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Echinococcosis: an emerging or re-emerging zoonosis?

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Abstract

The aim of this review is a critical discussion of factors actually or potentially contributing to persistence or emergence of echinococcosis in humans. Alveolar echinococcosis (AE), a life-threatening infection of humans, is caused by a larval stage of *Echinococcus multilocularis*. The adult parasite inhabits the intestine of foxes and other carnivores and has a wide distribution in the northern hemisphere (North America and northern and central Eurasia). Recent surveys in central Europe have extended the known geographical occurrence of *E. multilocularis* in foxes from four countries at the end of the 1980s to at least 11 countries in 1999. Cases of human AE previously regularly reported from only four countries are now recorded from seven countries, but the annual incidences are low. Since adequate information from earlier surveys is not available, it is not possible to conclude if the new findings reflect a recent extension of the parasite's range or just the first identification of hitherto unnoticed endemic areas. Evidence of parasite spreading has been reported from North America and Japan. Factors with the potential of enhancing the infection risk for humans in the future include increasing fox populations and parasite prevalences, progressing invasion of cities by foxes, the establishment of urban cycles of the parasite, and the spill-over of the *E. multilocularis* infection from wild carnivores to domestic dogs and cats. In view of the potential severity and fatality of AE in humans health authorities should initiate internationally coordinated countermeasures. Although control programmes against human cystic echinococcosis (CE), caused by *E. granulosus*, have been established in some countries and effective control strategies are available, the parasite has still a wide geographical distribution affecting many countries of all continents. Thus, human CE is persisting in many parts of the world with high incidences, and in some areas it is a re-emerging problem. For example, alarming increases of the number of human cases have been reported from Bulgaria and Kazakhstan, and the People's Republic of China. Progress in control can only be expected if health authorities attribute a higher priority to this disease and if all modern diagnostic and control options (for example vaccination of intermediate host animals) can be used.

Keywords: Echinococcosis; *Echinococcus multilocularis*; *Echinococcus granulosus*; Geographical distribution; Epidemiology; Control

1. Introduction

A first case of human alveolar echinococcosis (AE) was described in 1852 by Buhl in Munich (Germany) as a tumor-like lesion of the liver designated as 'alveolar colloid'. In 1855 the German pathologist Virchow identified the lesion as a 'multiocular and ulcerating echinococcosis tumor', but at this time it was unclear whether this form of echinococcosis was caused by the well known *Echinococcus granulosus* or another species [1]. In 1901 Posselt in Austria infected a dog with alveolar parasite material from a human liver and found in the dog's intestine small tapeworms clearly differing from *E. granulosus* and showing characteristics of another species described as *Echinococcus multiocularis* by Leuckart in 1863 [1]. After about 100 years of discussions on the aetiology of AE, Rausch and Schiller in Alaska (1954) and Vogel in Germany (1957) unequivocally demonstrated that *E. granulosus* and *E. multiocularis* are separate species and that the latter is the causative agent of human AE (Ref. in [2]). Today it is known that *E. multiocularis* is widely distributed in northern and central Eurasia and North America. This parasite is of increasing public health concern as it may cause severe and even lethal disease in humans, new endemic areas have been detected in recent years, efficient control measures are not available, and treatment of human cases is difficult and expensive. Furthermore, there are several epidemiological factors which may increase the infection risk for humans in the future [3].

Hydatid cysts, the larval stages of *Echinococcus granulosus* and causative agents of human cystic echinococcosis (CE), were already known in the Greek antiquity [1]. Although control of *E. granulosus* had been successfully

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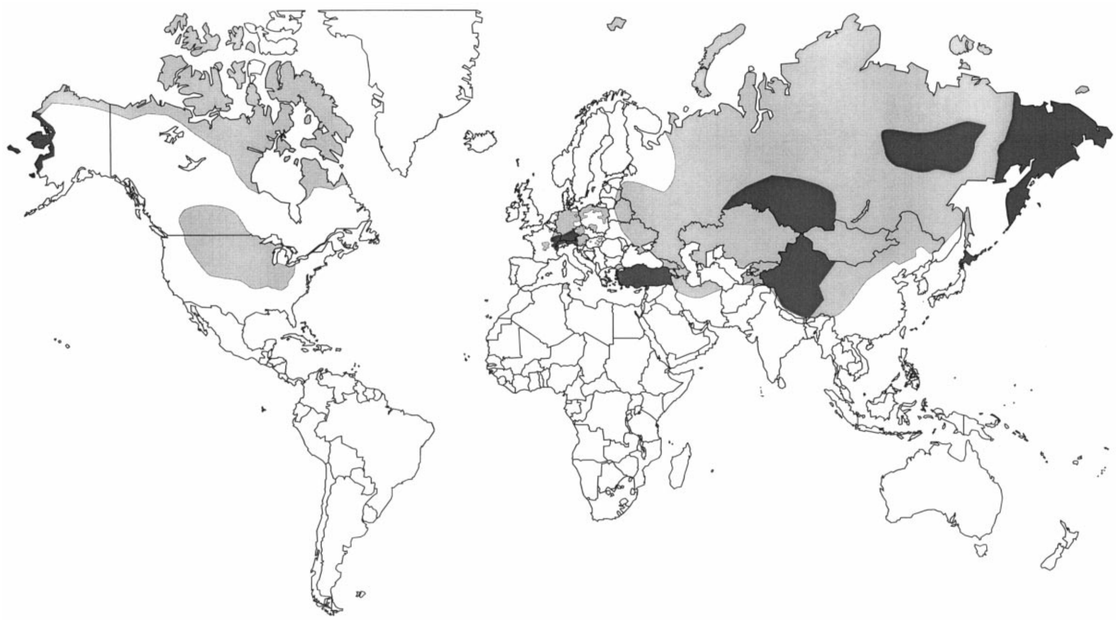

Fig. 1. Approximate geographical distribution of *Echinococcus multilocularis* (status 1999). Sources of data: Schantz et al. [9] and Eckert et al. [10]. ©Institute of Parasitology, University of Zurich (J. Eckert, F. Grimm. H. Bucklar).

performed in Iceland in the middle of the 19th century, and control programmes were established in the 20th century in different areas, recent surveys show that CE has still a wide geographical distribution affecting many countries of all continents. Thus, CE is persisting in many parts of the world, and in some areas it is a re-emerging problem [3].

