1 **Lyme neuroborreliosis and bird populations in northern Europe**

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Abstract

Many vector-borne diseases are transmitted through complex pathogen-vector-host networks, which makes it challenging to identify the role of specific host groups in disease emergence. Lyme borreliosis in humans is now the most common vector-borne zoonosis in the northern hemisphere. The disease is caused by multiple genospecies of *Borrelia burgdorferi* sensu lato bacteria transmitted by ixodid (hard) ticks, and the major host groups transmit *Borrelia* genospecies with different pathogenicity, causing variable clinical symptoms in humans. The health impact of a given host group is a function of the number of ticks it infects as well as the pathogenicity of the genospecies it carries. *B. afzelii*, with mainly small mammals as reservoirs, is the most common pathogen causing Lyme borreliosis, and it is often responsible for the largest proportion of infected host-seeking tick nymphs in Europe. The bird-borne *B. garinii*, though less prevalent in nymphal ticks, is more likely to cause Lyme neuroborreliosis, but whether *B. garinii* causes disseminated disease more frequently has not been documented. Based on extensive data of annual disease incidence across Norway from 1995-2017, we show here that 69 % of disseminated Lyme borreliosis cases were neuroborreliosis, which is three times higher than predicted from the infection prevalence of *B. garinii* in host-seeking ticks (21 %). The population estimate of migratory birds, mainly of thrushes, explained part of the annual variation in cases of neuroborreliosis, with a one-year time lag. We highlight the important role of the genospecies' pathogenicity and the host associations for understanding the epidemiology of disseminated Lyme borreliosis.

1. Introduction

Ecosystems provide vital services and goods to humanity, but they also cause disservices in terms of spillover of pathogens circulating in the ecosystems [1]. An important part of disease mitigation is to understand the ecology and circulation of the pathogens and their effects on the epidemiology of human diseases. However, the dynamics of zoonotic diseases can be difficult to unravel due to the complexity of the natural transmission networks [2,3]. In particular, the transmission of some vector-borne diseases may involve multiple hosts, parasites and pathogens. Such complexity makes it difficult to assess how each host type contributes to the epidemiology of disease. Lyme borreliosis is now the most common vector-borne disease in the northern hemisphere and has a particularly complex epidemiology [4-6]. The disease is caused only by some of the 19 members of the *Borrelia burgdorferi* sensu lato (s.l.) complex [5], which consists of multiple genospecies. In western Europe, the transmission of these pathogenic agents to humans occurs via one tick, *Ixodes ricinus*, and the density of infected nymphs typically determines disease hazard to humans [7]. In Europe, *B. afzelii* is often the most common genospecies in questing (host-seeking) nymphs due to the ubiquity of its small mammal reservoirs [8,9]. *B. garinii* is mainly bird-borne and is usually the second most common genospecies in questing nymphs. However, *B. garinii* is the main causal agent for the more severe infection, Lyme neuroborreliosis [10,11]. Hence, bird populations may have a more important role in spreading the pathogen causing disseminated Lyme borreliosis in humans than is currently documented and assumed based on the prevalence of *B. garinii* in questing nymphs.

Early clinical symptoms (stage 1) of Lyme borreliosis in humans may include erythema migrans [6,12], which is an expanding skin lesion, as well as fatigue, fever, headache, mild stiff neck, muscle and joint pains [13]. If untreated, the infection can progress to early disseminated infection (stage 2, up to 6 months), involving neurological abnormalities in the

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69   case of neuroborreliosis. The most common signs of early neuroborreliosis is Lymphocytic

70   meningoradiculitis (Bannwarth's syndrome) and central nervous system (CNS)

71   manifestations, while late stage (stage 3, more than 6 months) neuroborreliosis include both

72   peripheral nervous system (PNS) and CNS manifestations [14]. Other common clinical

73   symptoms of late disseminated infections may involve arthritis in North America and

74   acrodermatitis chronica atrophicans (ACA) in Europe, and sometime also carditis [6,12].

