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# Spatial distribution patterns of *Echinococcus multilocularis* (Leuckart 1863) (Cestoda: Cyclophyllidea: Taeniidae) among red foxes in an endemic focus in Brandenburg, Germany

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## SUMMARY

Over a period of 40 months, 4374 foxes were randomly sampled from an area located in northwestern Brandenburg, Germany, and examined parasitologically for infections with *Echinococcus multilocularis*. Spatial analysis of the origin of infected animals identified two (one central and one southeastern) high-endemic foci with an estimated prevalence of 23·8%. By contrast, a prevalence of 4·9% was found in the remaining (low-endemic) area. The prevalences among juvenile and adult foxes were compared in the high-endemic and the low-endemic areas. To analyse the central high-endemic focus further, the random sample was stratified by zones representing concentric circles with a radius of 13 km (zone 1) or $x_{n-1}+7$ km for the remaining three zones from the apparent centre of this focus (anchor point). Prevalences calculated for each zone showed a decrease from zone 1 (18·8%) to zone 4 (2·4%) with significant differences for all zones but zones 3 and 4. The relative risk of an infection decreased rapidly in a distance range of 26 km around the high-endemic focus, whereas the relative risk remained unchanged within a distance of 5 km around the anchor point. The importance of heterogeneous spatial distribution patterns for the diagnosis and epidemiology of the infection is discussed.

## INTRODUCTION

Alveolar echinococcosis (AE), caused by the larval stage of *Echinococcus multilocularis*, is considered as the most dangerous autochthonous parasitic zoonosis in Central Europe [1]. The presence of the parasite is limited to the northern hemisphere; the most southern country where the parasite has been detected is Tunisia [2, 3]. In recent years, our knowledge about the distribution of *E. multilocularis* in Europe has changed completely. In nearly all regions of Germany, in Switzerland, Austria, Liechtenstein and France infected foxes were detected, though with great differences in prevalences [4–19]. Recently, infections in foxes were also reported from Poland, the Czech Republic and Belgium [20–22].

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The obligate two-host parasitic cycle of *E. multilocularis* is predominantly silvatic. In the carnivorous definitive hosts the adult worms parasitize the posterior small intestine. In Europe, the red fox represents the main definitive host. Different species of rodents are involved in the parasitic cycle as intermediate hosts. They get infected by oral uptake of oncospheres ('eggs'), which definitive hosts start to shed with their faeces after a prepatent period of nearly 4 weeks. Humans are believed to possess only limited susceptibility for *E. multilocularis* and represent rare intermediate hosts, at least in Central Europe (annual incidence less than 1/100000 inhabitants) [16]. The precise sources of human infections are unknown. Vegetables or contact with infected definitive hosts are suspected as risk factors. In the countryside in central European regions, suburban human populations and

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especially farm workers seem to be at higher risk [23–25]. In areas hyperendemic for AE (Alaska, northern Siberia and central China), annual incidences of up to 98–170/100000 inhabitants were reported and often dogs were involved in the parasitic cycle [2]. Whether a correlation exists between the frequency of the parasite within the fox population and the human risk of infection is unclear [25].

Current knowledge about the epidemiology of the parasitic cycle is limited. Especially, the spatial distribution patterns of the parasite and their changes in time and space are unknown, though of great importance for the description of areas with an infection risk for humans, for prognostic purposes and for a better estimation of regional prevalences.

In the study presented the spatial distribution pattern among red foxes was monitored over a period of 4 years in an area where *E. multilocularis* was first detected in 1991 [26, 27]. Until then, the regional presence of this helminth was unknown, perhaps due to a lack of investigations with suitable diagnostic methods.

## MATERIALS AND METHODS

### Study area and sampling

Between January 1992 and April 1995, 4374 foxes were randomly sampled from two predominantly rural counties in the Northwest of the Federal State of Brandenburg (Germany). The study area is situated between 11·5–13·0° N and 52·5–53·5° E and covers approximately 4450 km$^2$.