The aim of this review is a critical discussion of factors actually or potentially contributing to persistence or emergence of alveolar and cystic echinococcosis with emphasis on the former. Polycystic echinococcosis, caused by *Echinococcus vogeli* or *Echinococcus oligarthrus*, is not considered in this paper.

2. *Echinococcus multilocularis* and alveolar echinococcosis

Human AE is caused by the metacestode stage of *E. multilocularis*. This parasite is typically perpetuated in a silvatic cycle with foxes as definitive hosts and small mammals, predominantly rodents, as intermediate hosts. Some other species of wild canids as well as domestic dogs and cats are also susceptible and may act as definitive hosts. The metacestode stage in natural intermediate hosts or aberrant hosts, including humans, is characterized by a tumorlike proliferation which leads to infiltration of the affected organs, primarily the liver, and in progressive cases to severe disease and even death [3,4]. In previous years AE was lethal within 10–15 years after diagnosis in 94–100% of untreated or inadequately treated human patients [4]. Nowadays, the 10–15 year lethality rate is much lower as AE is more often diagnosed in an early phase of the infection and options for treatment (surgery and chemotherapy) have greatly improved since the mid 1970s [3–7]. Modern treatment can significantly prolong the patients' survival time, but cure is only achieved if the metacestode is completely eliminated by radical surgery and complementary chemotherapy [3–5]. Therefore, AE remains a life-threatening infection which should attain adequate attention from public health authorities [8].

Echinococcus multilocularis is widely distributed in the northern hemisphere, including regions in central Europe, most of northern and central Eurasia (extending eastward to Japan) and parts of North America. In North America the cestode's range reaches from Alaska southward through Canadian provinces to the US states of Wyoming, Nebraska, Iowa, Illinois, Indiana, Ohio and Missouri [9,10] (Fig. 1).

A number of key factors and parameters are used in this review for assessing the actual or potential determinants for persistence or emergence of *E. multilocularis* and human AE in selected geographical regions, but only some of these factors can be discussed here (Table 1).

2.1. Risk areas

Recent surveys in central Europe have revealed that *E. multilocularis* has a much wider geographical distribution than previously anticipated. By the end of the 1980s, endemic areas of *E. multilocularis* were known to exist in only four countries, including Austria, France, Germany, and Switzerland, but at the end of 1999 the parasite was known to occur in red foxes of at least 11 central European countries, namely Austria, Belgium, the Czech Republic, France, Germany, Liechtenstein, Luxembourg, Poland, the

Table 1
Key factors and parameters used for assessing the epidemiological status and risk of emergence of the *Echinococcus multilocularis* infection

Key factor	Main parameters to be determined
1. Risk area	Geographical and spatial distribution of adult *E. multilocularis* in definitive hosts, of larval stages (metacestodes) in intermediate hosts, and occurrence of AE in humans
2. Sources of infection	Definitive host species and their population sizes, frequency and intensity of infection with *E. multilocularis*, capacity for egg production and excretion; relationships between definitive and intermediate host populations
3. Transmission dynamics	Habitats of definitive and intermediate hosts, population dynamics; contacts of animal hosts with humans and their environments; egg dispersal and survival in the environment; routes of egg transmission to humans
4. Incidence and significance of human AE	Annual number of human cases per 100 000 inhabitants, severity of cases, costs of diagnosis and treatment
5. Awareness of the disease and countermeasures	Public awareness of the disease, monitoring of the infection and countermeasures

Slovak Republic, The Netherlands and Switzerland [8,10,11] (Fig. 2). In 1999 metacestodes of *E. multilocularis* were found in rodents on the Spitsbergen island, belonging to the Norwegian Svalbard Island group situated in the Barent's Sea [12], and in foxes in Denmark (Kapel, personal communication [73]). It can be anticipated that further surveys will detect *E. multilocularis* in other regions and countries. Findings of *E. multilocularis* metacestodes in rodents have been reported from Slovenia, Bulgaria and Romania [13], but they require confirmation by the identification of the adult parasite in foxes or other carnivores. Since adequate information from earlier surveys is not available, it is not possible to conclude if the new findings reflect a recent extension of the parasite's range or just the first identification of hitherto unnoticed endemic areas which may have existed for long periods.

Whereas the occurrence of *E. multilocularis* in red foxes or other definitive hosts is an indicator of a potential infection risk for humans, the diagnosis of autochthonous human cases of AE provides definite evidence for an actual risk in a given area. In previous years autochthonous cases of human AE have been regularly reported only from Austria, France, Germany and Switzerland. Since 1993 such cases were recorded from at least 7 of 11 endemic countries, namely from Austria, Belgium, France, Germany, Switzerland, Liechtenstein and Poland [8]. Furthermore, sporadic cases had been reported in previous years from the Czech Republic, Slovakia, Hungary, Slovenia, Bosnia, and Greece [9,13]. These data allow the conservative conclusion that an actual infection risk for humans exists in the majority of the endemic countries of central Europe. However, it cannot be excluded that such a risk exists in all endemic areas, as rare cases may be overlooked or misdiagnosed (predominately as liver cancer) in countries which lack medical awareness of the disease. For example, in Poland a first report on the occurrence of *E. multilocularis* in red foxes was published in 1995 [14]. Shortly thereafter, a few historical and actual human cases of AE in humans were described [15], and by the end of 1999 a total number of 13 cases were registered [13,16,17] (Pawlowski, personal communication). On the other hand, it might be that *E. multilocularis* has spread to this area in recent decades and gradually established an infection pressure posing a risk for humans.

