INTRODUCTION TO THE SYMPOSIUM ON ECHINOCOCCOSIS

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Echinococcosis and cysticercosis are the major taeniid cestode zoonoses worldwide (Craig and Pawlowski, 2001; Singh and Prabhakar, 2001; Engels *et al*, 2003; Ito *et al*, 2003a; McManus *et al*, 2003). During the 3rd Seminar on Food- and Water-borne Parasitic Zoonoses (3rd FBPZ) held in December 2000, a symposium on Cysticercosis was chaired by A Ito and the late Dr C Urbani (Ito and Urbani, 2001). During this 4th FBPZ in 2003, we have another symposium on Echinococcosis. A similar symposium on Cestode Zoonoses including echinococcosis and cysticercosis (Craig and Pawlowski, 2001) may be better for a mutual understanding of the major cestode zoonoses, but is too big a topic for one symposium during 4th FBPZ 2003. So, today, we are having an Echinococcosis symposium, and tomorrow we will have a Cysticercosis symposium, organized by KD Murrell. Although we have no special session on taeniasis and cysticercosis in Asia during this 4th FBPZ 2003, it is also highly topical and may have more impact on us, at least in Asia (Ito *et al*, 2003b).

The Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT) has decided to support joint or collaborative projects for the control of parasitic infections in Asia, from 2002. The first one, a 3-year project started in 2002, and is organized by Prof Akihiko Yano of Chiba University, for "Asian unique strategy against Asian parasitic diseases for Asian people by Asian parasitologists (AAA)". His main subject is molecular and immunological study of *Toxoplasma* infections. He organized the First Congress of the Federation of Asian Parasitologists (FAP) in Chiba, in November 2000, and has successfully organized the Second Congress of FAP in Chiba, in November 2003. The main project, other than the FAP meeting, is publication of a series on Asian parasitology.

The second one started in 2003, and is organized by Akira Ito. It is for "The establishment of a network for the control of taeniasis/cysticercosis and echinococcosis in Asia and the Pacific". The main projects are (1) transfer of technology useful for immunological and/or molecular biological diagnosis of these cestode zoonoses through collaboration, (2) the organization of an international Congress on "Toward the control of taeniasis/cysticercosis and echinococcosis in Asia and the Pacific" to be held in Asahikawa, Hokkaido, between 5-8 July 2005. It is expected to be good timing, five years after the Cestode Zoonoses: Echinococcosis and Cysticercosis meeting held in Poland, in September 2000 (Craig and Pawlowski, 2001) and another symposium on the control of echinococcosis and cysticercosis, held in China, in July 2000 (Ito *et al*, 2003b). The WHO and FAO will join us for this 2005 meeting. The 2005 meeting will, simultaneously, be the Third Congress of the FAP focusing not only on these cestode infections, but also on parasitic infections in general, in Asia and the Pacific. Transfer of technology is based on the recognition that (a) we live together in Asia and the Pacific, at least, and (b) the establishment of each national or local diagnostic reference center for these serious cestode infections in endemic countries is based on the transfer of technology, which may function well in setting up home-made systems.

It is my pleasure to join local personnel digging wells and obtaining good spring water for their every day life, and their future life with better QOL, instead of commercially-available mineral water or soft drinks. It is recommended that purification of highly specific antigens for diagnoses available in endemic countries is prepared using their own, home-made antigen sources (Ito *et al*, 2003c).

Seminars for technical transfer will start from February 2004. This is a preliminary seminar but larger seminars will be held in September-October 2004 or February 2005, and also in September 2005. The first course covers immunological diagnosis of cysticercosis and taeniasis and echinococcosis. The second will be molecular diagnosis of cysticercosis/taeniasis and echinococcosis (Ito and Craig, 2003). It depends on the public health impact in each country. In February 2004, Indonesian researchers came to Asahikawa and did serological work on cysticercosis and taeniasis for 4 weeks, whereas Chinese researchers are doing serology on echinococcosis, and some others will be

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invited to join us. It is a preliminary seminar for the 2004 and 2005 seminars.

This Symposium on Echinococcosis at the 4th FBPZ 2003 is organized to introduce this project sponsored by MEXT, and for scientific exchange of mutual knowledge through up-dated topics on echinococcosis research from various points of view. There is no doubt that this symposium is a good start for our further discussion for the establishment of the network to control these taeniid cestode zoonoses in Asia, with expansion into the world.

Today's Symposium on Echinococcosis consists of two sessions. One focuses on an overview of the present echinococcosis situation worldwide. Craig PS (UK) summarizes the US-NIH project on transmission ecology of echinococcosis in China. Romig T (Germany) overviews the past and present situation of echinococcosis of alveolar and cystic types in Europe, and Jenkins D (Australia) overviews the current situation of cystic echinococcosis in Australia. The other covers the recent advances in technology including the clinical treatment of echinococcosis, by Wen H (China), spatial modeling within a geographic information system (GIS) for alveolar echinococcosis in China and Europe by Danson M (UK), molecular epidemiology of cystic echinococcosis by McManus DP (Australia), and recombinant vaccine against echinococcosis by Lightowlers MW (Australia), ending with a brief summary of immunological and molecular tools for echinococcosis by Ito A (Japan).

The main purpose of this symposium is not only to exchange up-dated mutual information on echinococcosis but also to communicate for the establishment of the network system for controlling taeniasis/cysticercosis and echinococcosis in the Asia-Pacific regions.

