


An intervention in general practice to improve the management of Lyme borreliosis in Denmark

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Background: Our objectives were to improve the following outcomes in patients with Lyme borreliosis (LB) through an educational intervention in general practice: (i) increase the number of hospital referrals on suspicion of LB, (ii) increase the number of cerebrospinal fluid (CSF) tests examined for *Borrelia burgdorferi* antibody index, (iii) decrease the number of serum-*B. burgdorferi* antibody tests ordered, (iv) shorten delay from symptom onset to hospital in Lyme neuroborreliosis (LNB) patients, (v) increase LB knowledge among general practitioners. **Methods:** A prospective non-blinded non-randomized intervention trial on the island of Funen, Denmark. The intervention included oral and written education about LB and was carried out in areas with an LNB incidence $\geq 4.7/100.000$ between 22 January 2019 and 7 May 2019. Results were compared between the intervention group (49 general practices) and the remaining general practices in Funen (71 practices) 2 years before and after the intervention. **Results:** In the study period, 196 patients were referred on suspicion of LB, a 28.9% increase in the intervention group post-intervention, 59.5% increase in the control group ($P = 0.47$). The number of CSF-*Borrelia*-antibody index tests increased 20.8% in the intervention group, 18.0% in the control group ($P = 0.68$), while ordered serum-*B. burgdorferi* antibody tests declined 43.1% in the intervention group, 34.5% in the control group ($P = 0.30$). 25.1% had the presence of serum-*B. burgdorferi* antibodies. We found no difference in LNB pre-hospital delay before and after intervention or between groups ($P = 0.21$). The intervention group performed significantly better on a follow-up questionnaire ($P = 0.02$). **Conclusion:** We found an overall improvement in LB awareness and referrals among general practitioners but could not show any effect of the intervention on clinical outcomes of LNB.

Introduction

Lyme borreliosis (LB), caused by the spirochete *Borrelia burgdorferi* sensu lato (*Bb*), is the most common tick-borne infection in the northern hemisphere.¹ One severe manifestation of European LB is Lyme neuroborreliosis (LNB), which can present with a wide range of symptoms from both the central and peripheral nervous system.^{1,2}

In the Danish health care system, the general practitioners are the first medical professionals to see the majority of LB patients, including LNB patients, through their gatekeeper role into the public health care system. General practitioners using serum-*Bb* antibodies as a screening tool when suspecting LB is discouraged in the Danish clinical guidelines, due to the following available evidence³: erythema migrans (EM), the most common LB manifestation in Europe, is a clinical diagnosis, with only ~50% of patients having serum-anti-*Bb* antibodies at the time of diagnosis.⁴ LNB should be diagnosed based on clinical symptoms and testing of cerebrospinal fluid (CSF) and cannot be diagnosed or excluded based on serum-anti-*Bb* antibodies.² Screening patients with non-specific symptoms for serum-*Bb* antibodies is not recommended due to the non-negligible prevalence of serum-*Bb* antibodies in the background population, and hence the risk of false-positive tests.^{4,5}

The incidence of LNB in Denmark is ~0.9–4.7/100.000 persons,^{5–8} with the highest reported incidence on the island of Funen.^{7,8} Residual symptoms after treatment are a frequent problem, and there is an association between the delay from symptom onset to antibiotic treatment.^{8–11} In a previous study on LNB patients on Funen, we found the delay from symptom onset to antibiotic treatment to be a median of 24 days.⁸ This delay did not change in the 20-year study period, and several patients described multiple contacts to their general practitioners prior to hospital referral, where classic symptoms of LNB were not recognized.⁸ The lack of knowledge among general practitioners of correct handling of patients with suspected LNB was confirmed in another Danish study where 470 (18%) of the 2643 serum-*Bb* antibodies registered were ordered based on suspicion of LNB.⁵

Using the islands of Funen, Langeland and Ærø as study area, the objectives of this study were as follows:

- To educate general practitioners working in Funen, focusing on ticks and LB including epidemiology, symptoms and correct hospital referrals.
- To assess the impact of this educational intervention through registration of (i) the number of suspected LB patients referred to a hospital, (ii) the number of CSF samples tested for intrathecal

anti-*Bb* antibody production, (iii) the number of ordered serum-*Bb* antibody tests from general practice, (iv) the delay from symptom onset to first hospital contact in LNB patients; before and after the intervention in the group of general practitioners that had been educated compared with the remaining general practitioners in the study area and (v) the response to a questionnaire about ticks and LB sent out 2 years after the educational intervention.

We hypothesized that an educational intervention in general practice would shorten the delay from LNB symptom onset to diagnoses and thereby improve treatment outcomes in LNB patients, that more patients suspected of having LNB would be referred to the regional reference center for tick-borne infections, the Clinical Center for Emerging and Vector-borne Infections (CCEVI) at Odense University Hospital (OUH), that fewer serum-*Bb* antibody tests would be ordered by the general practitioners after the intervention and that the general practitioners who had undergone the educational intervention would perform better on the questionnaire.

