Epidemiology of alveolar echinococcosis with particular reference to China and Europe

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SUMMARY

Human alveolar echinococcosis (AE), caused by the metacestode of the fox tapeworm *Echinococcus multilocularis*, is the most pathogenic zoonosis in temperate and arctic regions of the northern hemisphere. Prospective collection of human cases in some areas and mass screenings using ultrasound imaging and confirmation with serological techniques have markedly improved our knowledge of the epidemiology of the disease in humans during the past two decades. Transmission occurs when eggs of the tapeworm, excreted by the final hosts (usually foxes but also dogs, wolves and cats), are ingested accidentally by humans or during normal feeding by a variety of rodents and small lagomorphs. However, the species of host animals differ according to regional changes in mammalian fauna. This review mostly focuses on epidemiology of alveolar echinococcosis in those parts of the world where new and more accurate epidemiological data are now available, i.e. China and Europe, as well as on new epidemiological trends that can be suspected from recent case reports and/or from recent changes in animal epidemiology of *E. multilocularis* infection. The People's Republic of China (PRC) is a newly recognized focus on AE in Asia. Human AE cases were firstly recognized in Xinjiang Uygur Autonomous Region and Qinghai Provinces at the end of 1950s and infected animals were first reported from Ningxia in central China and north-east of Inner Mongolia in the 1980s. *E. multilocularis* (and human cases of AE) appears to occur in three areas: (1) Northeastern China (northeast focus): including Inner Mongolia Autonomous region and Heliongjiang Province (2) Central China (central focus): including Gansu Province, Ningxia Hui Autonomous Region, Sichuan Province, Qinghai Province and Tibet Autonomous Region and (3) Northwestern China: including Xinjiang Uygur Autonomous Region, bordered with Mongolia, Russia, Kazakhstan and Kyrgyzstan. The highest prevalence of the disease, up to 15 per cent of the population in some villages, is reached in China. In Europe, data from the European Echinococcosis Registry (EurEchinoReg: 1982–2000) show 53 autochthonous cases of AE in Austria, 3 in Belgium, 235 in France, 126 in Germany, 1 in Greece, and 112 in Switzerland, and 15 'imported' cases, especially from central Asia; 14 cases were collected in Poland, a country not previously considered endemic for AE. Improved diagnostic technology, as well as a real increase in the infection rate and an extension to new areas, can explain that more than 500 cases have been reported for these 2 decades while less than 900 cases were published for the previous 7 decades. New epidemiological trends are related to an unprecedented increase in the fox population in Europe, to the unexpected development of urban foxes in Japan and in Europe, and to changes in the environmental situation in many countries worldwide due to climatic or anthropic factors which might influence the host–predator relationship in the animal reservoir and/or the behavioural characteristics of the populations in the endemic areas.

Key words: Alveolar echinococcosis, *Echinococcus multilocularis*, epidemiology, animal hosts, risk factors, geography.

INTRODUCTION

Human alveolar echinococcosis (AE), caused by the metacestode of the fox tapeworm *Echinococcus multilocularis*, is considered to be the most pathogenic zoonosis in temperate and arctic regions of the northern hemisphere. In fact no cases have ever been observed in the southern hemisphere, and the lowest latitude for endemic areas is about 28°N in Asian territories. AE cases in humans have been reported from three continents: North America, Europe and Asia. Three human cases reported from Tunisia may indicate that the disease is also present in North-Africa (Robbana *et al.* 1981); however, no confirmation of the species of *Echinococcus* involved in these cases, in that country where *E. granulosus* infection is highly prevalent, has ever been given, and no new cases have been reported since 1981. Fig. 1 summarises the geographic distribution of *E. multilocularis* in the world and the countries which are considered either as endemic areas, or potential ones when only isolated cases have been reported.

The primary target organ for the larva is the liver where it proliferates slowly, but it also spreads into extrahepatic structures and even metastasises to distant organs. Prognosis of AE has improved during

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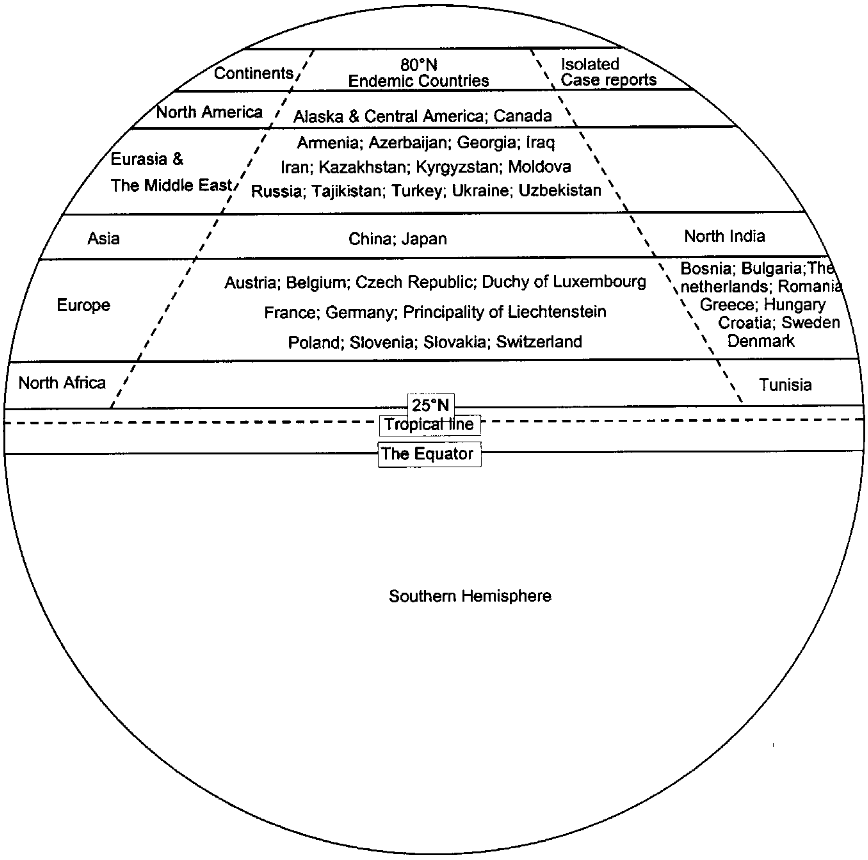

Fig. 1. Schematic representation of alveolar echinococcosis distribution in the world. Neither human cases nor *E. multilocularis* infection in animals have ever been reported in southern hemisphere. For most of the reported isolated cases, confirmation of the diagnosis of echinococcosis and/or of the species of *Echinococcus* involved was not given.

the past 2 decades in those countries where the appropriate and always complex therapeutic strategy may be applied; it remains poor if diagnosed late, and/or when access to medical care is not available or difficult (Vuitton, 1990; Ammann & Eckert, 1995; Bresson-Hadni *et al.* 2000). Diagnosis of the disease, which has a long (5–20 yrs) asymptomatic stage, mainly relies on the availability of good quality imaging techniques, which explains why accurate epidemiological data in many parts of the world have been only available in the past 2 decades. Ultrasound imaging has transformed the diagnostic approach of AE, and has made diagnosis of asymptomatic cases possible in hospital settings, even in remote parts of the world. CT-scan and Magnetic Resonance Imaging are mainly used for confirmation and pre-treatment assessment and staging (Ammann & Eckert, 1995; Bresson-Hadni *et al.* 2000). Especially, mass screenings using ultrasound imaging and confirmation with serological techniques have markedly improved our knowledge of the epidemiology of the disease in humans (see Macpherson, Bartholomot & Frider, in this supplement). Many excellent reviews on epidemiology of AE in Europe have been published (Stössel, 1989; Fessler, 1990; Eckert, 1996, 1997; Eckert & Deplazes, 1999; Eckert *et al.* 2000, 2001) and a comprehensive analysis of the data available on the spread of the disease in the world until the beginning of the 1990s can be found in Schantz *et al.* (1995).

Presence of human cases of AE is highly dependent of the presence of an actively functioning parasitic cycle in nature and thus understanding the local aspects of this cycle in a given region is essential to understand human epidemiology (Deplazes & Eckert, 2001). The natural transmission cycle of *E. multilocularis* is universally uniform in pattern, i.e. small mammals (rodents, pikas) act as intermediate hosts and carnivores of various species are definitive hosts. Transmission to humans occurs when eggs of the tapeworm, excreted by the final hosts (usually foxes but also dogs, wolves and cats), are ingested accidentally. However, the species of the host animals differ according to regional changes in mammalian fauna. Throughout the holarctic tundra zone, the cycle is completed through the predator–prey relationship existing between foxes, primarily the arctic fox (*Alopex lagopus*) and rodents of the genera *Microtus*, *Clethrionomys* and *Lemmus*. In central Europe, the cycle involves red foxes (*Vulpes vulpes*) and voles of various species, whereas in North America, the natural cycle involves coyotes (*Canis latrans*) and *V. vulpes* as final hosts. The predator–prey interactions between definitive and intermediate hosts (Rausch,

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Table 1. Definitive hosts (carnivores) recorded as susceptible species for *E. multilocularis* infection in the world (according to Zhou, H. X., 2001)

Carnivores	Places
Arctic fox (*Alopex lagopus*)	Former USSR; North America
Red fox (*Vulpes vulpes*)	Asia; Eurasia; The middle East Europe; North America
Corsac fox (*Vulpes corsac*)	China; Former USSR
Tibetan fox (*Vulpes ferrilata*)	China
Dog (*Canis familiaris*)	Alaska; Europe; China; Former USSR
Wolf (*Canis lupus*)	China; Former USSR
Coyote (*Canis latrans*)	North America
Wild cat (*Felis libyca*)	Former USSR
Cat (*Felis catus*)	Europe; Former USSR
Raccoon-dog (*Nyctereutes procyonoides*)	Former USSR
Grey fox (*Urocyon cinereoargenteus*)	Central North America

1995), as well as susceptibility and immunity of hosts (Vuitton, 2003), play a key role in the parasite transmission cycle. This includes seasonal fluctuations in numerical density of the intermediate host and the diversity of diet of the definitive host (see Giraudoux *et al*. 2002, and in this supplement) and fertility of the adult as well as larval stages of the cestode in animal hosts (Vuitton *et al*. 2002; Craig *et al*. in this supplement). Tables 1 and 2 give a list of the definitive and intermediate hosts respectively recorded as susceptible species for *E. multilocularis* in the world.

