Echinococcosis on the Tibetan Plateau

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Dedicated to my family

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Summary

The Tibetan plateau of western China has been shown to have a very high prevalence of human cystic echinococcosis (CE) caused by *Echinococcus granulosus* and human alveolar echinococcosis (AE) caused by *Echinococcus multilocularis*, with the domestic dog suspected of being the primary definitive host for the transmission of both parasites to humans in this locality. A purgation study of 371 dogs in Shiqu County, Sichuan Province during 2002 – 2003 resulted in an *E. multilocularis* prevalence of 12% and an *E. granulosus* prevalence of 8%. These crude prevalences were then adjusted, based on the known sensitivity of arecoline purgation for the detection of *E. granulosus* and a suggested sensitivity for the detection of *E. multilocularis*. In addition, it was assumed that some immature parasites of either species could be misidentified morphologically and wrongly assigned. This resulted in credible true prevalence intervals of between 13 – 33% for *E. multilocularis* and 8 – 19% for *E. granulosus*. Risk factors associated with the acquisition of canine echinococcosis were evaluated based on responses to a questionnaire administered to dog owners. Male dogs were more likely to be infected with *Echinococcus* spp. than female dogs ($P < 0.05$) and dogs allowed to roam were more likely to be infected with *E. multilocularis* ($P < 0.05$). *E. granulosus* and *E. multilocularis* abundance and prevalence were then fit to mathematical models to evaluate transmission parameters. Abundance based models, assuming the presence and absence of immunity, were fit for both parasites using Bayesian priors, maximum likelihood techniques, and Monte Carlo resampling techniques. When the models were compared, using the likelihood ratio test for nested models, the model assuming the presence of immunity was the best fit for *E. granulosus* infection, with a mean abundance of 80 parasites per dog and an average infection pressure of 560 parasites per year. In contrast, the model assuming the absence of immunity was the best fit for *E. multilocularis* infection, with a mean abundance of 131 parasites per dog, and an average infection pressure of 334 or 533 parasites per year assuming a 5 or 3 month parsite lifespan respectively. The prevalence data for both parasites was then fit to a set of differential equations modeling the transition between infection states in order to determine number of infectious insults per year. Infection pressure was 0.21, with a 95% credibility interval of 0.12 – 0.41, infections per year for *E. granulosus* and 0.52, with a 95% credibility interval of 0.29 – 0.77, infections per year for *E. multilocularis*, assuming a 5 month

parasite lifespan or 0.85, with a 95% credibility interval of 0.47 – 1.25, infections per year, assuming a 3 month *E. multilocularis* lifespan in dogs.

Since Shiqu County has an extremely high prevalence of both human AE and CE, the SF-12 v2 quality of life survey was utilized to evaluate the extent to which morbidity associated with echinococcosis should be accounted, and verified a significant reduction in mean health scores for individuals diagnosed with abdominal echinococcosis compared to an age and gender cross-matched population. Results of an ultrasound survey, which screened 3135 subjects, indicated a prevalence of approximately 5% for both AE and CE and an adjusted overall combined prevalence of 9.5%. The burden of disease associated with echinococcosis, utilizing disability adjusted life years (DALYs), was calculated using Monte-Carlo techniques to model uncertainty in the prevalence estimates and disability weights. Total numbers of DALYs lost due to echinococcosis, for the current population of 63,000, was estimated to be 50,933 (95% CI 41,995 – 61,026) and suggests an average of approximately 0.81 DALY lost per person. Human losses, associated with treatment costs and loss of income due to morbidity and mortality, in addition to production losses in sheep, goats, and yaks due to *E. granulosus* infection were also evaluated. A control program based on the biannual deworming of dogs with praziquantel and the vaccination of sheep and goats was then suggested based on the infection pressure of *E. granulosus* and *E. multilocularis* for the region. The median estimated cost of the program would be approximately U.S.$56,000 per annum, which is a fraction of the estimated combined livestock and human financial losses due to the disease. Overall cost for the proposed control program is within the World Health Organization's second most cost-effective band of less than U.S.$150 per DALY averted, however, cost per DALY averted would be less than U.S.$25 dollars for the human health sector if cost-sharing was implemented between the public health and agricultural sectors based on proportional benefit from control.

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Abbreviations

AE:	Alveolar Echinococcosis
CE:	Cystic Echinococcosis
CI:	Confidence Interval
DALYs:	Disability Adjusted Life Years
ELISA:	Enzyme Linked Immunosorbant Assay
GDP:	Gross Domestic Product
PAIR:	Puncture Aspiration Injection Re-aspiration
PCR:	Polymerase Chain Reaction
RMB:	Renminbi (Chinese currency)
SF-12 v2:	Short-Form 12 Version 2 Health Survey
U.S.$:	United States Dollar