Methods

Study design and setting

This prospective, non-blinded, non-randomized interventional trial was conducted on the island of Funen including the surrounding islands, with a population of ~500 000 on 1 January 2019.¹² At this time, there were 120 registered general practices in the area, with 333 general practitioners. The general practitioners can order serum-*Bb* antibodies but have to refer patients to OUH for lumbar punctures. CCEVI is a secondary referral center based at OUH, and all patients with suspected tick-borne diseases in the Region of Southern Denmark including Funen should be referred to this center. Patients can be referred from general practitioners, from private specialists or from hospital departments. CCEVI investigates and diagnoses patients suspected of tick-borne infections, primarily LB, and treats and follows patients after diagnosis. Around 100 patients are referred to CCEVI yearly, of whom ~25 patients from Funen are diagnosed with LNB. The Department of Clinical Microbiology at OUH analyzes all serum-*Bb* antibodies and *Bb* intrathecal antibody index tests from inhabitants in the study area.

Study intervention

General practices located in the area codes on Funen, Langeland and Ærø with an LNB incidence $\geq 4.7/100.000$ inhabitants were eligible for the intervention (figure 1). The intervention group was chosen as these areas consisted of half of the general practices in the area with 40% of the population on Funen at the time of intervention but contained 50% of the LNB patients from the study area in the 20 years before the intervention. The eligible general practices received a study invite by e-mail and/or telephone in January 2019. If they did not respond, up to three subsequent attempts of contact were made in the following 2 months. The educational intervention took place between 22 January 2019 and 7 May 2019. General practitioners in areas with an LNB incidence $< 4.7/100.000$ inhabitants were not contacted and were included in the control group.

The educational program consisted of a face-to-face oral presentation lasting approximately 1 hour supported by a powerpoint presentation and provided information about *Ixodes ricinus* ticks, tick-bites and prevention thereof, transmission of *Bb*, LB symptoms focusing on LNB, how to diagnose the different LB manifestations, and correct referrals in suspected cases of LNB. The content taught was in agreement with Danish and European guidelines, and emphasis was made on the limited indications for ordering serum-*Bb* antibody tests in general practice.^{2,3} At the educational intervention, all participants received written, laminated take-home messages (see

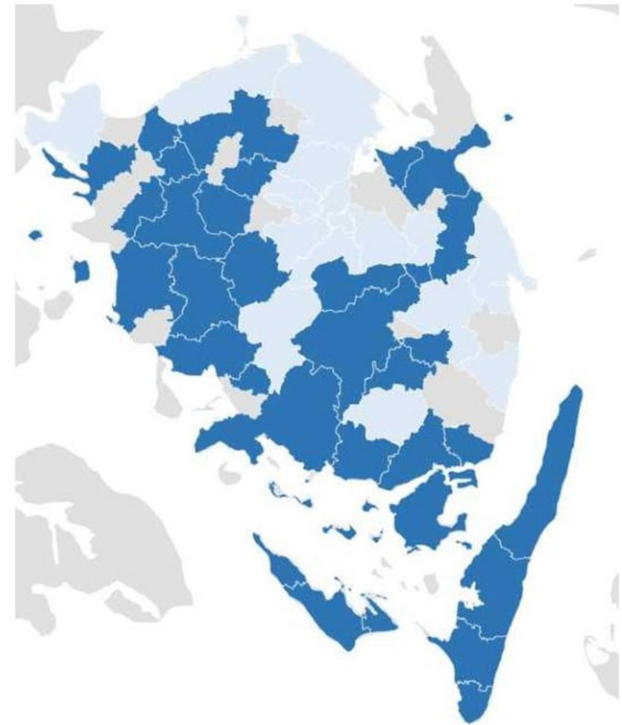


Figure 1 Map of the island of Funen, Langeland and Ærø. Divided by postal codes into areas with a Lyme neuroborreliosis incidence of $\geq 4.7/100.000$ population per year, where general practices were eligible for inclusion (dark blue), and areas with Lyme neuroborreliosis incidence $< 4.7/100.000$ population per year, not eligible for inclusion (light blue). The areas of grey color are serviced by general practitioners with addresses in other postal codes.

Supplementary appendix S1) which included a direct contact phone number and e-mail address to CCEVI that they were encouraged to use with questions related to tick-borne diseases. In May 2020, a reminder of the contact data and another set of take-home messages were sent by e-mail and postal mail. In February 2021, all general practitioners in the study area—intervention group and control group—with an available e-mail address were sent a questionnaire consisting of eight questions about ticks and LB (see Supplementary appendix S2).