The territories of the municipalities were used as the regional grid in which the foxes examined in this study (hunted or killed by accidents) were localized. Prior to autopsy, foxes were collected on a weekly basis, first stored at −20 °C and then deep-frozen for 1 week at −80 °C to decrease the infection risk for the laboratory personnel. In the partial parasitological dissection the whole intestine was removed. The age of each fox was determined – whenever exactly possible – as adult (born in a previous year) or juvenile (born in the current year) according to Wagenknecht [28]. The isolated intestine was stored at −80 °C for another week followed by parasitological detection of adults of *E. multilocularis* according to the WHO standard method [29]. In brief, smears of intestinal mucosa from at least one-third of the entire surface of the small intestine were investigated microscopically (enlargement between ×8 and 40). *E. multilocularis* was identified according to the size of the whole adult cestode (in rare cases only typical proglottids with oncospheres inside) and the relative size of the last proglottid as compared to the whole worm.

### Computing

A programme written in CLIPPER (Computer Associates International Inc., New York, USA), was used for the documentation of the data in a DBASE (5.0 for WINDOWS, Borland International Inc., Scotts Valley, CA, USA) file. EPI-INFO 6.0 (CDC, Atlanta, Georgia, USA, and World Health Organization, Geneva, Switzerland), STATISTICA for Windows (StatSoft, Inc., Tulsa, OK, USA), Harvard Graphics 3.0 (Software Publishing Corporation, Santa Clara, CA, USA), Regio-Graph 2.0 (MACON, GmbH, Waghäusel, Germany) and ArcView (ESRI, Redlands, USA) were used for statistical analysis, geographical and graphic documentation of the results. 95% confidence intervals (CI) were calculated according to Willer [30]. Differences in prevalences were compared by the $\chi^2$ test and, when appropriate, according to Cochran [31]. To analyse the spatial changes in the infection risk for foxes, density estimations according to Silverman [32] were carried out, applying the uniform distribution as the kernel function for the simulation of the home range of foxes. The average diameter of the home range was assumed to be 5 km.

## RESULTS

Over a period of 40 months, a total of 4374 foxes were randomly sampled and examined for intestinal infections with *E. multilocularis*. To analyse the geographical distribution patterns of the parasite in the fox population within the study area, the localization of each fox was plotted on a map (Fig. 1; large dots for infected, small dots for uninfected foxes). The municipality where a fox originated from was assumed as its home range. Therefore, the precise positions of the dots within the territory of that municipality were chosen randomly. Obviously positive foxes concentrated in a central and a southeastern region of the study area, despite heterogenous investigation densities. On the background of this result, an estimation of the prevalence of *E. multilocularis* in the whole random sample is inconclusive, especially because the random sample is not homogeneously distributed within the area and confounding effects are possible. Therefore, the random sample

