Neuroborreliosis in patients hospitalised for Lyme borreliosis in the Czech Republic in 2003 – 2013

Kříž B.[1, 2], Malý M.[1], Daniel M.[1]

[1]National Institute of Public Health, Prague, Czech Republic
[2]3rd Faculty of Medicine, Charles University, Prague, Czech Republic

ABSTRACT

Study objective: The objective was to analyse and evaluate a cohort of Lyme borreliosis (LB) patients with neuroborreliosis (LNB) hospitalised in the Czech Republic in 2003–2013.
Material and methods: Data analysed in this study were obtained from the National Register of Hospitalised Patients, which is a nationwide population register maintained at the Institute of Health Information and Statistics of the Czech Republic. Data collection from all departments of bed care establishments are regularly processed every year. Registration of basic hospitalisation diagnoses is performed in accordance with the 10th revision of the International Classification of Diseases (ICD-10). The study cohort consisted of 23,631 patients with clinically and laboratory confirmed LB hospitalised between 2003 and 2013.
Results: Nervous system involvement, i. e. LNB (ICD-10 codes G00-G99) was recorded in 27.1% (6,392) of LB patients. Hospital admissions for LB exhibited a slight downward trend with year-on-year fluctuations over the study period. In contrast, LNB showed an upward trend with slight year-on-year fluctuations (345–779 cases) (p = 0.003). Overall, 6,392 persons, 3,220 males and 3,172 females, were diagnosed with LNB over the 11-year study period. Some patients presented with multiple concomitant neurological symptoms. Overall, 6,392 hospitalised patients were diagnosed with 8,168 diseases of the nervous system. The most common diagnoses were facial nerve disorders (21.1%), meningitis (18.3%), polyneuropathies (13.6%), encephalitis, myelitis, and encephalomyelitis (11.3%), and nerve root and plexus disorders (4.9%). The average age of male and female patients hospitalised with LNB was 44.4 and 44.7 years, respectively. It varied significantly between the ICD-10 code groups (p < 0.001) from 38.0 to 63.0 years. The relative incidence of LB by five-year age group showed the first peak at the age of 5–9, followed by a considerable drop at the age of 20–24 and then by another higher peak at the age of 55–59 (the hospitalisation rate ratio comparing the peaks in the adults and children was 1.78). For LNB, the second peak shifted to the age of 65 to 74 years and was similar to the peak in children age groups (hospitalisation rate ratio of 0.95). The distribution of hospital admissions for LNB by month of admission showed the highest numbers of admissions in July and September and the lowest numbers of admissions in December and April. The length of hospital stay was significantly higher (mean of 12.4 days and median of 13 days) in LNB patients (p < 0.001) than in other LB patients (mean of 10.3 days and median of 10 days).
Conclusion: The basic prerequisite for reliable diagnosis of LNB is a multidisciplinary collaboration of highly experienced neurologists, infection disease specialists, and microbiologists. The cohort of 6,392 patients hospitalised for LNB was analysed by gender, length of hospital stay, and month of hospital admission. The study found LNB cases to occur in all age groups. LNB diagnosis performed in accordance with the ICD-10 enables valid comparison between neurological outcomes of LB patients at both the national and international levels.

KEYWORDS

Lyme borreliosis – neuroborreliosis – nervous system involvement – National Register of Hospitalised Patients – International Classification of Diseases and Related Problems – ICD-10 – medical importance

SOUHRN

Kříž B., Malý M., Daniel M.: Neuroborrelióza u pacientů hospitalizovaných s Lymeskou borreliózou v České republice za období let 2003–2013

Cíl práce: Cílem práce bylo analyzovat a vyhodnotit soubor celonárodní databáze hospitalizovaných případů onemocnění Lymeskou borreliózou (LB) neuroborreliózou (LNB) v České republice za období let 2003–2013.
Materiál a metody: Data využitá v této studii byla získána z Národního registru hospitalizovaných pacientů, jehož správcem na celostátní úrovni je Ústav zdravotnických informací a statistiky ČR. Data jsou každoročně získávána a zpracována z nemocnic včetně fakultních a nemocnic následné péče. Registrace diagnóz hospitalizovaných pacientů je prováděna podle Mezinárodní klasifikace nemocí, 10. revize. Celkem byly ve studii zpracovány údaje 23 631 pacientů s klinicky a laboratorně prokázanou LB hospitalizovaných v uvedených letech.
Výsledky: Onemocnění LB s postižením nervového systému (LNB) označená kódy MKN-10 (G00-G99) byla zjištěna v 27,1 % (6 392 případů). Počet hospitalizací nemocných LB měl ve sledovaném období mírně sestupný trend s meziročním kolísáním. Trend LNB byl však naopak vzestupný s mírným meziročním kolísáním (345–779), (p = 0,003). Celkem bylo ve sledovaném období 11 let postiženo LNB 6 392 osob, z toho 3 220 mužů a 3 172 žen. V některých případech bylo detekováno více neurologických diagnóz (či symptomů) u jednotlivých nemocných souběžně. Celkově bylo při 6 392 hospitalizacích LNB zaznamenáno 8 168 diagnóz ze skupiny G (Nemoci nervové soustavy) podle MKN-10. Nejčetnější byly poruchy lícního nervu – nervi facialis (21,1 %), meningitidy (18,3 %), polyneuropatie (13,6 %), encefalomyelitidy (11,3 %), onemocnění nervů, nervových kořenů a pletení (4,9 %). Průměrný věk hospitalizovaných pacientů s LNB byl 44,4 roku u mužů a 44,7 u žen. Průměrný věk byl mezi jednotlivými podkapitolami kapitoly G statisticky významně odlišný (p < 0,001) a pohyboval se v rozmezí 38,0–63,0 let. Relativní nemocnost LB v pětiletých věkových sku-

pinách měla první maximum ve skupině 5–9letých následované extrémním poklesem hodnot u 20–24letých a druhým vyšším maximem ve skupině 55–59letých (rate ratio hospitalizovaných pro srovnání vrcholu u dospělé a dětské populace je 1,78). V případě LNB bylo druhé maximum posunuto až do věku 65–74 let a bylo na podobné úrovni jako maximum u dětí (rate ratio 0,95). Rozdělení onemocnění LNB podle měsíce přijetí k hospitalizaci ukázalo nejvyšší počet přijatých v měsících červenec a srpen a nejnižší v prosinci a dubnu. Doba hospitalizace pacientů s LNB (průměr 12,4, medián 13 dní) byla signifikantně delší ($p < 0,001$) než doba hospitalizace ostatních pacientů LB, (průměr 10,3, medián 10 dní).