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EPIDEMIOLOGY OF ECHINOCOCCOSIS IN CHINA

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Abstract. China is one of the world's most highly endemic countries for the cestode zoonosis- echinococcosis. In the northwest of the country, both *Echinococcus granulosus* and *E.multilocularis* are transmitted between domestic livestock or wildlife hosts respectively, over vast and relatively remote regions. Traditional pastoralist communities of Tibetan, Kazakh and Mongol ethnic minorities appear to be most at risk of human cystic echinococcosis or alveolar echinococcosis, as are also Han Chinese that reside in the endemic Prefectures. This mini-review summarizes the situation of parasite transmission in animal hosts in China and focuses on the epidemiology of human disease in those regions where in-depth studies have been undertaken.

INTRODUCTION

Echinococcosis refers to infection of humans or animals with the larval cystic (metacestode) or adult stages (tapeworm) of any of the currently recognized 4 tapeworm species belonging to the genus *Echinococcus* (Family: Taeniidae, Order: Cyclophyllidea). Hydatidosis is the traditional term for human or animal infection with the larval cystic stage. *Echinococcus granulosus* causes cystic echinococcosis (CE) in humans, and *E.multilocularis* is the cause of human alveolar echinococcosis (AE). Both CE and AE are potentially highly pathogenic following a variable period of chronic incubation or lesion growth (Craig, 2003; McManus *et al*, 2003).The two other species in the genus, *E.vogeli* and *E.oligarthrus* occur only in Central and South America and may cause polycystic echinococcosis in humans though infections are very rare (D'Alessandro, 1997).

Only two *Echinococcus* species are currently considered to occur in Asia *ie E.granulosus* and *E.multilocularis*. The species *E.granulosus* has the greatest geographical distribution in the Region and this parasite infects humans and animals in eastern Russia, Mongolia, all the five Central Asian Republics (Turkmenistan, Uzbekistan, Kazakhstan, Kyrgystan, and Tadjikistan), China (including Tibet), India, Pakistan, Afghanistan, Bangladesh, Sri Lanka, Nepal, and Bhutan. Sporadic human cases of cystic echinococcosis have also been reported in Thailand, Vietnam, Cambodia, Lao PDR, Malaysia, Indonesia, the Philippines, North and South Korea, and Japan, however, clear evidence for active transmission of *E.granulosus* within these latter countries has not been confirmed (WHO/OIE, 2001). *E.granulosus* and CE are also currently endemic in Australia, and formerly throughout New Zealand prior to the end of the National Hydatid Control Program (1959-1989) in that country (Gemmell and Roberts, 1998). The distribution of the fox tapeworm *E.multilocularis* and human AE is much more restricted over its known range in Asia. Clear evidence for sustained transmission is available only for northeastern Russia, north and west China, and northern Japan; largely unconfirmed reports of human AE cases have also been made in Pakistan, India, Afghanistan, Kazahkstan, Kyrgystan, Uzbekistan, and Mongolia (WHO/OIE, 2001; PSCraig and P Torgerson, unpublished observations).

As in other regions of the world, it is very difficult to determine or even estimate the total numbers of human CE and AE cases in Asia. This is because of the long asymptomatic period (usually >5 years), the difficulty in diagnosis, poor record keeping, failure of patients to seek medical attention for a chronic condition, and also poor access to medical facilities especially for remote communities. Nevertheless, it is clear that for the Asian region the greatest numbers of both CE or AE cases occur in China and eastern Russia (Wen and Yang, 1997; WHO/OIE, 2001; Bessonov, 2002). It also appears, however, that human CE has re-emerged since the early 1990s as a significant public health problem in parts of Central Asia including Kazahkstan and Kyrgystan (Torgerson *et al*, 2002). Furthermore, human AE disease is an emerging or newly recognized public health problem in remote Tibetan communities in areas of Qinghai and Sichuan Provinces of China (Qiu *et al*, 1999; Schantz *et al*, 2003).

Human CE and AE are typically chronic cystic mass/lesion infections of the liver, and these helminthic

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diseases occur predominantly in children and adults living in rural pastoral or agricultural communities respectively. Nomadic, or more usually semi-nomadic (transhumant) pastoralism is an important risk factor for CE in Asia, but also surprisingly for AE in parts of western China. Human AE is also a medical problem for upland agricultural communities especially in regions of Gansu and Ningxia Provinces in central west China (Schantz *et al*, 1995). Hepatic CE and AE usually manifest after 2-15 years post-infection with non-specific symptoms, including upper abdominal discomfort, dyspepsia and jaundice. Both CE and AE may result in significant morbidity and even mortality if left untreated for long periods. CE is more likely to be detected than AE because of likelihood of the presence of a palpable liver or abdominal cyst, the occurrence of cyst rupture, or the appearance of a clear cystic image on ultrasound or after chest x-ray. In contrast to CE, human AE generally has a longer asymptomatic period followed by a more rapid deterioration in health often associated with severe cholestatic jaundice, epigastric pain, and weakness; untreated AE may result in a >90% fatal outcome. Further details regarding the pathology of CE/AE can be found in recent reviews (WHO/OIE, 2001; Craig, 2003; McManus *et al*, 2003).