Registered data

We registered the number of patients referred to CCEVI with a diagnosis of suspected LB (WHO ICD-10 code including DA69.2) during the study period; 2 years prior to (2017 and 2018) and 2 years during/after the intervention (2019 and 2020), in the intervention group and the control group. For all patients in the study area during the study period, we registered the number of lumbar punctures examined for CSF-*Bb*-intrathecal antibody index (CSF-*Bb*-AI) and the number of serum-*Bb* antibody tests ordered from general practitioners in the two groups during the study period. Furthermore, LNB patients from the study area registered with a positive CSF-*Bb*-AI at the Department of Clinical Microbiology, OUH, were compared in terms of symptom debut and frequency of residual symptoms at last hospital contact. The pre-hospital delay, defined as the delay from LNB symptom onset to first hospital contact, was compared between LNB patients with a general practitioner in the intervention group and the control group. Finally, the number of correct answers on the questionnaire was compared between general practitioners in the intervention group and the control group.

Borrelia burgdorferi serological assays

The second-generation IDEIA LNB test (Oxoid, Hampshire, UK) was used for detection of intrathecal synthesis of *Bb*-specific antibodies, and the Liaison *Borrelia* IgG (REF 310880) and IgM (REF 310020) CLIA assays (Diasorin, Saluggia, Italy) for serum-*Bb* antibodies.

Statistics

To test for significance between groups, the *t*-test was performed for normally distributed data, Wilcoxon–Mann–Whitney test, Kruskal–Wallis test and the Median test for non-normally distributed data, and the chi-squared test and Fisher's exact test were used for categorical data. A *P* value of <0.05 was considered statistically significant.

Ethical considerations

The study was approved by the Danish Data Protection Agency (J.nr. 19/4351) and the Legal Office at the Region of Southern Denmark (J.nr.20/58889). The protocol is published on clinicaltrials.gov (Identifier: NCT03820999).

Results

Inclusion of general practices

Of the 120 general practices in the study area by 1 January 2019, 59 practices were invited to participate in the intervention, of which 49 practices were included (figure 2). These practices covered ~34% of the population in the study area. The remaining 71 practices constituted the control group.

Outcome 1: patients referred to CCEVI

During the study period, 196 patients were referred to CCEVI with an LN diagnose directly from general practitioners in the study area (table 1, referrals). We found a 28.9% increase in referrals from the general practitioners in the intervention group in the 2 years during and after the intervention compared with the 2 years before the intervention. However, in the control group, the increase in referrals was 59.5% in the same time period (*P* = 0.47).

Outcome 2: patients examined for LNB

In all, 1818 CSF-*Bb*-AI samples from 1750 patients who had a general practitioner in the study area were included for analysis (table 1, intrathecal antibody tests). There was a 19.0% total increase in the number of CSF-*Bb*-AI tests performed from 2017/2018 to 2019/2020: 20.8% in the intervention group, 18.0% in the control group (*P* = 0.68). In all, 63 tests (3.5%) were positive. A positive CSF-*Bb*-AI was significantly more frequent in the intervention group (*n* = 35, 5.0%) compared with the control group (*n* = 28, 2.5%), *P* = 0.005. In both groups, the percentage of positive tests declined in the second half of the study period. There was a significant difference in the percentage of positive tests found between the different hospital departments ordering the lumbar punctures (Supplementary appendix S3).

Outcome 3: serum *Borrelia burgdorferi* antibodies

Of the 8242 serum-*Bb* antibody tests performed at the Department of Clinical Microbiology, OUH, in the study period, 1977 tests from 1616 persons were ordered by general practitioners from Funen and the islands (table 1, serum antibody tests; Supplementary appendix S4). This represents a mean 1.5 tests per general practitioner per year. Of these, 1117 (56.5%) tests were from females and 68 (3.4%) from children <18 years of age. There was a significant reduction in tests ordered in 2019/2020 (*n* = 754) compared with 2017/2018

(*n* = 1223), *P* < 0.001, corresponding to 122 tests/100.000 population/year before the educational intervention, 75 tests/100.000 population/year after. The reduction in testing from 2017/2018 to 2019/2020 was 43.1% in the intervention group and 34.5% in the control group, *P* = 0.30 (details in Supplementary appendix S5). Of the 1977 serum-*Bb* antibody tests, 497 (25.1%) were positive, 204 (10.3%) IgM positive, 183 (9.3%) IgG positive and 110 (5.6%) IgM and IgG positive.

Outcome 4: Lyme neuroborreliosis treatment delay

During the 4-year study period, 63 patients from the study area had a positive CSF-*Bb*-AI test: 18 in 2017, 16 in 2018, 17 in 2019 and 12 in 2020 (table 2). We found no difference in pre-hospital delay between the patients in the intervention group after the intervention, compared with the intervention group before intervention and the control group (*P* = 0.40). Of the 63 patients, 10 (15.9%) were not seen after ended antibiotic treatment. At 6-month follow-up after ended treatment, we found 22 patients (34.9%) to have one or more residual symptoms after infection, the most common being radicular pain (*n* = 8) and altered sensitivity (*n* = 5). We found no reduction in risk of sequelae in the intervention group after the intervention compared with the other patients (*P* = 0.33). Seventeen patients had cognitive symptoms (fatigue, memory impairment and/or concentration difficulties) at 6-month follow-up, and again we found no correlation between patient group and risk of cognitive residual symptoms (*P* = 0.37).