75   Therefore, Lyme borreliosis involves a variety of clinical symptoms, and it is becoming

76   increasingly clear that the different genospecies within the *Borrelia burgdorferi* s.l. complex

77   usually cause different clinical symptoms in humans [15-21]. In Europe, coupling of the

78   clinical diagnosis and the presence of genospecies show that most late-stage dermatological

79   manifestations (ACA) were caused by *B. afzelii*, while *B. garinii* usually causes

80   neuroborreliosis [14,22]. There is still limited knowledge about the extent to which different

81   genospecies lead to disseminated disease, which may depend on both the likelihood of the

82   patient receiving antibiotic treatment at an early stage and the human immune system's ability

83   to tackle different genospecies. One study indicated that *B. afzelii* caused more localized

84   infection and was significantly less associated with disseminated infection in patients

85   compared to *B. burgdorferi* s.s. [16]. Skin infections caused by *B. afzelii* may be more readily

86   identifiable and treated in an early stage. Hence, since *B. garinii* cause qualitatively more

87   severe cases of neuroborreliosis [8], infections with *B. garinii* may become overrepresented

88   among cases of disseminated Lyme borreliosis in humans compared to their proportion in

89   infected nymphs (Fig. 1).

90   Ixodid ticks are expanding in geographical distribution in elevation and towards the north in

91   both Europe [23] and North America [24]. Lyme borreliosis is currently emerging in northern

92   Europe [25-27] as well as in Canada [28], and understanding the causes is urgent. In Norway,

93   Lyme borreliosis has a status as a 'notifiable disease', and data across the whole country for

94 the period 1995-2017 is available [26]. The data include cases of disseminated Lyme

95 borreliosis (stage 2-3), as well as cases with the specific diagnosis of Lyme neuroborreliosis.

96 We here quantify for the first time the proportion of disseminated Lyme borreliosis cases

97 being neuroborreliosis across space and time at a broad (national) spatial scale. We

98 specifically test the hypothesis (H_1) that *B. garinii* more often causes disseminated infection

99 than does *B. afzelii* by comparing the local proportion of neuroborreliosis in official Lyme

100 statistics patients to the local proportion of *B. garinii* and *B. afzelii* in questing nymphs.

101 Because neuroborreliosis in northern Europe is linked to *B. garinii* and birds [10], we

102 calculated an annual bird disease hazard as the number of *B. garinii* infected nymphs

103 produced by a given bird population the previous year. We test the hypothesis (H_2) that

104 annual variation in disseminated Lyme neuroborreliosis incidence can be predicted by annual

105 variation in bird disease hazard.

106 **2. Material and Methods**

107 **(a) Study area**

108 The Lyme borreliosis data cover the whole of Norway with a latitudinal range of 57º58'-

109 71º08'N [26,27]. Due to the favourable mild and humid climate for *I. ricinus* and its hosts, the

110 south and south-west part of the coast is an endemic area for the occurrence of Lyme

111 borreliosis in Norway [29]. A mountain range in the south separates the western coastal

112 region from the eastern inland region, with the latter having a more continental climate. The

113 temperature is colder with increasing latitude, which affects both vegetation and tick

114 distribution [30]. The Gulf Stream also warms the western coast considerably with a humid

115 climate that is favourable for ticks [31]. Further inland and towards the east, with a colder and

116 drier climate, the forest is boreonemoral or boreal with coniferous forests dominating [32].

117 There are smaller areas of (deciduous) nemoral forest requiring a warmer climate along the

118   southernmost coast, i.e., deciduous forest trees such as oak (*Quercus* spp.) requiring a warmer

119   habitat.

120   **(b) Notifiable Lyme borreliosis in humans**

121   Lyme borreliosis has been a nominally notifiable disease in Norway since 1991; but we

122   restricted data to 1995 onwards when disseminated cases was consistently reported [33]. We

123   provide a detailed account for criteria to be notified as Lyme borreliosis in the Supplementary

124   Info. The data has been used previously to study the distribution of ticks [30] and the role of

125   deer populations for Lyme borreliosis incidence [26,27]. All data in Norway included 4685

126   cases of Lyme borreliosis, of which 3254 (69 %) was Lyme neuroborreliosis. As in previous

127   analyses [26,27], we limited the data to cases for which the municipality of the tick bite was

128   confirmed (Lyme borreliosis: n = 2844, neuroborreliosis: n = 1940). There may be a time lag

129   between tick bite and disseminated infection [12], and hence, the time of registration in the

130   disease statistics may differ from the time of the tick bite. However, there were very few cases

131   reported in January-May, while numbers peaked in August-October and subsequently

132   declined [34]. Therefore, the year of disease testing is usually the same year as the tick bite.