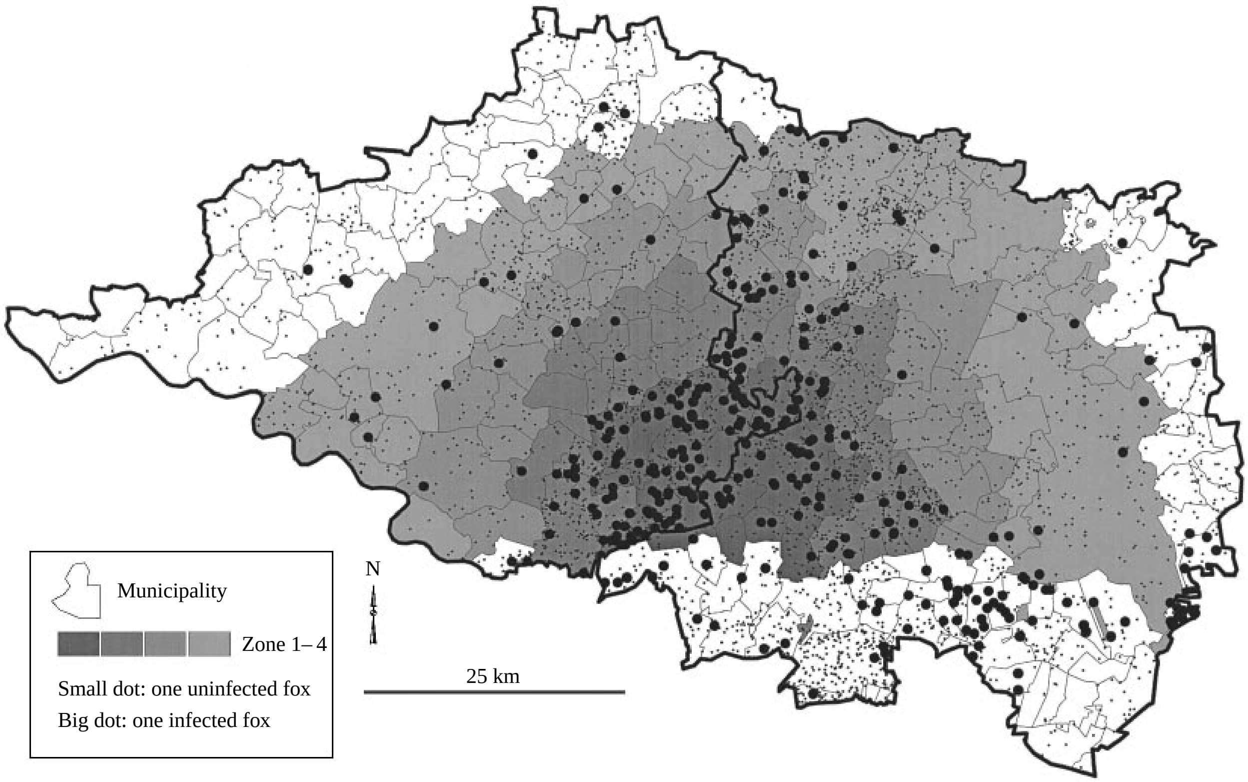


**Fig. 1.** Parasitological investigations for *E. multolocularis* among red foxes in two counties in the Northwest of the Federal State of Brandenburg. The origin of each examined fox is plotted on a map of the study area. Foxes found infected with *E. multilocularis* are represented by large dots, uninfected animals by small dots. The attribution of the municipalities to prevalence zones (see Table 2) is shown by the shading.

was stratified by distinguishing foxes from high-endemic and foxes from low-endemic municipalities. To this end, the prevalence was estimated for each municipality. By summarizing municipalities with higher prevalences and considering their respective neighbourhood, two endemic foci were identified, a central and a southeastern focus. All municipalities within these foci were regarded as high-endemic, whereas the remaining municipalities were considered as low-endemic. In the territory of the two high-endemic foci, *E. multilocularis* was detected in 183 out of 768 foxes investigated. The estimated prevalence in this area was 23·8% (20·9% $< P <$ 27·9%). By contrast, only 178 out of 3606 foxes investigated in the low-endemic region were positive. This corresponds to an estimated prevalence of 4·9% (4·2% $< P <$ 5·9%). The prevalence differences between the high-endemic and the low-endemic region were statistically significant by the $\chi^2$ test (Fig. 2, Table 1).

The influence of age on the prevalence was analysed with respect to the different epidemiological situations in the high-endemic and the low-endemic regions (Fig. 2, Table 1). This analysis had to be carried out only at a time of the year when nearly the same exposure of juvenile and adult foxes to the parasite could be expected. With regard to the biological development of the population, it is important to note that cubs are able to act as predators in the study area from June onwards. Before this time of the year, the food of cubs and juvenile foxes is quite different from that of adult foxes resulting in a lower exposure of juvenile animals to the parasite. On the other hand, a precise differentiation between adult and juvenile foxes becomes increasingly difficult and finally impossible from October onwards [33, 34]. Therefore, the influence of the age of the foxes on the prevalence was tested between July and September. In this analysis, the random sample was also stratified by the regional endemic situation. Under high-endemic conditions, juveniles were found more frequently infected than adults. This effect is statistically significant (Table 1); 46 out of 135 juvenile foxes investigated during this period were positive for *E. multilocularis*, resulting in an estimated prevalence of 34·1% (26·2% $<$ $P <$ 43·7%) among juvenile animals. By contrast, only 28 out of 150 adult foxes were positive, resulting