Outcome 5: follow-up questionnaire

After the intervention and until 31 December 2020, 33 inquiries were received at CCEVI by telephone or e-mail from 22 of the 49 clinics (44.9%) in the intervention group. The inquiries were regarding possible LNB (*n* = 16), dermatological manifestations of LB (*n* = 6), serum-*Bb* antibody test results (*n* = 3), unspecific symptoms after tick-bite (*n* = 3), tick-borne encephalitis virus (*n* = 3), ticks (*n* = 1) and possible Lyme arthritis (*n* = 1). The inquiries led to 12 referrals for lumbar punctures on suspicion of LNB, 2 referrals to other departments, 3 recommendations of antibiotic treatment, while 16 inquiries needed no further follow-up.

The questionnaire was sent to the 107 general practitioner clinics in the study area from which an e-mail address was available: the 49 clinics in the intervention group and 58 in the control group. In all, 42 general practitioners answered the questionnaire, of whom 21 (50.0%) were in the intervention group. Of eight questions, the median correct number of answers was 7 [interquartile range (IQR) 7–8] in the intervention group, 6 in the control group (IQR 6–7), *P* = 0.02. Only three general practitioners in the intervention group (14.3%) had >1 incorrect answer on the questionnaire, compared with 12 (57.1%) in the control group (*P* = 0.004). The general practitioners were also asked how often the patient's requests contributed to them ordering serum-*Bb* antibody tests. Here, 23 (54.8%) responded that the patient request never contributed, 7 (16.7%) in up to 10% of times, 4 (9.5%) 11–25% of times and 7 (16.7%) >25% of times. A significantly higher proportion of the general practitioners in the intervention group never felt pressured by patients request, compared with the control group (71.4% vs. 38.1%, *P* = 0.03).

Discussion

Summary of main findings

This study intended to improve the clinical behavior among general practitioners through an educational intervention about ticks and LB. The outcomes were reached with a decrease in ordered serum-*Bb* antibodies and an increase in number of CSF samples examined by CSF-*Bb*-AI test. There were also an increase in the number of patients referred from the general practitioners to the regional

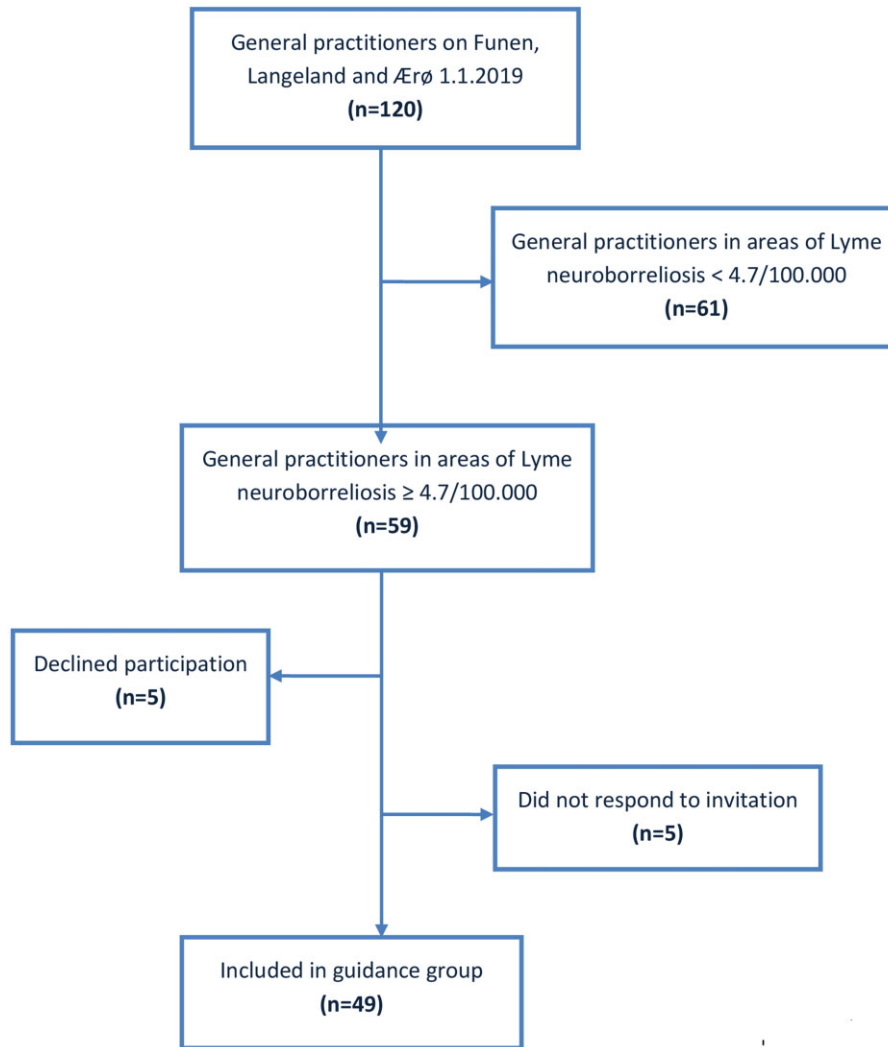


Figure 2 Flow chart of inclusion of general practices into an educational intervention about ticks and tick-borne infections on the islands of Funen, Langeland and Ærø.

reference center for tick-borne diseases, CCEVI, on suspicion of LB. However, we could not show any intervention effect on treatment delay and thereby risk of sequelae in LNB patients.