133   **(c) Indexing Lyme neuroborreliosis hazard from birds**

134   Lyme borreliosis hazard is typically defined as the abundance of infected nymphs in a given

135   year [7]. This is a function of both the number of larvae fed and the prevalence of *B.*

136   *burgdorferi* s.l. in hosts during the previous year. The most common way to estimate the

137   contribution of a given host species or group to the disease hazard is to use the estimated

138   population size of each species/group multiplied by the mean estimated tick load [35,36]. The

139   latter is the total tick load found on infested and non-infested birds divided by the total

140   number of birds sampled. In addition, transmission competence is important for calculating

141   the number of infected nymphs [8]. We, therefore, used metrics based on population numbers

142   of birds (below), their expected average larval tick load and the average infection prevalence

143   by *B. garinii*. This is expected to predict the number of *B. garinii*-infected nymphs the

144   following year, which can be termed the neuroborreliosis disease hazard.

145   Ground-feeding birds carry the most ticks [37], but they differ in their transmission

146   competence of *B. garinii* [38]. Thrushes as a group that have been identified as the main

147   group for hosting *B. garinii* across Europe [8], with some 11 species of birds contributing

148   notably [38]. Based on current reviews from across Europe, we calculated two indices of

149   neuroborreliosis disease hazard from birds. The basis for calculating the two hazard indexes

150   below is the annual abundance of a given bird species from within Norway multiplied by the

151   mean *B. garinii* infection prevalence of ticks from that bird species based on studies from

152   across Europe [38] (ESM Table S1). These patterns of the mean *B. garinii* infection

153   prevalence from across Europe are consistent with studies on birds from the Lista Bird

154   Observatory (see below), in terms of relative tick loads [39], the estimated prevalence of *B.*

155   *burgdorferi* s.l. [40,41] and the genospecies [42].

156   *Bird hazard index 1 Thrushes*. The Blackbird (*Turdus merula*), Songthrush (*Turdus*

157   *philomelos*) and Redwing (*Turdus iliacus*) are regarded to be, by far, most important

158   contributors to the transmission of *B. garinii* [38], and their *B. garinii* infection prevalence

159   was 18.3 %, 12.0 % and 28.1 %, respectively. This hazard index is the sum of the hazard (bird

160   abundance*infection prevalence) of the three species of thrushes.

161   *Bird hazard index 2 Important birds*. In addition to the three thrushes (above), the Common

162   Chaffinch (*Fringilla coelebs*), the Great Tit (*Parus major*), the Winter Wren (*Troglodytes*

163   *troglodytes*), the Blackcap (*Sylvia atricapilla*), the European Robin (*Erithacus rubecula*), the

164   Dunnock (*Prunella modularis*), and the Tree Pipit (*Anthus trivialis*) were added to this index.

165   The Hawfinch (*Coccothraustes coccothraustes*), the Common Redstart (*Phoenicurus*

166   *phoenicurus*), and the Common Whitethroat (*Sylvia communis*) are also listed as important for

167   the transmission of *B. garinii* in Europe [43]. However, they were not sufficiently common in

168   the current sample to allow for population estimates, and they are subsequently unlikely to

169   contribute to disease hazard index with such low numbers. This is likely related to the fact

170   that the bird capture data in mist nets may not be equally representative for all birds breeding

171   in the affected regions.

172   **(d) Bird population data**

173   Data on migratory bird populations were available from Lista Bird Observatory (58°07′53″N

174   6°42′10″E). The Observatory is located at the southwestern edge of Norway. It is the first

175   point that migrant birds along the western route meet when they enter the Norwegian coast in

176   spring. It is, hence, a major immigration route to Norway, and we assumed a strong

177   correlation to the number of breeding birds in Norway [44]. Standardized bird counts and bird

178   trapping are carried out at the observatory every spring and autumn [45]. Most birds were

179   trapped in mist nets during periods of the day when a constant effort approach was applied

180   [46], in which the total net area and net positions were held constant and playback was never

181   used to increase the trapping efficiency [47]. From the 15th of March to the 10th of June each

182   year, mist nets were used on a daily basis as the weather conditions permitted. Nets were

183   opened 30 minutes prior to sunrise and closed no earlier than five hours after sunrise. We used

184   data on all the birds ringed on those dates as well as those from the nests, which we expect to

185   be a good predictor for available bird hosts covering the main tick questing season in spring

186   [31]. From 2012 onwards, a standardized 6-hour daily catching period was introduced, which

187   slightly lowered the total number of observations (see analysis for how this was accounted

188   for). The same data have been used previously for the study of bird migration phenology [48].