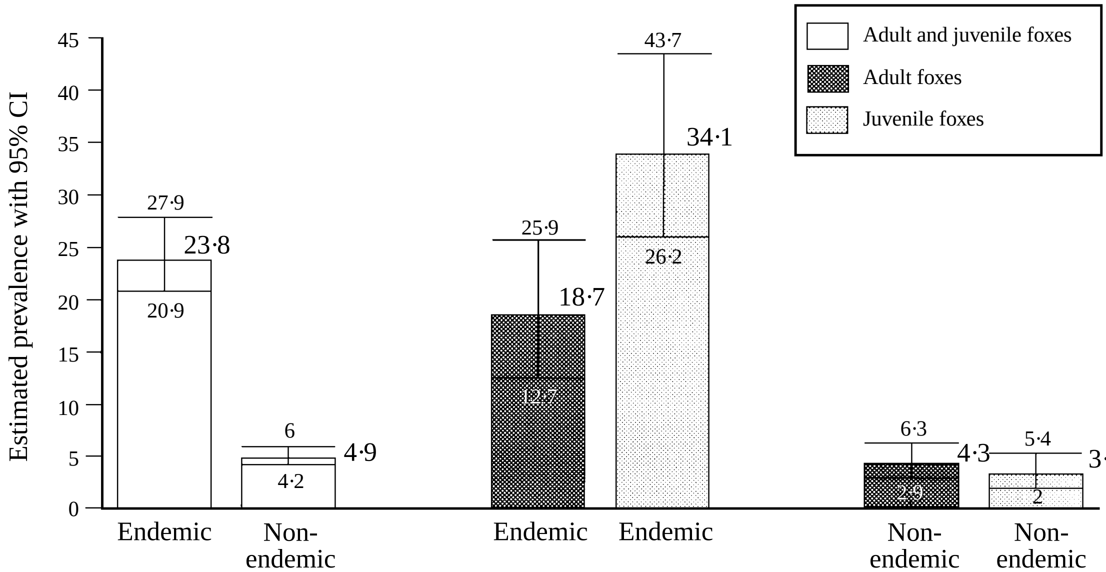


**Fig. 2.** Prevalence of *E. multilocularis* in random samples stratified by region and age. Estimated prevalences (bars) and 95% confidence intervals are shown for the endemic and the non-endemic region as well as juvenile (light grey bars), adult (dark grey bars) and all (white bars) foxes.

Table 1. *Influence of the factors 'endemic status of the municipality' and 'age' on the prevalence of* E. multilocularis *in red foxes and comparison of the age structure of infected foxes in the endemic and non-endemic areas*

| Variables | Selection | Exposure | Outcome | $n$ | $\chi^2$ | $P$ value | Odds ratio | Relative risk | Cochran | $P$ value |
|---|---|---|---|---|---|---|---|---|---|---|
| Area vs. E.m. | All data records | Endemic > non-endemic area | Positive/ negative | 4374 | 298·43 | < 0·001 | 6·02 (4·78–7·59) | 4·83 (3·99–5·84) | — | — |
| Age vs. E.m. | Endemic area | Juvenile > adult | Positive/ negative | 285 | 8·77 | < 0·001 | 2·25 (1·26–4·02) | 1·83 (1·21–2·75) | 2·938 | 0·002 |
| Age vs. E.m. | Non-endemic area | Adult > juvenile | Positive/ negative | 1100 | 0·59 | > 0·05 | — | — | 0·879 | 0·189 |

in an estimated prevalence of 18·7% (12·7% < $P$ < 25·9%) among adult animals (Fig. 2).

Under low-endemic conditions, adult foxes tended to be more frequently infected than juveniles (Fig. 2, Table 1). In 26 out of 602 adult foxes investigated in the low-endemic area the parasite was detected corresponding to an estimated prevalence of 4·3% (2·9% < $P$ < 6·3%), whereas 17 out of 498 juvenile foxes were positive in this region, resulting in an estimated prevalence of only 3·4% (2·0% < $P$ < 5·4%) among juvenile foxes in the low-endemic region. In this area, however, the difference in prevalence between adult and juvenile foxes was not statistically significant. The age structure in the whole random sample was not different between the high-endemic and low-endemic area.

