THE PRESENT SITUATION OF ALVEOLAR AND CYSTIC ECHINOCOCCOSIS IN EUROPE

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INTRODUCTION

In Europe, parasitic zoonoses are usually not of major public health importance. This is caused by a combination of temperate climate and favorable economic conditions which, in turn, enable high standards of medical and veterinary infrastructure. Exceptions are vector-transmitted zoonoses (*eg* tick-borne diseases) and parasitoses with a wildlife reservoir, which are both difficult to control. Therefore, alveolar echinococcosis (AE), despite moderate numbers of patients, is a major health issue in central Europe. In contrast, the livestock-associated cystic echinococcosis (CE) has decreased in importance over most of Europe, but persists *eg*, in the Mediterranean region under conditions of extensive sheep farming.

ALVEOLAR ECHINOCOCCOSIS

The typical transmission pattern of *Echinococcus multilocularis* in Europe involves red foxes (*Vulpes vulpes*) as final hosts, and arvicolid rodents (especially the common vole *Microtus arvalis*, the water vole *Arvicola terrestris,* and the muskrat *Ondatra zibethicus*) as intermediate hosts. Most of the parasite's biomass is estimated to be present in this wildlife cycle (Eckert, 1996). Dogs and cats appear to be of secondary importance for the parasite's propagation, but may still play an important role in transmission to humans. Dogs are known to be suitable hosts, and the low infection rate reported from Europe is clearly due to low exposition; dogs with high-risk behavior are frequently infected (Deplazes *et al*, 1999). The suitability of cats as final hosts has been long debated. While the number of worms and the number of eggs per worm are usually low, some cats show high infection intensities (Thompson and Eckert, 1983; Jenkins and Romig, 2000). Published low prevalence rates in cats are difficult to interpret because of the type of cat-keeping (pets, farm cats, etc) and, therefore, the infection risk is usually unknown. Other wildlife species are numerically of no importance as final hosts in Europe: the raccoon dog (*Nyctereutes procyonoides*), an accidentally introduced caniid from East Asia was recently confirmed as a natural host of *E. multilocularis* in Germany. The wolf (*Canis lupus*), lynx (*Lynx* spp) and wild cat (*Felis sylvestris*) are very rare, while jackals (*Canis aureus*) could be of regional importance in southeastern Europe, but data from that area are not available. The first European record of the arctic fox (*Alopex lagopus*) as a host of *E. multilocularis* in Europe came recently from the arctic islands of Svalbard where an introduced vole, *Microtus rossiaemeridionalis*, acts as an intermediate host (Henttonen *et al*, 2001).

Almost all data describing the epidemiological situation of alveolar echinococcosis (AE) in Europe are derived from animal hosts. Human incidence data are difficult to evaluate for various reasons. The generally low prevalence level, which is typical for regions where *E. multilocularis* predominantly affects wild animals, makes it difficult to recognize temporal developments and differences in spatial distribution. The long asymptomatic period of AE (which is likely to vary between patients) makes any estimation of time and place of infection very uncertain. Lastly, differential diagnosis from cystic echinococcosis is often not achieved or unreliable, especially with retrospective data (Eckert *et al*, 2001; Pawlowski *et al*, 2001). Prevalence estimates for human AE in highly endemic areas of central Europe ranged between 2 and 40 per 100,000 (Romig *et al*, 1999a; Eckert *et al*, 2001). The highest published value was reported from eastern France, with 152 / 100,000, although this study included cases of inactive AE and concentrated on farmers, a putative risk group (Bresson-Hadni *et al*, 1994). Obtaining data on epidemiologically important routes of infection is hampered by the low number of patients available for analysis. However, in a recent review of 210 AE cases from central Europe, 61.4% of patients were engaged in professional or part-time farming, gardening, or other outdoor activities, while 70.5% owned dogs or cats (Kern *et al*, 2003).