Human echinococcosis is one of the most difficult invasive helminthic infections to diagnose, to treat effectively, and also to undertake post-treatment evaluation. Pre-treatment diagnosis of human CE and AE relies on a combination of clinical history and radiographic imaging (CT scan, MRI, ultrasound, x-ray), preferably with serological confirmation (Craig *et al*, 1996). Surgical removal or drainage/sterilization of cysts remains the main form of treatment for CE in Asia, however, percutaneous aspiration (PAIR technique) which was pioneered in China, together with albendazole chemotherapy are increasingly recognized as important alternatives to surgery for a significant group of CE patients (Wen and Yang, 1997; McManus *et al*, 2003). More than 98% of human AE cases involve the liver (compared to about 70% for CE) and radical liver resection of an isolated AE lesion remains the best chance for cure. Albendazole therapy for AE is not usually curative but can significantly increase survival times (WHO/OIE, 2001). Another problem is that the cost of surgical treatment for CE and AE is high *eg* at least $700 in China, and this will have an effect on treatment rates in rural communities.

ECHINOCOCCOSIS IN CHINA

In China, both cystic and alveolar echinococcosis are highly endemic over large areas of northwestern Provinces and Autonomous Regions (Figs1 and 2). It has been estimated that 600,000-1.3 million existing cases of human echinococcosis occur in China, of which approximately one third are in children (Ito *et al*, 2003). Human CE cases are responsible for more than 98% of infections, with AE disease in the remainder. At least 10 cases of rare mixed CE and AE infections have also been identified in some patients in co-endemic areas of Xinjiang Uygur Autonomous Region (XUAR), Ningxia Hui Autonomous Region (NHAR) and from Ganze Tibetan Autonomous

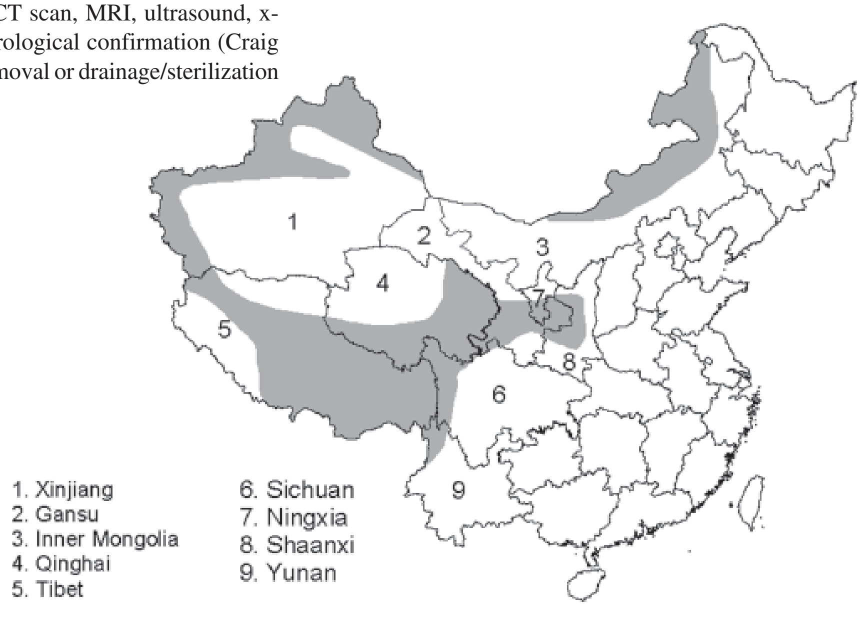

Fig 1- Provincial map of China showing the areas of highest endemicity for *E.granulosus* and CE disease.

Prefecture (Sichuan Province) (Wen *et al*, 1992; Qiu J and Yang Y, personal communication). Of China's 33 provinces, autonomous regions and municipalities, at least 20 are considered to be endemic for *E.granulosus* and at least 5 for *E.multilocularis* (Craig *et al*, 1991; Chai, 1995; Vuitton *et al*, 2003). Those provinces or autonomous regions with the highest risk are also co-endemic for both human CE and AE *ie* Xinjiang, Qinghai, Sichuan, Gansu, and Ningxia (Figs 1 and 2). In addition, significant numbers of CE cases also occur in the Tibet Autonomous Region, Shaanxi Province and Inner Mongolia, however, AE case reports for these areas are not clear or unknown (Fig 1 and Table 1).