This review will mostly focus on epidemiology of alveolar echinococcosis in those parts of the world where new and more accurate epidemiological data are now available, i.e. China and Europe, as well as on new epidemiological trends that can be suspected from recent case reports and/or from recent changes in animal epidemiology of *E. multilocularis* infection. The land-mass of PR China is a huge, and detailed epidemiological data mainly obtained from the scientific literature in Chinese and from mass screenings performed in the past decade, have relatively recently become available. In the absence of data published in international journals, published materials of various sources (non-English language, PhD thesis dissertations) have been used whenever necessary, after checking carefully for accuracy and reliability. Whenever available, data on the animal hosts of *E. multilocularis* have been given for every region studied, especially when particularities might explain risk factors in a given area and/or when they were associated with land use or behavioural characteristics useful to understand human epidemiology.

ALVEOLAR ECHINOCOCCOSIS IN NORTH AMERICA

The parasite has been recorded in two distinct geographic regions, the north tundra zone (western Alaska) and central north America (centred on southern Manitoba and North Dakota) (Storandt *et al*. 1993, 2002). Very high prevalence of AE in Eskimo communities in Alaska, especially on St Lawrence Island, in the northern part of the Bering Sea, was observed between 1950 and 1990 (Rausch & Schiller, 1956; Wilson & Rausch, 1980; Stehr-Green *et al*. 1988). A mass survey using specific serology was undertaken in the 1980s and led to the discovery of 'abortive cases' (or 'aborted cases'), i.e. patients with a positive highly specific serology and calcified lesions in the liver that were found sterile when operated on (Rausch *et al*. 1987). This endemic focus does not seem to have progressed, since no reports on a significant number of new cases have been published in the past 10 years. Transmission to humans occurred through arctic foxes, with a prevalence of infection averaging 77% and could be in excess of 90%, that preyed on northern voles, especially *Microtus oeconomus* considered as the main intermediate host for *E. multilocularis*, and a varying lemming (*Dicrostonyx exsul*), the northern red-backed vole (*Clethrionomys rutilus*) and shrews (*Sorex cinereus*) (Rausch, Fay & Williamson, 1990). Village dogs, found infected in 1951 with a prevalence of 12%, were also considered important in the spreading of the parasite close to human communities (Rausch & Fay, 2002) and baiting of these dogs with praziquantel was adopted as a control measure on St Lawrence Island in the 1980s (Rausch, Wilson & Schantz, 1990).

In central North America, despite the presence of infected definitive and intermediate hosts, in North and South Dakota, Iowa, Minnesota, Montana, Wyoming, Nebraska, Illinois, Wisconsin, Indiana, and Ohio, and 3 contiguous Canadian provinces, with prevalences quite similar to those found in highly endemic areas elsewhere in the world, only 2 human cases have been reported; the first, diagnosed in 1957, from Winnipeg, and the second, in 1977, from southeastern Minnesota. Serological screening of 120 fox trappers in South Dakota failed to detect any positive cases (Storandt & Kazacos, 1993; Storandt *et al*. 2002; Schantz *et al*. 1995). Behavioural more than genetic factors may be hypothesised to explain

Table 2. Intermediate hosts (small mammals) recorded as susceptible species for *E. multilocularis* infection in the world (according to Zhou, H. X., 2001)

Family	Species	Location
Soridae (1 genus)	*Sorex jacksoni*	St Lawrence
Talpidae (1 genus)	*Talpa altaica*	Altai Krai
Sciuridae (3 genera)	*Sciurus vulgaris*	Iakutiia
	Citellus ungalatus	St Lawrence; Buriat-Mongolia
	C. alashanicus	Ningxia
	Marmota bobak	Pavlodarsk Oblast'
Cricetidae (6 genera)	*Neotoma cinerea*	Wyoming
	Peromyscus maniculatus	North America
	Cricetus cricetus	Western Siberia
	Meriones unguiculatus	Buriat (Mongolia); Inner Mongolia
	M. erythourus	Kazakhstan
	Meriones spp.	Iran
	Rhombomys opimus	Aktiubinsk-Oblast'; Kazakhstan
	Myospalax myospalax	Kazakhstan
	M. fontanieri	Ningxia
Muridae (3 genera)	*Apodemus agrarius*	Kazakhstan
	A. sylvaticus	Tselinogradsk Oblast'
	Mus musculus	Europe; Xinjiang
	Nesokia indica	Iran
Arvicolidae (7 genera)	*Microtus arvalis*	Germany; France; Switzerland; Russia
	M. oeconomus	Kurile Islands; St Lawrence; West Alaska
	M. socialis	Georgia
	M. roerti	Georgia
	M. irene	Sichuan
	M. hyperboreus	Iakutiia
	M. gregalis	Kazakhstan; Kyrgyzstan
	M. brandti	Inner Mongolia
	M. pennsylvanicus	North America
	Arvicola terrestris	France; Western Siberia
	Ondatra zibethicus	Russia; Kazakhstan; France; Germany; North America
	Lagurus lagurus	Tselinogradsk Oblast'
	Ellobius talpinus	Kyrgyzstan
	Lemmus sibiricus	Eurasia tundra
	Clethrionomys glareolus	Latvia
	C. rufocanus	Iakutiia
	C. rutilus	Hokkaido; Karaginsk; Kamachatka Novosibirsk Oblast'
Dipodidae (1 genus)	*Allactaga elater*	Azerbaizhan
Ochotonidae (1 genus)	*Ochotona daurica*	Tuva
	O. pricei	
	O. roylei	Kyrgyzstan
	O. curzoniae	Sichuan; Qinghai
Leporidae (1 genus)	*Lepus oiostulus*	Sichuan

the apparent discrepancy between the prevalence of animal and human infection in this area.

ALVEOLAR ECHINOCOCCOSIS IN CENTRAL ASIA

Human cases were reported from the former USSR, throughout Russia and most of the newly independent states including Ukraine, Byelorussia, Moldova, Georgia, Armenia, Azerbaijan, Kazakhstan, Uzbekistan, Tajikistan, and Kyrgyzstan (Lukashenko, 1968; Yarotskii *et al*. 1988; Schantz *et al*. 1995). Reviews by Bessonov (1998; 2002) report that some of the highest prevalence rates ever reported before the Chinese focus was studied (i.e. 10/100 000 and more) were recorded in Yakutia, Chukot, and Korjak autonomous districts, Kamchatka, Omsk and Tomsk regions and Altai territory. Medium prevalence rates (1–10/100 000) were recorded in Tuva republic, at the south of Krasnoiarsk territory, Magadan region and northern areas of Kazakhstan. Lower prevalence rates were recorded in some zones of west Siberia, East Povolzhje, Byelorussia, north Caucasus, and Azerbaijan. Most cases in the highly endemic region of Kamchatka were limited to indigenous people with activities in hunting and herding (Yarotskii *et al*. 1988). Unfortunately no update in the epidemiology of AE in Russia is available. Data given in the most recent publications are often old and fragmentary and need to be reviewed; no systematic mass-screening has ever been performed and/or published in Russia and the independent states of central Asia, which certainly represent one of the most endemic areas in the world. In fact nine species of carnivores (arctic fox, red fox, corsac fox, wolf, golden jackal, rural dog, racoon dog, wild cat and domestic cat) have been found naturally infected, as well as 30 species of small mammals, including voles, mice, shrews, lemmings, marmots, jirds, muskrats, ground squirrels, jerboas, hares and hamsters (Bessonov, 1998). It is likely that the parasite cycle is still very active, and that human cases still occur. The situation regarding AE was recently re-assessed in Kazakhstan: an average of 20 new human cases are observed each year in the eastern part of the country; the larval stage was found in 18 species of rodents, including marmots, steppe marmot (*Marmota bobac*) and grey marmot (*Marmota baibacina*), and gerbils, red-tailed gerbil (*Meriones libycus*) and great gerbil (*Rhomomys opimus*), especially in the forest-steppe, steppe zones and river valleys, and the adult stage in 4 species of definitive hosts, foxes (*Vulpes vulpes* and *V. corsac*), domestic dog (*Canis familiaris*), especially hunters' dogs, and wild cat (*Felis lybica*) (Shaikenov & Torgerson, 2002).