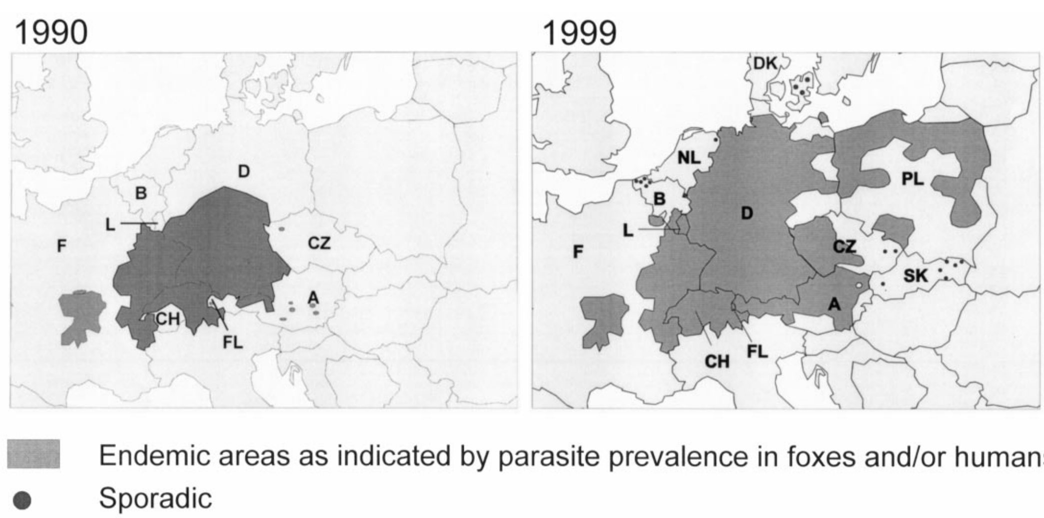

Fig. 2. Approximate geographical distribution of *Echinococcus multilocularis* in central Europe 1990 and 1999. Sources of data: Eckert and Deplazes [8], Eckert et al. [10], Romig et al. [11], Kolarova [13]. A, Austria; B, Belgium; CH, Switzerland; CZ, Czech Republic; D, Germany; DK, Denmark; F, France; FL, Liechtenstein; L, Luxembourg; NL, The Netherlands; PL, Poland; SK, Slovak Republic. ©Institute of Parasitology, University of Zurich (J. Eckert, F. Grimm, H. Bucklar).

Data from Japan provide epidemiological evidence for spreading and emergence of the *E. multilocularis* infection. *E. multilocularis* is believed to have been introduced into Japan in red foxes translocated from one of the Kurile Islands to Rebun Island, northwest of Hokkaido, during the years 1924–1926, for the purpose of controlling the vole population [18,19]. On Rebun Island 131 human cases of AE have been observed between 1937 and 1989 but no further cases thereafter due to effective control measures [9,20]. Another outbreak occurred around 1960 in eastern Hokkaido, followed by the spread of *E. multilocularis* to central and western parts of the island [9,20]. Between 1981 and 1991 the parasite spread across approximately 8 to 90% of the area of Hokkaido [19] (Fig. 3). Concurrently the number of human cases of AE in Hokkaido has increased from only 6 new cases between 1937 and 1964 to a total of 110 cases between 1985 and 1994 [20].

In North America, *E. multilocularis* occurs in two geographical regions, one in the Northern Tundra Zone (NTZ) of Alaska (USA) and Canada and the other further south, in the North Central Region (NCR) [9,18,21]. The range of *E. multilocularis* in the NTZ is roughly equivalent to that of the arctic fox and extends along the coast of Alaska from the mouth of the Kuskokwim River northward and eastward to Canada, and southward along the western shore of Hudson Bay [9,10,18]. There is no evidence of the presence of *E. multilocularis* within the forested interior (taiga) between the NTZ and NCR, although fairly large numbers of foxes and rodents have been examined [9]. The NCR currently includes parts of three Canadian provinces (Alberta, Saskatchewan, Manitoba) and 13 contiguous US states (Fig. 1).

It is assumed that prior to the 1960s, *E. multilocularis* had spread from the NTZ and became established in central North America (Fig. 1). Previous surveys of endoparasites of canids and rodents in the NCR had failed to reveal *E. multilocularis* [18,21]. The first finding of *E. multilocularis*

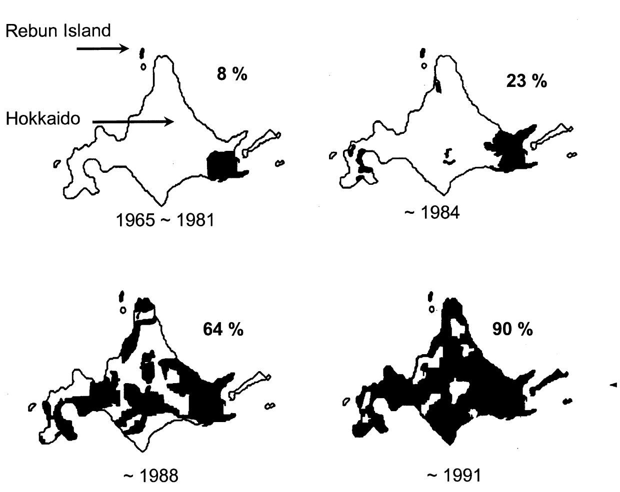

Fig. 3. Spreading of *Echinococcus multilocularis* in Hokkaido, Japan (after Suzuki et al. [19], with kind permission).

was in 1964 in a red fox in North Dakota. Subsequently, the parasite was identified in wild canids or rodents in South Dakota, Iowa, Minnesota, and Montana in 1965–1969, in Wyoming in 1976, in Nebraska and northern Illinois in 1981–1982, and in Wisconsin in 1982–1983. Further surveys extended its known occurrence to as far east as east-central Illinois, Indiana, and Ohio and as far south as Missouri. Given the abundance of suitable definitive and intermediate hosts throughout the US, it may be assumed that *E. multilocularis* will become established in contiguous states. Translocation of foxes and coyotes from endemic states and their release in hunting enclosures of non-endemic areas may contribute to parasite spreading [9,18].

Interestingly, despite the widespread occurrence of *E. multilocularis* in animal hosts in North America, nearly all cases of AE in humans have been diagnosed in Eskimos of a limited number of communities in Alaska. On St. Lawrence Island, among a small population of about 1000 inhabitants, 53 cases have been diagnosed between 1947 and 1990 [9]. In the extensive areas of Canada where *E. multilocularis* is endemic, cases of human AE have never been recorded, and only two cases of AE were diagnosed to date in the NCR of the USA, one in 1937 and the other in 1977 [18].