For a detailed analysis of the spatial distribution patterns, the investigation area was further differentiated into four zones defined according to their distance from a virtual centre point located in the central high-endemic focus of the study area. For this analysis, the study area was limited in the South to the southern border of the central high-endemic focus (Fig. 1), i.e. municipalities south of this border line were excluded. An anchor point was marked in the apparent centre of the central high-endemic area. From this point a circle was described with a radius of 13 km. All municipalities situated with more than 50% of their area within a circle of 13 km (radius) around the anchor point were included in zone 1 (Fig. 1). The following three concentric circles have a radius of $x_{n-1}+7$ km around the anchor point of zone 1, and

Table 2. *Prevalences of* E. multilocularis *in red foxes from the different zones*

| Zone | External limit (radius in km) | Area ($km^2$) | No. of foxes | Lower CI | Prevalence | Upper CI |
|---|---|---|---|---|---|---|
| Zone 1 | 13 | 393·7 | 778 | 16·4 | 18·8 | 22·2 |
| Zone 2 | 20 | 529·9 | 834 | 6·3 | 8 | 9·9 |
| Zone 3 | 27 | 678·5 | 577 | 2·9 | 4·5 | 6·6 |
| Zone 4 | 34 | 1318·5 | 889 | 2·4 | 3·5 | 4·9 |
| Total | 34 | 2920·6 | 3078 | 7·8 | 8·8 | 9·8 |

Table 3. *Statistical examination of the prevalences of* E. multilocularis *in red foxes in the different zones*

| Exposure | $\chi^2$ | *P* value | Odds ratio | Relative risk |
|---|---|---|---|---|
| Zone 1 > zone 2 | 40·43 | < 0·001 | 2·64 (1·92–3·64) | 2·34 (1·78–3·07) |
| Zone 1 > zone 3 | 60·79 | < 0·001 | 4·9 (3·12–7·73) | 4·16 (2·78–6·23) |
| Zone 1 > zone 4 | 102·6 | < 0·001 | 6·39 (4·21–9·75) | 5·38 (3·7–7·83) |
| Zone 2 > zone 3 | 6·89 | < 0·01 | 1·85 (1·14–3·03) | 1·78 (1·15–2·77) |
| Zone 2 > zone 4 | 16·58 | < 0·001 | 2·42 (1·53–3·83) | 2·3 (1·52–3·49) |
| Zone 3 > zone 4 | 0·97 | > 0·05 | — | — |

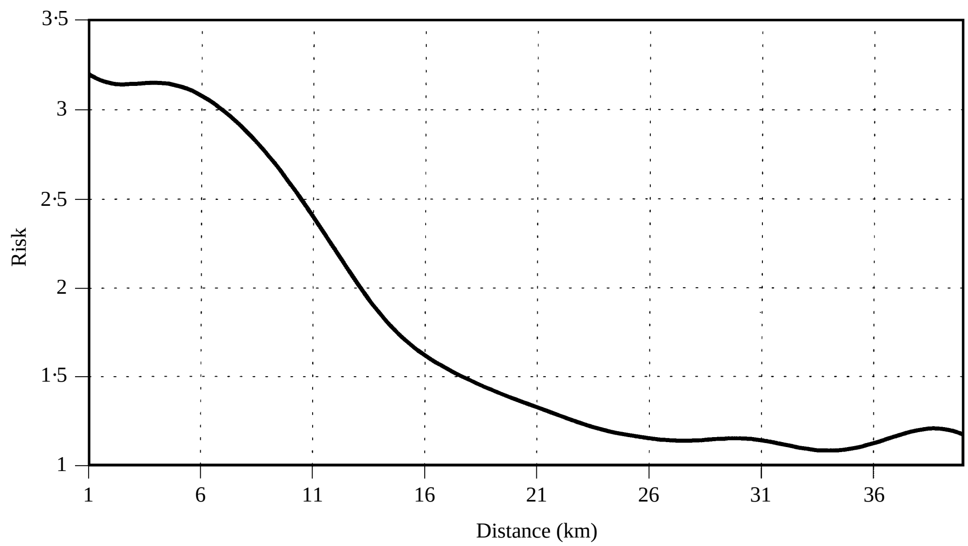


**Fig. 3.** Risk of infection as a function of distance from the endemic focus. The relative risk of infection with *E. multilocularis* was plotted against the distance from the endemic focus.

the respective municipalities were included in zones 2, 3 or 4 (Fig. 1). The random sample was stratified by the four zones and the respective prevalences of the zones were statistically analysed (Table 2). As there were no differences in the age structure in the various zones, it was not necessary to stratify the random sample for this potential influence. A distinct decrease of the estimated prevalence from zone 1 (18·8%) to zone 4 (3·5%) was observed (Table 2). The prevalence differences for all zones except for zones 3 and 4 were statistically significant by the $\chi^2$ test (Table 3).