Isolated cases have been reported from northwest Iran, northern Iraq, southern Azerbaizhan and Afghanistan (Zarrifar, 1997; Al Irhayim, personal communication), and the natural cycle is known to be present in this area (Rausch, 1995), but most cases in central/western Asia have been diagnosed in Turkey. Cases of non-European origin recorded in the EurEchinoReg registry from 1982 to 2000 were born (and likely contracted infection) in the Newly Independent States (3 cases), Kazakhstan (1 case), Afghanistan (1 case) and in Turkey (3 cases). Among the 157 autochtonous Turkish cases reported from 1934 to 1983, 90% originated from central, eastern Anatolia and the Black sea and only 2% from the European part of Turkey (Uysal & Paksoy, 1986; Stössel, 1989). In a series of 39 surgical cases, more than 90% came from the eastern, Asian, part of Turkey. Between 1980 and 1998, 189 AE cases were collected from different regions. The ages ranged from 7 to 70 years for these 119 cases; 49 (41%) were males and 70 (59%) were females. The origin of most of the patients was from eastern Anatolia (57%), especially from Erzurum (Altintas, 1997). Associated with the EurEchinoReg programme described below, Altintas collected 202 cases from 1980 to 1998 (Kern *et al.* 2003). In all Middle East and central Asian countries where AE cases were reported from, both *Echinococcus* spp. are responsible for human disease and confusion is possible. However, in Turkey, the collection of AE cases originated mostly from surgery, and the cases were confirmed by pathological examination. The role of the various potential definitive and intermediate hosts in transmission to humans is still unknown; presence of *E. multilocularis* in a fox, in the north-west of Turkey, was reported by Merdivenci in 1965 (cited in Altintas, 1997). Research projects are currently considered for both Turkey and Iran.

ALVEOLAR ECHINOCOCCOSIS IN EASTERN ASIA

Japan

The first human case of AE was recognised in 1936 in Hokkaido, the northern island of Japan (Tunoda, Mikami & Aoki, 1937; Suzuki, Sato & Uchino, 1993). *E. multilocularis* was introduced with infected foxes transferred to Rebun Islands, northwest of Hokkaido from the Kuriles islands, to fight against rodents, in years 1924–26. Another transfer of foxes took place in the 1960s. A total of 383 human AE cases were detected since then, up to 1999, and 5–9 cases per year are newly disclosed by the Committee for Echinococcosis Control in Hokkaido (Tsukada *et al.* 2000). Periodic serological screening of potentially exposed populations over the past 25 years has shown that farm residents were the population group the most at risk in Japan, due to faecal contamination by foxes that scavenge in the proximity of farms. The fox is the animal symbol of Hokkaido Island and rather well tolerated by farmers; approaching foxes has become a tourist attraction in some parts of Hokkaido, and this could be a reason of extension of the diseases to the subjects from other islands of Japan (Takahashi, personal communication). In fact, a report of 60 AE cases on Honshu, the main island of Japan, has been published (Kamiya, 1988; see also Ito *et al.* in this supplement); 17 would be autochtonous, however, evidence of a definitive clinical confirmation of these cases has not been given. In endemic areas of Japan (i.e. nearly the entire territory of Hokkaido Island and Rebun Island), *E. multilocularis* circulates between foxes, stray dogs, and voles (Yamashita, 1973); cats were occasionally found infected but there is no evidence that they participate in human contamination. *Clethrionomys rufocanus*, *C. rutilus* and, more recently, *C. rex* have been identified as the main intermediate hosts involved in the cycle in nature (Takahashi *et al.* 1989; Takahashi & Nakata, 1995). Horses, rats and especially pigs, raised in farms and fed with contaminated grass, were also found infected but their role in the natural cycle is doubtful.

People's Republic of China

The People's Republic of China (PRC) is a newly recognized focus of AE in Asia. Human AE cases were first recognized in Xinjiang Uygur Autonomous Region (XUAR) and Qinghai Provinces (QP) at the end of 1950s and infected animals were first reported from Ningxia in central China and north-east of Inner Mongolia in the 1980s (Li *et al.* 1985; Tang *et al.* 1988). To date, eight provinces or autonomous regions in China have been found endemic (Ito *et al.* 2003) (Fig. 2). *E. multilocularis* appears to occur in three areas: (1) Northeastern China (northeast focus): including Inner Mongolia Autonomous region (IMAR) and Heliongjiang Province (HP) (mainly

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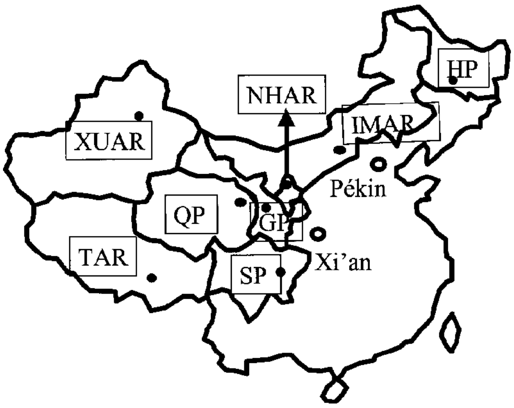

Fig. 2. Provinces and autonomous regions of PR China where alveolar echinococcosis is endemic. GP: Gansu Province; HP: Heilongjiang Province; QP: Qinghai Province; SP: Sichuan Province; IMAR: Inner Mongolia Autonomous Region; NHAR: Ningxia Hui Autonomous Region; TAR: Tibet Autonomous Region; XUAR: Xinjiang Uigur Autonomous Region.

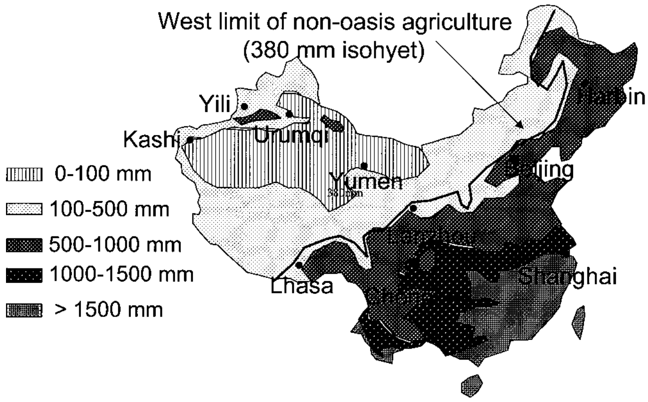

Fig. 3. Climatic map of PR China. Numbers art mean annual rainfall in mm.

covers the area of Hulunbeier Pasture, Da-xing-an-ling, Xiao-xing-an-ling mountains at the border with Russia and Mongolia). (2) Central China (central focus): including Gansu Province (GP) (mainly southern part on the confluence area of Qinghai–Tibet plateau and Loesis plateau): Ningxia Hui Autonomous Region (NHAR) (mainly Liupan mountains area in southern part on the Loesis plateau); Sichuan Province (SP) (mainly in Ganzi, Arba prefecture on Qinghai–Tibet plateau); Qinghai Province (QP) and Tibet Autonomous Region (TAR) (mainly at the border area with GP, SP) on Qinghai–Tibet plateau. (3) Northwestern China: including Xinjiang Uygur Autonomous Region, especially in Altai, Western Junggar and Tianshan mountains, Pamir Plateau bordered with Mongolia, Russia, Kazakhstan and Kyrgyzstan. The known foci are all situated in the mountainous areas covered with grassland or steppe, but no epidemiological details are available to make the distribution limits of the three foci in PRC more precise. Considering the climate and land-use pattern in China, the location of endemic areas likely overlap the places with annual precipitation of 300–500 mm and grassland (Fig. 3). The distribution range of *E. multilocularis* approximately fits the areas close to the 380 mm isohyet (Western Limit of non-oasis agriculture line) where mountain pastures, river canyons and steppe are typical landscape, and terraced farmland has been extended to the valley of lower altitude during the past five decades. The social and economic conditions within these areas are comparable; for instance, poor economic condition, isolated communities of minority ethnic groups with Muslim or Buddhist religions, animal herding with little agriculture. Although Xinjiang is far towards the west from the isohyet, its mountain areas have similar climate and social economic conditions as other endemic areas. The enzootic areas likely occur only in the areas of grassland, steppe and scrubland landscape at certain altitude with annual rainfalls more than 300 mm and mean temperature lower than 20 °C in July. The exact correlation between landscape, climate conditions and *E. multilocularis* distribution in China still requires appropriate studies which are currently being undertaken by several coordinated Chinese and international research multidisciplinary teams (Ito *et al.* 2003). Table 3 gives a summary of prevalence rates of AE in humans in central China, based on community surveys using ultrasound imaging and serology. The following description of AE in humans in the eight provinces or autonomous regions of PR China involved gives a synthesis of all sources available in international and Chinese literature together with some unpublished data obtained in the most recent studies in this area.

Heilongjiang Province (*HP*). HP (43°20′–53°20′N, 122°10′–135°5′E), located in the most northeastern part of China, shares the border with Russia by Heilong River to the north. It covers an area of 460 000 square kilometres with a population of 35 570 000 (the population density is 77·33 per square kilometre). Mean annual precipitation is 400–700 mm. Four human AE cases have been documented in three counties of the province (Yu *et al.* 1994). Cases from Nahe County and Jamusi City were reported respectively (Li *et al.* 1985; Wen, 1990). These two cities are close to Da-xin-an-ling and Xiao-xin-an-ling mountains where deforestation and farmland extension were noted as early as the 1950s (Xia, 1996). No data are available on animal infection and the characteristics of the local cycle of the parasite are unknown.