189   An extended index, including bird observations from March to September, was highly

190   correlated with this period (r = 0.96).

191   **(e) Other covariates**

192   We used similar spatial covariates as used in previous analyses on the Lyme borreliosis

193   incidence [26,27]. The deer population density index is based on harvest numbers of roe deer

194   (*Capreolus capreolus*), red deer (*Cervus elaphus*) and moose (*Alces alces*) divided by the size

195   of the deer habitat at the scale of municipality. At the scale of municipality, we retrieved the

196   proportion of human settlement, the proportion of agricultural areas, the proportion of habitat

197   above 200 m a.s.l. and the distance to the fjord. Due to its strong impact along the coast of

198   Norway [49], we used the North Atlantic Oscillation (NAO) as a proxy for the climate, as

199   well as the PCA-based index for December through February

200   (https://climatedataguide.ucar.edu/climate-data/hurrell-north-atlantic-oscillation-nao-index-

201   pc-based). We considered the regions in the east (Østfold, Akershus, Oslo, Hedmark, Oppland

202   and Buskerud counties), the south (Vestfold, Telemark, Aust-Agder and Vest-Agder

203   counties), and the west (Rogaland, Hordaland, Sogn and Fjordane, and Møre and Romsdal

204   counties) of Norway, because there were very few cases in northern Norway.

205   **(f) Statistical analyses**

206   We analysed all data using R x 64 v. 3.3.3 software (http://www.r-project.org/). Cases of

207   Lyme borreliosis and neuroborreliosis were modelled with negative binomial mixed effects

208   regressions using the R package lme4. To analyse the incidence, we used the human

209   population size in a given municipality as an offset variable. We excluded the 4 northernmost

210   counties due to few positive cases (<4 % of sample) and being too distant from the Lista Bird

211   Observatory. We also restricted the analysis to 204 (of 292) municipalities with at least one

212   case of Lyme borreliosis. An overview of raw data is given in ESM Table S2.

213   As a starting point for our model selection, we used an established model structure that was

214   found to fit our data well [26,27]. The parameters included were chosen based on minimizing

215   the AIC corrected for small sample sizes (AICc) but also to fit the data in terms of having no

216   spatial or temporal pattern in the residuals. We used a linear or quadratic year term to quantify

217   and remove trends. To account for remaining dependency in the nested data structure, we also

218   tested both spatial dependency (i.e., the presence of Lyme borreliosis or neuroborreliosis in a

219   neighbouring municipality the previous year) and temporal autocorrelation (incidence the

220   previous year) terms. The established model [26,27] included the region (west/east/south), the

221   NAO winter index, the spatial deer population density, proportion of human settlement,

222   proportion of agricultural areas, proportion of habitat above 200 m a.s.l. and distance to the

223   fjord. A second-order polynomial of the year was used to quantify the long-term trend in the

224   incidence data. The model also included a year interaction term with the region, to account for

225   a regional difference in the temporal trend of Lyme borreliosis cases. We then added the bird

226   hazard index to this model. The Lyme borreliosis data, land use variables and deer densities

227   were all gathered at a municipality scale. The bird data do not have a specific spatial scale, as

228   they are one value per year. In the analysis, we lag the disease hazard index by one year, as

229   questing larvae typically moult after their blood meal and overwinter before they emerge and

230   quest as nymph the year after. When we had achieved a good model, we challenged the model

231   fit by removing one variable at a time and seeing how it changed the AICc. We standardized

232   the coefficients to enable direct comparisons of the effect sizes of the different variables.