Hypothetically, the prevalence differences detected between different radial zones could be due to deteriorating environmental conditions for the parasite, resulting for instance in a decreased number of live oncospheres taken up by intermediate hosts. To test this hypothesis, the infection risk in any distance from the anchor point within the high-endemic focus was calculated relative to the general risk of infection of any definitive host living in the study area [35, 36]. The resulting relative risk decreased rapidly in a distance range of 26 km (Fig. 3). Moreover, within a

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distance of 5 km around the anchor point the relative risk remains unchanged, thus providing further evidence for the existence of the suspected central high-endemic focus.

## DISCUSSION

This study shows the existence of a distinct high-endemic focus for *E. multilocularis* in the Northwest of Brandenburg which has been present within the same boundaries at least since 1992. The small size of the focus may indicate the presence of factors limiting the parasitic cycle outside the focus. Heterogeneous spatial distribution patterns of *E. multilocularis* were observed by several investigators [13, 37, 38]. Recently, a study conducted in Switzerland detected a hyperendemic area with high prevalences in both definitive and intermediate hosts suggesting that *E. multilocularis* may be encountered in wild-ranging intermediate hosts in the form of at least focal hyperendemicity [39]. Our results indicate that this may also be true for definitive hosts. Thus, heterogeneous spatial distribution patterns appear to be a particular epidemiological feature of the parasite. This notion is of great importance for the design of studies aiming at the estimation of an *E. multilocularis* prevalence. A prevalence estimation in a given regional grid requires a homogeneous distribution of the infection within the grid. For *E. multilocularis* this seems only to be true for small areas, at least in those regions which are not high endemic. This implies that prevalence estimations in suspected low or moderate endemic regions should be carried out in regional units of a maximal area of 500 $km^2$ with a sufficient investigation density. Prevalence reported from studies with larger regional units should be interpreted carefully, particularly because random samples of foxes cannot be assumed to be homogenously distributed in the study area and data concerning the precise origin of individual foxes are often not available.

Due to the strictly local association of postulated limiting influences on the parasitic cycle, microclimate and habitat can be suspected as potential influencing factors. Environmental conditions seem to be of the utmost importance for the survival of the oncospheres and may thus represent key factors for the parasitic cycle and the distribution patterns of the infection [15, 23, 40, 41]. Elevated temperatures and desiccation are known limiting factors for the infectivity of the oncospheres [42]. Geological and climatic factors as well as vegetation types have been proposed as important influences on the persistence of the parasite and its distribution in France [23, 43, 44].

The study area we report on is an intensively land-used area lacking hills or major rises. No infected foxes were found in areas with sandy soils or obviously dry habitats. In addition, large forests which are also represented in the study area appear to be unfavourable for the parasitic cycle of *E. multilocularis*. We believe that in the intensively land-used area microclimatic factors (e.g. low soil humidity) restrict the parasitic cycle, whereas in the forest regions host-associated influences (e.g. population densities of intermediate and/or definitive hosts, predator behaviour of foxes) may limit the infection. Delattre and colleagues observed a correlation of microtine rodent indices with land-use variables in France [45]. Due to the lack of infected foxes in forest areas, the exposure of humans to *E. multilocularis* through contaminated berries or mushrooms from the forest, as frequently discussed, is unlikely, at least in the region studied here.

The prevalences in the study area did not change significantly during the investigation period, although the fox population density increased sharply in the same interval, maybe due to rabies control which has been carried out since 1991 and a decreased hunting pressure in the years 1990–3 caused by the political changes in eastern Germany [46]. The lack of major prevalence fluctuations indicates the low influence of fox population densities on the prevalence of *E. multilocularis* in the investigation area.