Inner Mongolia Autonomous Region (*IMAR*). IMAR (37°–54°N, 97°–126°E) covers an area of 1 100 000 square kilometres with a total population of 22 170 000. The region is bordered with Mongolia to the north and Russia to the northeast. The main

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Table 3. Prevalence rates of alveolar echinococcosis in humans in central China (based on community surveys; cases were diagnosed with ultrasound and/or serological test)

Source	Wang *et al.* (1991)	Craig *et al.* (1992, 1997)	
Location	Liu-pan Mountains on the Loesis Plateau	Qinghai–Tibet Plateau	
Province	Ningxia Hui Autonomous Region	Gansu Province	
Prefecture	Guyuan Prefecture	Dingxi Prefecture	
County	Xiji 5·90% 141/2389	Zhang 4·95% 65/1312	Zhang & Ming 3·4% 84/2482
Sex			
Female	6·67% 90/1349	7·79% 47/603	4·83% 52/1077
Male	4·90% 51/1040	2·54% 18/709	2·82% 32/1402
Occupation			
Farmer	9·70% 137/1413	4·95% 65/1312	3·34% 83/2482
Herdsman	no	no	
Others	0·41% 4/976	no	
Ethnicity			
Han	5·1% 73/1433	4·95% 65/131	3·4% 84/2482
Hui	7·11% 68/956	no	no
Tibetan	no	no	no
Age range	19–72	11–73 (40·9)	12–70 (38·7)
Diagnostic methods	Ultrasound + ELISA	Ultrasound + ELISA	Ultrasound + ELISA
Peak value Age group	25–55	31–50	
Survey year	1988	1991	1994–1997

Source	Qiu *et al.* (1999); Schantz *et al.* (1998); Liu *et al.* (1998)					
Location	Qinghai–Tibet Plateau					
Province	Sichuan Province			Qinghai Province		
Prefecture	Ganzi Tibetan Prefecture			Yushu Tibetan Prefecture		Huangnan Tibetan Prefecture
County	Shiqu 2·96% 37/1251	Shiqu & Gahnzi 1·9% 76/3999	Ganzi 1·42% 39/2748	Gengduo 2·96% 37/1251	Yushu 2·03% 8/394	Zeku 0·29% 3/1046
Sex						
Female	5·27% 30/569	2·62% 45/2080	no data	no data	no data	0·29% 3/1046
Male	no data	1·62% 31/1919	no data	no data	no data	no data
Occupation						
Farmer	no data	1·14% 6/526	1·35% 7/520	no data	no data	no data
Herdsman	6·59% 27/410	5·44% 44/809	3·19% 10/313	2·12% 12/565	no data	no data
Others	no data	0·98% 26/2664				
Ethnicity						
Han	no data	no				
Hui	no	no				
Tibetan	no data	1·90% 76/3999				
Age range	13–81 (45·6)					
Diagnostic methods	Ultrasound + ELISA			Ultrasound + ELISA		
Peak value Age group	no data			no data		
Survey year	6/1997–8/1998			1997–1998		

inhabitants are Mongols with herding activities. The annual precipitation is 80–450 mm (higher in east and lower in west). One male case from Hulunbeier pasture was reported in 1987 (Ji, Xing & Xu, 1987). The case lived in Chen-bai-hu-qi where infected rodents were recorded (Tang *et al.* 1988). Although more human AE cases were diagnosed in the province, according to local reports, no more cases were formally published from this region. Corsac foxes were found infected in this area; *Microtus brandti* (a cyclic species) and *Meriones unguiculatus* have been recorded as naturally infected, but other small mammals from the rodent and lagomorph families (e.g. *Ochotona daurica*) are present and may also serve as intermediate hosts.

Ningxia Hui Autonomous Region (*NHAR*). NHAR (35°14′30″–39°23′N; 104°17′–107°38′50″E), located on the Loesis in central China, covers an area of 66 000 square kilometres with a population of

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5 040 000. One third of inhabitants are Hui Muslims with farming activities. Annual precipitation is between 200 and 600 mm; it is higher in Liupan Mountains in the southern area connected to Gansu province and lower in the northern area connected to Inner Mongolia Autonomous Region. Human AE cases were found in three counties (which belong to Guyuan Prefecture): Xiji, Haiyuan and Guyuan Counties in the Liupan Mountains area, in southern NHAR (Lin & Hong, 1991; Wang *et al*. 1991). Up to 1989, 304 human AE cases from XHG were diagnosed (E.P.S.N.R., 1999). A community mass-screening survey was conducted in Xiji County in the 1980s (Wang *et al*. 1991). A total of 2389 subjects from two villages (Xinyeng village with a majority of Han people, and Bai Ai village with a majority of Hui people) and one town (Xiji county city, civil servants) were examined with ultrasound and serological tests (ID and ELISA). A total of 141 human AE cases were diagnosed as AE by ultrasound and confirmed by serological tests (prevalence rate 5·9%). The age of infected people ranged from 19 to 72 years. No significant differences of prevalence were observed between sexes and ethnic groups, but a higher prevalence (9·7%: 137/1413) was recorded in farmers living in rural areas and a lower prevalence in those living in cities (0·4%: 4/976) (Wang *et al*. 1991); 4 cases from the same family of 8 members were diagnosed. This family used to hunt ground squirrels (*Spermophilus* spp.) for meat and gave the raw viscera to their dogs. A community ultrasound screening in Yumu village (which belongs to Xiazhai community of Xiji County) showed a prevalence rate of AE of 4·6% (6/130) in this village (E.P.S.N.R., 1999). A total of 113 clinical cases diagnosed in Guyuan Hospital between 1965 and 1991 were reported (Mu & Sueng, 1991): mean age was 31 yrs, 80% of the patients aged from 20 to 40 yrs and the male to female ratio was 1·1 : 1. Preliminary results of a mass screening performed in 2114 subjects living in the northern area of Xiji county in 2002 showed an overall prevalence of 2·4%, with a prevalence over 6% in 3/9 communes (Nan Wen, Bai Ai and Zhuang Cun Pu). (P. S. Craig and Yang Yurong, personal communication). The mean and lower age of the patients disclosed with AE lesions suggest that patients were infected more than 20 years ago and that the local parasitic cycle could have been interrupted after dog populations dramatically declined following campaigns to kill rodents using anti-coagulant drugs at the beginning of the 1990s. Infection of red fox (*Vulpes vulpes*) in this province in 1985 by Li and co-workers was the first report of animal infection by *E. multilocularis* in China. Dogs were likely involved in transmission to humans in the rural communities of south Ningxia in the past (Rausch, 1995; P. S. Craig, personal communication); however no dog infection has formally been identified. Infected *Spermophilus dauricus* and *S. alashanicus* were found in 1985 (Li *et al*. 1985), both *Spermophilus* spp. and *Myospalax fontanieri* were infected with fertile cysts containing protoscolices in 1987 (Hong & Ling, 1987), though experimental infection in the genus *Spermophilus* has generally shown a poor fertility of cysts (Rausch, 1995; Zhou *et al*. 1998). *Ochotona* spp., lagomorphs involved in *E. multilocularis* transmission in other provinces, were not infected in this autonomous region. Other suitable intermediate hosts such as *Cricetulus* spp. and *Meriones unguiculatus* were recorded in scrub-grassland in Liupan Mountains (Wang, 1989); evidence of infection by *E. multilocularis* is, however, missing from parasitological reports. The situation of northern Ningxia, close to Inner Mongolia, regarding AE in humans is not clear: no human cases were spontaneously reported in this area.

Gansu Province (*GP*). GP (32°30′–42°47′N, 92°13′–108°40′E) has border with NHAR towards northeast, SP towards south, QP towards west; it covers about 390 000 square kilometres of area with a population of 23 520 000. Mean annual precipitation is 40–800 mm (lower in west and higher in southeast). Human cases were recorded only in southern GP. The first community mass screening performed at the end of the 1980s in Zhang County of Dingxi Prefecture revealed that a serious public health problem occurred in this province (Craig *et al*. 1992). Prevalence rate in humans averaged 5% (65/1312) and was significantly higher in females than in males. This high prevalence was attributed to infected dogs combined with poor hygienic conditions (Craig *et al*. 1992). In 1994, a collaborative Chinese, British and French study was initiated to better understand the epidemiology of the disease in this area. An ultrasound mass screening (with serological confirmation) carried out in Zhang and Ming Counties between 1991–1997 revealed that prevalence rates ranged between 0–16% in villages and a peak value of 16% was recorded within a small region (20 km radius). Overall mean prevalence was 4% (135/3331) within the two connected counties (Zhang and Ming) (Craig *et al*. 1992, 2000; Bartholomot *et al*. 2002). Among 2482 subjects from 28 villages, a typical lesion of progressive AE was disclosed in 84 subjects; in addition various types of calcifications were observed in the liver of 451 examined subjects, suggesting a high prevalence of 'abortive cases'. Females found with AE lesion were more frequent than males: 52 women and 32 men, mean age 38·7 yrs (extremes 12–70 yrs). This seems to reflect special conditions of human contamination, with dogs as an important definitive host, and more frequent contact of children and women with these dogs. In fact, dogs seem to play (or to have played) a major role in human contamination. Six of 59 dogs examined (10%) were found infected in Zhang County. Numbers of *E. multilocularis* worms in dog intestines ranged from 20 to 5000 worms (Shi, 1995; Craig *et al*.