Increase in referred patients

We observed an overall increase in referrals to CCEVI for suspected LB from general practitioners in both groups. We can only speculate if this represents an increased general awareness of LB over time among general practitioners. The lower increase in referrals from the intervention group could represent more confidence in clinical assessment of LB after the intervention, as well as the opportunity to contact CCEVI for guidance.

Increase in patients examined for LNB

More patients were examined for LNB after the intervention. But this increase was seen in both groups, and therefore not likely to be caused by the intervention itself. The percentage of positive CSF-*Bb*-AI tests was higher in the intervention group, as expected by the higher LNB incidence in this area, but the positive rate did not increase after the intervention. The overall positive percentage of

3.5% in the study area is in accordance with previous Danish findings.¹³

*Decrease in serum *Borrelia* testing and potential consequences thereof*

One of our main teaching points was the limited indications for ordering serum-*Bb* antibody tests in general practice. The aim, a marked reduction in ordered tests in the intervention group after the intervention, was accomplished. But with the comparable reduction seen in the control group, this was more likely due to general awareness among general practitioners about the clinical limitations of *Bb* serology rather than the intervention itself.

The reduction in ordered serum-*Bb* antibody tests, and thereby a decrease in false-positive tests has several positive implications. Besides the economic gain, it will likely mean less prescribed antimicrobial treatments for patients without active infection.^{14–17} False-positive serum-*Bb* antibody tests may cause stress and anxiety in patients with unspecific symptoms and lead to delayed diagnosing and overlooking other causes of symptoms.^{18–22} As some LNB patients have no serum antibodies at time of positive CSF-*Bb*-AI, referring for lumbar puncture instead of screening with serum-*Bb*

Table 1 Presenting the impact of an educational intervention among an intervention group of 49 general practices, compared with a control group (71 general practices) on Funen, Langeland and Ærø, Denmark, in the 2 years before (2017 + 2018) and during/after (2019 + 2020) the intervention

	Before educational intervention		After educational intervention		All	
	2017	2018	2019	2020		
Referrals						
						Increase after educational intervention
Intervention group	16	22	28 ^a	21	87	28.9%
Control group	11	31	43	24	109	59.5%
All	27	53	71	45	196	45.0%
Intrathecal antibody tests						
						Increase after educational intervention
Intervention group	128 (9; 7.0%) ^b	190 (10; 5.3%)	203 ^c (10; 4.9%)	181 (6; 3.3%)	702 (35; 5.0%)	20.8%
Control group	224 (9; 4.0%)	288 (6; 2.1%)	306 (7; 2.3%)	298 (6; 2.0%)	1116 (28; 2.5%)	18.0%
All	352 (18; 5.1%)	478 (16; 3.3%)	509 (17; 3.3%)	479 (12; 2.5%)	1818 (63; 3.5%)	19.0%
Serum antibody tests						
						Decrease after educational intervention
Intervention group	293	255	179 ^d	133	860	43.1%
Control group	337	338	252	190	1.117	34.5%
All	630	593	431	323	1.977	38.3%

Referrals: Number of patients referred from the general practitioners in the two groups under the diagnosis Lyme borreliosis to the Clinical Center for Emerging and Vector-borne Infections at Odense University Hospital. Intrathecal antibody tests: Number of cerebrospinal fluid samples tested for intrathecal production of *Borrelia burgdorferi* antibodies in patients from the two groups. Serum antibody tests: Number of ordered serum anti-*B. burgdorferi* antibody tests from the general practitioners in the two groups.

a: Three tested before intervention.

b: Number of tests (number positive; % positive).

c: Thirty-seven tested before intervention (4 positive).

d: Twenty-one samples ordered before the educational intervention.