233   **(g) Literature survey**

234   We retrieved all studies of the genospecies composition of *B. burgdorferi* sl in questing

235   nymphs from across Norway (ESM Table S3). We did this by searching in ISI on "Borrelia

236   AND Norway" and by searching publication lists of the most prominent tick researchers in

237   Norway and screening for relevant publications. We conducted this survey to compare the

238   regional disease hazard in questing ticks caused by *B. garinii* relative to the proportion of

239   disseminated Lyme borreliosis that had clinical signs of neuroborreliosis (Fig. 2). For those

240   studies reporting an average that was based on several nearby locations, we plotted the pie

241   chart around the approximate middle location of the cluster of locations. For each study, we

242   retrieved the proportion of neuroborreliosis cases out of the total number of Lyme borreliosis

243   cases at a county scale for the given year. If data included more years or areas, we used the

244   average numbers. We then used a paired Wilcoxon-test to test if the proportion of *B. garinii* in

245   nymphs differed from the proportion of neuroborreliosis cases.

246   **3. Results**

247   The proportion of neuroborreliosis among the disseminated Lyme borreliosis cases varied

248   across years from 50 % to 84 % (minimum 58 % after year 2000), and between regions from

249   61 % in the south (averaged across years), over 69 % in the east to 81 % in the west. We

250   found a consistently much higher proportion (overall mean 69 %) of neuroborreliosis cases

251   among patients with disseminated borreliosis (stage 2-3) than expected from the proportion of

252   *B. garinii* in questing nymphal ticks (overall mean 21.4 %) for all regions of Norway (Fig. 2,

253   ESM Table S3, paired the Wilcoxon signed rank test, p = 0.02), i.e., we found strong support

254   for H_1 that *B. garinii* more often causes disseminated borreliosis compared to *B. afzelii*.

255   The two bird hazard indices were highly correlated (r = 0.99), they provided similar model fit

256   (AIC = 0.01) and parameter estimates, and we therefore only report results using bird disease

257   hazard index 2. The annual variation in bird disease hazard, which was calculated from the

258   expected production of *B. garinii*-infested nymphs that were produced by migratory birds

259   coming to Norway, correlated with the number of neuroborreliosis cases the following year

260   (H_2, Fig. 3, Table 1). The mean incidence per 1000 inhabitants was 0.049. The model predicts

261   an increase in incidence from 0.049 to 0.056 (0.049*exp (0.066)^2) per 1000 inhabitants if we

262   increase the bird hazard by 2 SD. The effect of bird abundance was significant, with a p-value

263   below 0.05, also when varying the model structure in terms of other covariates included. The

264   effect was quantitatively stronger when excluding data before 2000. The result was robust to

265   deleting the last five years (with a slight change in bird survey effort) or using a detrended

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266   series of annual bird hazard, but a significant effect was dependent on the inclusion of the

267   year 2007, with a peak in both cases of neuroborreliosis and bird hazard. There was also an

268   effect linked to the annual variation in the NAO climate index. The effect of annual bird

269   hazard was slightly weaker (but significant) if including all Lyme borreliosis cases and not

270   restricted to Lyme neuroborreliosis cases only (ESM Table S4).

271   The variance of the mean spatial incidence was ~7.9 times higher than the variance of the

272   mean annual incidence. Due to this, the effect size of the parameters estimated as the annual

273   variation was, in general, weaker than the effect sizes of spatial covariates for explaining the

274   incidence of neuroborreliosis (Fig. 3). As reported also earlier [26], the incidence of Lyme

275   neuroborreliosis increased spatially with the cervid population density, and it decreased with

276   the proportion of human settlement, agricultural fields, areas > 200 m a.s.l. and with

277   increasing distance from the coast. The incidence of neuroborreliosis increased over time. The

278   increase was less strong for the south region compared to the pooled west and east, but it was

279   at a diminishing rate (i.e., a significant $year^2$ term for the west and east regions pooled; Table

280   1).