1992). Wolf, red fox, corsac fox (*Vulpes corsac*) and Tibetan fox (*V. ferrilata*) are present in Gansu. Only the red fox, and very rarely the wolf, were believed by farmers to be present in the study area of Zhang and Ming counties where the highest prevalence of AE in humans was found; however they were not systematically studied for *E. multilocularis* infection (Zhang, 1997). An ecological survey of small mammals in the endemic area has shown that the deforestation which occurred twenty years ago had resulted in the succession of small rodent communities in this area (Giraudoux *et al*. 1998). Shrub-lands and pastures, a vegetation stage occurring after deforestation, might have supplied favourable habitats for susceptible species such as *Microtus limnophilus* and thus enhance *E. multilocularis* transmission dynamics in this area (for a review, see Giraudoux *et al*. 2002, and Giraudoux *et al*. in this supplement). However, no formal demonstration of infection of the various small mammal species present in the area has ever been given. Transmission to humans may well have been interrupted in this region: because of massive deforestation, the populations of wild carnivores have markedly decreased: foxes have been rarely seen in the past ten years; and the local villagers confirmed that dogs were eliminated at beginning of the 1990s; as in Ningxia autonomous region, dogs as well as foxes might have been killed by secondary poisoning during rodent-control campaigns. It is thus unlikely that active transmission still occurs in this area which had the highest prevalence of AE ever reported in the world. In fact, taking the population size in the two counties into account, the prevalence rate may be estimated to be 200 per 100 000 inhabitants in comparison to 65 per 100 000 in St Lawrence (Alaska), 10 per 100 000 in Franche-Comté (eastern France) or in northern Switzerland (Schantz *et al*. 1995; Bresson-Hadni *et al*. 1997; Eckert, 1997).

Qinghai Province (*QP*). Qinghai Province (31°30′–39°30′N; 89°30′–103°40′E) is located totally on the Qinghai–Tibet plateau. It covers the area of 720 000 square kilometres with 4 610 000 inhabitants. Mean altitude is 3000 m with summer pastures above 4500 m. Most areas are covered with steppe pastures for animal husbandry and bare ground. Farmland only occupies small areas close to Xining City (capital of the province) at a lower altitude. The mean annual precipitation is about 100–600 mm. Human AE cases were discovered at the end of 1950s and the first clinical report from this province was published in 1964 (Liu & Qu, 1964). This is probably the earliest report of a human AE case in China. The first reported patient was 22 yr-old man who died of AE brain metastases in 1959. Twenty cases of liver AE were reported from the same hospital. Qinghai Endemic Disease Control Office has reported 143 cases of AE coming from 18 counties over the province, diagnosed from 1980 to 1992. Most cases lived in the south-eastern part where herding is the main activity (Wang *et al*. 1999). Epidemiological information is available from a community screening (by ultrasound) carried out in Yushu Tibetan Prefecture (including Yushu and Chengduo counties which are close to Sichuan Province) and in Huangnan Tibetan Prefecture (Zeku County which is close to Gansu Province) in 1997 and 1998. The prevalence rate in humans was of 2·0% (8/394) in Yushu County, 1·52% (19/1253) in Chengduo County, and 0·29% (3/1046) in Zeku County (all 3 cases were Tibetan women) (Liu, Qiu & Schantz, 1998; Schantz, 1998). Two out of fifteen feral dogs (13·3%) in Chengduo County of Yushu Tibetan Prefecture were found to be infected in 1994 (Schantz, 1998); 3/9 foxes (*Vulpes corsac* and *V. ferrilata*) were found infected in Haibei Prefecture (Wang *et al*. 1999). Naturally infected *Ochotona curzoniae*, 'pikas', have been reported in this province (Guo, 1986; Wang *et al*. 1999; Liu *et al*. 1998; He, Han & Wu, 1994). Very high prevalence rates of 3·5% were found in Huangnan Tibetan Prefecture (Wang *et al*. 1999), 3·5% to 7·7% in Yushu County and 3·5% in Chengduo County of Yushu Tibetan Prefecture (Liu *et al*. 1998; He *et al*. 1994). *Ochotona* has been reported as the main pest on the alpine meadows of this region (Wang, 1996). One hare (*Lepus oiostolus*) in Huangnan Prefecture, 18/384 yaks and 31/578 sheep were also naturally infected with *E. multilocularis* in this area (Wang *et al*. 1999); however, these species are unlikely involved in the maintenance of the parasitic cycle. It is, conversely, likely that the parasitic cycle responsible for human infection involves all 3 species of foxes (including *Vulpes ferrilata*) present in the province as well as feral dogs, and *Ochotona curzoniae*, which are known to serve as prey to foxes and dogs as well (Liu *et al*. 1998; Schaller, 1998). Microtine species (noticeably *Microtus oeconomus*) are widely spread on the plateau and may also be involved locally. The dog population is steadily increasing especially in Buddhist communities for religious reasons. Wolves may also be involved in the parasite cycle: Schaller (1998) reported that they preyed heavily on marmots and *Ochotona*.

Sichuan Province (*SP*). SP (26°–34°40′N, 97°30′–108°30′E) covers areas of 478 000 square kilometres with a population of 80 820 000 (Chongqin city, which became an independent metropolis in 1997, not included). It is one of the provinces with the highest population density in China. Its western part is located on Qinghai–Tibet plateau and bordered with Tibet, Qinghai and Gansu Provinces. Mean annual precipitation ranges from 500 to 1200 mm. Human cases of AE were only identified in Arba and Ganzi Tibetan Autonomous Prefectures located on the Qinghai–Tibet plateau. In these two autonomous prefectures, human cases were found in Shiqu, Derger, Ganzi, Seda, Kangding and Nuoergai counties

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(Lin & Hong, 1991; Qiu, Liu & Schantz, 1999). The areas where AE cases have been documented are endemic for both AE and cystic echinococcosis (see Schantz *et al*. in this supplement). An epidemiological survey of echinococcosis (including AE and CE) in Ganzi and Shiqu County of Ganzi Prefecture was undertaken between June 1997 and July 1998. Among 3999 subjects from 8 communities (36°19′–31°24′N; 97°20′–100°25′E) who were screened using B-ultrasound, X-ray and Dot-ELISA, 76 AE cases were diagnosed which represents a prevalence rate of 1·9%. In Shiqu County where most of the landscape was dominated by pastures and populated with pastoralists, the mean prevalence rate nearly reached 3% of the total population and 6·6% in the herdsmen population (most of them are Tibetan). In Ganzi County, where semi-pasture and semi-agriculture areas are present, the mean prevalence was 1·4% in the total population, and 3·2% in herdsmen (Qiu *et al*. 1999; Liu *et al*. 1998). The prevalence rates were statistically different between the two counties. Potential risk factors for human infection with *E. multilocularis* were analysed: the prevalence rate was strongly and positively linked with low economic income of the family, drinking pool water rather than tap water, dog ownership, fox pelt ownership (Qiu *et al*. 1999; Wang *et al*. 2001). Surveys on *E. multilocularis* in wildlife at Ganzi Tibetan Prefecture (including Shiqu and Ganzi Counties) from 1983 to 1997 revealed prevalence rates of 57% in red fox, 59·1% in Tibetan fox, and 17% in feral dogs. High prevalence rates of *E. multilocularis* were found in *Microtus irene* (up to 25%), *Ochotona curzoniae* and *Lepus oiostolus* (Qiu *et al*. 1999). Several species of livestock were also infected with *E. multilocularis* such as yak, sheep (3·1%) and pigs. Due to the concomitant presence of both *E. multilocularis* and *E. granulosus* in this area, misidentification of the lesions is possible; however, the substantial number of livestock reportedly infected with *E. multilocularis* both in Qinghai and Sichuan Provinces, by researchers well aware of the parasitological characteristics of both *Echinococcus* species, is puzzling and needs further confirmation using molecular characterization of the species.

Tibet Autonomous Region (*TAR*). Like Qinghai Province, Tibet Autonomous Region (26°30′–36° 30′N, 78°–100°E) is entirely located on the Qinghai–Tibet plateau and covers an area of 1 200 000 square kilometres with a population of 2 320 000. The population density is the lowest in China (1·9 inhabitants per square kilometre). Annual precipitation ranges 200–500 mm. Some areas can reach 2000 mm in south TAR (Himalaya Mountains area). Fourteen human AE cases have been documented in the northeast part of Tibet (Changdu and Naqu Prefectures) near Qinghai and Sichuan Provinces (Peng, 1988; Yixi, 1992; Luo, 1993; Pu, 1999). Ten clinical AE cases were reported from People's Hospital of Tibet in Lhasa (Yixi, 1992). No more information on epidemiology in humans, especially from systematic surveys, is available. Feral dogs were infected with *E. multilocularis* in eastern TAR close to Sichuan Province (F. J. Liu, personal communication). *Ochotona* is the dominant genus of small mammal in the pasture areas and also a main prey for Tibetan foxes (Schaller, 1998). To date no more investigations on *E. multilocularis* cycle in this region have been reported.

Xinjiang Uygur Autonomous Region (*XUAR*). XUAR (34°32′–49°31′N, 73°32′–96°21′E) in northwestern China covers an area of 1 600 000 square kilometres with a population of 16 050 000 inhabitants. It is the largest province (or autonomous region) of China. Mean annual precipitation ranges from 20 to 500 mm (higher in north and lower in south). It shares a border, from northeast to southwest, with Mongolia, Russia, Kazakhstan, Kyrgyzstan, Tajikistan, Afghanistan, Pakistan and India. Except for Afghanistan and Pakistan, most of the former USSR countries bordered with Xinjiang are known to be endemic for *E. multilocularis* (Bessonov, 1998).