Závěr: Základní podmínkou spolehlivé diagnostiky LNB je spolupráce kvalifikovaných neurologů, infekcionistů a mikrobiologů. Soubor 6 392 pacientů hospitalizovaných s LNB byl analyzován podle pohlaví a věku, délky hospitalizace a rozdělení dle měsíce přijetí k hospitalizaci. Studie prokázala výskyt onemocnění LNB ve všech věkových skupinách. Vyjádření LNB diagnózy pomocí MNK-10 umožní validní srovnávání výsledků neurologických vyšetření případů onemocnění LB jak na národní, tak i mezinárodní úrovni.

KLÍČOVÁ SLOVA:
Lymeská borrelióza – neuroborrelióza – nemoci nervové soustavy – hospitalizace – Národní registr hospitalizovaných – ÚZIS – Mezinárodní klasifikace nemocí – MKN-10 revize – lékařská důležitost

Epidemiol. Mikrobiol. Imunol., 66, 2017, č. 3, s. 115–123

INTRODUCTION

Lyme borreliosis (LB) is a disease caused by gram-negative spirochetes from the *Borrelia burgdorferi* sensu lato complex. The following spirochetes have been detected in the Czech Republic (CZ): *Borrelia burgdorferi* sensu lato (s.l.)/(BBSL), *Borrelia afzelii, B. garinii, B. burgdorferi* sensu stricto (s.s.), *B. bavariense, B. bissettii, B. valaisiana, B. spielmanii*, and *B. lusitaniae* [6].The tick *Ixodes ricinus* is the most important vector of LB in the Czech Republic.

Borrelia genomospecies have diverse reservoirs and vectors, differ in organotrophy, and cause various clinical symptoms. Their prevalence varies between ecosystems and geographical regions [11, 14]. Serotyping studies of *Borrelia* isolates from Europe revealed a striking correlation between infection caused by *B. garinii* and neuroborreliosis. *B. garinii* is the most common causative agent of neuroborreliosis in Europe [31, 37]. Neurotropism of *B. garinii* was detected in a study conducted in an LB endemic area in Norway [41]. Birds are the core reservoir of *B. garinii* and *B. valaisiana* in the CZ and Slovakia [9, 39]. In Slovenia, *B. garinii* causes a more severe clinical disease than *B. afzelii* [38].

In the Czech Republic, the geographical distribution pattern of LB cases does not overlap with those of other tick-borne infections. The differences result from the fact that the animal reservoirs of various infections are diversely distributed in nature. Rodents, birds, and small animals, all contribute to the spread of LB infection [4]. Compared to other infections, e.g. tick-borne encephalitis, active LB focal points occur more often in parks and gardens of urban agglomerations [1, 30, 45]. LB risk in periurban forest areas and the importance of its mapping for public health in France has been pointed out by [42].

The disease involves several phases and variable symptoms. It can be symptom-free or can have severe symptoms culminating in Lyme neuroborreliosis (LNB). Most infections begin with a dermal manifestation, erythema migrans [11, 14, 35]. It is typically a red spot, with a diameter greater than 5 cm, that is paler in the centre. The incubation period is from three to 32 days (exceptionally longer), but it averages 7–10 days. In later stages of the disease, the joints, nerves, heart, brain, and other organs can be affected. The disease can be treated by antibiotics, but symptoms may persist, such as joint pain.

Table 1. Numbers of LB patients hospitalised in 2003–2013, CZ

Year	No. of patients	Percentage
2003	2385	10.1
2004	2205	9.3
2005	2137	9.0
2006	1943	8.2
2007	2046	8.7
2008	2312	9.8
2009	1975	8.4
2010	2243	9.5
2011	2338	9.9
2012	2055	8.7
2013	1992	8.4
Total	23631	100.0

LB can be considered as one of the most common vector-borne diseases. In Europe, approximately 85,000 cases of LB were diagnosed in 2011. The annual total of LB cases in the world might be as many as 255,000 [31]. However, LB incidence varies widely across European countries. In the CZ, it ranged from 27.6/100,000 to 46.1/100,000 population between 2006 and 2015.

The surveillance of LB in the CZ is comprehensive: LB has been a mandatory reportable disease since 1988. The case definition is provided in Ministerial Decree 275 [8]. Reports received from paediatricians, GPs, and hospital physicians at the district level are sent to the regional authorities and to the National Institute of Public Health (NIPH). Reliable LB disease data have been available since the beginning of the nineties of the last century. Data of hospitalised persons are reported additionally by hospital administrations to a separate register.

MATERIAL AND METHODS

Data used in this study were obtained from the National Register of Hospitalised Patients (NRHOSP), which is a nationwide population register that builds on the information system Hospitalisation maintained in the CZ since 1960 by the Institute of Health Information

Table 2. Patients hospitalised with LB and its manifestations, 2003–2013, CZ

Diagnosis	No. of patients	Percentage
Lyme disease (A69.2) without any additional diagnosis	6486	27.5
Manifestation involving the nervous system – LNB (G00–G99)	6392	27.1
Manifestation involving the circulatory system (I00–I99)	2405	10.2
Manifestation involving the musculoskeletal system and connective tissue (M00–M99)	3044	12.9
Manifestation involving symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00–R99)	1293	5.5
Manifestation involving diseases or symptoms from other chapters of ICD-10	4011	17.0
Total Lyme borreliosis cases	23631	100.0

and Statistics founded by the Ministry of Health of the Czech Republic. Data collection from all bed departments of bed care establishments have been regularly processed every year since 1992. Since 1994, registration of basic hospitalisation diagnoses is performed according to the 10th revision of the International Classification of Diseases and Related Health Problems (ICD-10) [www.who.int/classifications/icd/en/]. The basic diagnosis is recorded and possibly added with up to four other health problems as additional diagnoses [http://www.uzis.cz/en/registers/national-health-registers/nr-hospitalised-patients]. The mid-period population data were obtained from the Czech Statistical Office [https://www.czso.cz/]. The hospitalisation records studied were those of patients diagnosed with LB and classified into the basic diagnosis (A 69.2 Lyme disease, ICD-10). The study patients were those with manifestations involving the nervous system (LNB) with at least one of four additional diagnoses from ICD-10 group G. The remaining patients were classified into the respective ICD-10 groups based on their additional diagnoses.