2.2. Sources of infection

The study and monitoring of the infection sources (Table 1) can indicate epidemiological changes and emergence of the infection. In central Europe, the life cycle of *E. multilocularis* is predominantly silvatic, involving red foxes (*Vulpes vulpes*) as definitive hosts and various species of rodents as intermediate hosts [8,22]. Epidemiological evidence suggests that humans and other aberrant hosts contract the infection predominantly from this cycle by ingestion of parasite eggs released in the faeces of infected foxes. According to a large number of recent data, the prevalence of *E. multilocularis* in red foxes differs widely between countries, larger areas, and smaller territories from about 1 to over 60% [8,10,11]. Also, infection intensities vary in a given fox population. In a Swiss study the total biomass in 57 urban and 76 rural foxes sampled during two winters was 398 653 *E. multilocularis* specimens [23]. Using a highly sensitive technique infections with less than 1000 specimens were found in 69% (92/133) of the foxes and with more than 1000 specimens in 31% (41/133); the average worm number in 133 adult and subadult foxes was 2997 (range 1–56 970) per animal. Only 7.5% of the foxes (10/133) harboured more than 10 000 specimens corresponding to 72% of the total biomass [23].

Several parameters related to definitive hosts and possibly associated with epidemiological changes and emergence of the *E. multilocularis* infection are currently discussed in central Europe: (1) increasing fox populations and parasite prevalences, (2) invasion of villages and cities by foxes, and (3) the role of domestic dogs and cats in disease transmission to humans.

2.2.1. Increasing fox populations and parasite prevalences

It is widely believed that in parts of Europe fox population densities have increased in recent years [11,24,25], possibly due to reduced fox mortality after anti-rabies vaccination and other factors. However, scientific verification is difficult because exact methods for determining fox population densities are not available. Therefore, indirect parameters for population size estimation are used, such as the annual hunting index (AHI) (number of foxes shot per km^2 and year) and the numbers of foxes killed by car accidents or other events. During 1974–1976, the AHI in large parts of central Europe ranged between approximately 1 and 1.4 foxes [26], and between 0.9 and 1.2 according to another source [27]. In 1990/1991 the average AHI in 13 Cantons of Switzerland was 1.7 (range 0.1–2.5) [28]. The average AHI in western Germany has increased 3.7 times from about 0.6 in 1960 to 2.2 in 1988 (data extracted from a graph) [24]. In Baden-Württemberg, south-western Germany, the number of foxes sampled by hunting has increased 2.7 times from approximately 30 000 in 1975/1976 to 80 000 in 1997 (data extracted from a graph) [11], equivalent to estimated AHIs of 0.8 and 2.2, respectively (calculated for a total area of 35 751 km^2). The AHI is a rather 'weak' parameter as it is only based on the assumption that a linear relationship exists between the number of shot foxes and population densities. Furthermore, the AHI is extremely sensitive to several sources of bias, since fox hunting itself is influenced by many variables [29,30]. Therefore, the AHI can only be used to describe trends if data from larger areas (>1000 km^2) [31,32] are analysed over longer periods of time (approximately 5 years). For these reasons AHIs have to be interpreted with great caution, especially if data from different regions are to be compared.

Another approach for estimating fox population densities is counting of breeding dens per km^2 and multiplying their number with the average number of foxes presumably living in each den, for example 2.5 animals (this number is based on random observations of fox families). Using this method, in a large (270 km^2) former military testing ground, the estimated number of adult foxes in spring was 0.61 individuals per km^2 [25]. There was no indication of an increase in population density shortly after introduction of anti-rabies vaccination [25].

In a Swiss study a significant positive correlation was found between regional prevalences of *E. multilocularis* in foxes and AHIs [28]. In one of the Federal States of Germany (Rhineland-Palatinate) the total number of foxes shot by hunters has increased 2.6 times from 18 872 in 1989/90 to 49 326 in 1995/1996 [33]. Coincidentally the average annual prevalence of *E. multilocularis* in foxes has increased from 13.1% (121/923) in 1991 to 29.7% (340/1145) in 1996 [33]. Also from another Federal State (Baden-Württemberg) regional increases of *E. multilocularis* prevalences have been reported [11], while in other states (Brandenburg, Lower Saxony, Thuringia) the prevalences of *E. multilocularis* remained stable over periods of several years [34–36].

Data on increasing prevalences of *E. multilocularis* in foxes have to be interpreted with caution, as potentially confounding effects are often neglected in the statistical evaluation of the results, such as the spatial heterogeneity regarding the prevalence of *E. multilocularis* in foxes, differences in the age structure of sampled animals and the sensitivity of diagnostic techniques. The average diagnostic sensitivity of the intestinal smear technique, most frequently used in epidemiological surveys, is 78% [23]; it does not detect a proportion of infected foxes, especially those which harbour only a low number of parasites. Furthermore, the spatial distribution of infected foxes in a given area is typically heterogeneous, and prevalences or infection intensities of *E. multilocularis* are influenced by several variables, including host age (due to differences in exposure to the infection and possibly also in susceptibility), season, and regional endemic factors [34]. In an endemic district of northern Germany (Brandenburg) *E. multilocularis* infected foxes were not found in areas with sandy soils or dry habitats [34]. It might be that disease transmission was impaired by reduced survival periods of oncospheres in eggs exposed to dry environmental conditions. Also in other countries (i.e. France, China) geological, climatological variables and land-use patterns were identified as factors influencing distribution and transmission dynamics of *E. multilocularis* [37–38].

This implies that a large number of variables and potentially confounding factors have to be considered in exact comparisons of prevalences in relation to time and area. Moreover, it is not clear whether the relationships of variables governing the life cycle follow continuous or discontinuous functions. In the latter case, there may be threshold values for certain variables (e.g. for egg production capacity) which must be reached to allow the life cycle to persist.

2.2.2. Invasion of villages and cities by foxes

In the UK, in the middle of the 1980s, an increasing invasion of cities by red foxes was noticed, and a few years later they had established in approximately 200 cities [39]. In the city and in suburbs of Oxford population densities of between 2.7 and 10 foxes per km^2 have been determined by radiotelemetry [39]. The same phenomenon is now also recognized in other regions, such as continental Europe [23] and Japan [40–42]. Such foxes have been identified as carriers of *E. multilocularis* which can contaminate public grounds, recreational areas and gardens with infective eggs of the parasite. A recent study (1996/1998) in Zurich, Switzerland, revealed *E. multilocularis* prevalences of 47% (61/129) in foxes from the city and of 67% (82/123) in foxes from the adjacent rural area during the winter period; prevalences in summer were lower [23]. Furthermore, metacestodes of *E. multilocularis* were found in 14% (19/135) of water voles (*Arvicola terrestris*) in a park in the city of Zurich, but only two animals harboured protoscoleces of the parasite [23]. These data provide evidence for an urban cycle of *E. multilocularis* [23] that has to be regarded as a potential infection risk for humans.