In 1956, the first human case (a 33 yr-old Kazakh male) from Yili valley was hospitalized in the first affiliated hospital of Xinjiang Medical University (formerly Xinjiang Medical College) in Urumqi. This case was not diagnosed clearly until the second patient (a 24-yr old Kazakh female) was seen in the same hospital in 1958. The first 6 clinical cases diagnosed in this hospital were reported in 1965 (Yao *et al*. 1965). After then, new cases have been diagnosed regularly in the same hospital: 52 clinical cases from the whole region were reported in 1986 (Yao *et al*. 1986). However, in most reports, little information on epidemiology is available (Yao *et al*. 1965, 1986; Wang, 1978), and until the end of the 1990s, endemic areas were considered to be located along central Tianshan mountains and Kazakhstan border (Schantz *et al*. 1995). Epidemiology of AE in XUAR has been updated in 2000 by the analysis of data collected from the medical records of 157 clinical cases, all diagnosed after 1980, who had attended the four main hospitals in the region (in Urumqi, Yili, and Karamay) where imaging equipment available after 1980 has made correct identification of cases possible (Zhou *et al*. 2000). These data indicate that the disease is relatively common in the Altai, western Junggar, and Tianshan mountain ranges, whereas the Tarim and Junggar basins are likely to be of low endemicity. The highest prevalence (3·9/100 000) was observed in the Altai mountain zone. The prevalence of the disease in the Kunlun Mountain appears low but could have been underestimated. Semi-nomadic groups, especially those of Kazakh and Mongol origin, have a higher risk of infection than other ethnic groups. However changes in the

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Table 4. Alveolar echinococcosis in humans; annual incidence rates of symptomatic cases per 100 000 inhabitants, and asymptomatic AE cases found at mass screenings, from published data

Country	Period	Incidence	Reference
Austria			
Whole country	1983–1990	0·02	Auer & Aspöck (1991)
France			
Franche-Comté	1971–1988	0·5	Bresson-Hadni (1988)
Dépt du Doubs	*1960–1992*	*1·4*	*Bresson-Hadni et al. (1994)*
Dépt du Doubs, mass screening (dairy farmers)	*1987–1992*	*8/7, 884*	*Bresson-Hadni et al. (1994)*
Franche-Comté	1983–1998	0·7	Bresson-Hadni *et al.* (2000)
Germany			
Bavaria	1985–1989	0·03	Nothdurft *et al.* (1995)
Baden-Württemberg, mass screening (endemic village)	*1997*	*3/2, 560*	*Romig et al. (1999)*
Switzerland			
Whole country	1970–1983	0·18	Gloor (1988)
Whole country	1984–1992	0·10	Eckert *et al.* (1995)
Canton du Jura	*1970–1983*	*0·74*	*Gloor (1988)*
Western Switzerland, mass screening (blood donors)	*1986*	*2/17, 166*	*Gottstein et al. (1987)*

In italics: studies performed in limited areas where average fox infection by *E. multilocularis* reaches 50%.
Number of AE cases/number of screened subjects in endemic areas is given for mass screenings.

behaviour of communities, and especially sharing of winter settlements with Han sedentary communities, could also change epidemiological features of the disease in the endemic areas. Prevalence of the disease appears to be correlated with aspects of the local climate such as relatively high annual precipitation (higher than 400 mm) and low temperatures (averaging −22 °C in January and 17 °C in July). In four Counties (Ermin, Toli, Tacheng and Yumin counties) in Western Junggar Mountain at the border area with Kazakhstan, adult *E. multilocularis* were found in 11 of 36 red foxes and 1 of 2 wolves. The role of dogs in the transmission to humans is doubtful: Liu (1993) noted that a total of 27 186 dogs had been examined for the presence of *Echinococcus* spp. after autopsy from 1957 to 1991 in Xinjiang: no occurrence of *E. multilocularis* was reported in dogs by investigators. Except very few reports of naturally infected *Mus musculus* and *Spermophilus erythrogenys* without protoscoleces, which still have not been confirmed, no formal identification of the small mammals involved in the parasite cycle in XUAR has been done. Bone remains of *Marmota* were found in dog faeces collected from the western Junggar mountains in July 1996, and the Altai mountains in 1998 (Zhou, 2001); this suggests that dogs could also be involved in human transmission in this region. Microtines, *Ochotona* spp., and *Marmota* spp., which are abundant in mountain areas and were reported as prey for foxes and wolves in the Kunlun mountain (Schaller, 1998), could well serve as intermediate hosts and contribute to maintain the local natural cycle, as well as species of cold semi-desert as *Allactaga* spp., *Dipus* spp., *Cricetulus* spp. and *Meriones* spp. Actually, small mammal communities, landscape and ecological conditions may be very diverse within some hundred kilometres. The respective role of each community regarding sustainable transmission still remains unknown.

ALVEOLAR ECHINOCOCCOSIS IN EUROPE

Western Europe

Some incidence rates from European countries based on well documented published studies up to the beginning of the 1990s are summarised in Table 4. The average incidence rates, referred to the total population of a country, are rather low: 0·18 (1970–1983) and 0·10 (1984–1992) cases per 100 000 inhabitants per year in Switzerland; 0·02 and 0·03 in Austria and Bavaria in Germany. However, locally, because of the geographically-focused nature of the parasitic cycle, the incidence rates may be higher, for example in the Canton du Jura in Switzerland with 0·74, or in the Département du Doubs in France with 1·4. This has to be taken into account when examining the actual risk in a given European region. Between 1980 and 2000, autochthonous human cases of AE have been documented and published from several European countries, namely Austria, France, Germany, Switzerland and the European part of Turkey (see Bresson-Hadni *et al.* 1988, 1997, 2000; Stössel, 1989; Vuitton *et al.* 1990; Schantz *et al.* 1995; Ammann & Eckert, 1995; Eckert, 1997; Eckert & Deplazes, 1999; Eckert *et al.* 2001). The number of verified and published cases from Europe (Austria, France, Germany and Switzerland) between 1900 and 1980 amounted to 844 cases (Fesseler, 1990). Sporadic ‘imported’ cases were described from Belgium (Claudon, 1983). A systematic recording

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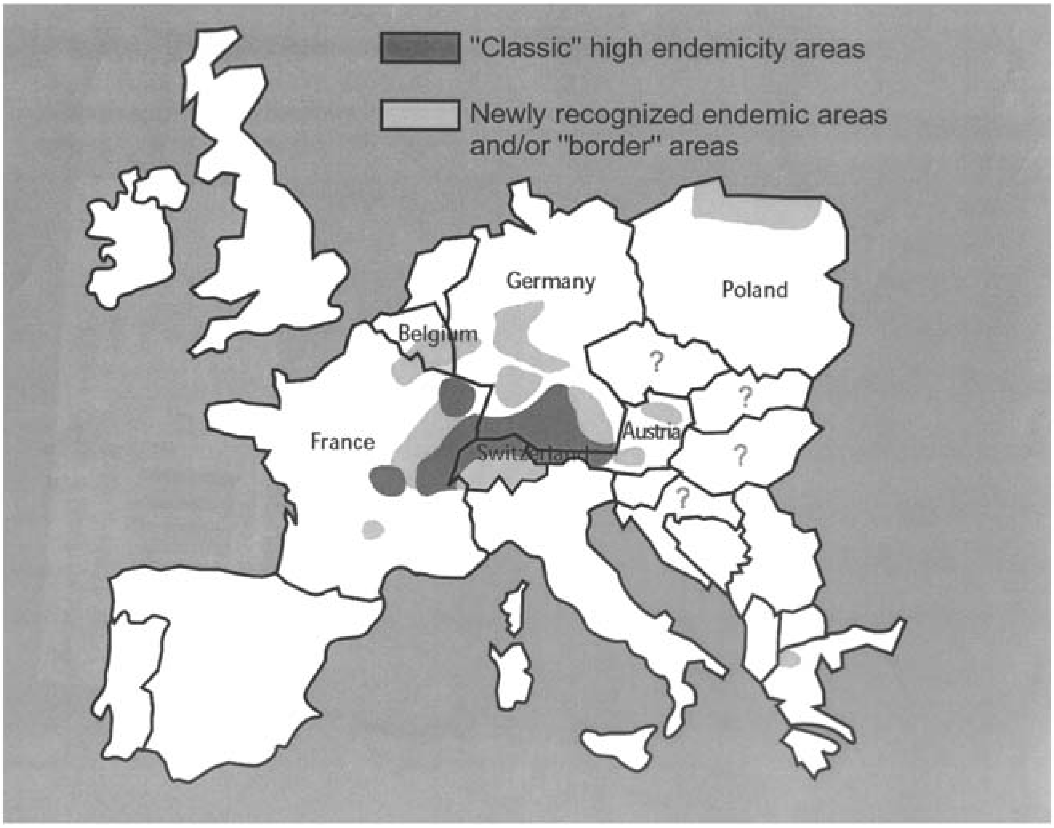

Fig. 4. 'Old' and 'new' endemic areas for human alveolar echinococcosis in Europe (adapted from the geographic location of human cases, according to Kern *et al.* (2003); data from the EurEchinoReg).

of cases was only done in Switzerland in the past 20 years, until 1997, and most of the reports in the various countries of Europe were based on hospital collection of cases, single case reports and not on a systematic epidemiological study. Systematic mass screenings were performed in endemic areas of Switzerland (Gottstein *et al.* 1987), southern Germany (Romig *et al.* 1999; Jensen *et al.* 2001), and eastern France (Bresson-Hadni *et al.* 1994).