Table 2 Characteristics of 63 patients with Lyme neuroborreliosis in the period 2017–20 from Funen, Langeland and Ærø, Denmark, divided into an intervention group and a control group

	Control group N = 32	Intervention group before N = 18	Intervention group after N = 13	All N = 63	
Sex, male (%)	17 (53.1)	10 (55.6)	7 (53.9)	34 (54.0)	P = 0.99
Age, median (IQR)	53 (36–68)	68 (48–71)	58 (45–70)	58 (40–70)	P = 0.20
Comorbidities ^a (%)					
0	25 (78.1)	13 (72.2)	8 (61.5)	46 (73.0)	P = 0.08
1	6 (18.8)	5 (27.8)	2 (15.4)	13 (20.6)	
≥2	1 (3.1)	0	3 (23.1)	4 (6.4)	
Pre-hospital delay, days, median (IQR)	21 (9–47)	23 (9–64)	29 (17–121)	23 (9–56)	P = 0.40
Residual symptoms after 6 months (%)	13 (40.6)	6 (33.3)	3 (23.1)	22 (34.9)	P = 0.33
Cognitive symptoms after 6 months (%)	8 (25.0)	5 (27.8)	4 (30.8)	17 (27.0)	P = 0.37

a: Comorbidities measured by use of the Charlson comorbidity index.

antibodies in general practice will reduce the risk of overlooking LNB based on false-negative serum-*Bb* antibody tests.^{8,23,24}

In our study, we have limited data regarding the general practitioners motives for ordering serum-*Bb* antibodies. Other studies have demonstrated that general practitioners test patients for the presence of serum-*Bb* antibodies for multiple reasons including suspected EM and after tick-bites. These practices are not supported by international guidelines and recommendations.^{5,25–27} In a qualitative Dutch study, general practitioners admitted to referring patients with unspecific symptoms for *Bb* serology on patients' request, hoping for a negative result.²⁸ In our questionnaire, almost half the general practitioners admitted ordering serum-*Bb* antibodies partly on patients' request. However, the number of tests was low with 1.5

tests/general practitioner/year in a highly endemic LB area. Of these, 25% were positive, a higher prevalence than previously found in similar settings.^{5,24} Our high positive-rate matches that of Danish hunters, a highly tick-exposed group.²⁹ This supports the theory that these patients were a selected group with a higher risk of LB than the background population. It also confirms the study area as highly endemic for LB.

Increased LB knowledge but unchanged pre-hospital delay

The pre-hospital delay among LNB patients with the general practitioners in the intervention group remained unchanged after the

intervention. As these numbers were small, no conclusions can be drawn from these results. However, we found the general knowledge about LB to be increased 2 years after the intervention among general practitioners in the intervention group, as was their confidence in ordering serum-*Bb* antibodies.

Study implications for future research

While the knowledge on tick-borne infections improved among the general practitioners over the study period, our intervention had a limited impact on clinical decision-making and LNB pre-hospital delay. This important finding has future implications. Our classical teaching-based intervention was resource- and time-consuming and suggests it is not cost-effective with similar interventions going forward. But, as the knowledge of tick-borne diseases among the general population is limited, other approaches are crucial to influence clinical behavior and thereby reduce the LNB pre-hospital delay.³⁰ Two such approaches could be utilization of Citizen Science and Nudging campaigns, focusing on increasing awareness and educating the population.^{31–33} Also, based on the myriad of hospital departments and private specialists ordering serum-*Bb* tests, limiting the number of physicians diagnosing LB in the future will likely have a positive impact. More effort should be directed towards awareness of the rare LB complications in Europe (arthritis, carditis, acrodermatitis chronica atrophicans) where serum-*Bb* antibody tests are still indicated to establish the diagnosis, and towards more knowledge of the relatively high false-positive rates of serum-*Bb* antibodies, especially isolated serum-*Bb* IgM.^{17,34}

Study limitations

Our study has several weaknesses. The general practitioners in the intervention group were contacted in January 2019, but the teaching period lasted until primo May. The 2019 numbers therefore do not represent the entire year. However, the tick-season with the highest activity, disease burden and referrals of patients, ranges from May to October.^{8,35} Only 11.7%, 18.2% and 10.7% of the serum-*Bb* antibodies, CSF-*Bb*-AI and patients referred to CCEVI in 2019 from the intervention group were prior to the intervention. We therefore chose to include all 2019 results in this group. We cannot know whether the intervention group and the control group differed in their knowledge about ticks and LB prior to the intervention. Sending out a questionnaire prior to the intervention could have uncovered any differences between the groups. This was not done, and this represents a limitation in the study setup.

Furthermore, we observed a reduction in all of our outcome parameters from 2019 to 2020, likely due to the COVID-19 pandemic. Since March 2020, Denmark has had periods with lockdown, and the general practitioners have had less consultations.³⁶ On the other hand, with restrictions on international travel and indoor activities, the Danish population has spent more time outdoors during the COVID-pandemic.³⁶ This might have led to increased risk of tick-bites and tick-borne diseases in 2020 compared with previous years, as seen in other European countries.³⁷ There is also cause for concern regarding overlooked cases or delayed diagnosing of LB due to COVID-19.³⁸ The 2020 decline is more likely to represent a change in access to health care and testing rather than declining cases of LB.

