systems should be considered when comparing surveillance data between countries and when estimating LB disease burden.

Introduction

Lyme borreliosis (LB), an infection caused by the spirochete *Borrelia burgdorferi* sensu lato complex (Bbsl), is the most common tick-borne disease in Europe [1]. Although LB commonly presents as erythema migrans (EM), Bbsl infection can disseminate resulting in Lyme neuroborreliosis (LNB), arthritis, or carditis [1].

The purposes of public health surveillance for LB include identifying geographic areas with a risk of disease transmission, monitoring disease trends, estimating disease burden, and supporting public health decision-making. Many European countries publish LB surveillance data online [2]. There are, however, marked differences in the approaches for LB surveillance between countries. Some countries conduct LB surveillance for both clinician-diagnosed and laboratory-diagnosed cases and include all clinical

* Corresponding author: Frederick J. Angulo, Vaccines and Antivirals Medical Affairs, Pfizer US Commercial Division, Collegeville, 500 Arcola Road, PA 19426, USA.
E-mail address: frederick.angulo@pfizer.com (F.J. Angulo).
Current affiliation: Julia Olsen, Hologic, Inc.

https://doi.org/10.1016/j.ijid.2024.107242

manifestations of LB (e.g., cases of EM and cases of disseminated LB). Other countries conduct surveillance only for laboratory-diagnosed disseminated LB cases or only for laboratory-diagnosed LNB cases. Most countries that conduct LB surveillance have governmental statutes that require notification of LB cases to public health authorities, but some countries conduct LB surveillance via voluntary sentinel networks of clinicians. In countries where LB is statutorily notifiable, the responsibility for reporting cases of LB varies; some countries require reporting by both clinicians and laboratories, some require reporting only by clinicians, and some require reporting only by laboratories. Furthermore, there are differences within and between countries on the ability of clinicians and laboratories to diagnose LB, contributing to differences in reporting of LB cases to surveillance. The marked differences in the approaches for LB surveillance between countries make it challenging to compare LB disease burden [2].

Regardless of how LB surveillance is conducted, to be detected by surveillance a Bbsl-infected person must seek medical care; this is unlikely to occur if the infected individual does not have symptoms. To achieve the purposes of public health surveillance, LB surveillance systems do not need to detect all cases of symptomatic Bbsl infections. Reasons why a symptomatic Bbsl-infected individual may not be included in public health surveillance include that persons: (1) do not seek medical care, (2) seek medical care but are not diagnosed with LB, and (3) are diagnosed with LB but are not reported as a case to the surveillance system. Seroprevalence studies provide estimates of the prevalence of people with anti-Bbsl IgG antibodies and are a useful tool for understanding the population-based LB burden. The aim of this study was to enable between-country comparisons of the incidence of symptomatic Bbsl infection and improve the understand of the LB disease burden in Europe by using data from seroprevalence studies, along with estimates of the symptomatic proportion and the duration of antibody detection and LB surveillance data, to estimate the incidence of symptomatic Bbsl infection.

Methods

General population seroprevalence studies were identified through two literature searches. The first literature search, the results of which are summarized in an article published in 2023, was a systematic literature review of literature of articles published from 2005 to 2022 [3]. The second literature search, which was conducted to identify articles published prior to or after the first search, was a search of articles published in 1998-2023. Details of first search, including the PRISMA diagram, have been published [3]; briefly, the searches were conducted in PubMed, Embase, and CABI Direct (Global Health) and had no language restrictions and used the search terms "Lyme," "*Borrelia*," "borreliosis," and "surveillance." If an identified seroprevalence study only reported on results obtained using a single-tier diagnostic testing protocol, the results were adjusted to estimate the seropositivity that would have been observed if a two-tier diagnostic testing protocol had been used. In addition to seroprevalence studies, LB surveillance data for countries in Europe were identified by searching public health institute websites and contacting public health institutions.

The number of incident Bbsl-infected individuals in the area where, and at the time when, the seroprevalence studies were conducted was estimated from the number of individuals with anti-Bbsl IgG antibodies from the seroprevalence studies using the formula: I=P/D, where *I* is the number of incident Bbsl-infected individuals, *P* is the number of individuals with anti-Bbsl IgG antibodies, and *D* is the median duration of detection of anti-Bbsl IgG antibodies. Population estimates from Eurostat (https://ec.europa.eu/eurostat) were then used to estimate the incidence of Bbsl infection (incident cases per 100,000 population per year [PPY]), for the area where, and the year when, the seroprevalence studies were conducted.