Cystic echinococcosis (CE) in humans

Human CE was first reported in China in 1905 (Wen and Yang, 1997). At least 35,000 cases have been treated surgically in China since the 1950s, however, that figure reflects only symptomatic cases that had access to treatment (availability of health care and/or financial ability to pay). In Xinjiang, of 21,560 CE patients identified from 58 hospitals, 72.8% were hepatic cases and 19.1% pulmonary CE, in addition, 36.4% of patients were under 14 years of age (Xu, 1995). Accurate surgical incidence data for CE is not, however, readily available in all areas, but is as high as 80 per 100,000 per year in north central Xinjiang (Chi *et al*, 1990). Active mass screening surveys using portable ultrasound (US) scanners (which can accurately identify abdominal CE *ie* hepatic, spleen , pancreas, kidney, and abdominal cavity sites), have been applied in some endemic areas of China since the 1980s. Many of these US surveys have also employed serological tests (*eg* ELISA or IHAT) for antibody confirmation. The ultrasound based survey data indicates human CE prevalence rates of 0.5-7% in the high endemic zone that stretches from western Xinjiang to Sichuan (Fig 1, Table 1). The highest ultrasound prevalence rates for human CE in China appear to occur in Tibetan pastoral communities of the eastern Tibetan plateau (at or above 4,000 meters altitude), located in southwest Qinghai and northwest Sichuan Provinces (Qiu *et al*, 1999; Schantz *et al*, 2003), and CE case rates are also high in Tibetan autonomous areas of south Gansu (Bai *et al*, 2002). The disease is also a public health problem in central areas of the Plateau in the Tibet Autonomous Region itself especially Nakqu and Lhasa Prefectures (Gong *et al*, 2000). In northwest Xinjiang Uygur Autonomous Region (which by surface area at 1.7 million km^2 is the largest administrative region of China), ultrasound based screening surveys indicate significant CE rates (>3%) in traditional semi-nomadic pastoral communities of Kazakh or Mongolian ethnicity (Wang *et al*, 2000). In south Ningxia Hui Autonomous Region of central China, Moslem Chinese (Hui) especially that practice transhumance (seasonal movement of livestock between high and low altitude pastures), also appear to be at risk of CE disease (Li *et al*, 1990; Yurong Y and Wang Y, unpublished observations) (Table 1, Fig 1). In all endemic CE areas where Han Chinese reside, especially if they keep dogs and small numbers of livestock, they too are at risk of CE disease (Chi *et al*, 1990; National Hydatid Disease Center of China, 1993; Wang *et al*, 2000).

Cystic echinococcosis in animals

Livestock pastoralism is a major industry in western and northern China with national herds of sheep/goats above 250 million and other large livestock species > 100 million. Those regions of high stocking and rangeland density correlate with available grassland and with the endemic foci of CE caused by infection with *E.granulosus.* This parasite has been

Table 1
Human cystic echinococcosis (CE) in China.

Province or region	Approx. number cases diagnosed	Incidence per 10^5	Prevalence (% range)
Xinjiang	>22,000	0.07-80	0.6-3.1
Qinghai	>5,500		4-6.6
Gansu	>2,000	43	1-2
Sichuan	>1,500		2.1-7
Tibet	>2,000		>1
Inner Mongolia	>1,200		?
Ningxia	>1,000		0.6-2.3

(After: Andersen *et al*, 1991; Chai, 1995; Schantz *et al*, 1995; Qiu *et al*, 1999; WHO/OIE, 2001).

recorded in domestic livestock mammals in all of China's 20 or so endemic provinces and autonomous regions (Craig *et al*, 1991; Chai, 1995). Domestic ungulates most commonly infected are sheep, goats, cattle, yak, and pigs (Table 2). High prevalence of CE (> 30%) occurs in all livestock groups especially sheep and yak (Wang *et al*, 1993a). For example, of 28,083 sheep slaughtered in abattoirs in Xinjiang in 1991, 36% were recorded infected with CE (Liu *et al*, 1993), and of 670 yak examined at slaughter in Qinghai Province 577 (86%) were infected with hydatid cysts (Wang *et al*,1993a).

Camels (bactrian variety only in China) and equids have also been reported as intermediate hosts for *E.granulosus* in China. Mis-identification of cystic hydatidosis does, however, occur in slaughterhouses, in particular the possible confusion with hepatic cysts of *Taenia hydatigena* (also called *Cysticercus tenuicollis*) (Ming *et al*, 1992; Craig P and Gemmell M, unpublished).

E.granulosus is considered to be a species complex with up to 8 or 9 intra-specific variants, strains, or genotypes (Thompson and McManus, 2001). Molecular taxonomic approaches have shown that the common domestic sheep/dog strain (G1 genotype) appears to be the dominant strain in China (McManus *et al*, 1994), and this strain may also infect other livestock species *eg* yak (Xiao *et al*, 2004). Importantly, the sheep strain (G1 form) is also responsible for the majority of human infections world-wide and the only strain so far identified in surgically treated Chinese CE patients (McManus and Thompson, 2003). The camel strain (G6) has also been identified in China in *Camelus bactrianus* from Xinjiang (Zhang *et al*, 1998) though it has not yet been identified from human CE isolates in China, in contrast to other parts of the world *ie* North Africa and South America (McManus and Thompson, 2003). Yak (*Bos grunniens*), like cattle (*Bos taurus*, *B.indicus*), appear to exhibit a high rate of calcified and non-fertile hydatid cysts in comparison to that observed in sheep (Wang *et al*, 1993a). The bovid (cattle) strain or G5 genotype, has not been identified in China, however, morphological comparison of experimentally derived dog-sheep *vs* dog-yak adult worms indicated significant differences between the two isolates, and also between the yak derived worms and Swiss cattle strain specimens. This suggests possibility of a dog-yak genotype/strain at least in Qinghai (Wang *et al*, 1993b). The occurrence of both cattle and a yak strains of *E.granulosus* has been suggested to occur in Xinjiang and Qinghai, respectively (Chai, 1995). However, to date DNA analysis of yak hydatid cysts from northwest Sichuan indicates only the presence of the sheep strain (Heath *et al*, 2004; Xiao *et al*, 2004).