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By the end of the 1980s, the European range of *E. multilocularis* was thought to be restricted to central and western France, southern Germany, northern Switzerland, and western Austria, with a few old human records outside this range. The range limits were largely determined by the historical occurrence of human cases. Only one decade later, numerous studies on animal hosts, mainly foxes, have drastically increased this range (Romig, 2002) (Fig 1). Transmission seems to be most intense in the northern pre-alpine regions, the French, Swiss and German Jura mountains and the mountainous areas stretching from southern Belgium to central Germany; there, prevalence rates are often above 50% and approach 100% locally. Recent data suggest that this highly endemic area further continues into the eastern parts of the Slovak Republic. In contrast, prevalence rates are usually <5% in the area north of this region (the Netherlands, northern and eastern Germany, Denmark, Poland). No positive records of *E. multilocularis* exist from the Iberian peninsula, Finland, Sweden, the Norwegian mainland, and the British Isles. No reliable or recent data are available from a large part of France and from the regions east of Poland and the Slovak Republic, although the presence of the parasite in these areas is strongly suspected. Recently, *E. multilocularis* was found in foxes from the northern part of Hungary, and from northern Italy (Manfredi *et al*, 2002; Sreter *et al*, 2003). Whether the increased range of *E. multilocularis* as recognized today does constitute a real expansion, or is an artifact due to the intensified search for the parasite, remains open to debate. Focussed surveys for *E. multilocularis* in animal hosts before 1990 were confined to the region known to be endemic, while in almost all 'new' areas the first surveys already resulted in positive records. Therefore, hardly any negative baseline data exist, and discussions about possible changes of the parasite's geographical range have to remain speculative. In areas where the parasite is found today in prevalence rates of 5% or less (*eg* from northern Germany to western Poland), its previous presence may have gone unnoticed, and the absence of human cases may be due to low infection pressure. In areas recognized today as highly endemic (*eg* parts of Belgium and central Germany), the lack of previous records (even with sporadic examinations) is as difficult to understand as the absence of previous cases of human AE. In such areas, it is therefore highly probable that the parasite was either absent before, or present at far lower prevalence levels than today. This intrinsic uncertainty also applies when discussing the apparent absence of the parasite *eg* from the British Isles and mainland Scandinavia. Therefore, efforts to determine precise 'range limits' using retrospective data appear pointless and should be redirected to establishing regional prevalence levels, both in endemic and 'non-endemic' areas, using appropriate sampling strategies, in order to provide a reliable basis for future analyses of spatial and temporal transmission dynamics.

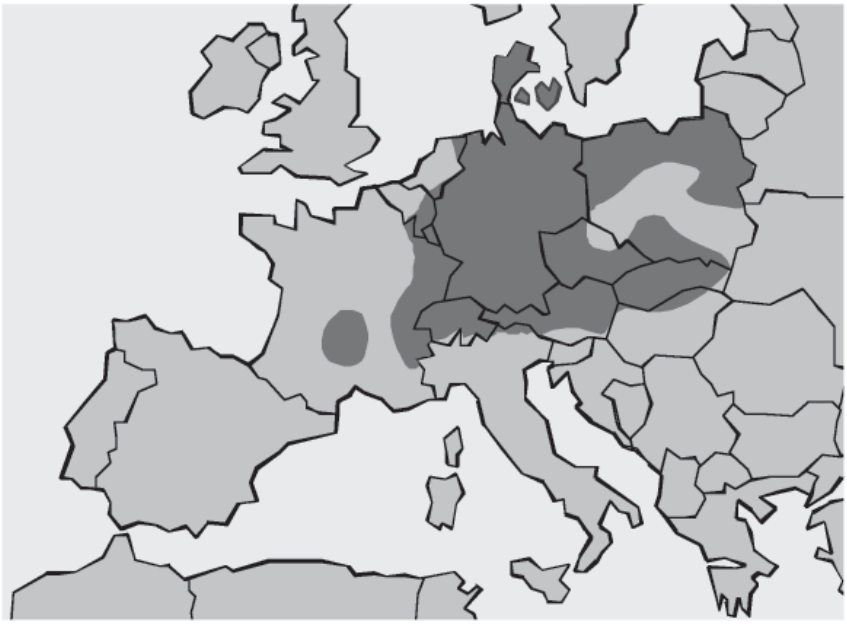

Fig 1- Confirmed distribution of *E. multilocularis* in Europe (based on numerous authors).