We then derived estimates of the proportion of incident Bbsl-infected persons (i.e., individuals who seroconverted from anti-Bbsl IgG antibody negative to positive) who reported symptoms of LB and the persistence of anti-Bbsl IgG antibodies in a person with anti-Bbsl IgG antibodies from a PubMed search of literature published from 1990 to 2023 (Supplementary Material). These estimates were then used to estimate the under-detection of cases of symptomatic Bbsl infection by surveillance (i.e., the under-detection multiplier), by comparing the incidence of symptomatic Bbsl infection derived from the seroprevalence studies with the incidence of surveillance-reported LB in the area where, and time when, the seroprevalence studies were conducted. Finally, the under-detection multiplier for each country was applied to the national incidence of surveillance-reported LB in 2018-2022 to derive the estimated national incidence of symptomatic Bbsl infection in 2018-2022. A sensitivity analysis was conducted, using the same methodology to estimate the incidence symptomatic Bbsl infection but using the upper and lower bound of the 95% confidence interval (CI) of the pooled estimate of the symptomatic proportion instead of using the pooled estimate of the symptomatic proportion.

Results

Population-based seroprevalence studies of anti-Bbsl IgG antibodies were identified in nine (39%) of the 23 countries that conduct LB surveillance (Figure 1): the Czech Republic, Denmark, Finland, Germany, Ireland, Norway, Poland, Romania, and Switzerland. The approaches for LB surveillance varied in the nine countries: the Czech Republic, Finland, Germany, Poland, Romania, and Switzerland had statutory reporting of all clinician-diagnosed and laboratory-diagnosed LB cases, Norway had statutory reporting of all laboratory-confirmed disseminated LB cases, and Denmark, and Ireland had statutory reporting of all laboratory-confirmed LNB cases. LB surveillance in Germany was conducted in nine federal states: Bavaria, Berlin, Brandenburg, Mecklenburg-Vorpommern, Rhineland-Palatinate, Saarland, Saxony, Saxony-Anhalt, and Thuringia. LB surveillance in Switzerland was a voluntary sentinel surveillance network of clinicians which the public health institute extrapolates to derive nationwide estimates.

Of the nine countries with seroprevalence studies and LB surveillance, three countries had two studies each resulting in 12 seroprevalence studies (Table 1) [4–14]. In Norway and Poland, the second study was conducted in the same geographic area as the first study, so an average seroprevalence was derived from the two studies by weighting the seroprevalence of each study by the number of participants in each study. In Finland, the second study was conducted in a geographic area not included in the first study, so an overall nationwide seroprevalence was derived from the two studies by weighting by the seroprevalence in each study by the population represented in each study. The participants in the 12 seroprevalence studies were adults (age range 18-80 years) except for the Czech Republic study which also included children. Seroprevalence study participants were selected from the nationwide general population in Denmark, Finland, Germany, and Ireland, the general population in subnational areas in the Czech Republic (6 of the 14 regions), Norway (5 of the 15 counties), Poland (1 of the 16 provinces), and Romania (6 of the 41 counties), and the nationwide general population in rural areas in Switzerland. The number of participants per country in the studies ranged from 95 in Poland to 6965 in Germany, and the prevalence of individuals with anti-Bbsl IgG antibodies ranged from 2.3% in Romania to 9.4% in Germany.