The domestic dog is the main definitive host of *E.granulosus* in China as it is also throughout the world where domestic cycles of the parasite occur (WHO/OIE, 2001). It has been estimated that in 1991 there were 100 million dogs in China despite the Government's general policy against dog rearing (Liu, 1993). In Xinjiang, the ratio of dogs to humans in the early 1990s was 1:10-15 in agricultural areas and 1:6 in pastoral areas (Liu, 1993). Provincial data on the prevalence of canine echinococcosis is sporadic and often concerns only small numbers of necropsies. Necropsy data from dog studies in endemic areas of Xinjiang, Qinghai, Gansu, and Sichuan Provinces indicates canine prevalence rates of *E.granulosus* that range from 6->80% (Table 3).

Table 2
Prevalence (% range) of CE in livestock in China.

Province or region	Sheep	Goats	Yak	Cattle	Pigs
Xinjiang	1-99	4-42	41	2-88	2-38
Gansu	8-77	14-32	30-76	51	30-70
Qinghai	10-99		5-99	72	5-20
Ningxia	52	3		81	24
Sichuan	82	41	51		
Inner Mongolia	15-48				
Tibet	56			66	

(After: Liu *et al*, 1993; Wang *et al*, 1993 a, b; Jiang *et al*, 1994; Chai, 1995; WHO/OIE, 2001).

Table 3
Prevalence (% range) at necropsy for *E.granulosus* in dogs in China.

Province or region	Prevalence %
Xinjiang	6.9-70
Qinghai	19.5-82.3
Gansu	6.6-16.6
Sichuan	21.2
Ningxia	55.9

(After: Liu, 1991; Craig *et al*,1992; Chai, 1995; He *et al*, 2000; Schantz *et al*, 2003)

Table 4
CE in wild ungulates in Qinghai Province, China.

Species	Number infected	(%)
Blue sheep (*Pseudois nayaur*)	21/327	(6.4)
Tibetan gazelle (*Procapra picticaudata*)	13/198	(6.6)
Red deer (*Cervus elaphus*)	?	(15.0)

(After: Guo *et al*, 1994; He D and Jenkins D, unpublished).

Average prevalence rates for dogs are usually around 15-30%. A large post-mortem study of 4,318 dogs examined between 1986-1990 in northern Xinjiang showed that the average rate was 17.6% with a local prevalence range of 7-70% (Liu, 1993). Mean worm burden of *E. granulosus* in 40 dogs necropsied in Altai Prefecture (Xinjiang) was 300 (range 10-14,000) (P Craig and Z Ding, unpublished observations). Transmission of *E.granulosus* within wildlife predator-prey host cycles may also occur in more remote parts of north and western China, but few studies have been made (Craig *et al*, 1991). The wolf (*Canis lupus*) is an excellent host of the parasite throughout its northern hemisphere range (Rausch, 2003), and in parts of the Tibetan Plateau, the adjacent mountainous areas, and in Xinjiang, wolf populations though threatened are present in sustainable numbers (Schaller, 1998; Sheng *et al*, 1999). Wolves are known to predate on large ungulates in their range in China (Schaller, 1998). Hydatid cysts of *E.granulosus* have been recorded in wild blue sheep (*Pseudois nayaur*), Tibetan gazelle (*Procapra picticaudata*), and the red deer (*Cervus elaphus*) in Qinghai Province (Table 4) (Guo *et al*, 1994). To date, however, no genotypic studies of Chinese wildlife isolates of *E.granulosus*, have been published.

Risk factors for human CE in China

Relatively few CE case-control studies have been published, and as far as is known by the author, none for China. In some endemic areas in European (Spain, UK) and Middle East countries (Jordan) case-control studies indicated that significant risk factors for human CE were: livestock ownership, an occupation in pastoralism, dog ownership (number and years owned), feeding of uncooked viscera to dogs, and source of drinking water (Campos-Bueno *et al*, 2000; Dowling *et al*, 2000; Dowling and Torgerson, 2000). In China, case data derived retrospectively from hospitals or from cross-sectional mass screening studies using ultrasound scanners and questionnaire analyses, revealed a range of potential risk factors for human CE. In Xinjiang Region of northwest China, hospitalized CE patients were most likely to be of Han Chinese, Kazakh, Mongolian or Uygur ethnic origin and from farming or pastoralist households and between ages of 6 and 15 years with no difference between sexes (National Hydatid Disease Center of China, 1993). Serological surveys in Xinjiang indicated that females were more likely to be seropositive regardless of ethnicity and involvement in husbandary especially involving semi-nomadic practices (Chai, 1993). Analysis of data from 3,700 ultrasound scanned persons in two communities in Tacheng and Altai Prefectures in northern Xinjiang showed a prevalence of abdominal CE of 1.8% (range 0.9-2.7%), and significant CE risk factors were: a previous history of CE and knowledge about CE, a pastoral/herdsman occupation, and involved in practice of home slaughter; however, dog ownership per se was not significant (Wang *et al*, 2000). A similar survey in south Ningxia Hui Autonomous Region in central northwest China revealed a 2% ultrasound prevalence of CE in ~2,000 persons screened, with higher risk for the > 30-years age group, however, difference between sexes or ethnicity (Han-Chinese *vs* Hui-Moslem) or dog ownership were not significant for CE (Wang YH and Yang Y, unpublished).