2.2.3. The role of domestic dogs and cats in disease transmission to humans

In several European countries, domestic dogs and cats have been identified as definitive hosts that acquire the infection from the silvatic cycle by ingesting rodents harbouring the metacestode stage with protoscoleces [43]. However, little information exists on the prevalence of *E. multilocularis* in European populations of dogs or cats and their actual role in disease transmission to humans. In one older study in France 5.6% of 36 dogs [44], and in a further five studies in Germany and France 0.5 to 3.7% of 58 to 498 cats were identified as carriers of *E. multilocularis* [43,45]. New diagnostic tools can now be employed for screening larger populations of living domestic carnivores. Using the ELISA for coproantigen detection as a screening test and PCR for DNA detection and/or necropsy for confirmation, 660 dogs and 265 cats originating from the endemic area of eastern Switzerland were examined for *E. multilocularis*; 0.30% of the dogs and 0.38% of the cats were infected [46]. If the results were related only to 130 free-roaming cats and not to the total population which included 135 cats kept in households, the proportion of infected animals was 0.77% [46]. In a highly endemic focus in western Switzerland (Canton Fribourg) 12% of 41 dogs were identified (by ELISA and PCR) as carriers of *E. multilocularis* [47].

In order to estimate the relative capacities of foxes, dogs and cats to contaminate the environment with *E. multilocularis* eggs, the following calculation can be made using the Canton of Zurich as an example. The estimated fox population size in 1992 was 4700 and the prevalence of *E. multilocularis* 33%, equivalent to 1551 parasite carriers in that population [8]. On the other hand, if 0.30 and 0.38% of the estimated dog (48 400) and cat (145 200) population in the Canton would be infected with *E. multilocularis*, then 145 dogs and 552 cats were carriers of the parasite, hypothetically representing 9.3 and 35.5% of the carrier capacity of the infected 1551 foxes. An increase of the infection rate in the cat population to 0.5%, would result in 726 parasite carriers and an increase of the carrier capacity to 47% of the fox capacity. These data underline the epidemiological importance of population sizes of definitive hosts since not only the relative but also the absolute number of infected animals in a given area is a significant factor. Furthermore, their susceptibility and egg production capacity have to be considered. Foxes and dogs are highly susceptible to *E. multilocularis* whereas the susceptibility of cats appears to be reduced [48]. Therefore, the contribution of cats to environmental contamination might be relatively low. On the other hand, the close association of domestic dogs and cats with humans could selectively enhance their actual role in disease transmission to humans, but little information exists in this respect. In an Austrian study the habits and activities of 21 patients with AE were retrospectively (1967–1997) compared with those of 84 control persons matched by sex, age and residence [49]. Cat ownership and hunting were found as independent risk factors, but caution with regard to this result is justified as *E. multilocularis* infected cats had not been found in the study area (see also 2.3). In certain epidemiological situations dogs may become the predominant definitive hosts being mainly responsible for human infections (for example in Alaska and China) [9,10].

2.2.4. Factors associated with spreading of E. multilocularis

Factors potentially responsible for spreading of the *E. multilocularis* infection have been discussed by Tackmann et al. [34]. In Japan *E. multilocularis* has apparently been imported by dislocation of foxes from one of the Kurile Islands to Rebun Island, and there are reports from the USA that foxes and coyotes have been moved from endemic to non-endemic areas for hunting purposes posing the risk of disease spreading ([34], see chapter 2.1). In Europe, spreading of *E. multilocularis*, if it happened at all, would most likely be associated with spatial migration of foxes out of endemic areas [34]. Most foxes migrate less than 5–10 km, and only a few over 50–70 km [34]. Spreading of *E. multilocularis* by infected dogs and cats was also considered but regarded as most likely unimportant due the low prevalence of the parasite in these hosts [34]. Rodents could play a role in spreading of the infection only over small distances. Long-distance (over 60 km) transport of eggs by birds as described for *Taenia hydatigena* [50] could be another way of spreading *E. multilocularis*.

2.3. Transmission dynamics

Exposure of humans to eggs may be influenced by occupational and behavioural factors, but the few available data are conflicting. There are some hints from various European countries that persons working in agriculture and living in areas with high prevalences of *E. multilocularis* in red foxes may be at increased risk [4,44]. A recent study in an endemic focus in southern Germany could not identify any risk factor since only one human case with AE among 2560 examined persons was detected. Also, for 60 seropositive cases found in this study, a statistically significant association of considered potential risk factors (agricultural occupation, dog and cat ownership, hunting, outdoor activities, eating raw garden products or wild berries and herbs, etc.) was not detected [51]. In a statistical analysis in France it was shown that a high density of voles (*Arvicola terrestris*) and certain geomorphologic and climatic conditions are significant risks factors for the acquisition of human AE [38]. In periods of high vole densities, foxes feed almost exclusively on grassland rodents (including *A. terrestris*), and it can be hypothesized that this could lead to higher prevalences and infection intensities of *E. multilocularis* in local fox populations and finally to increasing contamination of the environment with infective parasite eggs [38]. Among the geomorphologic and climatic factors intermediate temperature, rainfall, permanent grassland surface and some other factors may contribute to an ecosystem favourable for survival and transmission of *E. multilocularis* eggs [38]. It has thus been assumed that increased grassland rodent populations and certain changes of geomorphologic and climatic factors could enhance disease transmission to humans. However, as long as there is no evidence of a temporal change in the incidence of AE and due to the lack in knowledge of the real risk factors for humans, discussions about potential influences of geomorphologic and climatic factors on acquisition of human AE remain largely speculative. The wide distribution and high prevalences of *E. multilocularis* in foxes on the one hand and the low incidence of human AE (see below) on the other suggest that the infection risk for humans may be limited by certain factors, for example by human behaviour leading to reduced exposure or by immunogenetic predisposition for resistance [52].