The influence of age on the prevalence of the infection with *E. multilocularis* among foxes is controversial. Some authors found infections more often in juveniles than in adults [10], others could not detect statistically significant differences [13, 34, 37, 47]. The results of our study suggest that the relationship between the age of the fox and an infection with *E. multilocularis* depends on temporal and regional epidemiological factors. As long as the cubs are not weaned, they are less exposed to the parasite, resulting in the lower prevalence as compared with adults. In our study, the earliest infection of cubs was detected around 20 May every year. This finding is in accord with the results of Schott & Müller [34], who found first infections in approximately 6-week-old cubs. In the following weeks the prevalences in young foxes increased steadily in our study area (data not shown). Later in the year, the influence of other, regional endemic factors prevailed. Under high-endemic conditions, between July and September the prevalences among young foxes (born in the same year) were significantly higher than in adult foxes. This phenomenon can be caused by differences in exposure or susceptibility. According to Witt [48], the proportion of rodents in the food of young foxes is decreased in June/July, when the animals become less dependent on adults. This also implies a lower exposure of young foxes to *E. multilocularis* as compared to adults. From August onwards, the diet of young foxes is similar to that of the adults. Taken together, these findings suggest that young foxes are more susceptible to infection and that adult foxes may acquire a partial immunity to the parasite under high-endemic conditions. An intestinal immunity to related parasites such as *E. granulosus* and to *Taenia hydatigena* has been suggested [3, 49].

Interestingly, more adult foxes tended to be infected under low-endemic conditions during the same period of time. This finding also supports the notion of a surprisingly limited spatial migration of foxes outside the high-endemic focus. If the animals did migrate further, more infected juvenile foxes would have to be expected in the low-endemic area around the focus because of the temporarily higher spatial migration rate of the young animals as compared with adults. Also, the fact that more adult foxes tended to be infected under low-endemic conditions does not contradict the concept of partial immunity, because immunity may restrict *E. multilocularis* infections only under high-endemic conditions due to lack of sufficient contact with the parasite under low-endemic conditions. The time of exposure may also limit the parasitic cycle under low-endemic conditions, i.e. often foxes may have grown up before they had contact with *E. multilocularis*. The possibility that the age-structure of the random sample of foxes influences the estimated prevalence under high-endemic conditions has also to be considered in prevalence studies. Due to the potential confounding effect of different age structures, a prevalence estimation may only be valid in age-stratified random samples, as shown above. This if particular importance when different age structures are considered in different regions.

Heterogeneous, though at least under low-endemic conditions temporally constant, spatial distribution patterns of foxes infected with *E. multilocularis* may also be regarded as an alternative to the hypothesis of a possible spread of the parasite across Europe during the past decade. A spread of *E. multilocularis* over long distances would be predominantly associated with the spatial migration of foxes out of endemic areas. The import of the parasite by moving foxes to a different region as supposedly practised by hunters in the USA [50, 51] is in Europe extremely unlikely. The spread by infected dogs and cats does most probably not play a role due to the extremely low prevalence of the parasite in these populations [52, 53] and the limited spatial migration of these animals. Rodents appear to play a role in the spread of the infection only over small distances. Therefore, the description of the spatial distribution pattern of infected foxes, especially in newly recognized endemic regions, and their changes with time are of special interest. Our findings indicate a limited spatial migration of foxes in the study area. Although data reported from different areas vary grossly, most foxes seem to migrate less than 5–10 km, with males walking further than females [54]. Only few individuals migrate over 50–70 km [55].

The question whether the parasite has spread is of particular importance in view of the zoonotic character of the infection: if transmission of the parasite to hitherto non-endemic areas has taken place, an exposure of the human population in these region must be assumed. The present lack of human cases of AE outside the traditional endemic areas could be explained by the long incubation period (5–15 years) of the infection in humans. Other possible explanations for regional discrepancies between the detection of infection foxes and the lack of clinical cases of human AE are (i) little contact to the infection sources, (ii) the occurrence of less pathogenic or nonpathogenic strains of *E. multilocularis* or (iii) a lower susceptibility for the infection or the disease in the regional human population [14, 23, 56, 57]. This view is supported by the fact that even in hyper-endemic regions (as judged by the local fox population) human cases of AE can be rare [39]. By contrast to the situation in Alaska [2], infected dogs and cats most probably do not influence the human AE prevalence since the prevalence of the parasite in these animals is extremely low in Europe, even in areas high endemic for *E. multilocularis* infections in foxes [52, 53].

Due to the lack of human AE cases, it is at present unclear whether the high-endemic focus describes in this publication should be considered as a risk area for human infections. The prevalences in this focus are at a level comparable with that documented for the Swabian Alb between 1970 and 1980. During this period, many humans undoubtedly contracted AE in the latter region. Nevertheless, the particular epidemiological situation of the focus initiated a project investigating the possibility to control the parasite by treating foxes with baits containing praziquantel, based on the experiences of Schelling [58].


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