Alveolar echinococcosis (AE) in humans

Human AE was first described in China in the 1950s, and one of the first formal reports in 1965 in a patient with a hepatic lesion admitted to the First Teaching Hospital at Xinjiang Medical College in Urumqi City (Yao, 1965). At that time, human AE was considered globally to be a rare disease for which the causative parasite had only been confirmed to be *E.multilocularis* approximately 10 years previously. Prior to the early 1950s the disease was referred to in Europe as colloid carcinoma whose etiology was usually considered to be due to aberrant growth of *E.granulosus* (Grove, 1990). Due to difficulty in diagnosis and treatment options for human AE in China, there are limited studies of hospital-based records. One of the few good studies of AE surgical records was carried out in four main hospitals in Xinjiang for the period 1956-1997, from which 157 AE cases were identified representing 0.6 cases per 100,000 for the whole Region (Zhou *et al*, 2000). AE case age ranged from 6-62 years (mean 35.7 years) with no significant difference in rates between the sexes, though incidence among Kazakh (5.4 per 100,000) and Mongol (10.6 per 100,000) ethnic groups was significantly higher, while most of the AE cases in Xinjiang resided in the northern Altai Mountain zone, western Junggar, or the Yili Valley/Tianshan zones (Zhou *et al*, 2000).

In China, mass ultrasound screening studies in the last 10 years indicated that human AE is highly endemic in 3 main foci, all in western regions (Vuitton *et al*, 2003). These are: (i) the northwest and western areas of Xinjiang (especially Yili and Altai Kazakh Autonomous Prefectures); (ii) south Ningxia (especially Xiji, Haiyuan and Guyuan counties) and south Gansu (especially Zhang and Puma counties); (iii) a region of the eastern Tibetan plateau comprising northwest Sichuan (especially Ganze and Aba Tibetan Autonomous Prefectures) and southwest Qinghai (Yusu and Huangnan Tibetan Autonomous Prefectures) (Fig 2). Average human AE prevalence rates using ultrasound scanning were 4-6% for northwest Sichuan and south Gansu with individual village AE prevalences up to 15%; a prevalence range of 0.4-1.5% was obtained for southwest Qinghai and south Ningxia with discrete village prevalences up to 8% (Craig *et al*, 2000; Wang *et al*, 2001; Schantz *et al*, 2003; Yang Y *et al*, unpublished) (Table 5). The good ability to correctly differentiate hepatic AE from CE using ultrasound alone, or preferably supported by serological confirmation, also means that absence or low rates of AE disease in highly CE endemic regions may be reliably confirmed from the > 10,000 scans already performed in rural communities in parts of western China (Craig *et al*, 1992; Qiu *et al*, 1999; Zhang *et al*, 2001; Bartholomot *et al*, 2002).

E.multilocularis in animal hosts

In China as elsewhere in the world, *E. multilocularis* is transmitted between canid definitive hosts (primarily fox species) and small mammal intermediate hosts (primarily rodent species). Zoologically, the small mammal species assemblage in China is complex and includes both Palearctic and Indo-Malay endemic species (Giraudoux *et al*, 1998). It is not perhaps surprising that with new ecological investigations the range of families, genera, and species of potential small mammal intermediate hosts is far greater than in the endemic areas of either North America, Western Europe or Japan (Giraudoux *et al*, 1998). Microtine vole species which are generally a highly susceptible group of rodents, are well represented in central, north, and western China, including the Tibetan Plateau (>4,000m altitude), and probably provide among the most important intermediate host species for *E.multilocularis eg Microtus limnophilus, M.irene* and *M.brandti* (Giraudoux *et al*, 1998; He *et al*, 2000). In addition, gerbils (*Meriones* spp), ground squirrels (*Citellus* spp or *Spermophilus* spp), pikas (*Ochotona* spp), and hares (*Lepus* spp) may also act as susceptible intermediate host species (Table 6). Small mammal ecology studies in the south Gansu AE endemic zone, revealed a variable species assemblage in relation to landscape profiles within an upland agricultural area that has been fragmented by deforestation and farming. Risk of human AE by village correlated with landscape features (characteristics and size) within a 2-km radius around settlements, which may be explained by provision of optimal habitats for susceptible rodent host species (Giraudoux *et al,* 1996; Craig *et al*, 2000; Danson *et al*, 2004). On the eastern Tibetan Plateau at least two lagomorph host species *ie* plateau pika (*Ochotona curzoniae)* and the Tibetan hare (*Lepus oiostolus)* were also shown to

Table 5
Human alveolar echinococcosis (AE) in China.

Province or region	Approx number of cases diagnosed	Prevalence -% range (mean %)
Ningxia	>250	0.2-8 (1.5)
Gansu	>150	0.8-15.8 (4.0)
Sichuan	>200	0.3-14 (6.5)
Qinghai	130	0.8
Xinjiang	150	3.9/100,000
Tibet AR	10	?
Helionjiang	4	?

(After: Li *et al*, 1990; Lin and Hong, 1991; Schantz *et al*, 1995; Zhang *et al,* 2001, WHO/OIE, 2001; Vuitton *et al*, 2003) be infected with *E.multilocularis* and these hosts may contribute to both sylvatic and peri-domestic transmission through predation by foxes or dogs, respectively (He *et al*, 2000; Xiao *et al*, 2004).