2.4. Distribution and incidence of human AE

The average annual incidence values of human AE are not well documented in many regions, but appeared to be low in previous years in some of the endemic countries and regions, for example in central Europe and Japan where they vary between 0.03 and 1.2 per 100 000 population [4]. However, higher values of 98–170 per 100 000 have been reported from highly endemic foci in Alaska, northern Siberia and China [4,9].

Some recent ultrasound and immunodiagnostic surveys have revealed high prevalences in highly endemic foci. For example in a rural area of Gansu, China, between 1991 and 1997 among 3331 examined persons 135 (4%) had AE [53]. In a highly endemic rural area of southwestern Germany 1 of 2560 examined persons was infected, corresponding to a hypothetical prevalence of 40 per 100 000 (95% confidence interval 15–205/100 000) [51]. It has to be underlined, however, that AE has a focal distribution, that group or local prevalence or incidence values may not be representative for larger regions, and local and methodological variables have to be taken into account if comparisons of values from various locations are made.

The detection of cases of human AE in countries where the disease was not known to occur in previous periods, for example in Poland and Belgium, may be an indication for an emerging infection risk for humans. However, as mentioned above, the possibility that rare cases may have previously been overlooked has to be considered.

Little reliable long-term data exist which could reflect changes in the epidemiological situation. In Switzerland the country-wide average annual incidence of human AE did not markedly vary (0.10–0.18) during a 36-year period (1956–1992) suggesting a stable epidemiological situation [8]. However, it cannot be excluded that increasing fox populations, the invasion of urban areas by foxes, high or increasing prevalences of *E. multilocularis* in foxes, spill-overs from the silvatic to the synanthropic cycle, changes in land use patterns, and other factors may modify transmission patterns and increase the infection risk for humans in the future. In Japan (Rebun Island and Hokkaido) the average annual number of new human cases has steadily increased from 4.2 per 100 000 inhabitants during 1937–1964 to 11.2 during 1985–1994 in coincidence with the spread of *E. multilocularis* in Hokkaido. In the following period between 1995 and 1997 there was a decline of the average annual case number to 9.7 [20]. Influences of potential confounding factors, such as improved diagnosis and effects of preventive measures, are not considered in these statistics.

2.5. Awareness of the disease and countermeasures

Some diseases, such as rabies and Creutzfeldt–Jacob disease, have attained special public attention mainly because of their severity and high fatality rate and stimulated health services to initiate countermeasures. Although human AE is a severe and often lethal infection, its significance is not adequately recognized by public health authorities of many countries [8]. In view of the potential severity and fatality of AE in humans, the persistence of an infection risk in wide areas, growing fox populations and other unpredictable risk factors, health authorities should initiate internationally coordinated countermeasures, including effective systems of continuous surveillance, using new tools for the diagnosis of *E. multilocularis* in definitive hosts, and certain measures of prevention and control which have been described by Eckert and Deplazes [8]. Even if control of *E. multilocularis* in a silvatic cycle is extremely difficult, studies to investigate the chances and limitations of various intervention strategies aiming at reducing the risk for humans are urgently needed. For example, in Germany, two different field studies using praziquantel-containing baits are carried out to treat fox populations against *E. multilocularis* under initially different epidemiological conditions (highly endemic versus focal endemic) [54]. The results of these studies should help to answer the question whether or not such a type of intervention is effective and feasible. As long as effective control strategies are not available, special attention should be given to all possible measures of prevention, including continuous monitoring of the epidemiological situation, registration of cases of the *E. multilocularis* infection in definitive hosts and humans, and combined sero-epidemiological and ultrasound screening of human population groups at risk. Several studies, for example in Hokkaido, Japan, have shown that such mass-screening programmes can detect AE in an early stage and significantly increase the chances of successful and curative treatment [19]. If basic measures of surveillance and prevention are neglected, a risk of emergence of the infection cannot be excluded.

3. *Echinococcus granulosus* and cystic echinococcosis

Transmission of *E. granulosus* occurs predominantly in a synanthropic cycle with domestic dogs as final hosts and livestock animals as intermediate hosts. The spectrum of intermediate hosts in this cycle depends on the *E. granulosus* strain, regional or local differences in the availability of various intermediate host species and other factors [22]. Highest prevalences of CE in humans are found among populations involved in sheep raising, thus emphasising the overwhelming public health significance of the dog-sheep cycle and the sheep strain of *E. granulosus* [55]. In some regions or countries silvatic cycles of *E. granulosus* exist and may play a role as infection source for both domestic animals and humans.

In the human host, metacestode cysts may develop virtually in all anatomic sites following oral ingestion of *E. granulosus* eggs, but liver and lung are the most frequently affected organs [3,56]. The initial phase of the infection is always asymptomatic. Small, well encapsulated, or calcified cysts typically do not induce major pathology and may remain asymptomatic for years or permanently [3,56]. According to an Italian study, asymptomatic cases accounted for 36 to >60% of all cases [57]. After a highly variable incubation period of months or years, the infection may become symptomatic, particularly if the cysts are growing, causing a variety of tumorlike symptoms related to the number and size of cysts and the organ site. Rupture of cysts may cause anaphylactic and other reactions [3,56].

Echinococcus granulosus has a worldwide geographical range and occurs in all continents and in circumpolar, temperate, subtropical and tropical zones [10] (Fig. 4). The highest prevalence of the parasite is found in parts of Eurasia, Africa, Australia and South America. Within the endemic zones the prevalence of the parasite varies from sporadic to high, but only a few countries can be regarded as free of *E. granulosus*.

The principles of epidemiology and control of *E. granulosus* have been studied in great detail and described in recent reviews [58]. Current control programmes are predominantly based on control of dog populations, regular dosing of dogs with praziquantel to eliminate *E. granulosus*, improved control of animal slaughter, and health education. Control programmes are costly and may last for more than 30 years, depending on the control option used in a given area [59]. Vaccination of livestock animals is a realistic new option of control but not yet widely available [60].