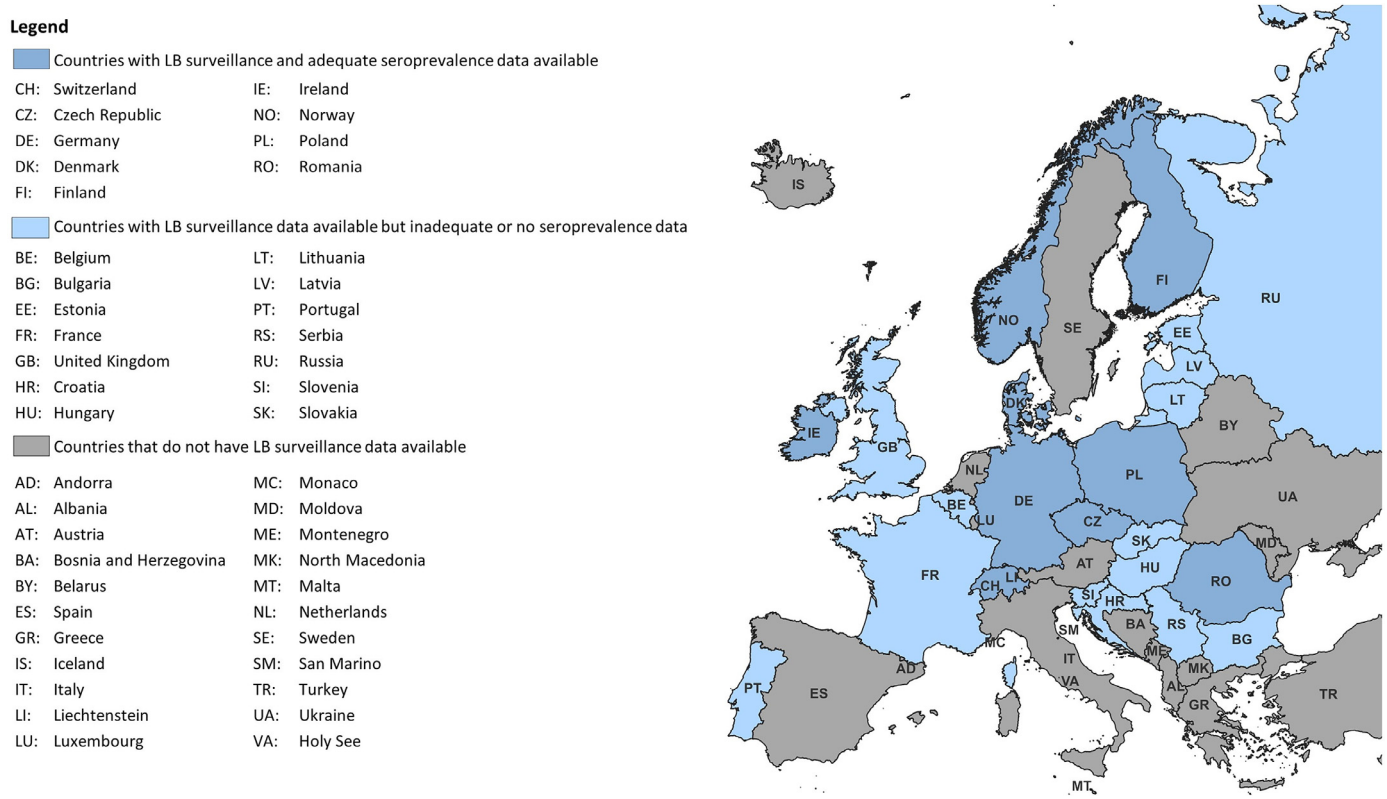

Figure 1. European countries with online Lyme borreliosis surveillance data ($n = 23$) in which there are seroprevalence studies that report the prevalence of anti-*Borrelia burgdorferi* sensu lato (Bbsl) IgG antibodies among participants selected from the general population ($n = 9$).

Table 1
Seroprevalence of individuals with anti-*Borrelia burgdorferi* sensu lato (Bbsl) IgG antibodies among individuals selected from the general population in the European countries with online Lyme borreliosis surveillance data.

Country	Sample collection location, year(s)	Number of participants	Participant age range in years	Prevalence of individuals with anti-Bbsl IgG antibodies in area of seroprevalence study or studies
Czech Republic	Central Bohemia, Moravia-Silesia, Plzeň, South Bohemia, South Moravia, and Vysočina Districts, 2001 [4]	270	10-59	5.5%[a]
Denmark	Nationwide, 2022 [5]	1000	32-56	6.2%
Finland	Mainland Finland, 2011 [6], Åland Islands, 1993-1997 [7]	5748[b]	29-80	4.0%[c]
Germany	Nationwide, 2008-2011 [8]	6965	18-80	9.4%
Ireland	Nationwide, sample collection years not specified [9]	1224	[f]	3.4%
Norway	Agder, Møre og Romsdal, Rogaland, Vestland, and Vestfold og Temark counties, 2010 [10], and 2012-2013 [11]	1713[b]	18-75	6.8%[d]
Poland	Lublin district, 1998-2007 [12] Lublin district, 2013 [13]	95[b]	33-70	5.2%[e]
Romania	Alba, Bistrița-Năsăud, Cluj, Maramureș, Sălaj, and Satu-Mare counties, 2019-2020 [14]	1200	18-75	2.3%
Switzerland	Rural regions (specific regions not specified), 2008-2009 [15]	4580	[f]	6.3%[a]