The main definitive hosts for *E.multilocularis* in China appear to be the red fox (*Vulpes vulpes*), Corsac fox (*V.corsac*) and the Tibetan fox (*V.ferrilata*), with domestic dogs as a significant host involved in peri-domestic transmission and thus of zoonotic importance (He *et al*, 2000; Craig *et al*, 1992; 2000) (Table 7). Prevalence of adult *E.multilocularis* infection in foxes as high as 60% have been recorded in Sichuan, as well as rates of 5-15% in domestic dogs in Tibetan communities in both Sichuan and Qinghai Provinces, and also in Han farming communities in Gansu Province (Lin and Hong, 1991; Craig *et al*, 1992; He *et al*, 2000; Schantz *et al*, 2003). Recent unpublished data from 2002-2003 using arecoline purgation and specific coproPCR testing of owned dogs in Ganze Tibetan Prefecture (Sichuan), showed canine prevalence rates of *E.multilocularis* of at least 9% with a mean intensity of 1,200 worms (range 1-20,000) (C Budke and M Campos-Ponce, unpublished).

Risk factors for human AE in China

Data from hospital records and mass screening surveys in endemic areas of China indicate that ethnicity (Han, Tibetan, Kazakh, Hui or Mongol), sex (females appear at higher risk), age (>20 years), occupation (agriculture or pastoralism), environment (rural upland grassland/scrubland above 1,500m altitude) and dog ownership were significant risk factors for human AE (Craig *et al*, 2000; Wang *et al*, 2001; Schantz *et al*, 2003; Vuitton *et al*, 2003; Danson *et al*, 2004).

The role of definitive hosts in transmission of *E.multilocularis* is of critical importance as they provide the source of eggs for infection of small mammals and also to humans. Traditionally, it has been considered that hunting associated contacts with wild foxes would be expected to be a major risk factor for human AE. This, however, does not appear to be the case in most endemic regions when specific case-control, case-risk analysis, or serological (exposure) studies were carried out in rural populations, for example in North America (Stehr-Green *et al*, 1988; Hildreth *et al*, 2000), Europe (Kern *et al*, 2003), and northern Japan (Yamamoto *et al*, 2001), and also for China (Craig *et al*, 2000; Wang *et al*, 2001). Rather, risk factor analysis for human AE disease appears to indicate that the role of domestic dogs is of significant zoonotic importance. This appears to be the case in the China foci so far investigated in cross-sectional mass screening studies in Gansu (Craig *et al*, 2000) and Sichuan Provinces (Wang *et al*, 2001). Though these communities were ethnically and culturally very different (*ie* Han farmers *vs* Tibetan pastoralists, respectively), a history of dog ownership and numbers of dogs owned over a period of time were highly significantly correlated with relative risk for AE disease. It is known that dogs are generally highly susceptible to infection with *E.multilocularis*, and this

Table 6
E.multilocularis infection in small mammals in China.

Host	Nos. infected (%)	Province or region
Microtus brandti	64/2,635 (2.3)	Inner Mongolia
M.irene	3/12 (25)	Sichuan
Meriones spp	1/61 (16.7)	Inner Mongolia
Mus musculus	1/6,890 (0.014)	Xinjiang
Spermophilus erythrogenys	2/2,211 (0.09)	Xinjiang
Citellus spp	12/2,156 (0.6)	Ningxia
Citellus dauricus	3/1,500 (0.2)	Ningxia
Myospalax fontanierii	1/321 (0.3)	Ningxia
Ochotona curzoniae	13/322 (5.6)	Sichuan
	11/319 (3.5)	Qinghai
Lepus oiostolus	6/89 (6.7)	Sichuan

(After: Li *et al*, 1985; Lin and Hong, 1991; Lin *et al*, 1993; He *et al*, 2000; WHO/OIE, 2001; Schantz *et al*,2003)

Table 7
Definitive hosts of *E.multilocularis* in China.

Host	No. infected	(%)	Province or region
Red fox *(Vulpes vulpes)*	16/48	(33)	Xinjiang
	19/32	(59.4)	Sichuan
	3/20	(15)	Ningxia
Tibetan fox *(V. ferrilata)*	89/193	(46)	Sichuan
Corsac fox *(V. corsac)*	2/33	(6.1)	Inner Mongolia
Wolf *(Canis lupus)*	1/2		Xinjiang
Dog *(C. familiaris)*	46/295	(15.6)	Sichuan
	6/58	(10.3)	Gansu
	3/27	(5.1)	Qinghai

(After: Lin and Hong, 1991; Schantz *et al*, 1995, 2003; WHO/OIE, 2001)