A consortium of European research teams involved in the management of AE cases undertook the establishment of a European registry of alveolar echinococcosis cases (EurEchinoReg) in 1998 and thus allowed a more accurate collection of human case data. Data collected from January 1982 up to August 2001 were recently published (Kern *et al.* 2003). From 1982 to 2000, a total of 559 AE cases from Western and Central Europe were reported to the Registry; 258 patients were males (46%), 301 were females (54%) (Gender ratio 1:1·2). The median age at first diagnosis was 56 years (mean 52·5, range 5 to 86 years) and was almost equal in men and women. Proportion of patients under 20 years was 2% (121/559) and of patients over 69 years 16% (88/559). By December 2000, 73·0% of the patients, whose diagnosis was ascertained in 1982 and afterwards, were alive, 21·3% had died and 5·7% were lost to follow-up. For countries of the European Union and Switzerland, there were 53 autochthonous cases of AE in Austria (highest annual incidence: 6), 3 in Belgium (diagnosed in 1997 and 1999), 235 in France (42%; highest annual incidence: 26), 126 in Germany (24%; highest annual incidence: 20), 1 in Greece, and 112 in Switzerland (21%; highest annual incidence: 11). For most of the 530 autochthonous cases, the residences correspond most closely to the area of infection. A complete documentation of the residences during the patients' whole lifetime was available for about 30% of patients. Mobility of this patient subgroup was low, obviously in conjunction with long-term farming. Among the 15 'imported' cases reported by the various European centres, 7 originated from neighbouring countries and 8 from central Asia.

The number of incident cases per year varied between years with a peak incidence of 36 patients in 1988; notifications ranged between 15 and 27 patients. The median numbers of patients reported to the registry per year did not vary during the two decades under study (1980s: 24; 1990s: 22). Thus, low but constant incidences are characteristic of the occurrence of human AE in Europe today. Underreporting from previous years can be responsible for an apparent increase of incidence in Germany (Lucius & Bilger, 1995); conversely, under-reporting since 1998 may explain a decline in Switzerland. Mass screenings performed at the middle of the 1980s in the endemic areas of Franche-Comté (east of France

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at the border with Switzerland), which disclosed several cases within 5 years and more generally raised the awareness of the disease in this region, might explain the observed increase in the number of cases in France.

Improved diagnostic technology (ultrasound examination of the liver, CT-scan, MR-imaging as well as improved serological tests) has taken place in Europe since the beginning of the 1980s, and has probably led to an optimal detection rate. This could explain why more than 500 cases have been reported for these 2 decades, while less than 900 cases were published for the previous 7 decades. Nevertheless, changes in animal infection and in risk exposure for humans cannot be excluded totally. Information on potential risk factors was available for 38% patients from Austria, Germany, Greece and France, 97 men and 113 women. Twenty two percent were farmers; 46·2% of the patients with other professions, housewives and students were regularly engaged in farming, gardening or related activities as a pastime, as well as 62% of pensioners and unemployed. A majority of the patients (70·5%) had owned or formerly kept dogs and cats. Among the pet owners, 105 persons were also actively farming or gardening. Only 15 patients (7·1%) were neither farming nor gardening and did not own pets. In Europe, only one case-control study including 21 patients and 84 controls from Austria has been published (Kreidl *et al*. 1998). A high association of the disease was found with cat ownership and hunting, but due to the low case number the study was of limited power. Farming did not seem to have an impact on infection risk. However, comparisons of professions in an endemic area of Eastern France have shown that farmers were over-represented among patients with AE, compared with the proportion of farmers in the same area (Vuitton *et al*. 1990; Bresson-Hadni *et al*. 1997). A case-control study that involved 100 highly seropositive subjects found at mass screening in eastern France as cases, and 200 seronegative subjects matched for age, gender and place of residence as controls did not find any significant relationship with hunting, owning dogs or eating dandelions, but a significant association with frequent consumption of non-cooked berries collected in nature (Vuillemin, 1997). Data from the European registry on occupational and recreational activities among patients suggest a high frequency of putative exposure (farming, gardening, owning dogs and cats) but the lack of a comparison group does not allow an evaluation of the risk potential of these behaviours. They may be characteristic for the majority of the population from rural communities in Europe, as indicated from the preliminary results of a sociological study which is being performed in Eastern France (D. Jacques-Jouvenot, personal communication). Individual cases point to very specific factors of contamination, such as keeping a fox as a pet (Bresson-Hadni *et al*. 1988). However, for Europe, the question of how risk behaviour could be defined and how exposure can best be prevented is, therefore, still unclear.

Most residences are clustered in defined regions: central France, Lorraine, French Jura and Savoy, Swiss Jura and Swiss northeast, southern Germany, and western Austria. Single cases were identified in Belgium, in the northern regions of France, Germany, and in northeastern Austria (Fig. 4). The patient from Greece lived in the Greek province Macedonia. The distribution of AE in Europe shows high densities of cases in the classic endemic regions in Austria, France, Germany, and Switzerland. These regions are those where the index cases from each of these countries were identified since 1855 (Fesseler, 1990). In areas at the border of these 'classic endemic regions', clusters of a few patients or single cases were observed. In the well-known endemic areas, recent screening studies detected not only a small number of patients with the disease (12/12 000 subjects screened using serology followed by ultrasound and/or CT-scan examinations in Franche-Comté, France, from 1987 to 1994) (Bresson-Hadni *et al*. 1994, 2000), but also self-cured infections, also called 'aborted lesions', first described by Rausch *et al*. (Rausch *et al*. 1987). Such 'aborted lesions' were also disclosed in China (Bartholomot *et al*. 2002), as well as seropositivity rates of up to 2% in various endemic areas (Bresson-Hadni *et al*. 1994; Romig *et al*. 1999; Gottstein *et al*. 2001). Fifteen persons with aborted hepatic lesions (lesions with characteristic calcifications) and positive serology were notified to the Registry. They are not included in the numbers reported above. Together with a persistent *E. multilocularis* seroprevalence in the screened populations, they point to a previous contact with the infectious agent and to a high level of 'infection pressure' in the endemic areas. They also show that transmission of *E. multilocularis* to humans occurs rarely, and that incidence of the disease is far lower than exposure of the 'at risk' human communities to the parasite (estimated to 1/10). Genetic susceptibility, especially related to genes within the Major Histocompatibility Complex (Eiermann *et al*. 1998; Zhang *et al*. 2003), plays a role in the actual emergence of the disease in human population, and various levels of tolerance towards *E. multilocularis* may explain the spectrum of immunological interactions between the larva and its human host (Godot *et al*. 1997, 2000*a*, *b*) and thus the spectrum of clinical expression of the disease (Bresson-Hadni *et al*. 1997, 1999). Acquired immunodeficiency, such as AIDS, therapeutic immune depressants or, to a lesser degree, young age or pregnancy may also promote parasitic growth and clinical symptoms (Seiler *et al*. 1997; Vuitton *et al*. 2002; Kern *et al*. 2003). This has obvious consequences when considering the epidemiology of the disease in humans and its counterpart in the animal hosts (Vuitton *et al.* 2002).

In most European endemic areas the transmission cycle is predominantly sylvatic involving red foxes as definitive hosts and arvicolid rodents, mainly *Arvicola terrestris* and *Microtus arvalis* as intermediate hosts. Prevalence of the disease in a given region of Eastern France has been shown to be significantly correlated to the occurrence of high densities of *A. terrestris* in the same area (Viel *et al.* 1999). The risk of rodent population outbreaks are themselves related to land use, and particularly permanent pastures devoted to dairy cow breeding, in Europe (Giraudoux *et al.* in this supplement). Muskrats have also been found infected in Eurasia (Rausch, 1995); they were found infected in France and are likely to be much involved in the parasite cycle in Southern Germany; *E. multilocularis* infection rates in muskrats have been increasing within the past decade and may reach nearly 40% of trapped muskrats in some areas of Baden-Württemberg (Romig *et al.* 1999). Such high prevalence of *E. multilocularis* infection in rodents is rare. Except in very specific 'hot spots' (Giraudoux *et al.* 2001; Gottstein *et al.* 2001) where it can reach 40%, infection of voles by *E. multilocularis* has a low prevalence (Deplazes & Eckert, 2001; Giraudoux *et al.* 2002). Conversely, prevalence of infection in foxes is often over 60% in the highly endemic areas (Deplazes & Eckert, 2001; Raoul *et al.* 2002).

Central Europe

Sporadic, presumably autochthonous cases have been reported from the Czech Republic (Slais *et al.* 1979), Slovak republic (Krcmery *et al.* 1989), Poland (Pawlowski, 1996) and Greece (Theodoropoulos *et al.* 1978). Cases in Bulgaria have been reported in several publications collected by Genov, Silenov & Polydkova-Krusteva in 1980: in the absence of formal confirmation of these cases, and due to the high prevalence of cystic echinococcosis in this country, the actual presence of AE in this country cannot be ascertained. The same applies for Romania: among 638 cases of 'hydatidosis' collected during the period 1981–1990, lesions with multiple cysts were detected in 15% of cases: this, and the location of cases, might suggest that AE could be found in mountain shepherds in Romania (Coroiu, Rusu & Stefanoiu, 1992). One case was also reported from Hungary (Jakab & Faller, 1988). All references on single case reports and on the situation regarding animal contamination in central and Eastern Europe until 1999 can be found in a review by Kolarova (1999).