281   **4. Discussion**

282   Annual estimates of Lyme borreliosis suggest some 300,000 cases in the USA and 85,000

283   cases in Europe, and yet, Lyme borreliosis is often assumed to be underreported. A recent

284   topic is the extent to which the genospecies of *B. burgdorferi* s.l. differ in pathogenicity and in

285   their ability to escape the immune system of humans [50,51] and cause disseminated infection

286   [15]. In Norway alone, in the period 2005-2009 [52], approximately 11,000 persons visited a

287   medical doctor after a tick bite, while some 7,000 received antibiotic treatment against

288   borreliosis each year. However, official statistics of disseminated Lyme borreliosis are only in

289   the range of some 400 annually in recent years. As predicted from the medical knowledge that

290 the bird-borne *B. garinii* is the main (97 %) cause of neuroborreliosis in Norway [10]; our

291 study documents a 3-fold overrepresentation of neuroborreliosis among the cases of

292 disseminated Lyme borreliosis compared to the prevalence of *B. garinii* in questing nymphal

293 ticks (Fig. 2, Table 1). This result is additional evidence that *B. garinii* more often causes

294 disseminated Lyme borreliosis than does *B. afzelii* at these northern latitudes. Hence, bird

295 populations play a more important role for severe Lyme borreliosis than was predicted from

296 the prevalence of *B. garinii* in ticks. Although current knowledge suggests that the highest

297 proportion of the infected ticks have *B. afzelii* in many places in Europe [8,9], our study

298 highlights that this hazard is not representative of the more severe disseminated infections.

299 For the period 1995-2017, 69 % of the reported cases of disseminated infections in Norway

300 was neuroborreliosis. Therefore, we would expect annual variations in cases of disseminated

301 Lyme borreliosis to be linked to fluctuations in bird population numbers, mainly that of

302 thrushes [38]. Our analysis provided some evidence that annual variations in incoming

303 migratory birds to northern latitudes affects next year's incidence of disseminated Lyme

304 borreliosis (Fig. 3), but the effect was dependent on inclusion of the year 2007, which had a

305 peak in both cases of neuroborreliosis and bird numbers (the previous year).

306 **(a) Clinical symptoms, diagnostics and treatment before dissemination**

307 As in many places of Europe [8,9], *B. afzelii* is the most common genospecies in questing

308 ticks in Norway, with estimates between ~60-80 % (ESM Table S3). *B. garinii* is typically the

309 second most common, with ~20-30 %. Hence, with 69 % of disseminated Lyme borreliosis

310 being neuroborreliosis, this is a 3-fold overrepresentation in patients compared to the mean

311 hazard of 21.4 %. The proportion of neuroborreliosis among all Lyme borreliosis cases has

312 increased slightly over time. The notification criteria has been consistent, and adequate

313 treatment have been available with only minor changes over the time period [53]. However,

314 improved ELISAs for diagnostic appeared around 2005-08 [54], and the use of spinal

puncture became a more standard way to diagnose the disease in children (age group 0-9

years) from 2015. Whether increased public attention and awareness to Lyme borreliosis play

a role for the temporal trend is less clear. We correct for temporal trend in our analysis

looking at year-to-year variation in numbers, and the proportional change in neuroborreliosis

cases over time was not sufficiently strong to markedly affect the overrepresentation relative

to genospecies found in questing ticks (Fig. 2). However, Lyme borreliosis is challenging to

diagnose due to a range of clinical manifestations and low sensitivity and specificity of

available diagnostic tests [13]. The wide variation in antigenicity among *Borrelia* genospecies

may affect the sensitivity and specificity of diagnostics [55]. If genospecies differ in the

presentation of clinical symptoms, this may in turn bias disease statistics directly or indirectly

if it leads to a differential treatment. Therefore, both different pathogenicity and the likelihood

of receiving treatment may affect the extent to which infections by different genospecies lead

to disseminated disease.

The ability of the different genospecies to cause erythema migrans (EM) may affect

the likelihood of causing systemic infection [17,56], because it affects the likelihood of

receiving treatment, as EM is readily identified as Lyme borreliosis and then treated with

antibiotics. Most neuroborreliosis patients in Norway have not had any EM (medical doctor

and neuroborreliosis expert Bjørn Barstad, pers. comm.). Similarly, in the Netherlands, the

genospecies *B. bavariensis* (formerly grouped with *B. garinii*) was found to be rare in EM

patients compared to *B. burgdorferi* s.s., which may explain the high prevalence of *B.*

bavariensis in neuroborreliosis patients despite it being a rare pathogen in questing ticks due

to the restricted reservoir linked to hedgehogs (*Erinaceus europaeus*) [15]. Hence, also *B.*

bavariensis can in areas with hedgehogs be expected to be disproportionally represented in

neuroborreliosis patients in way similar to *B. garinii*. In Norway, *B. bavariensis* has not yet

been recorded, probably due to the rarity of hedgehogs. Also in *B. burgdorferi* s.s., different