The most important factors influencing persistence, re-emergence and spread of the *E. granulosus* infection have recently been described in Bulgaria [61]. They are also relevant in many other endemic countries in the world and can be summarized as follows: (1) presence of large numbers of dogs (especially stray dogs!) with high prevalences of *E. granulosus*, (2) easy access of dogs to organs of livestock infected with *E. granulosus* cysts, especially in the countryside, (3) insufficient anthelminthic treatment of dogs, (4) a restricted number or lack of small municipal slaughterhouses, (5) inefficient slaughter animal and meat inspection, (6) inefficient or lacking facilities for destruction of infected viscera, (7) illegal or uninspected home slaughter of livestock animals, and (8) lack of adequate health education. Furthermore, financial restrictions and political instability

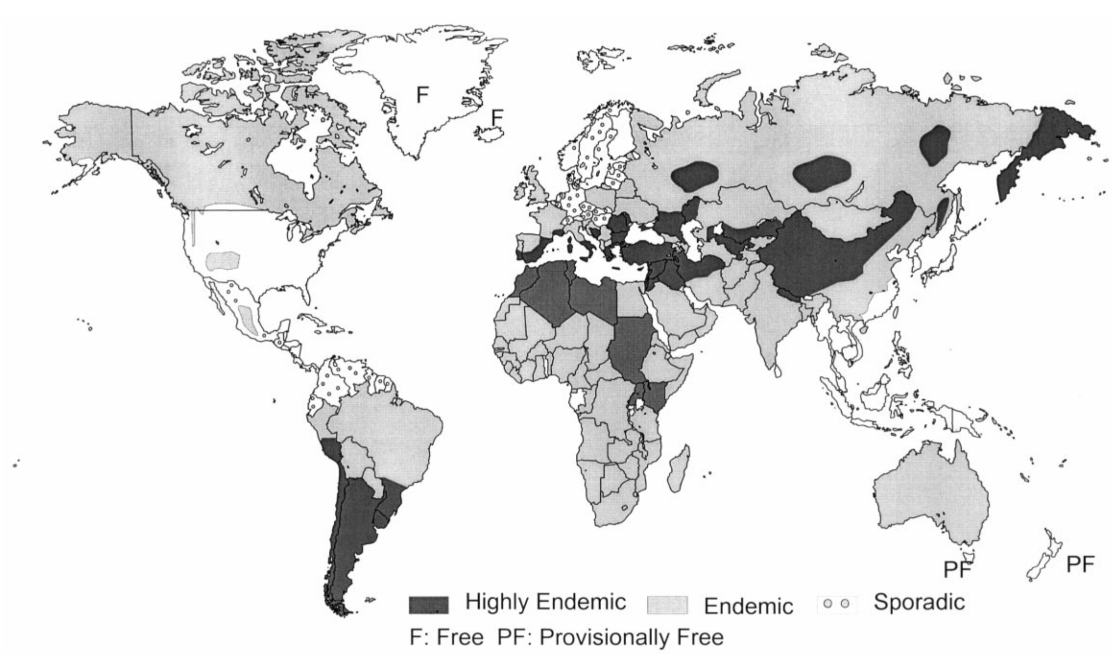

Fig. 4. Approximate geographical distribution of *Echinococcus granulosus* (status 1999). Sources of data: Schantz et al. [9], Eckert et al. [10], Craig et al. [55]. ©Institute of Parasitology, University of Zurich (J. Eckert, F. Grimm, H. Bucklar).

are major obstacles in control and prevention of echinococcosis and other communicable diseases.

As mentioned previously, options for effective control of *E. granulosus* are available but they require adequate long-term finance. Therefore, public awareness of the problem and the availability of economic resources are important factors influencing persistence or emergence/re-emergence of the *E. granulosus* infection.

3.1. Examples of emergence, re-emergence or increasing concern

There are several recent reports describing the *E. granulosus* infection and CE in humans as an emerging or re-emerging disease or a problem of increasing concern.

In Bulgaria the *E. granulosus* infection was highly endemic during the period 1950–1962 with a total of 6469 new surgical cases of CE in humans, equivalent to an annual incidence rate of 6.5 per 100 000 population and a high parasite prevalence in dogs and livestock animals [61]. A control programme, initiated in 1960, led to a considerable improvement of the situation in the period 1971–1982 with a decrease of the annual incidence of human CE to 2.0 per 100 000. Owing to administrative irregularities and economic changes, funds for the control campaign were reduced and control structures dismantled [61]. As a result, the *E. granulosus* infection in humans and animals has re-emerged. Between the periods 1971–1982 and 1983–1995 the proportions of infected dogs and sheep have increased from 4 to 7% and from 19 to 32%, respectively [61]. During the same periods the average nationwide annual number of surgical cases (new and readmitted) of human CE has increased from 176 to 291, and the corresponding annual incidence rose from 2.0 to 3.3 per 100 000. In 1995, the average incidence by district showed wide variations, ranging from 1.9 to 15.8 per 100 000, with high endemicity especially in southern parts of the country [61].

In Kazakhstan, the political changes, the emergence of a free market, economic reforms, the deterioration of the financial situation and of the veterinary field services appeared to be associated with an increased transmission of *E. granulosus* to humans and an alarming resurgence of CE [62]. The annual incidence of surgical cases has increased from 0.9 to 1.4 cases per 100 000 population during 1974–1990 to 2.0 and 2.5 cases per 100 000 in 1996 and 1997, respectively, representing an increase in actual numbers from 221 cases in 1990 to 415 in 1997. This increase of incidence has been most marked in the south of the country in the Zhambyl Oblast from 3.8 in 1990 to 10.3 per 100 000 in 1997, and the South Kazakhstan Oblast from 2.7 in 1990 to 3.6 per 100 000 in 1997 [62].

In the People's Republic of China human CE constitutes one of the major public health problems and is of increasing concern [9,55,63,64–66]. *E. granulosus* is endemic in at least 21 of China's 31 provinces, autonomous regions and municipalities, covering approximately 87% of the country's entire territory [66]. The highest prevalences in animals and man occur in the pastoral and semi-pastoral western provinces and regions (representing about 46% of the country's territory), including the provinces of Xinjiang, Qinghai, Gansu, Ningxia, Inner Mongolia, Tibet, and parts of Sichuan and Yunnan and a wide range of geographical, climatic and socio-ecological conditions [55,63,65].