Collection of cases in central Europe countries was undertaken in association with the EurEchinoReg in Poland and in Czech and Slovak republics. Fourteen cases were collected in Poland (highest incidence: 4 cases per year). No cases could be formally confirmed for Czech and Slovak republics.

Preliminary results from the Echinorisk programme (Romig, for the Echinorisk programme, personal communication) show that 53% of foxes were infected in the Carpathian foothills in the south of Poland. This regional focus of transmission is mirrored by data from the bordering region of Slovakia, and appears to be of recent origin since a previous survey only five years ago showed a much lower infection rate of 8%. A general increase in prevalence rates, although less dramatic, was also observed in other regions of Poland. Infection of 5/100 foxes in Hungary was recently reported by Streter *et al.* (2003); all five infected foxes were shot in 2 northern counties of Hungary, in the Northern Mountain Range, at a distance of 60–120 km from the nearest known *E. multilocularis* endemic region, the Muránska Planina Mountains in Slovakia.

NEW EPIDEMIOLOGICAL TRENDS

Increase in fox population and in fox infection in Europe

Comparisons between prevalence rates measured in the 1980s and the end of the 1990s seem to indicate a significant increase, at least in two areas of Western Europe where suitable data were available (Romig, for EurEchinoReg, 2002). In Baden-Wurtemberg, southern Germany, large-scale monitoring showed that prevalence ranged from 0% to 30% in the period 1973 to 1984, and then ranged from 0% to more than 50% in the period 1995 to 1999 (Romig *et al.* 1999). In the plateau area of the Jura Mountain (France), prevalence in the Jura Département increased from 27% to 53% between the period 1981–1989 and the period 1996–1999, and prevalence increased from 46% to 65% in the Doubs Département (Raoul *et al.* 1999; Giraudoux *et al.* 2001). A similar increase was also observed in Belgium, province of Luxembourg, a rather recently identified endemic area (Losson *et al.* 1997), and it is worth noting that the first autochthonous Belgian human cases were found within the past 5 years (Kern *et al.* 2003).

A concomitant increase in fox populations has been observed in several countries of Europe since the beginning of the 1990s: regionally in Spain, Bulgaria, Sweden, France, Germany, Switzerland, Belgium and Czech Republic (Artois, 1997; Chautan, Pontier & Artois, 2000), a combination of rabies vaccination and modification in human-fox interactions (fox control, habitat changes) may account for higher survival and fertility (Chautan *et al.* 2000).

For the first time the presence of *E. multilocularis* in foxes has been reported in Italy, Bolzano Province, at the border of Austria (Manfredi *et al.* 2002). No infected foxes have been found at the French-Italian border, despite the presence of human cases in the French Alps. This is of specific significance for the definition of the southern limit of the parasite's range in Europe, and, together with data from Southern Switzerland and southern Austria, it provides an added opportunity to identify factors responsible for its absence in most Mediterranean regions. Preliminary results from the Echinorisk programme, a European Commission-sponsored project to assess the current risk factors of transmission to humans indicate that, for the first time too (Romig *et al.* report to the European Commission, personal communication), *E. multilocularis* was recorded in foxes from Burgenland, the easternmost federal state of Austria. Locally, the prevalence there was found to be up to 18%, while no infected fox was recorded in surveys ten years ago. Based on these results, transmission in eastern Austria appears to increase, and the occurrence of the parasite in bordering Hungary is likely. The latter is supported by the fact that *E. multilocularis* also occurred with moderate prevalence levels in Slovakia at the border to Hungary. The extension of the endemic area towards Scandinavian countries is also suggested by the presence of infected foxes in the Netherlands (Van Der Giessen *et al.* 1999) and by the discovery of an infected fox in the city of Copenhagen, Denmark (Petersen & Kapel, 2000; Saeed & Kapel, 2001). The specific problem of Great Britain, which is still considered as free of *E. multilocularis*, is particularly relevant since infected animals could enter the territory in the future because of suppression of the quarantine regulation. Studies on fox infections in England are currently being done within the Echinorisk programme mentioned above.

Urban foxes and the risk of AE in urban human populations

The continuing adaptation of wild foxes to living conditions in settlement areas and cities is on record from many areas in Western Europe, e.g. in Switzerland (Gloor *et al.* 2001). Infection of these 'urban foxes' by *E. multilocularis*, causes concern that a far bigger section of the human population might be at risk to contract AE than previously assumed. The current situation in Hokkaido and in the city of Sapporo shows that the risk is not only a possibility but a reality: an *E. multilocularis* coproantigen survey suggested the presence of the parasite in 58% of foxes from 19 den sites, most of these 'positive' dens being located in the peripheral area of the city (Tsukada *et al.* 2000). High infection rates of 'city foxes' increase the probability of transmission to pet dogs and cats (via rodents in parks and recreational areas). Specific studies were performed in Europe, in Stuttgart, Germany (mean prevalence 17%) (Romig *et al.* 1999), Zurich, Switzerland (prevalence ranged from 44% in urban foxes to 67% in foxes from the outskirt) (Hofer *et al.* 2000) and Geneva, Switzerland (mean prevalence 40%) (Romig *et al.* report of the Echinorisk programme to the European Commission; and Fisher, personal communication). The data show that *E. multilocularis* infection does exist in foxes living in the public parks located in the centre of cities, but the prevalence is rather low (under 30%); it may reach up to 75% in the public or private parks of the suburban areas, on the city territory (Romig *et al.* 1999). The actual risk for urban populations is still unknown. It is, however, clear that permanent presence of *E. multilocularis* eggs in urban environments and especially in recreational areas where children may play, could lead to a major change in the epidemiology of the disease. Complementary studies are currently performed in big cities of various countries and in smaller cities of the endemic areas in Germany, Switzerland, Austria, Czech Republic and France.

Socio-economic factors, deforestation, overgrazing and emergence of AE cases

Various economic and political reasons have led to deforestation in PR China. Field and Geographic Information System-aided studies have revealed a significant relationship between occurrence of high densities of rodents, increase in the surface of shrub and scrub-lands after deforestation and high prevalence of AE in humans in central China (Gansu, Ningxia) (addressed in detail by Giraudoux *et al.* in this supplement). The extremely high number of cases in these areas could have been directly related to a specific environment at a given period of time. Disappearance of the main source of contamination (dogs) and either reforestation or conversion of shrub and scrub-lands to ploughed lands could as well lead to an interruption of the parasite cycle and transmission to humans. Follow-up of this quasi-experimental situation should give interesting insights into the complex landscape/animal hosts/humans interplay which underlies AE epidemiology in humans.

A preliminary exploratory analysis of risk factors for AE transmission in Qinghai–Tibetan plateau of China has suggested that partial fencing around the settlements in winter pastures might promote AE prevalence rate in Tibetan herdsmen villages. A significant correlation was recently found between the surface of fenced areas and the prevalence of AE in 11 villages of Shiqu County, Ganzi Tibetan autonomous prefecture, Sichuan province, PR China (Wang *et al.* 2003). The underlying reason may lie in the overgrazing, an assumed cause of a population outbreak of small mammals in Qinghai–Tibetan plateau, which was exacerbated by the reduction of common grassland due to partial fencing nearby the settlements. In Tibetan herdsmen communities, grassland is roughly split into summer and winter pastures. From October to the next early May, the herdsmen stay in winter settlements and the livestock grazes in winter pasture. From early or middle May to late September, the majority of livestock grazes in summer pasture. At the beginning of the 1980s, the tenure of winter grassland was distributed to group-based individuals (group tenure). The herdsmen collectively use the group tenure pasture and their houses are usually set up near each other for security and mutual aid. Within the group tenure pasture, fenced areas are owned exclusively by individuals. Overgrazing is considered to be a key factor of grassland degradation and an assumed reason of population outbreak of small mammals, especially *Ochotona* spp. (Hou, 2001). It is generally assumed that a higher ratio between the number of livestock and the area of grassland means higher grazing pressure. However, grazing behaviour, controlled by humans, should also be taken into account. Further researches should pay attention to this issue.

CONCLUSION

Several examples show how changes in economic status, regulations and policies may generate conditions that favour interactions between animal hosts and maintenance of the parasite cycle. Epidemiological studies on alveolar echinococcosis performed in the past 30 years have stressed the various links between apparently unrelated collective decisions which resulted in changes in landscape, thus in rodent densities, and the emergence of the disease. Deforestation in China, suppression of ploughed fields and hedges in mid-mountain areas in Europe are other examples. On the other hand, individual or community-related human behaviour may also strongly influence the occurrence of contacts with the infecting parasite eggs, through attitudes towards wild animals, in rural as well as urban areas, contacts with domestic animals, or food.

Alveolar echinococcosis in humans is the overall result of a complex network of interactions between genetic, biological, behavioural, sociological, economic and political factors; this indicates that a multidisciplinary approach is not only fruitful but quite necessary to elucidate the reasons of its occurrence in humans and to plan for prevention.

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