Conclusion

In conclusion, we found an overall improvement in LB awareness and referrals among the general practitioners during the study period. This was, however, more likely due to a general increased attentiveness than due to our intervention, and it did not improve treatment delay and thereby risk of residual symptoms in LNB patients. Our results confirm that educational teaching cannot stand

alone and that a multifaceted approach is needed to decrease the diagnostic delay in LB.

Supplementary data

Supplementary data are available at *EURPUB* online.

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Conflicts of interest: All authors declare no conflicts of interest.

Data availability

The protocol, including more details on the intervention, is published on *clinicaltrials.gov* (Identifier: NCT03820999). The dataset generated for the cohort study is not publicly available due to the Danish Data Protection Law in accordance with the study approval by the Danish Data Protection Agency (J.nr. 19/4351). It is available from the corresponding author upon reasonable request.

Key points

- There is a lack of knowledge about the symptoms of Lyme borreliosis and how to diagnose it, both among physicians and the general population.
- An educational intervention teaching general practitioners about ticks and Lyme borreliosis was conducted.
- We found improved behavior after the intervention with more patients referred to hospital on suspicion of neuroborreliosis, more cerebrospinal fluids examined for *Borrelia burgdorferi* antibodies, and less blood tests screened for *B. burgdorferi* antibodies ordered by the general practitioners.
- There was no significant difference between the behavior of the general practitioners in the intervention group and the control group on any of our outcomes.
- Going forward, a multifaceted approach targeting not only physicians but also the general population must be used to improve outcomes of Lyme borreliosis.

References

- 1 Stanek G, Wormser GP, Gray J, Strle F. Lyme borreliosis. *Lancet* 2012;379:461–73.
- 2 Mygland A, Ljostad U, Fingerle V, et al. EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis. *Eur J Neurol* 2010;17:8–16, e1–4.