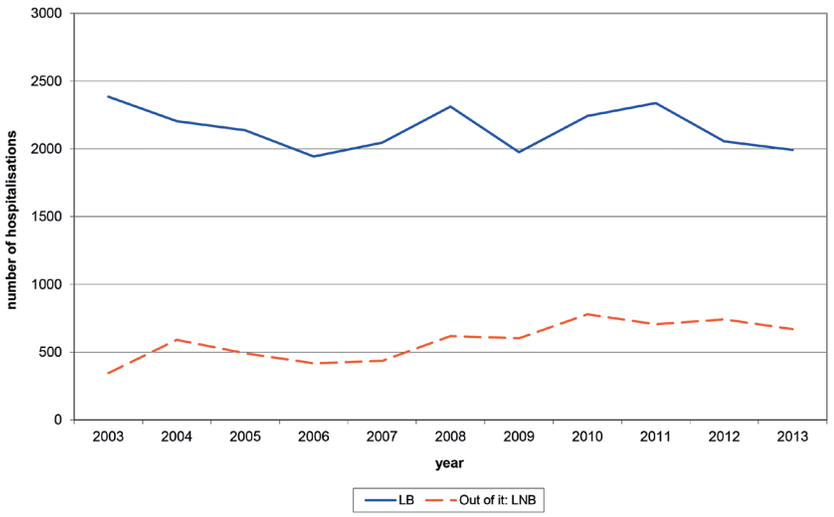

Figure 1. Hospital admissions for LB and LNB in 2003–2013, CZ

Laboratory diagnosis consists in the detection of IgM and IgG antibodies against *Borrelia* in the serum or cerebrospinal fluid and synovial fluid by the enzyme-linked immunosorbent assay (ELISA). In clinically ambiguous cases, the result is confirmed by immu-

Table 3. Distribution of the diseases of the nervous system – LNB (G00–G99) by gender and ICD-10 code, 2003–2013, CZ

ICD-10 code	Diagnosis	Male		Female		Total	
		No.	%	No.	%	No.	%
G01–G05	Inflammatory diseases of the central nervous system	1098	34.1	1141	36.0	2239	35.0
G10–G13	Systemic atrophies primarily affecting the central nervous system	15	0.5	5	0.2	20	0.3
G20–G26	Extrapyramidal and movement disorders	45	1.4	45	1.4	90	1.4
G30–G32	Other degenerative diseases of the nervous system	19	0.6	14	0.4	33	0.5
G35–G37	Demyelinating diseases of the central nervous system	51	1.6	108	3.4	159	2.5
G40–G47	Episodic and paroxysmal disorders	192	6.0	383	12.1	575	9.0
G50–G59	Nerve, nerve root and plexus disorders	968	30.1	764	24.1	1732	27.1
G60–G64	Polyneuropathies and other disorders	535	16.6	366	11.5	901	14.1
G70–G73	Diseases of myoneural junction and muscle	11	0.3	13	0.4	24	0.4
G80–G83	Cerebral palsy and other paralytic syndromes	107	3.3	109	3.4	216	3.4
G90–G99	Other disorders of the nervous system	179	5.6	224	7.1	403	6.3
Total		3220	100.0	3172	100.0	6392	100.0

Table 4. Distribution of diseases of the nervous system taking into account hospital admissions with multiple diagnoses, 2003–2013, CZ

ICD-10 code	Diagnosis	No.	%
G00–G03	Meningitis	1496	18.3
G04–G05	Encephalitis, myelitis and encephalomyelitis	922	11.3
G40–G41	Idiopathic epilepsy and epileptic syndromes	146	1.8
G43–G44	Migraine and other headache syndromes	500	6.1
G51	Facial nerve disorders	1726	21.1
G52–G53	Multiple cranial nerve palsies and other disorders	102	1.2
G54	Nerve root and plexus disorders	397	4.9
G56–G58	Mononeuropathies	213	2.6
G60–G63	Polyneuropathies	1109	13.6
G80–G81	Cerebral palsy and hemiplegia	91	1.1
G82	Paraplegia and tetraplegia	179	2.2
G83	Monoplegia (paralysis), diplegia	97	1.2
G93	Other disorders of brain including cerebral oedema	379	4.6
G97	Postprocedural disorders of nervous system	155	1.9
	Other	672	8.2
G00–G99	Total	8184	100.0

noblot (Western blot) or possibly by culture detection of *Borrelia burgdorferi* sensu lato from clinical specimens. Another option is non-culture detection of the antigen or borrelial genomic and plasmid nucleic acid (DNA).

The data presented are expressed as absolute frequencies and percentages. Tests for trend were based on Poisson regression model and on linear regression applied to transformed data. The comparison of continuous data between groups was performed using the Mann-Whitney test. To compare percentages of categorical data, the Pearson $\chi 2$ test was used. All statistical tests were evaluated as two-sided at a significance level of 0.05. Statistical analysis was performed by the statistical software Stata, release 9.2 (Stata Corp LP, College Station, TX).

Table 5. Average age distribution of 6392 patients hospitalised with LNB by ICD-10 code group and gender, 2003–2013, CZ

Diagnosis, ICD-10 code group	Male	Female	Total
G00–G09	41.9	44.7	43.3
G10–G13	56.7	62.0	58.0
G20–G26	58.7	62.0	60.4
G30–G32	61.7	64.9	63.0
G35–G37	42.3	45.0	44.2
G40–G47	41.0	38.4	39.3
G50–G59	37.6	38.5	38.0
G60–G64	59.3	57.2	58.4
G70–G73	54.4	56.2	55.3
G80–G83	58.6	56.7	57.6
G90–G99	41.1	44.9	43.2
Total	44.4	44.7	44.6

RESULTS

In 2003–2013, a total of 23,631 patients diagnosed with LB were recorded in the hospitalisation database of the CZ (Table 1).

In more than a quarter of patients hospitalised with LB (27.5%), LB was reported as the basic disease without additional diagnoses. Additional diagnoses were most often diseases of the nervous system – detected in 27.1% of LB patients. Musculoskeletal and circulatory system disorders were recorded in 12.9% and 10.2% of LB patients, respectively (Table 2). The number of hospital admissions for LB had a slight downward trend in the first years of the monitoring, peaking in 2003 (2385 cases) and being the lowest in 2006 (1943 cases), followed by year-on-year fluctuations approximately at the same level (Figure 1). In general, the trend is non-significant ($p = 0.415$). However, LNB showed an upward trend ($p = 0.003$), with the lowest number of cases in 2003 (345 cases) and a peak in 2010 (779 cases). Consequently, the percentage of hospital admissions for LNB was also on the rise ($p = 0.001$).