There are only a few regions where long-term studies allow direct comparisons of prevalence levels between different periods. The largest sets of data exist for the state of Baden-Württemberg in southwestern Germany. There, a prevalence of 15% (n=7,485) was found in the period 1974-1984, which had increased to 37% (n=6,013) in the period 1995-1998, despite the fact that highly endemic regions were over-represented in the earlier and underrepresented in the latter period (Romig *et al*, 1999a). In some other federal states of Germany a similar trend is on record, while in many other central European regions prevalence rates have appeared to increase, but due to small sample sizes the data are difficult to interpret. In addition, fox populations have increased drastically in central Europe since the beginning of the 1990s (Romig *et al*, 1999b). There is an obvious temporal correlation with the start of rabies immunization campaigns, which have by now removed rabies as a significant cause of fox mortality, but additional factors, like reduced hunting pressure and easier access to food sources in the vicinity of human settlements, are likely to have contributed to this situation. The parasite density (biomass) in foxes per area unit has, therefore, increased in southwestern Germany by an estimated factor of 10. This is reflected by data from intermediate hosts in the same region. Recent data from muskrats (*Ondatra zibethicus*) demonstrate a general prevalence increase from 2% (n=3,419) in the period 1980-1989 to 26% (n=947); in the period 1995-2000, a change in the same order of magnitude as observed in the final hosts (Romig *et al*, 1999b).

The adaptation of foxes to urban environments - known in Britain since the 1940s - occurred rather recently in continental Europe, possibly because the development was prevented by the low population density of foxes during the rabies period. Today 'urban foxes' are known from many towns and cities of south-central Europe, *eg* in southern Germany and Switzerland (Deplazes *et al*, 2004). Casual observations and basic research have shown that population densities (up to 20/km^2) can be much higher than in rural habitats due to the abundant availability of food. Infection rates with *E. multilocularis* can be high (Hofer *et al*, 2000), but are generally lower than in surrounding rural areas, probably depending on the presence of habitats suitable for voles as intermediate hosts. However, due to the high population density, the absolute number of infected foxes may be higher than in agricultural landscapes, and the close proximity between foxes and man poses a considerable risk to humans. Transmission to humans may not only occur directly from infected foxes, but also from pet dogs and cats that get infected by catching rodents in city parks and gardens (9% of *A. terrestris* caught in a city park in Zurich were found infected (Stieger *et al*, 2002).

CYSTIC ECHINOCOCCOSIS

Cystic echinococcosis (CE) is caused by '*E. granulosus*', which today is recognized as an assembly of different strains and species. The world-wide distribution of these parasites is closely linked to animal husbandry. Most life cycles include domestic dogs and livestock species as hosts, wildlife is involved in only a few places (*eg* in a cycle between dingoes and kangaroos in eastern Australia). The highest prevalence rates among humans and animals occur where livestock production is extensive (*eg* large-scale sheep farming), where large numbers of dogs are kept (*eg* for guarding livestock), and where dogs have access to carcasses of dead livestock or to offal after uncontrolled slaughter (Schantz *et al*, 1995). Although few regions in the world are completely free of any of the various forms of the *E. granulosus* group, transmission intensity is usually very low in regions with advanced slaughter supervision, which is the case for the larger part of Europe. Transmission to humans is thought to be by close contact with infected dogs carrying *Echinococcus* eggs on their fur, or indirectly by ingesting contaminated water or food. Geographically, prevalence rates of human CE are often linked to prevalence in livestock. However, additional factors are important, not the least being the strain of parasite that predominates in a given region. Within Europe, cystic echinococcosis is rare in animals in Scandinavia and central Europe (with the exception of Poland and regions further east), and human cases only occur sporadically. The most affected regions are parts of Spain, southern Italy and Sardinia, where annual incidence rates for human CE of 4-8/100,000 are reported (Eckert *et al*, 2001).