Bbsl, *Borrelia burgdorferi* sensu lato.
[a] Study conducted single-tier testing only; adjusted the single-tier seroprevalence from the study in the Czech Republic (10.6%) and Switzerland (12.1%) with the second-tier test results (52% seropositivity) from Finland seroprevalence study to estimate two-tier seroprevalence.
[b] Combined sample size from the two seroprevalence studies.
[c] Seroprevalence derived from two studies weighted by represented population in 2011 (mainland [population 5.3M] 3.9% and Åland Islands [population 28,000] 19.5%).
[d] Seroprevalence derived from two studies weighted by number of participants in study ([$n = 1213$] 5.8% and [$n = 519$] 9.2%) studies.
[e] Seroprevalence derived from two studies weighted by number of participants in study ([$n = 50$] 6.0% and [$n = 45$] 4.4%).
[f] Not specified.

Table 2
Two scenarios of the under-detection multiplier of symptomatic *Borrelia burgdorferi* sensu lato (Bbsl) infection by surveillance in the area and at the time-period that the seroprevalence studies were conducted in the European countries with online Lyme borreliosis (LB) surveillance data[a].

Country	Year(s) used to estimate multiplier	Incidence of surveillance-reported cases	Scenario #1: 10-year persistence of anti-Bbsl IgG antibodies		Scenario #2: 20-year persistence of anti-Bbsl IgG antibodies	
			Incidence of symptomatic Bbsl infection	Multiplier	Incidence of symptomatic Bbsl infection	Multiplier
Czech Republic	2001	36	204	5.7	102	2.9
Denmark	2022	4	229	54.6	115	27.3
Finland	2011	67	148	2.2	74	1.1
Germany[b]	2011	33	348	10.4	174	5.2
Ireland	2012	0.2	126	722.2	63	361.1
Norway	2011	9	252	28.1	126	14.1
Poland	2010	34	192	5.7	96	2.8
Romania	2020	8	85	10.5	43	5.3
Switzerland	2009	98	232	2.4	116	1.2

Bbsl, *Borrelia burgdorferi* sensu lato; LB, Lyme borreliosis.
[a] Derived using the base-case approach with 37% symptomatic proportion among incident *Borrelia burgdorferi* sensu lato (Bbsl)-infected cases.
[b] States of Bavaria, Berlin, Brandenburg, Mecklenburg-Vorpommern, Rhineland-Palatinate, Saarland, Saxony, Saxony-Anhalt, and Thuringia.

The symptomatic proportion literature search identified 4835 articles for title and abstract review, of which 176 (3.6%) were selected for full-text review (Supplementary Figure 1). From these, four (2.3%) articles met the inclusion criteria (Supplementary Table 1). One additional appropriate article was identified by co-authors, making 5 articles available for estimating the symptomatic proportion [16–20]. All were cohort studies; four enrolled individuals bitten by a tick and one enrolled individuals at high risk of being bitten by a tick. All study participants were adults. The total number of participants who reported recently being bitten by a tick within the past week was 2708; range of participants per study was 100-1546. The follow-up times after enrollment per study ranged from 42 to 120 days. Three studies reported the frequency of subsequent tick bites during follow-up; subsequent tick bites among participants ranged from 50% to 72%. The studies identified a total of 110 incident Bbsl-infected individuals. The pooled estimate of the symptomatic proportion among incident Bbsl-infected individuals was 37% (95% CI 28%-46%) (Supplemental Figure 2).

The literature search for articles on the persistence of IgG antibodies also identified 4835 articles for title and abstract review, of which 288 (6.0%) were selected for full-text review (Supplementary Figure 3). From these, five (1.7%) articles met the inclusion criteria (Supplementary Table 2). Three additional appropriate articles were identified by co-authors, making eight articles available for estimating symptomatic proportion [21–28]. Six were follow-up studies of individuals with anti-Bbsl IgG antibodies identified when they sought medical care and two were follow-up studies of individuals with IgG antibodies identified by general population seroprevalence studies. The total number of individuals with anti-Bbsl IgG antibodies in the studies was 3352; range of individuals with anti-Bbsl IgG antibodies per study was 22-2287. Five studies included adults and children, two included only adults, and one included only children. The median follow-up times after enrollment ranged from 0.8 to 12.0 years. The range in the estimated time for 50% of the individuals with anti-Bbsl IgG antibodies to seroreverte to IgG-negative was 0.4-33.3 years; the range was 0.4-30.0 years among the studies of medically-attended patients and 12.8-33.3 years among studies of the general population. Given the range in median time for persistence of IgG antibodies in Bbsl-infected individuals in the eight studies, two scenarios were used: a 10-year persistence of anti-Bbsl IgG antibodies (scenario #1) and 20-year persistence of anti-Bbsl IgG antibodies (scenario #2).