Table 3 summarizes LB cases with an additional neurological diagnosis listed under ICD-10 codes G00-G99 by gender. The highest proportion of admissions for LNB was due to inflammatory diseases of the central nervous system, particularly meningitis and encephalitis (35.0 %). Nerve, nerve root, and plexus disorders and polyneuropathies and other disorders were reported in 27.1% and 14.1% of cases, respectively. Over 11 years of the monitoring, LNB occurred in 3,220 males and 3,172 females. Females were less often affected by disorders

Table 6. The hospitalisation rates per 100,000 population and year by age group and gender – total of hospitalisation for LB and hospitalisations for LB with LNB, 2003–2013, CZ

	Total LB			Out of it LNB		
Age group	Male	Female	Total	Male	Female	Total
0- 4	4.9	6.1	5.4	2.0	2.7	2.3
5-9	24.7	23.9	24.3	10.0	9.7	9.9
10-14	22.1	20.4	21.3	6.7	5.8	6.3
15-19	13.6	19.0	16.2	4.0	3.7	3.8
20-24	9.4	11.1	10.2	2.5	2.4	2.4
25-29	11.4	12.5	11.9	2.6	2.6	2.6
30-34	12.3	15.7	14.0	3.6	3.9	3.8
35-39	15.7	18.4	17.0	3.9	4.2	4.1
40-44	17.1	23.1	20.0	4.1	4.7	4.4
45-49	22.4	28.1	25.2	5.4	6.6	6.0
50-54	29.9	36.8	33.4	7.2	8.0	7.6
55-59	35.2	32.3	33.7	9.5	7.9	8.7
60-64	30.1	27.5	28.7	9.0	7.2	8.1
65-69	33.7	30.1	31.7	10.1	8.7	9.3
70-74	32.5	26.2	28.8	11.1	8.0	9.3
75-79	26.7	16.3	20.3	10.5	5.1	7.2
80-84	14.4	10.6	11.8	3.9	3.3	3.5
85+	11.8	4.1	6.2	4.6	1.5	2.4
Total	20.1	21.3	20.7	5.8	5.4	5.6

under ICD-10 codes G50-G59 and G60-G64 and more often diagnosed with those under ICD-10 codes G40-G47 and G35-G37 than males.

Some patients presented with multiple concomitant neurological diagnoses (symptoms). Overall, 6392 hospitalised patients were diagnosed with 8168 diseases of the nervous system (codes G00-G99). Selected diagnoses that accounted for more than 1% of the total of these 8168 diseases are listed in Table 4. The most common diagnoses were facial nerve disorders (21.1%), meningitis (18.3%), mononeuropathies and polyneuropathies (16.2%), and encephalitis, myelitis, and encephalomyelitis (11.3%).

The average age of male and female patients hospitalised with LNB was 44.4 and 44.7 years, respectively. It varied significantly between ICD-10 code groups ($p < 0.001$) from 38.0 to 63.0 years (Table 5).

The age distribution of hospital admissions for LB and LNB calculated per 100,000 population and year within 5-year age groups and gender is shown in Table 6.

The highest total rates of hospital admissions for LB and LNB were found in children aged 5–9 (24.3/100,000 and 9.9/100,000, respectively). In adults, LB was most prevalent in age group 55–59 (33.7/100,000), and LNB in 65–74 (9.3/100,000).

The trends of LB curves by age and gender typically have two peaks, with the first peak in both males and females at the age of 5–9 years (24.7/100,000 and 23.9/100,000, respectively), followed by a drop to the lowest incidence in the age group 20–24 years (9.4/100,000 and 11.1/100,000, respectively) and another peak in males of the age group 55–59 years (35.2/100,000) and in females of the age group 50–54 years (36.8/100,000). Nevertheless, high morbidity levels are recorded in a wider age range from 55 to 74 years in males and from 50 to 69 years in females.

Similarly to the incidence of LB, the hospitalisation curves for LNB by age group show the first peak in the age group 5–9 years, but with lower levels (males 10.0/100,000 and females 9.7/100,000). In the following adolescent age groups, the proportion of LNB among LB cases declines rapidly. In the working-age population aged between 20 and 69 years, LNB exhibits an upward trend with age. The percentage increase between neighbouring age categories shows similar patterns in both the LNB group and the LB group without LNB up to the age of 54 years. LNB continues to be on the rise up to the age of 69 years, but the total of LB cases is declining ($p = 0.013$). The second peak of LNB is thus shifted to higher age groups, to the age of 70–74 years in males (11.1/100,000) and 65–69 years in females (8.7/100 000) .The second LNB peak is less pronounced than that in the total LB cases, particularly in females. While the hospitalisation rate ratio between second and first peak is 1.78 for the total of LB cases, it equals to 0.95 for LNB, which means that the hospitalisation rates for LNB are practically equal for both peaks, while second peak is markedly higher for the total of LB cases ($p < 0.001$) (Figures 2 and 3).

The age distribution of selected neurological disorders (LNB) in hospitalised LB patients in 2003–2013 is shown in Figure 4. In children, facial nerve disorders and meningitis were most often diagnosed

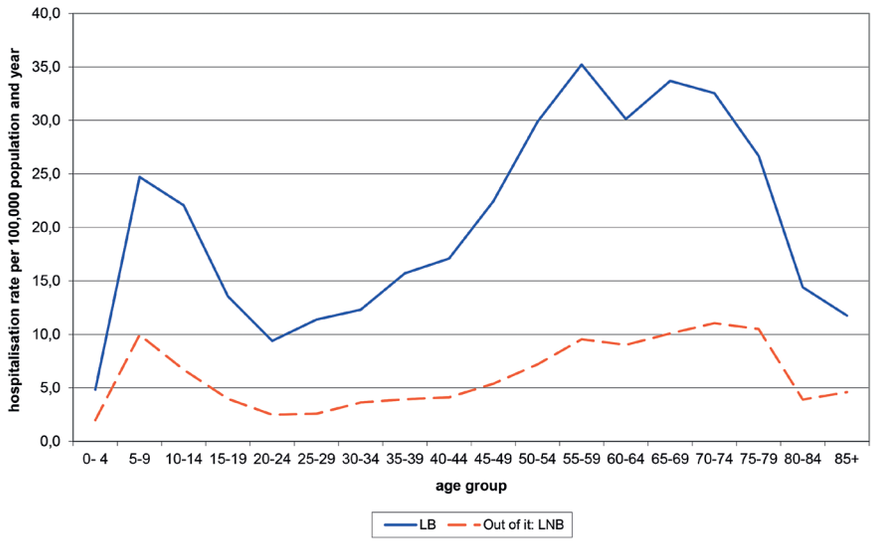

Figure 2. The hospitalisation rates for LB and LNB per 100,000 population and year by age group in males, 2003–2013, CZ