340 clinical symptoms have been found in different geographic regions in the USA due to strain

341 variation [19]. In some studies, *B. afzelii* was found in the cerebrospinal fluid, although

342 always in a much lower proportion than *B. garinii* [57-59]. This may nevertheless reflect the

343 role of strain variation within genospecies [60] and that *B. afzelii* may be more pathogenic in

344 some areas of Europe. The clinical spectrum of Lyme borreliosis in relation to genospecies

345 [21] and strains is still based on rather few studies. The European Centre for Disease

346 Prevention and Control now from 2019 include Lyme neuroborreliosis under EU

347 epidemiological surveillance, with a uniform EU case definition [61], but this will not enable

348 capturing disease burden from other genospecies.

349 **(b) Bird populations and Lyme borreliosis emergence**

350 We still have a limited understanding of the relative role of climate and the abundance of

351 different host groups on the current emergence of Lyme borreliosis. A systematic review

352 including 66 studies found that a few host species dominate the transmission of Lyme

353 borreliosis in Europe [8], with the most widespread host groups being rodents, thrushes

354 (*Turdus* spp.) and deer. Deer are important, because they are reproduction hosts to adult ticks,

355 and high deer population densities have been associated with increased tick abundance

356 [62,63]. For Norway, we have previously shown a link between the deer density and increased

357 Lyme borreliosis incidence [26]. Rodents and thrushes have a dual role, being both important

358 larval tick hosts and reservoirs for pathogens. The bird hazard was calculated as a mean

359 annual variable and had a weak, but significant impact on incidence. The spatial scale of

360 ecological processes can be important for estimation processes. A weakness of our study is

361 the lack of spatially explicit information on bird numbers. The bird hazard was calculated as a

362 mean annual variable and had a weak, but significant impact on incidence. In our case, the

363 variance in the spatial incidence of Lyme neuroborreliosis was ~7.9 times higher than the

364 variance of the mean annual incidence, which may explain the weaker effect sizes of both the

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365 NAO and the annual bird variation. The increased spatial resolution of bird numbers is

366 currently unavailable, but it may be important for assessing the relative importance compared

367 to other host groups, such as deer density.

368 Identifying the role of specific vertebrate host groups is critical for disease risk

369 assessment and management [15]. We found quantitative evidence for the role of annual

370 variation in bird numbers linked to the annual variation in neuroborreliosis cases. Most

371 markedly, we found a huge overrepresentation of Lyme neuroborreliosis cases among

372 disseminated Lyme borreliosis patients in Norway relative to the predicted hazard from *B.*

373 *garinii* in questing ticks. To further improve our understanding of the complex epidemiology

374 of Lyme borreliosis, we not only need a better understanding of how disease hazard depends

375 on the genospecies but also how human immune responses and the likelihood of getting

376 treatment contribute to the incidence of reported cases of disseminated Lyme borreliosis.

377 **Ethics**

378 This paper only contain data from databases gathered for other purposes.

379 **Data accessibility**

380 The data is available in Dryad.

381 https://datadryad.org/review?doi=doi:10.5061/dryad.114dg70
382 .

383 **Authors' contributions**

384 A.M. initiated the study. A.M., D.J.A.H. and E.M. developed the bird hazard index and

385 discussed initial design. A.M. did the literature survey and made Fig. 1 and 2. H.V. did the

386 statistical analyses and made Fig. 3. A.L.G provided bird data and knowhow. S.J. provided

387 the Lyme borreliosis data and knowhow on neuroborreliosis and diagnostic developments.

388 A.M. drafted the manuscript with notable input from D.J.A.H., E.M., S.J. and H.V. All

389 authors edited and approved the final manuscript.

Competing interests

Authors declare that they have no competing interests.

Footnotes

Electronic supplementary material is available online at ****.