Using the identified seroprevalence studies, LB surveillance data, a 37% symptomatic proportion, and the two scenarios of persistence of antibodies, estimates of the incidence of symptomatic Bbsl infection and the under-detection multipliers were derived in the area and time period of the seroprevalence studies (Table 2). Under scenario #1, the under-detection multipliers were 2.2 in Finland, 2.4 in Switzerland, 5.7 in the Czech Republic, 5.7 in Poland, 10.4 in Germany, and 10.5 in Romania, where all LB cases are reported; 28.1 in Norway, where only disseminated LB cases are reported; and 54.6 in Denmark, and 722.2 in Ireland, where only LNB cases were reported. The under-detection multipliers were 50% lower under scenario #2 compared to scenario #1.

Under scenario #1, the estimated incidence of symptomatic Bbsl infection from 2018 to 2022 was predominately >220/100,000 PPY in Finland, Germany, Norway, Poland, and Switzerland, 190-220/100,000 PPY in the Czech Republic and Denmark, and <190/100,000 PPY in Ireland and Romania (Table 3). The estimated incidence was 50% lower under scenario #2 compared to scenario #1. Results of the sensitivity analyses comparing the estimates of the incidence of symptomatic Bbsl infection in 2022 in the nine countries using symptomatic proportions of 28%, 37%, and 46% are shown in Supplementary Table 3; the incidence of symptomatic Bbsl infection increased with increasing symptomatic proportion.

Discussion

In this analysis, we demonstrate that several European countries have a high incidence of symptomatic Bbsl infection; in some countries, the incidence of Bbsl infection was several-fold higher than reported incidence of LB in national surveillance. Since disease incidence is a key measure for estimating disease burden, our results add to the growing evidence of the substantial LB burden in Europe. We have previously published data from Finland [29], Germany [30], and Poland [31] using a similar methodology. However, this report provides more detailed estimates of the proportion of incident Bbsl-infected persons that report symptoms and the persistence of anti-Bbsl IgG antibodies, the key inputs needed to derive the incidence of symptomatic Bbsl infection from seroprevalence studies and LB surveillance data and extends this approach to all countries in Europe with appropriate data. Using seroprevalence studies to estimate the incidence of symptomatic infection is a standard epidemiological approach and has been used for other infectious diseases, but this represents the first application to multinational LB estimates [32].

The aim of this study was to improve the understanding of the incidence of Bbsl infection and LB burden in Europe, where countries use a variety of approaches for public health surveillance for LB. Since surveillance systems are not intended to detect all cases of symptomatic Bbsl infection, it is expected that the estimated incidence of symptomatic Bbsl infection is notably higher than the

Table 3
Two scenarios of the incidence (per 100,000 population per year) of symptomatic *Borrelia burgdorferi* sensu lato (Bbsl) infection after adjusting surveillance-reported Lyme borreliosis (LB) cases for under-detection of symptomatic Bbsl infection in European countries with seroprevalence studies, 2018-2022[a].

A. Scenario #1: 10-year persistence of anti-Bbsl IgG antibodies

Statutory reporting of LB cases	Country	Multi-plier	Incidence of symptomatic Bbsl infection after adjusting for under-detection of cases of symptomatic Bbsl infection by surveillance				
			2018	2019	2020	2021	2022
Reporting of all LB cases	Czech Republic	5.7	254	220	198	154	191
	Finland	2.2	224	230	248	344	278
	Germany[b]	10.4	339	365	423	329	284
	Poland	5.7	300	305	193	187	262
	Romania	10.5	28	8	15	27	31
	Switzerland	2.4	479	260	384	216	214
Reporting of only disseminated LB cases	Norway	28.1	224	258	267	280	257
Reporting of only Lyme neuroborreliosis cases	Denmark	54.6	192	161	185	202	230
	Ireland	722.2	194	88	204	58	57