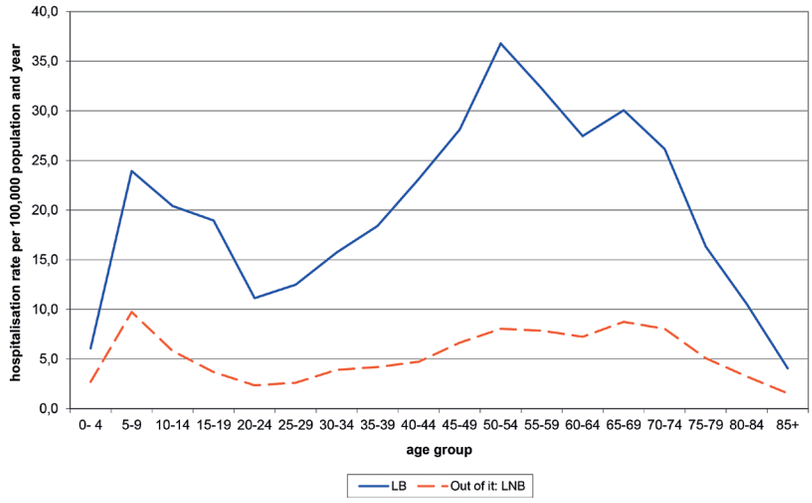

Figure 3. The hospitalisation rates for LB and for LNB per 100,000 population and year by age group in females, 2003–2013, CZ

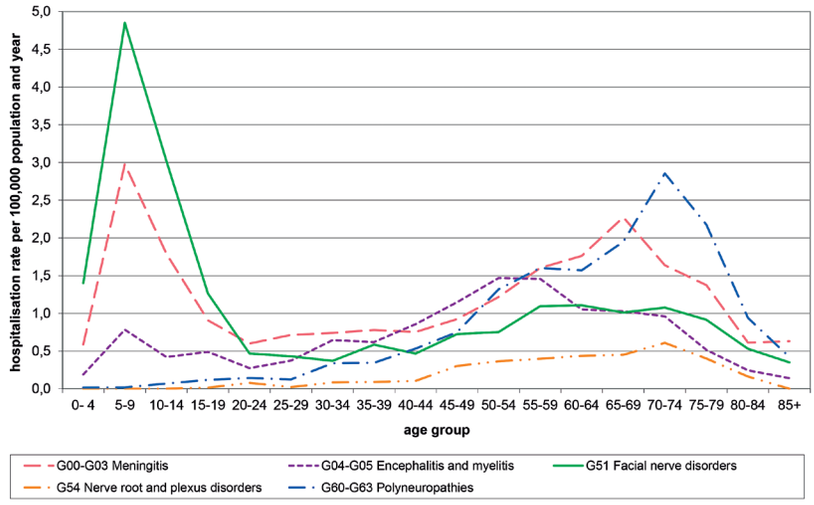

Figure 4. The hospitalization rates for selected additional diagnoses (LNB) per 100,000 population and year, by age group, 2003–2013, CZ

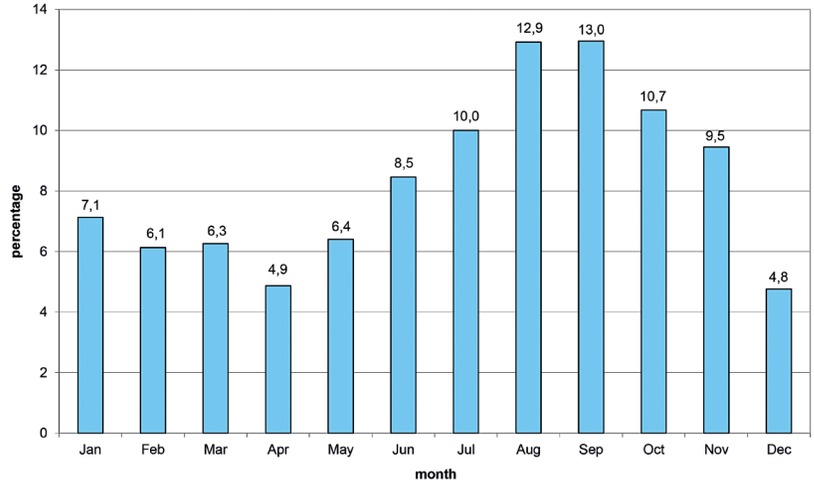

Figure 5. Distribution of hospital admissions for LNB by calendar month of admission, 2003–2013, CZ

at the age of 5–9 years (4.8/100,000 and 3.0/100,000, respectively). The same holds for encephalitis and myelitis but in less extend (0.8/100,000). Polyneuropathies and nerve root and plexus disorders were almost never reported in childhood. In adults, the most common conditions were encephalitis and myelitis at the age of 50–59 (1.6/100,000), meningitis at the age of 65–69 years (2.3/100,000), nerve root and plexus disorders at the age of 70–74 years (0.6/100,000), and polyneuropathies at the age 70–74 years (2.9/100,000).

Figure 5 shows the distribution of hospital admissions for LNB by calendar month of admission. A seasonal trend is evident in LNB cases, with a peak in August and September and the lowest incidence in the winter and spring months.

The length of hospital stay for LNB showed a slight downward trend during the study period from 2003 (mean of 14.1 days and median of 14 days) to 2013 (mean of 12.2 days and median of 13 days). Shortening took place mainly in 2008–2010. No marked difference was seen between years in 2003–2007 and then in 2010–2013, except for 2012 with the shortest hospital stays. The 25th percentile dropped from nine to six days, which means that in one of four patients, the length of hospital stay is now under one week.
Table 7 (see p. 121) summarizes the length of hospital stay data for the entire study period 2003–2013 by G code group (LNB). The longest median hospital stays were recorded for conditions from code groups G00–G09, G10–G13 and G50–G59 while the shortest ones for conditions from code groups G40–G47 and G90–G99. The length of hospital stay was significantly higher (mean of 12.4 days and median of 13 days) in LNB patients ($p < 0.001$) than in other LB patients (mean of 10.3 days and median of 10 days).