From six highly endemic provinces or autonomous regions (Xinjiang, Gansu, Qinghai, Ningxia, Tibet and Inner Mongolia) a total of 26 065 surgical cases of CE was recorded during four decades between 1951 and 1990 [67], equivalent to an annual average of 651 cases. The analysis of 15 289 surgical cases from Xinjiang has indicated a steady increase of case numbers which reached an average of 1218 cases per year during 1986–1990. This increase was thought to be due in part to the improvement of medical services [68]. Up to 1993 further cases were recorded increasing the total number to 27 716 cases in the period 1951–1993 [65]. Based on the analysis of 15 289 of the cases diagnosed between 1951 and 1990 in the province of Xinjiang, an average annual incidence of 8.7 cases per 100 000 population was calculated for 1990, but the local rates in the various prefectures ranged between 0.07 (Hetian Prefecture) and 28.4 (Tacheng Prefecture), with even higher incidences in some counties, for example in the Yumin County (Tacheng Prefecture) with 42.2 cases per 100 000 population [68]. These data, probably underestimating the real number of cases, are indicative for a very serious situation in some of the highly endemic areas. This is also supported by recent prevalence studies. For example, in western Sichuan 3999 individuals were examined in 1997–1998 by abdominal sonography and chest X-ray for echinococcosis; in 2.1% of them *E. granulosus* cysts were detected [69], representing a theoretical group prevalence of 2100 per 100 000 individuals. In another study in southern Qinghai 3702 individuals were examined in 1997–1998 using the same methods, and 7.6% had lesions indicative for CE or AE, but differentiation beyond doubt was difficult [70]. Data from this group allow the calculation of a theoretical group prevalence of 7590 per 100 000 individuals. Group prevalences, especially those from smaller population groups at high infection risk, may not be representative for larger populations or regions, but they can provide hints for the extend of the problem on a local basis.

In South America more than 2000 new human cases of CE are operated annually, including 464 in Argentina (1.42/100 000 inhabitants), 367 in Uruguay (12.4/100 000), 573 in Chile (3.4/100 000) and 244 in Peru (2.4/100 000) [71]. However, the number of surgical cases underestimates the real number of cyst carriers in some endemic areas. For example, the following group prevalences have been recently reported, based on sero-reactivity in the Double Diffusion Arc 5 test: 2050/100 000 in south Argentina and 5800/100 000 in the south of Brazil [71]. Even higher group prevalences of 6000 to 14 900/100 000 have been found in areas of Neuquen, Chubut and Rio Negro (Argentina) [71] by abdominal ultrasound examination which is highly specific but does not detect pulmonary cysts. Although these data reflect the situation in relatively small population groups and include asymptomatic cases, they have to be regarded as alarming signals.

3.2. The global situation of E. granulosus *control*

Up to date, long-term control has resulted in eradication of *E. granulosus* or reduction of parasite prevalence to very low levels only in a few island situations, including Iceland, New Zealand, Tasmania and southern Cyprus [10,59]. In continental situations control measures have been performed in endemic regions of several countries, including Argentina, Chile, Uruguay, Spain, Bulgaria, some north African countries, Australia, and others. Although control resulted in impressive reduction of parasite prevalence in animal populations and decrease of disease transmission to humans in various countries (i.e. Argentina, Chile, Uruguay, Spain), parasite eradication has not been achieved.

In some regions, for example in several countries of central Europe and North and Central America, the current prevalence of *E. granulosus* is low. However, in many other countries in Eurasia, Africa and other regions of the world *E. granulosus* is widely distributed and represents a considerable public health problem [10], specific control measures have not yet been initiated, and the prospects for improving dog control and treatment, slaughter hygiene, health education, etc. are desperate for economic and in some areas also for political reasons. Therefore, it has to be expected that *E. granulosus* and human CE will persist or re-emerge in many of the endemic countries in the world.

4. Discussion

This and other reviews [2,10] indicate that AE and CE are widely distributed zoonoses which may cause severe or even lethal disease in humans and considerable economic losses. According to a recent report from the Rio Negro Province, Argentina, the annual costs for an integrated control programme against the *E. granulosus* infection and human CE amount to US$ 700 278, including $ 243 208 for treatment of patients, $ 17 070 for serological and ultrasound surveys in 10 000 children from 6 to 13 years, and $ 440 000 dosing of 12 000 dogs 8× per year [71]. In view of the low medical and public health budgets in many countries such costs are considerable. In 1995, the costs for a surgical case of human CE have been estimated to be about US$ 14 000 [72]. Patients with AE may require long-term and even life-long chemotherapy with benzimidazoles. In Germany the annual costs per patient for chemotherapy alone were determined to range from US$ 5500 to 17 800, while treatment for life was estimated to amount to US$ 300 000 per case [51]. In Hokkaido, Japan, cost estimates for treatment of 60 AE patients, including surgery in 20 and chemotherapy in 60 cases, amounted to a total of US$ 5 534 000 or an average of US$ 95 567 per patient (Suzuki and Sato, personal communication, cited in [2]).

Although data on the global economic significance of AE and CE are not available, various examples, especially cost-benefit analyses of control programmes against *E. granulosus* [71], indicate that these infections have a rather high financial impact in certain endemic regions.

There is clear evidence from Japan and North America that the *E. multilocularis* infection may spread from endemic to non-endemic regions. In central Europe the known endemic regions have significantly increased since the end of the 1980s, but is unclear whether due to disease spreading or detection of hitherto undiscovered endemic regions. The fact that the endemic region is much wider then previously anticipated should be reason for awareness and concern. Furthermore, several factors have been identified which could possibly enhance spreading of the *E. multilocularis* infection and increase the infection risk for humans. These factors include inter alia the increase of fox population sizes, suspected or documented increase of *E. multilocularis* prevalences in foxes, the increasing invasion of cities by foxes, the establishment of urban cycles of the parasite, changes in land-use patterns and human behaviour. In some countries, for example in Russia, financial restrictions have led to decrease in research on zoonoses and efficiency of public health and veterinary services. A further reason for concern is that efficient and cost-effective methods for control of the *E. multilocularis* infection are still lacking. Therefore, special emphasis has to be laid on prevention and early diagnosis of AE in humans.

The situation is different with regard to CE. For the control of the *E. granulosus* infection in animal and human populations, clear strategies and efficient methods are available, but they are costly and have to be performed for years or decades. Persistence or re-emergence of this infection is well documented in some countries and is primarily caused by the lack or reduction of control measures due to economic or other reasons. Reinforcement of currently available control programmes could prevent re-emergence of the infection and result in effective control. However, easier and cheaper methods are required to improve control worldwide. A new potential in this respect is vaccination of livestock animals in order to interrupt the cycle on that level, in association with other measures.

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