B. Scenario #2: 20-year persistence of anti-Bbsl IgG antibodies

Statutory reporting of LB cases	Country	Multi-plier	Incidence of symptomatic Bbsl infection after adjusting for under-detection of cases of symptomatic Bbsl infection by surveillance				
			2018	2019	2020	2021	2022
Reporting of all LB cases	Czech Republic	2.9	127	110	99	77	95
	Finland	1.1	112	115	124	172	139
	Germany[b]	5.2	200	183	211	164	142
	Poland	2.8	150	152	97	94	131
	Romania	5.3	14	4	8	13	16
	Switzerland	1.2	240	130	192	108	107
Reporting of only disseminated LB cases	Norway	14.1	112	129	134	140	129
Reporting of only Lyme neuroborreliosis cases	Denmark	27.3	96	80	92	101	115
	Ireland	361.1	97	44	102	29	29

Bbsl, *Borrelia burgdorferi* sensu lato; LB, Lyme borreliosis.
[a] Derived using 37% symptomatic proportion among incident *Borrelia burgdorferi* sensu lato (Bbsl)-infected individuals.
[b] States of Bavaria, Berlin, Brandenburg, Mecklenburg-Vorpommern, Rhineland-Palatinate, Saarland, Saxony, Saxony-Anhalt, and Thuringia.

incidence of surveillance-reported LB. Under the 10-year persistence of antibodies scenario, in countries with reporting of all LB cases, the under-detection multipliers ranged from 2.4 to 10.5, indicating that there are 2.4 to 10.5 individuals with symptomatic Bbsl infection for each surveillance-reported LB case. In contrast, in countries with reporting of only LNB cases, the multipliers ranged from approximately 55-722. The high under-detection multiplier of symptomatic Bbsl-infected individuals by LNB-only surveillance is expected since LNB is a less common manifestation of Bbsl infection; only an estimated 3% of patients with medically-attended LB have LNB [1]. Quantifying the extent of the under-detection of symptomatic Bbsl infection by LB surveillance, including LNB surveillance, is a useful tool for understanding the LB burden.

Although online LB surveillance data are available in many European countries, anti-Bbsl IgG seroprevalence studies with specimens collected from a representative sample of the general population were identified for only nine countries. For our analysis, we did not use seroprevalence studies of persons at increased risk for tick exposure and/or LB (i.e., studies of forest workers) because such studies yield a higher prevalence of anti-Bbsl IgG antibodies [3] and are not appropriate for estimating the under-detection of symptomatic Bbsl infection by surveillance. Two-tier diagnostic testing protocols which utilize a screening test (with a high sensitivity) followed by a confirmatory test (with a high specificity) of specimens that are first-tier positive, is a recommended diagnostic approach in many countries [1]. To reduce the potential for false positive results which would inflate the seroprevalence estimates, thereby increasing the number of estimated incident cases and reducing the under-detection multipliers, our intention was to only use general population seroprevalence which used two-tier diagnostic testing. However, two of the seroprevalence studies that we identified used a single-tier diagnostic testing protocol to identify Bbsl-infected individuals. Therefore, in our study, we used the results from the seroprevalence study in Finland [6], which had the highest proportion of screening test-positive specimens that were confirmatory test positive (52%), to adjust the results in the two single-tier seroprevalence studies. The results from the study in Finland were chosen to adjust the results in the single-tier seroprevalence studies as a conservative approach to optimize specificity.

There are several limitations in the available seroprevalence studies and LB surveillance data that impact the estimates of the incidence of symptomatic Bbsl infection. Several of the seroprevalence studies had a small number of participants, reducing the robustness of the prevalence estimates. For example, the two seroprevalence studies in Poland only had a total of 95 participants. Also, to use the estimated under-detection multipliers to estimate the incidence of symptomatic Bbsl infection in 2018-2022, we assumed that the multipliers had remained unchanged since the conduct of the seroprevalence study. However, LB awareness may be increasing in some areas which could result in lower multipliers and lower estimated incidence. Furthermore, most of the participants in the seroprevalence studies were adults and most of the seroprevalence studies did not provide age-stratified prevalence estimates. Therefore, it was not possible to derive age-specific under-detection multipliers and we extrapolated the results of the seroprevalence studies to all ages. This is likely a conservative approach since the prevalence of anti-Bbsl IgG antibodies is probably higher in adults than children. Therefore, using seroprevalence estimates from adults probably over-estimated the population seroprevalence, resulting in a higher estimated incidence of symptomatic Bbsl infection at the time that the seroprevalence

study was conducted, which when compared to the incidence of surveillance-reported LB cases from the same time period resulted in a lower under-detection multiplier. Finally, when the lower under-detection multiplier was applied to the most recent incidence of surveillance-reported LB cases, it will result in a lower incidence of symptomatic Bbsl infection at the time of the most recent surveillance data.