DISCUSSION

The present study analysed LNB cases reported in 27.5% of hospitalised LB patients in the study period 2003–2013. The curve of annual hospital admissions for LB exhibited a slight downward trend (nonsignificant) with year-on-year fluctuations. In contrast, LNB showed an upward trend ($p = 0.003$). Interestingly, the length of hospital stay of LNB patients became significantly shorter during the study period. In this context, a question arises of how to interpret the reduced length of hospital stay. On the one hand, it might be a result

Table 7. Lengh of hospital stay for LNB in days by ICD-10 code, 2003–2013, CZ

ICD-10 code	Diagnosis	No. cases	Days mean	Days median	Days min	Days max
G00–G09	Inflammatory diseases of the central nervous system	2239	14.1	14	1	83
G10–G13	Systemic atrophies primarily affecting the central nervous system	20	28.4	14	2	304
G20–G26	Extrapyramidal and movement disorders	90	12.0	9.5	1	77
G30–G32	Other degenerative diseases of the nervous system	33	11.3	10	1	41
G35-G37	Demyelinating diseases of the central nervous system	159	9.8	8	1	28
G40–G47	Episodic and paroxysmal disorders	575	8.2	7	1	35
G50–G59	Nerve, nerve root and plexus disorders	1732	13.0	14	1	92
G60–G64	Polyneuropathies and other disorders of the peripheral nervous system	901	11.3	13	1	46
G70–G73	Diseases of myoneural junction and muscle	24	10.4	13	1	21
G80–G83	Cerebral palsy and other paralytic syndromes	216	14.2	13	1	110
G90–G99	Other disorders of the nervous system	403	9.1	7	1	50
Total		6392	12.4	13	1	304

of new therapeutic options that became available, but, on the other hand, it cannot be excluded either that administrative pressure to reduce the length of hospital stay, particularly in acute care beds, might have contributed to this reduction. In any case, it means lower hospital costs for LNB patients. The case definition of LB, including the principles of diagnosis, is specified in the annex Surveillance of L. borreliosis in the CR within the Ministerial Decree No 275/2010 Coll. [8].

LB was discovered in the last quarter of the last century. Clinical and laboratory diagnosis of the disease is constantly evolving. The implementation of novel diagnostic methods led to improved diagnosis of the disease in many European countries. Unfortunately, it cannot be stated that consensus has been reached on laboratory diagnosis of diverse manifestations of this vector-borne disease [19, 20]. A considerably improved precision in the diagnosis was achieved through the specific antibody index (AI) in the cerebrospinal fluid (CSF)/serum [15]. The standard diagnostic protocol is based on the demonstration of synthesis of intrathecal antibodies to Lyme borrelia, serological testing and clinical manifestation. Detection of *Borrelia burgdorferi* s. l. by culture or PCR could be used as additional methods. Important are previous well defined LB manifestations [10].

However, clinically manifest LNB cases can occur exceptionally in the absence of detectable antibodies in the CSF. The potential for use of PCR in the detection of *Borrelia* and monitoring of therapy response in LNB was tested in 57 clinically manifest cases of LNB with antibodies detected in the CSF. In comparison with the method of CSF antibody synthesis, nested PCR detected specific DNA concomitantly in the plasma, CSF, and urine in 63.1% of cases [27]. During a long-term follow-up of 57 LNB patients, the presence of specific DNA was detected in 48 patients after therapy, in 29 patients after three months, and in six patients after six months [28].

A controlled study tested a novel enzyme immunoassay (EIA) using recombinant fragments of the borrelial subspecies *B. garinii*, *B. afzelii*, and *B. burgdorferi* s. s., e.g. the highly specific antigen VIsE for IgG. In children diagnosed with LNB, elevated sensitivity of IgG antibodies was revealed, and the assay had comparable specificity to western blot [17]. VlsE peptide ELISA showed high specificity and sensitivity in the serological diagnosis of Lyme facial paralysis [24].

Another controlled study has confirmed the clinical relevance of the detection of chemokine CXCL13 (B cell chemoattractant) and anti-C6 peptide antibodies (C6 peptide is a synthetic antigen derived from the VlsE protein of *B. burgdorferi*) in LNB patients. The highest concentrations of chemokine CXCL13 in the CSF were detected in early-stage LNB. The detection of CXCL13 could be used mainly in patients with acute stage LNB who had an as yet negative AI [29].

A systematic literature review evaluated 78 publications on the diagnostic accuracy of serological tests for Lyme borreliosis. The sensitivity of the EIA or immunoblot (IB) in case-control studies was 0.77 (95% CI 0.67–0.85). The specificity was around 0.95 [10]. According to the EFNS guidelines, neurological symptoms, cerebrospinal fluid (CSF) pleocytosis, and Bb-specific antibodies produced intrathecally are the basic criteria for the diagnosis of LNB [21].

In the USA, neurological involvement occurs in 10–15% of untreated LB patients [12]. The prevalence of LNB in the USA is < 10% of all LB cases, whereas in Europe, the rate is 35% [33]. In the South of England, the incidence of LB was in the mean range of 9.8/100 000 in 1992–2012. Neurological involvement has been observed in up to 25% of Czech LB patients [17]. LNB cases have been reported practically from all countries where LB occurs.

The present study found the following conditions to be the most prevalent (in descending order): facial nerve disorders (21.1%), meningitis (18.3%), polyneuropathy (13.6%), encephalitis, myelitis, and encephalomyelitis (11.3%), migraine and other headache syndromes (6.1%), nerve root and plexus disorders (4.9%), and other disorders of the brain including cerebral oedema (4.4%).

The first symptom of LB is often erythema chronicum migrans, a red circular rash at the site of the tick bite. It may not appear or may remain unnoticed by the

patient. LB patients may develop LNB, nervous system involvement, in the early, acute stage of the disease three to six weeks after infection as well as in the later, chronic stage. LNB often manifests itself as a lymphocytic meningoradiculoneuritis [13] or facial nerve palsy, aseptic meningitis, and neuroradiculitis [19]. Common manifestations are facial nerve palsy, aseptic meningitis, and neuroradiculitis [24], and radiculopathy or cranial neuropathy (of facial nerve) [26]. Acute facial nerve palsy is one of five variables considered in the diagnosis of LNB in Sweden [35]. Bannwarth's syndrome, which consists of the triad of lymphocytic meningitis, cranial neuritis, and radiculitis, is relatively common [22], with painful meningoradiculitis, inflammation of the nerve roots, and lancinating, radicular pain [32]. Facial nerve palsy is considered as the most common neurological manifestation of LNB in children in Europe [34, 40]. The following clinical manifestations were diagnosed in 57 hospitalised LNB patients: Bannwarth's syndrome (50.9%), acute meningoencephalitis (8.8%), subacute encephalitis (5.2%), meningitis (10.5%), multiplex neuritis (15.8%), facial palsy (8.8%) [27]. Chronic stage LNB results from long-term infection accompanied by symptoms that develop for weeks to months. It manifests itself as progressive encephalitis, myelitis, and neuropathy; however, other neurological disorders are not ruled out [18]. One of the chronic manifestations of Lyme disease is Lyme encephalopathy described as the syndrome of cognitive slowing, memory impairment that complicates daily functioning of patients [5]. Late chronic organ involvement may occur months to years after infection [25]. Late chronic neuroborreliosis may present the following neurological manifestations: chronic progressive Lyme encephalitis or encephalomyelitis, cerebral vasculitis, myositis, and chronic polyneuropathy [26]. However, not even modern medicine can explain the causes of the persisting health problems, such as chronic pain, fatigue, and other disabling symptoms. Prolonged symptoms after successful treatment are rather rare, but may occur. Long-term antibiotic therapy not only fails to control such symptoms but also is a risk to human health [23].