It has long been recognized that *E. granulosus* possesses a high degree of genetic variability (Thompson and McManus, 2001). This has led to the recognition of various strains (G1 to G9), which are genetically distinct and exhibit a variety of differences in morphology, development rate, host range, pathogenicity, and geographical occurrence. While some of these strains are poorly known, for others the existing information is sufficient for preliminary epidemiological analysis. Two of these strains have most recently been elevated to species status (*E. equinus* and *E. ortleppi*) on the basis of their genetic distinctness, different intermediate host preferences and sympatrical occurrence in the identical definitive host without interbreeding (Thompson and McManus, 2002).

Two strains of *E. granulosus* appear to be specifically adapted to ovine intermediate hosts, although they may also affect other species. One of them, the common sheep strain (G1) occurs almost worldwide in areas of extensive sheep raising, and coincides with a high-prevalence of human CE. Data from Europe support this hypothesis, since G1 is mainly present in sheep raising areas of the Mediterranean and parts of Great Britain, where the majority of human CE cases are on record (Eckert *et al*, 2001).

E. equinus was formerly known as the horse strain (G4) of *E. granulosus*. It appears to use exclusively equines (horses, donkeys, and zebras) as intermediate hosts. It is known from parts of Great Britain, and epidemiological data suggest that it may not be infectious to humans (Thompson, 1995).

E. ortleppi, the former cattle strain (G5) of *E. granulosus*, is adapted to transmission by cattle (which is a poor host species for most other taxa of *Echinococcus*). The last stable cattle-based transmission cycles in Germany and Switzerland (Eckert *et al*, 2001) are likely to be attributable to this species. Autochthonous cases were reported until the 1980s, but the taxon is probably extinct or sporadic. Only one isolate from a human patient-from the Netherlands-could until now be allocated to this species (Bowles *et al*, 1992) which may be less infectious to humans than the sheep strain of *E. granulosus*.

A genetically closely related group of strains consists of the camel strain (G6), the pig strain (G7), the cervid strain (G8), and a genotype found in some human patients from Poland (G9). Recently, isolates from reindeer and moose in Finland were found to differ genetically from the North American G8, and were allocated to a new strain, G10 (Lavikainen *et al*, 2003). All these strains are difficult to distinguish from each other, and are likely to be geographical variants of the same taxon. However, epidemiological data on this group are limited and, although they are clearly distinct from the sheep strain, are tentatively retained in the species *E. granulosus* (Thompson and McManus, 2002). In Europe, the pig strain (G7) is found in domestic pigs in Poland, Slovakia, and probably in pig-raising areas of eastern and southeastern Europe. No human cases of this strain have yet been diagnosed, although a closely-related genotype (G9) of unknown animal reservoir was described from Polish patients (Scott *et al*, 1997). The cervid strains (G8/10) are known from arctic and subarctic regions of Europe, Asia, and North America. In northern Europe, dogs and domestic reindeer are typically involved, although this domestic cycle may be interlinked with sylvatic transmission between wolves and wild cervids. Human cases of G8 are known from North America, but the disease was described as more benign than the sheep strain of *E. granulosus* (Wilson *et al*, 1968). In total, human susceptibility/pathogenicity of this group of genotypes appears to be low (awaiting further data), and the predominant presence of these taxa may be the reason for the relative scarcity of human CE in some regions which are highly endemic for animal echinococcosis, *eg* parts of central and eastern Europe.

The epidemiology of cystic echinococcosis still suffers from lack of strain/species-based information. To date, relatively few isolates have been genetically diagnosed, since reliable methods for strain identification became only recently available (Pearson *et al*, 2002; Dinkel *et al*, 2004). More information, however, is urgently required, especially for prevention and control strategies which have previously not taken notice of relevant differences, *eg* intermediate host species, and different prepatency periods in the definitive hosts. From a medical view point information about human susceptibilty to the various forms is still inadequate, and no reliable data exist about pathogenicity in humans and putative differences in response to chemotherapy.

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