Another limitation of the seroprevalence studies is that the studies in the Czech Republic, Norway, Poland, and Romania were conducted among residents of subnational areas. To derive the estimate of the national incidence of symptomatic Bbsl infection, we assumed that the nationwide under-detection multipliers were the same as the multipliers derived from the seroprevalence studies and surveillance data in the subnational area. Depending on the LB incidence in the areas not included in the seroprevalence studies, the extrapolation of under-detection multipliers nationwide may result in an underestimation or overestimation of the national incidence of symptomatic Bbsl infection. Furthermore, LB surveillance in Germany is only conducted in part of the country, therefore, our estimate of the symptomatic LB incidence is only for the states in Germany that conduct LB surveillance. In addition, the LB surveillance in Switzerland is a voluntary sentinel surveillance network of clinicians which the public health institute extrapolates for a nationwide estimate of reported LB cases. Also, the LNB surveillance data from Ireland included a small number of cases, and therefore the under-detection multiplier in Ireland may be less reliable. This is reflected in the year-to-year variability in estimated incidence in Ireland; for example, the estimated incidence of symptomatic Bbsl infection was 204/100,000 population in 2020 based on 14 LNB cases and 58/100,000 population in 2021 based on 4 LNB cases. The less reliable estimates in Ireland probably contribute to the notably higher multiplier in Ireland than Denmark, the other country that conducts surveillance only for LNB cases.

Further limitations of our approach to estimate the incidence of symptomatic Bbsl infection are that the calculations are dependent on the estimates of the proportion of incident Bbsl-infected individuals who reported symptoms. We derived an estimate of the proportion of individuals with serological evidence of an incident Bbsl infection who reported symptoms during a 3-4 month follow-up period. However, some patients with LB do not have serological evidence of infection at the time of the LB diagnosis either because they will not develop detectable IgG antibodies or it is too early in the course of illness to have a detectable antibody response. For example, some persons with EM do not develop detectable IgG antibodies [1]. Furthermore, Bbsl-infected persons previously treated with antibiotics may no longer have detectable antibodies [1]. Therefore, the symptomatic proportion among persons with LB, which includes individuals with and without detectable anti-Bbsl IgG antibodies, will be higher than the symptomatic proportion among Bbsl-infected persons which includes only individuals with detectable IgG antibodies. In our study, the symptomatic proportion was estimated from five studies. Including the additional participants in these studies who developed EM during follow-up but did not seroconvert, the pooled symptomatic proportion among persons with incident LB was 52%, which represents a 15% increase in the symptomatic proportion compared to the proportion (37%) we used in our analysis. Our use of a lower symptomatic proportion can be considered a conservative approach since it results in lower estimates of the incidence of symptomatic Bbsl infection.

To identify studies to estimate the symptomatic proportion, we used strict inclusion and exclusion criteria. The included studies had to be follow-up studies that identified incident Bbsl-infected individuals and interviewed them about symptoms. Although the five identified studies included almost 3000 participants, the studies identified a small number of individuals with an incident Bbsl infection; therefore the CI of symptomatic proportion in each study is wide. Also, all participants in the five studies were adults, therefore we assumed that the symptomatic proportion in children is the same as in adults despite the possibility that the symptomatic proportion may vary by age. Furthermore, with the limited number of identified individuals with an incident Bbsl infection, there is insufficient data to stratify the symptomatic proportion among Bbsl-infected persons by various regions in European. It is possible that the symptomatic proportion varies by region because the Bbsl genospecies causing infections may vary by region. Furthermore, the five studies used different approaches to identify incident Bbsl-infected individuals and interview them about symptoms. Also, the studies followed participants for only three to 4 months to identify symptoms. A longer follow-up period of the participants with a Bbsl infection may have identified more symptomatic infected individuals. For example, some Bbsl-infected persons do not report symptoms until they have disseminated disease, which may occur more than 4 months after infection [25]. However, using a longer follow-up period to identify additional symptomatic persons is problematic because a high proportion of study participants reported subsequent tick bites. Despite these limitations, the symptomatic proportion was notably similar between the five studies. Furthermore, we used the upper and lower bond of the 95% CI of the pooled estimate of the symptomatic proportion in a sensitivity analysis. As the symptomatic proportion decreased, the estimated incidence of symptomatic Bbsl infection declined.