As it follows from our results, LNB affects both adults and children in the CR. The prevalence was higher in boys than in girls. The most affected childhood age group was 5–9 years.

The prevalence of LNB in children has also been reported by epidemiological studies from Sweden [34, 35]. Of 89 Dutch children diagnosed with LNB, 79% had one or more neurological manifestations. Most of them suffered from facial palsy, cranial nerve abnormalities, and meningeal signs [3].

In an epidemiolgical study involving 1,471 LB cases, conducted in southern Sweden, LNB occurred in 16% of patients. LNB incidence was the highest in the age groups 5–9 years and 60–74 years. Boys were affected more often than girls [2]. No difference in the total rates of LNB was found between boys and girls in a Norwegian endemic area [41]. A 10-year study of 142 children diagnosed with LNB has reported facial nerve palsy to be more common in girls (86%) than in boys (62%) [42]. Bannwarth's syndrome occurs more often in adults than in children, with less than 5% of children with LNB being affected. The most common manifestations of childhood LNB are acute facial nerve palsy in 55% of patients and lymphocytic meningitis in 27% of patients [4].

In the present study, the highest rates of hospital admissions for LNB were recorded in the summer and autumn months (55 % in the period from June to October); however, 4.8–7.1% of LNB patients were admitted to the hospital in the winter and spring months where the questing activity of *I. ricinus* ticks is close to zero. This can be explained, on the one hand, by the relatively long incubation period of LB and, on the other hand, by a delay in the diagnosis in some LB patients who were admitted to the hospital with a late-stage disease when presenting with severe complications. A six-year retrospective study of LNB in an Austrian endemic area has reported 74% of cases to occur in the period from June to October and 26% of cases in the remaining months of the year [16].

The authors of the present study are aware of the fact that some of the less common conditions listed in the additional diagnosis category (e.g. G10–G13) may not be causally linked to LB. However, the fact that the main reason behind the hospital admission of the study patients was LB should be taken into account. Given the size of the study cohort, possible detection of some uncommon neurological manifestations of LB cannot be ruled out.

REFERENCES

1. Bašta J, Plch J, Hulínská D, et al. Incidence of *Borrelia garinii and Borrelia afzelii* in *Ixodes ricinus* ticks in an urban environment, Prague, Czech Republic, between 1995 and 1998. *Eur J Clin Microbiol Infect Dis*, 1999;18(7): 515–517.

2. Berglund J, Eitrem R, Ornstein K, et al. An epidemiologic study of Lyme disease in southern Sweden. *N Engl Med*, 1995;33(20): 1319–1324.

3. Broekhuijsen-van Henten DM, Braun KP, Wolfs TF. Clinical presentation of childhood neuroborreliosis; neurological examination may be normal. *Arch Dis Child,* 2010;95(11): 910–914.

4. Christen HJ. Lyme neuroborreliosis in children. *Ann Med*, 1996;28(3): 235–240, Review.

5. Dandashi JA, Nizamutdinov D, Dayawansa S, et al. Texas Occurrence of Lyme Disease and Its Neurological Manifestations. *J Neuroinfect Dis*, 2016;7(2). pii: 217.

6. Daniel M, Rudenko N, Golovchenko M, et al. The occurrence of *Ixodes ricinus* ticks and important tick-borne pathogens in areas with high tick-borne encephalitis prevalence in different altitudinal levels of the Czech Republic Part II. *Ixodes ricinus* ticks and genospecies of *Borrelia burgdorferi sensu lato* complex. *Epidemiol Mikrobiol Imunol*, 2016;65(3): 182–192.

7. Danielová V, Daniel M, Rudenko N, et al. Prevalence of Borrelia burgdorferi sensu lato genospecies in host-seeking *Ixodes ricinus* ticks in selected South Bohemian locations (Czech Republic). *Cent Eur J Public Health*, 2004;12(3): 151–156.

8. Decree of the Ministry of Health of the Czech Republic No 275/2010 Coll. amending the Decree No 473/2008 Coll. on surveillance system for selected infectious diseases, Annex 23: Surveillance of Lyme borreliosis.

9. Dubska L, Literak I, Kocianova E, et al. Differential role of passerine birds in distribution of *Borrelia* spirochetes, based on data from ticks collected from birds during the postbreeding migration period in Central Europe. *Appl Environ Microbiol*, 2009;75(3): 596–602.

10. European Centre for Disease Prevention and Control. A systematic literature review on the diagnostic accuracy of serological tests