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621

622   **Table 1.** Parameter estimates for analysis (GLMM with negative binomial family) of the

623   number of cases of neuroborreliosis in Norway from 1995-2017. Population size was included

624   as an offset variable. Random effect variances of 204 municipalities nested in 14 counties

625   were 0.15 and 0.09, respectively. Variables were scaled to mean 0 and variance 1. Sqrt =

626   square root. NAO=North Atlantic Oscillation index. DJF-December, January and February.

Parameter	Estimate	SE	Z	P	ΔAICc
Intercept	-10.273	0.178	-57.83	< 0.001	
Log (spatial deer density + 0.1)	0.351	0.063	5.60	< 0.001	26.9
Bird *B. garinii* hazard (lag 1 yr)	0.066	0.028	2.38	0.018	3.6
Region (South vs. other)	0.099	0.252	0.39	0.695	40.6
Region (East vs. other)	-1.177	0.270	-4.36	< 0.001	11.9
year	0.460	0.044	10.36	< 0.001	126.1
I (year^2)	-0.240	0.043	-5.57	< 0.001	29.6
Sqrt (distance to coast)	-0.387	0.093	-4.15	< 0.001	15.1
Sqrt (prop. human settlement)	-0.533	0.060	-8.85	< 0.001	58.0
Sqrt (agricultural area)	-0.308	0.073	-4.24	< 0.001	15.6
area > 200 m a.s.l.	-0.314	0.086	-3.66	< 0.001	11.0
spatial dependency (lag 1 yr)	0.133	0.071	1.87	0.062	1.5
NAO – DJF (lag 1 yr)	0.107	0.026	4.12	< 0.001	15.4
year:Region (South vs. other)	-0.339	0.056	-6.03	< 0.001	41.6
I (year^2):Region (South vs. other)	0.267	0.059	4.55	< 0.001	18.8

627

Figure captions

Figure 1. A conceptual overview linking the different genospecies of *B. burgdorferi* s.l. to the most common clinical manifestations. This may potentially affect reporting on Lyme borreliosis statistics relying on disseminated infection. While *B. afzelii* is the most common pathogen due to a small mammal reservoir, it is a pathogen less likely to yield disseminated infection than *B. garinii*.

Figure 2. Lyme disease incidence per 100000 inhabitants at the scale of municipality across the whole of Norway. (A) The cases of neuroborreliosis relative to other diagnosis (summed at county scale) among the cases of disseminated infection in humans. (B) The proportion of *B. garinii* in questing nymphs (from ESM table S3). Note the higher proportion of neuroborreliosis in humans than proportion of *B. garinii* in questing nymphs.

Figure 3. The effect sizes of different covariates explaining spatial and temporal variation in the incidence of neuroborreliosis. Bird species are the number of migratory birds incoming to southern Norway and are restricted to those species known to infect larval ticks with *B. garinii*. The bird numbers were lagged one year relative to the disease cases, as engorged larvae on birds are expected to become a hazard to humans as questing nymphs the year after their first feeding. The incidence rate ratio (given by the exp(estimate) in Table 1) is the factor by which the incidence is changing by an increase of 1 SD (variables are standardized) in the respective variable, while the other variables are kept unchanged.

Disease stage/symptoms

Host → Pathogen → Stage 1 → Stage 2-3

→ *B. afzelii* ➡ EM → dermatities (ACA) →

→ *B. burgdorferi* ss → EM → arthrities →

→ *B. garinii* ➡ EM → neuroborreliosis ➡

Abundance in nymphs

Abundance in statistics

Disease statistics

A. Neuroborreliosis in humans

140

Neuroborreliosis

Other

Lyme disease incidence

0

0 - 0.05

0.05 - 0.10

0.10 - 0.25

0.25 - 0.40

N

0　80　160　　　320 Kilometers

B. Genospecies in questing ticks

44

- B. afzelii
- B. valaisiania
- B. burgdorferi ss
- B. garinii

Lyme disease incidence

- 0
- 0 - 0.05
- 0.05 - 0.10
- 0.10 - 0.25
- 0.25 - 0.40

0°0'0"
10°0'0"E
20°0'0"E
30°0'0"E

70°0'0"N
65°0'0"N
60°0'0"N

N

0   80   160   320 Kilometers