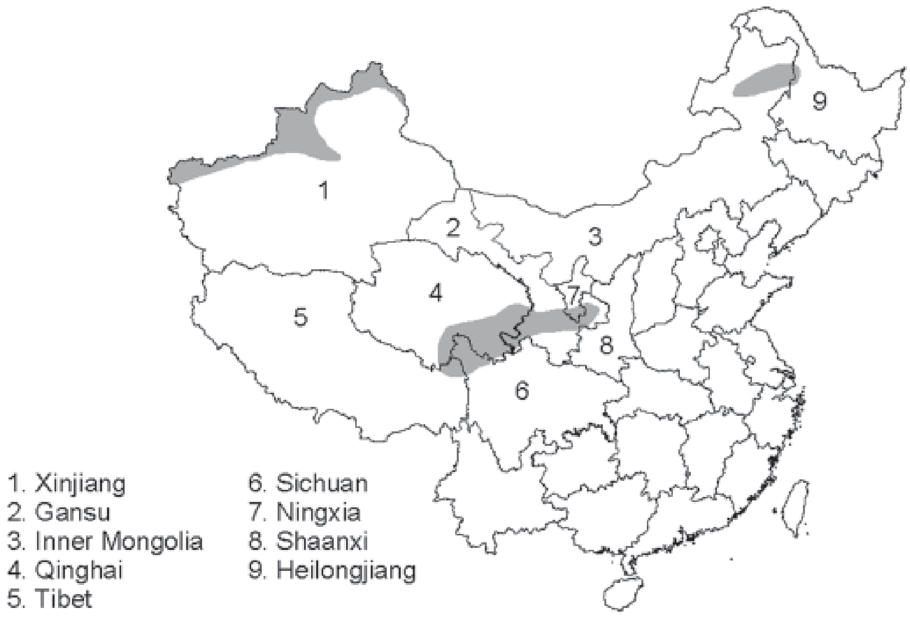

Fig 2- Provincial map of China showing the areas of highest endemicity for *E.multilocurlaris* and AE disease.

coupled with a free-roaming/scavenging behavior, especially in under-developed communities where dogs are poorly fed, appears to result in exposure of dogs to the parasite from predating small mammals. With close proximity or co-habiting of dogs in or immediately around households a higher zoonotic risk may develop (Rausch *et al*, 1990; Craig *et al*, 2000).

The role of the physical environment, in particular landscape characteristics, is also of growing interest in relation to the transmission ecology of *E. multilocularis* and the epidemiology of human AE disease. Associations between landscape and transmission of *E.multilocularis* were first made in France as a result of ecological studies on microtine rodent populations (Delattre *et al*, 1992; Giraudoux *et al*, 1996). Landscape approaches have since also been investigated for human AE risk assessment in China (Giraudoux *et al*, 1996; 1998; Craig *et al*, 2000; Danson *et al*, 2003). Recently, satellite remote sensing was used to measure land cover composition around villages in the endemic south Gansu AE area, and that analysis showed a significant positive correlation between human AE prevalence and proximity of villages to shrubland and grassland. Furthermore, a simple predictive model for human AE disease based on landscape spatial characteristics was developed (Danson *et al*, 2004). This spatial model could explain more than 70% of variation in village AE rates by analysis of landscape features within an optimal 2km zone around villages. That distance probably reflects proximity of resident small mammal populations as well as local movement of domestic dogs from home areas (Craig *et al*, 2000; Danson *et al*, 2003; 2004).

Whilst pastoralism has long been considered an occupational risk factor for human CE because of its association with domestic dogs and livestock, this has not been the case for human AE. Human AE is generally thought of as an occupational risk for rural workers/farmers and agriculturalists rather than semi-nomadic pastoralists (WHO/OIE, 2001; Kern *et al*, 2003). In China, human AE is however, an important public health problem in Tibetan pastoralists especially those that practice semi-nomadism (Wang *et al*, 2001; Schantz *et al*, 2003). The reasons for this still require investigation, but it appears that a relatively large range of potential small mammal intermediate host species occurs on the Tibetan Plateau, along with two species of foxes, and this coupled with the presence of large numbers of dogs owned by pastoralists also provides potential definitive hosts for *E.multilocularis*. Very recent studies on the Plateau in northwest Sichuan, in addition, showed a positive correlation between proximity of overgrazed pasture/rangeland and relative risk of human AE at village level (Wang *et al*, 2003). This observation may be due, in part, to increase in population densities of certain small mammal species in response to pasture degradation, and this coupled with large dog populations increased the risk of zoonotic transmission.

CONCLUDING REMARKS

Transmission of *E. granulosus* and *E. multilocularis* occurs readily between animal hosts over vast areas of north and western China, with associated risk of human cystic echinococcosis (CE) and alveolar echinococcosis (AE), respectively. China, therefore, is one of the world's most highly endemic countries for these cestode zoonoses. The majority of human cases of CE occur in persons within communities that practice semi-nomadic pastoralism *eg* Kazakh, Tibetan, and Mongol. While AE disease also occurs in agricultural based communities in addition to those of some of the major pastoralists *eg* Tibetan. Both CE and AE are considered to be important endemic diseases in northwest China that require special attention (Wen and Yang, 1997), however, control programs will be very difficult in these remote endemic zones (Ito *et al*, 2003). For *E.granulosus*, control is theoretically feasible at least in Xinjiang because the parasite in the sheep-dog cycle is likely to be in an endemic steady state (Ming *et al*, 1992). Practical approaches should emphasize registration and regular dosing of dogs with praziquantel, together with slaughterhouse improvements and health education to facilitate acceptance of control. In addition, the role of the new *E.granulosus* (EG95) vaccine for sheep (and bovids) may accelerate control intervention in China and elsewhere (Torgerson and Heath, 2002; Heath *et al*, 2003). Control of transmission of *E.multilocularis* will not be practicable or ethically acceptable in relation to wildlife hosts, however, in all endemic communities studied so far in China, the domestic dog appears to be a key factor in human disease risk, and therefore targeted anthelmintic dosing of dogs together with reduction in dog numbers (including stray animals) could significantly reduce transmission of *E.multilocularis* to humans and, therefore, the public health importance of AE disease.

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