for Lyme borreliosis. Stockholm ECDC, April 2016. ISBN 978-92-9193-724-0 doi 10.2900/309479.
11. Grubhoffer L, Golovchenko M, Vancová M, et al. Lyme borreliosis: insights into tick-/host-borrelia relations. *Folia Parasitol* (Praha), 2005;52(4): 279-94. Review.
12. Halperin JJ. Lyme disease and the peripheral nervous system. *Muscle Nerve*, 2003;28(2): 133–143.
13. Hansen K, Lebech AM. Lyme neuroborreliosis: A new sensitive diagnostic assay for intrathecal synthesis of *Borrelia burgdorferi*-specific immunoglobulin. *Ann Neurol*, 1991;30: 197.
14. Hubálek Z. Epidemiology of lyme borreliosis. *Curr Probl Dermatol*, 2009;37: 31–50. Review.
15. Kaiser R, Lücking CH. Intrathecal synthesis of specific antibodies in neuroborreliosis. Comparison of different ELISA techniques and calculation methods. *J Neurol Sci*,1993;118(1): 64–72.
16. Kindler W, Wolf H, Thier K, et al. Peripheral facial palsy as an initial symptom of Lyme neuroboreliosis in an Austrian endemic area. *Wien Klin Wochenschr*, 2016;128(21–22): 837–840.
17. Krbková L, Bednářová J, Čermáková Z, et al. Improvement of diagnostic approach to Lyme neuroborreliosis in children by using recombinant antigens in detection of intrathecally produced IgM/IgG. *Epidemiol Mikrobiol Imunol*, 2016;65,2: 112–117.
18. Ljøstad U, Mygland Å. Chronic Lyme, diagnostic and therapeutic challenges. *Acta Neurol Scand*, 20.13; 196(Suppl.): 38–47.
19. Melia MT, Auwaerter PG.Time for a Different Approach to Lyme Disease and Long-Term Symptoms. *N Engl J Med*, 2016;374(13): 1277–1278.
20. Melia MT, Lantos PM, Auwaerter PG. Laboratory testing for lyme neuroborreliosis. *JAMA Neurol*, 2015;72(1): 126. doi: 10.1001/jamaneurol.2014.3555.
21. 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.
22. Pachner AR, Steere AC. The triad of neurologic manifestations of Lyme disease: meningitis, cranial neuritis, and radiculoneuritis. *Neurology*, 1985;35(1): 47–53.
23. Paul M, Lantos MD, Chronic Lyme Disease. *Infect Did Clin North Am*, 2015 Jun;29(2): 325–340.
24. Peltomaa M, McHugh G, Steere AC. The VlsE (IR6) peptide ELISA in the serodiagnosis of lyme facial paralysis. *Otol Neurotol*, 2004;25(5): 838–841.
25. Pfister HW, Wilske B, Weber K. Lyme borreliosis: basic science and clinical aspects. *Lancet*, 1994;343: 1013–1016.
26. Pfister HW, Rupprecht TA. Clinical aspects of neuroborreliosis and post-Lyme disease syndrome in adult patients. *Int J Med Microbiol*, 2006 May;296 Suppl 40: 11–16. Review.
27. Pícha D, Moravcová L, Ždárský E, et al. PCR in Lyme borreliosis: a prospective study. *Acta Neurol Scand*, 2005;112: 287–292.
28. Pícha D, Moravcová L, Vaňousová D, et al. DNA persistence after treatment of Lyme borreliosis. *Folia Microbiol* (Praha), 2014;59(2): 115–125.
29. Pícha D, Moravcová L, Smíšková D. Diagnostický význam chemokinu CXCL13 a protilátek proti C6 peptidu u pacientů s neuroboreliózou. *Epidemiol Mikrobiol Imunol*. 2017;66(2):80–85.
30. Rizzoli A,Silaghi C, Oblegala A, et al. Ixodes ricinus and its Transitted Pathogens in urban and Peri-Urban Areas in Europe. New Hazard and Relevance for Public Health. *Front Public Health,* 2014: 251.
31. Rudenko N, Golovchenko M, Grubhoffer L, et al. Updates on *Borrelia burgdorferi sensu lato complex with respect to public health. Ticks Tick Borne Dis*, 2011 Sep;2(3): 123–128.
32. Rupprecht TA, Koedel U, Fingerle V, et al. The pathogenesis of lyme neuroborreliosis: from infection to inflammation. *Molecular Medicine*, 2008;14(3–4): 205–212.
33. Sindha A, Dietzman T, Ross D, et al. Lyme neuroborreliosis: a diagnostic headache. *Hosp Pediatr*, 2014;4(6): 400–404.
34. Skogman BH, Croner S, Nordwall M, et al. Lyme neuroborreliosis in children: a prospective study of clinical features, prognosis and outcome. *Pediatr Infect Dis J*, 2008;27(12): 1089–1094.
35. Skogman BH, Sjowall J, Lindgren PE. The NEBoP score – a clinical predoction test for evaluation of children with Lyme neuroboreliosis in Europe. *BMC Pediatr*, 2015; 15: 214.
36. Stanek G, Wormser GP, Gray J, et al. Lyme borreliosis. *The Lancet*, 2012; 379, (9814): 461–473.
37. Stanek G, Reiter M. The expanding Lyme *Borrelia* complex – clinical significance of genomic species? *Clin Microbiol Infect*, 2011;17: 487–493.
38. Strle F, Ružić-Sabljić E, Cimperman J, et al. Comparison of findings for patients with *Borrelia garinii* and *Borrelia afzelii* isolated from cerebrospinal fluid. *Clinical Infectious Diseases*, 2006;43(6): 704–710.
39. Taragelová V, Koči J, Hanincová K, et al. Blackbirds and Song Thrushes Constitute a Key Reservoir of *Borrelia garini* the Causative Agent of Borreliosis in Central Europe. *Appl Environ Microbiol,* 2008;74(4): 1289–1293.
40. Tveitnes D, Øymar K, Natås O. Acute facial nerve palsy in children: how often is it lyme borreliosis? *Scand J Infect Dis,* 2007;39(5): 425–431.
41. Tveitnes D, Natås OB, Skadberg Ø, et al. Lyme meningitis, the major cause of childhood meningitis in an endemic area: a population based study. *Arch Dis Child*, 2012;97(3): 215–220.
42. Tveitnes D, Øymar K. Gender differences in childhood Lyme neuroborreliosis. *Behav Neurol*, 2015;790762. doi: 10.1155/2015/790762.
43. Vourc'h G, Abrial D, Bord S, et al. Mapping human risk of infection with *Borrelia burgdorferi sensu lato*, the agent of Lyme borreliosis, in a periurban forest in France. *Ticks Tick Borne Dis*, 2016;7(5): 644–652.
44. Zeman P, Benes C. Peri-urbanisation, counter-urbanisation, and an extension of residential exposure to ticks: a clue to the trends in Lyme borreliosis incidence in the Czech Republic? *Ticks Tick Borne Dis*, 2014;5(6): 907–916.
45. Zeman P, Benes C, Markvart K. Increasing Residential Proximity of Lyme Borreliosis Cases to High-Risk Habitats: A Retrospective Study in Central Bohemia, the Czech Republic, 1987-2010. *Ecohealth*, 2015;12(3): 519–522.

Acknowledgement
Supported by Ministry of Health, Czech Republic – conceptual development of research organization („the National Institute of Public Health – NIPH, 75010330").

Do redakce došlo dne 2. 2. 2017.

Adresa pro korespondenci:

doc. MUDr. Bohumír Kříž, CSc.
Státní zdravotní ústav
Šrobárova 48
100 42 Praha 10
e-mail: bohumir.kriz@szu.cz