To be included in the studies on the persistence of anti-Bbsl IgG antibodies, studies had to be follow-up studies of individuals with anti-Bbsl IgG antibodies. There was a wide range (0.4-33.3 years) in the median time of persistence of antibodies in the eight identified studies, which included over 3000 individuals with anti-Bbsl IgG antibodies. Participants in the studies included children and adults, but it was not possible to stratify the persistence of antibodies by age despite the possibility that persistence may vary by age. Several factors may contribute to the lack of agreement between the studies. First, while the individuals with anti-Bbsl IgG antibodies in five studies sought medical care and may have been treated with antibiotics, the majority of individuals with anti-Bbsl igG antibodies in two general population studies were likely asymptomatic and therefore likely did not seek medical care. Antibiotic treatment of Bbsl-infected persons can shorten the persistence of antibodies [1]. Second, an individual with anti-Bbsl IgG antibodies could be subsequently bitten by an infected *Ixodes* tick which would further prolong the persistence of antibodies. In the studies used to estimate of the symptomatic proportion, three studies reported that 50%-72% of participants were subsequently bitten by ticks during the 3- to 4-month follow-up period. Given the lack of agreement between the studies used to estimate the persistence of antibodies, we elected to estimate the incidence of symptomatic Bbsl infection using two scenarios, a 10-year and a 20-year persistence of anti-Bbsl IgG antibodies. The incidence of symptomatic Bbsl infection is reduced by 50% using a 20-year persistence compared to a 10-year persistence.

Results from this study demonstrate a high incidence of symptomatic Bbsl infection in several European countries and provide estimates of the extent of under-detection of symptomatic Bbsl infection by surveillance. Furthermore, this study shows how under-detection of symptomatic Bbsl infection varies between different types of surveillance systems and that differences in surveillance need to be considered when comparing reported data across countries.

Ethical approval

Approval was not required.

Data sharing statement

Data available upon request from corresponding author.

Funding

This work was supported and jointly funded by Valneva and Pfizer as part of their co-development of a Lyme Disease vaccine.

Author contributions

FA and EC wrote the manuscript. FA, EC, JO, GB, PK, AP, JS, and JM planned and coordinated the study. FA, EC, JO were responsible for data collection. FA, EC, JO, GB, AV, HG, KH, PK, MS were responsible for data analysis, figure production, and writing of the methods. FA, EC, JO had direct access and verified the data reported in the manuscript. AL, PL, AM, AV, and FS reviewed the method and preliminary findings. All authors critically revised the manuscript.

Declarations of competing interest

Frederick J. Angulo, Gordon Brestrich, Emily Colby, Andrew Vyse, L. Hannah Gould, Kate Halsby, Patrick H. Kelly, Jennifer C. Moïsi, Andreas Pilz, Madiha Shafquat, and James H. Stark are employees of Pfizer and may hold stock or stock options. Per-Eric Lindgren has been an external scientific advisor to Valneva, Pfizer, and Bavarian-Nordic A/S.

Acknowledgments

Editorial assistance provided by Asees Bajwa, MPH, and Melissa Furtado, MPH, ISMPP CMPP, of Pfizer. We also acknowledge the assistance of the following Pfizer colleagues, Alex Davidson (maps), Rishi Srinivasan (spreadsheets), and the following colleagues at local Pfizer offices in Europe: Heidi Ahman (Finland), Dagmar Krivohlavkova (Czech Republic), Kristian Lie (Norway), Claudius Malerczyk (Germany), Sascha Nielsen (Denmark), Kate O'Keeffe (Ireland), Marta Popiel (Poland), Alexandra Popp (Switzerland), Veronica Purdel (Romania), and Mette Skovdal (Denmark). Volker Fingerle (Germany), Reto Leinhard (Switzerland), and Ram Benny Dessau (Denmark) contributed background information and commented on draft versions of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2024.107242.

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