- 3 Dessau RBB JM, Hansen K, Lebech AM, et al. Lyme Borreliose - Klinik, diagnostik og behandling i Danmark. Dansk Selskab for Klinisk Mikrobiologi. Available at: <https://dskm.dk/onewebmedia/Borrelia%20klaringsrapport%202.udgave%202014.pdf>.
- 4 Dessau RB, van Dam AP, Fingerle V, et al. To test or not to test? Laboratory support for the diagnosis of Lyme borreliosis: a position paper of ESGBOR, the ESCMID study group for Lyme borreliosis. *Clin Microbiol Infect* 2018;24:118–24.
- 5 Dessau RB, Bangsbo JM, Ejlersten T, et al. Utilization of serology for the diagnosis of suspected Lyme borreliosis in Denmark: survey of patients seen in general practice. *BMC Infect Dis* 2010;10:317.
- 6 Krabbe NV, Jensen TE, Nielsen HI. Neuroborreliosis in North Jutland. *Ugeskr Laeger* 2008;170:3420–4.
- 7 Hansen K, Lebech AM. The clinical and epidemiological profile of Lyme neuroborreliosis in Denmark 1985–1990. A prospective study of 187 patients with *Borrelia burgdorferi* specific intrathecal antibody production. *Brain* 1992;115:399–423.
- 8 Knudtzen FC, Andersen NS, Jensen TG, Skarphédinsson S. Characteristics and clinical outcome of Lyme neuroborreliosis in a high endemic area, 1995–2014: a retrospective cohort study in Denmark. *Clin Infect Dis* 2017;65:1489–95.
- 9 Eikeland R, Mygland Å, Herlofson K, Ljøstad U. Risk factors for a non-favorable outcome after treated European neuroborreliosis. *Acta Neurol Scand* 2013;127:154–60.
- 10 Dersch R, Sommer H, Rauer S, Meerpohl JJ. Prevalence and spectrum of residual symptoms in Lyme neuroborreliosis after pharmacological treatment: a systematic review. *J Neurol* 2016;263:17–24.
- 11 Berglund J, Stjernberg L, Ornstein K, et al. 5-y Follow-up study of patients with neuroborreliosis. *Scand J Infect Dis* 2002;34:421–5.
- 12 Denmark S. Population at the first day of the quarter by region, sex, age and marital status 2019. Available at: <https://www.statistikbanken.dk/statbank5a/default.asp?w=1920>.
- 13 Dessau RB, Espenhain L, Molbak K, et al. Improving national surveillance of Lyme neuroborreliosis in Denmark through electronic reporting of specific antibody index testing from 2010 to 2012. *Euro Surveill* 2015;20:21184.
- 14 Webber BJ, Burganowski RP, Colton L, et al. Lyme disease overdiagnosis in a large healthcare system: a population-based, retrospective study. *Clin Microbiol Infect* 2019;25:1233–8.
- 15 Hansmann Y, Leyer C, Lefebvre N, et al. Feedback on difficulties raised by the interpretation of serological tests for the diagnosis of Lyme disease. *Med Mal Infect* 2014;44:199–205.
- 16 Seriburi V, Ndukwe N, Chang Z, et al. High frequency of false positive IgM immunoblots for *Borrelia burgdorferi* in clinical practice. *Clin Microbiol Infect* 2012;18:1236–40.
- 17 Hillerdal H, Henningson AJ. Serodiagnosis of Lyme borreliosis-is IgM in serum more harmful than helpful? *Eur J Clin Microbiol Infect Dis* 2021;40:1161–8.
- 18 Garment AR, Demopoulos BP. False-positive seroreactivity to *Borrelia burgdorferi* in a patient with thyroiditis. *Int J Infect Dis* 2010;14(Suppl 3):e373.
- 19 Naesens R, Vermeiren S, Van Schaeren J, Jeurissen A. False positive Lyme serology due to syphilis: report of 6 cases and review of the literature. *Acta Clin Belg* 2011;66:58–9.
- 20 Keymeulen B, Somers G, Naesens A, Verbruggen LA. False positive ELISA serologic test for Lyme borreliosis in patients with connective tissue diseases. *Clin Rheumatol* 1993;12:526–8.
- 21 Feder HM Jr, Gerber MA, Luger SW, Ryan RW. False positive serologic tests for Lyme disease after varicella infection. *N Engl J Med* 1991;325:1886–7.
- 22 Reid MC, Schoen RT, Evans J, et al. The consequences of overdiagnosis and overtreatment of Lyme disease: an observational study. *Ann Intern Med* 1998;128:354–62.
- 23 Schwenkenbecher P, Pul R, Wurster U, et al. Common and uncommon neurological manifestations of neuroborreliosis leading to hospitalization. *BMC Infect Dis* 2017;17:90.
- 24 Dessau RB, Ejlersten T, Hilden J. Simultaneous use of serum IgG and IgM for risk scoring of suspected early Lyme borreliosis: graphical and bivariate analyses. *APMIS* 2010;118:313–23.
- 25 Coumou J, Hovius JW, van Dam AP. *Borrelia burgdorferi* sensu lato serology in the Netherlands: guidelines versus daily practice. *Eur J Clin Microbiol Infect Dis* 2014;33:1803–8.
- 26 Vanthomme K, Bossuyt N, Boffin N, Van Casteren V. Incidence and management of presumption of Lyme borreliosis in Belgium: recent data from the sentinel network of general practitioners. *Eur J Clin Microbiol Infect Dis* 2012;31:2385–90.
- 27 Eliassen KE, Berild D, Reiso H, et al. Incidence and antibiotic treatment of erythema migrans in Norway 2005–2009. *Ticks Tick Borne Dis* 2017;8:1–8.
- 28 Vreugdenhil TM, Leeftang M, Hovius JW, et al. Serological testing for Lyme Borreliosis in general practice: a qualitative study among Dutch general practitioners. *Eur J Gen Pract* 2020;26:51–7.
- 29 Andersen NS. Tick-borne infections in Denmark – with special emphasis on tick-borne encephalitis. PhD Thesis. Odense, Denmark: University of Southern Denmark, Odense, Denmark, 2019.
- 30 Slunge D, Jore S, Krogfelt KA, et al. Who is afraid of ticks and tick-borne diseases? Results from a cross-sectional survey in Scandinavia. *BMC Public Health* 2019;19:1666.
- 31 Hines D, Sibbald SL. Citizen science: exploring its application as a tool for prodromic surveillance of vector-borne disease. *Can Commun Dis Rep* 2015;41:63–7.
- 32 Seifert VA, Wilson S, Toivonen S, et al. Community partnership designed to promote Lyme disease prevention and engagement in citizen science. *J Microbiol Biol Educ* 2016;17:63–9.
- 33 Thaler RH, Sunstein CR. *Nudge: Improving Decisions about Health, Wealth, and Happiness*. New Haven & London: Yale University Press, 2008.
- 34 Strizova Z, Smrz D, Bartunkova J. Seroprevalence of *Borrelia* IgM and IgG antibodies in healthy individuals: a caution against serology misinterpretations and unnecessary antibiotic treatments. *Vector Borne Zoonotic Dis* 2020;20:800–2.
- 35 Nordberg CL, Bodilsen J, Knudtzen FC, et al. Lyme neuroborreliosis in adults: a nationwide prospective cohort study. *Ticks Tick-Borne Dis* 2020;11:101411.
- 36 The Danish Health Authority. COVID-19: Monitoring of activities in the Danish healthcare system. 2021. Available at: <https://www.sst.dk/da/Udgivelses/2020/COVID-19-Monitorering-af-aktivitet-i-sundhedsvaesenet-3-rapport> (27 December 2021, date last accessed).
- 37 Steffen R, Lautenschlager S, Fehr J. Travel restrictions and lockdown during the COVID-19 pandemic-impact on notified infectious diseases in Switzerland. *J Travel Med* 2020;27:taaa180.
- 38 Wormser GP, Jacobson E, Shanker EM. Negative impact of the COVID-19 pandemic on the timely diagnosis of tick-borne infections. *Diagn Microbiol Infect Dis* 2021;99:115226.