Chapter 1

Echinococcosis – an international public health challenge

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1.1. Abstract

This review aims to summarize some of the recent studies that have been undertaken on parasites of the genus *Echinococcus* and the diseases which they cause. Although the adult parasite, which inhabits the intestine of various carnivore species is not pathogenic, the larval or metacestode stages can be highly pathogenic, causing economic losses to livestock and various forms of echinococcosis in humans, some of which have a high fatality rate. There is growing evidence that there are at least 5 species of *Echinococcus* rather than the generally accepted 4 species. Within these species there are a number of genotypes or strains. This can have implications for surveillance and control. In some wealthy countries, cystic echinococcosis caused by *Echinococcus granulosus* has been successfully controlled or indeed eradicated. However, in most parts of the world it remains a serious threat to human health. In the former Soviet Union, the disease has rapidly increased in incidence after the end of communist administration. Human alveolar echinococcosis, caused by *Echinococcus multilocularis*, is more sporadic. However, in some Chinese communities there is a disturbingly high human prevalence and in Europe there has been an increase in the detection rate of *E. multilocularis* in animals in the last 10 years. Echinococcosis can present diagnostic challenges, particularly in the definitive host in areas of low endemicity. Much of the recent work relating to the use of coproantigen and PCR to overcome these difficulties is summarized. New ideas for controlling the parasite are becoming available and these include both the use of vaccination and the application of mathematical models to determine the most cost effective means of control. Effective measures that are affordable are vital if the parasite is to be controlled in poor countries.

1.2. Introduction

The genus *Echinococcus* is of great importance because it contains a number of zoonotic species that can cause serious ill health in man. There are at least 4 species in the genus, but recent molecular evidence suggests that there should be a taxonomic revision to at least 5 species (Table 1.1) or even possibly 6 (Le et al., 2002; McManus, 2002; Thompson and McManus, 2002). There is also significant strain variation in the species *Echinococcus granulosus*. With each species the definitive host is a carnivore, whilst the intermediate host can be one of a large number of mammalian species. The parasite is of pathogenic and economic significance in intermediate and aberrant intermediate hosts, where the larval parasite develops into a hydatid cyst. The genus is found throughout the world although a number of species have a limited geographical distribution.

1.3. Species and distribution

Cystic echinococcosis (CE) caused by the larval stage of *E. granulosus* is the most widespread of these parasites (Figure 1.1). Dogs are the usual definitive hosts whilst a large number of mammalian species can be intermediate hosts, including domestic ungulates and man. In the UK, the parasite has a restricted distribution, being found mainly in mid and southern Wales. In Europe, zoonotic strains of *E. granulosus* are present in every country with the exceptions of Ireland, Iceland and Denmark. It is most intensely endemic in the Mediterranean areas and parts of Eastern Europe such as Bulgaria. In Asia the parasite is intensely endemic in large parts of China and is an important re-emerging zoonosis in the former Soviet Republics in Central Asia (Torgerson et al., 2002a; Torgerson et al., 2002b). The parasite is also found throughout the Indian Subcontinent and the Middle East. In Africa, *E. granulosus* is widespread and is a particular problem in northern African countries such as Tunisia, Morrocco, Libya and Algeria. South of the Sahara the parasite is of specific concern in certain locations such as Turkana in Kenya. In North America the parasite is found in Canada and Alaska, but seems to assume mainly a sylvatic cycle. In the continental USA, the parasite is very sporadic with just a few foci such as certain communities in Utah and California. In South America the parasite is extensive, particularly in Argentina, Uruguay and the Peruvian Andes. In Australia the parasite is common due to a sylvatic cycle between dingoes and wallabies with over 25% of dingoes and up to 65% of macropod marsupials infected (Jenkins and Morris, 1995; Jenkins, 2002). In some developed countries, due to the application of successful control programmes, it is becoming increasingly uncommon. In Iceland, New Zealand, Tasmania and southern Cyprus the parasite has been effectively eradicated (Economides and Christofi, 2002). In many poorer parts of world, particularly where sheep husbandry is an important agricultural industry, the disease is widespread.

Table 1.1. Species and strains of the genus *Echinococcus*

Species	**Definitive hosts**	**Intermediate hosts**	**Approximate geographical location**	**Zoonotic significance**
E. granulosus sheep strain (G1)	Dog, fox, dingo, jackal, hyena	Sheep, cattle, pigs, camels, goats, macropods	World wide	Cystic echinococcosis
Tasmanian sheep strain (G2)	Dog, fox	Sheep	Argentina	Cystic echinococcosis
Buffalo strain (?)	Dog (fox?)	Buffalo (cattle?)	Asia	?
Cattle strain (G5)	Dog	Cattle	Europe, India	Cystic echinococcosis
Camel strain (G6)	Dog	Camels, goats, (cattle?)	Middle East, Africa, China, Argentina	Cystic echinococcosis
Pig strain (G7/G9?)	Dog	Pigs	Europe, Russia, South America	Cystic echinococcosis
Cervid strain (G8)	Wolf, dog	Cervids	Eurasia, North America	Cystic echinococcosis
Lion strain	Lion	Wild African ungulates	Africa	?
E. equinus[a]	Dog	Horse	Europe, Middle East	None
E. multilocularis	Fox, arctic fox, raccoon dog, coyote, dog, wolf, cat[b]	Rodents, lagomorphs, domestic and wild pig[b], dog[b], monkey[b], horse[b]	Eurasia, North America	Alveolar echinococcosis
E. vogeli	Bush dogs	Rodents	South America	Polycystic echinococcosis
E. oligarthrus	Wild felids	Rodents	Latin America	Polycystic echinococcosis

[a] G4 strain of *E. granulosus*. Molecular and epidemiological evidence suggests that it should be a separate species.
[b] Aberrant hosts.

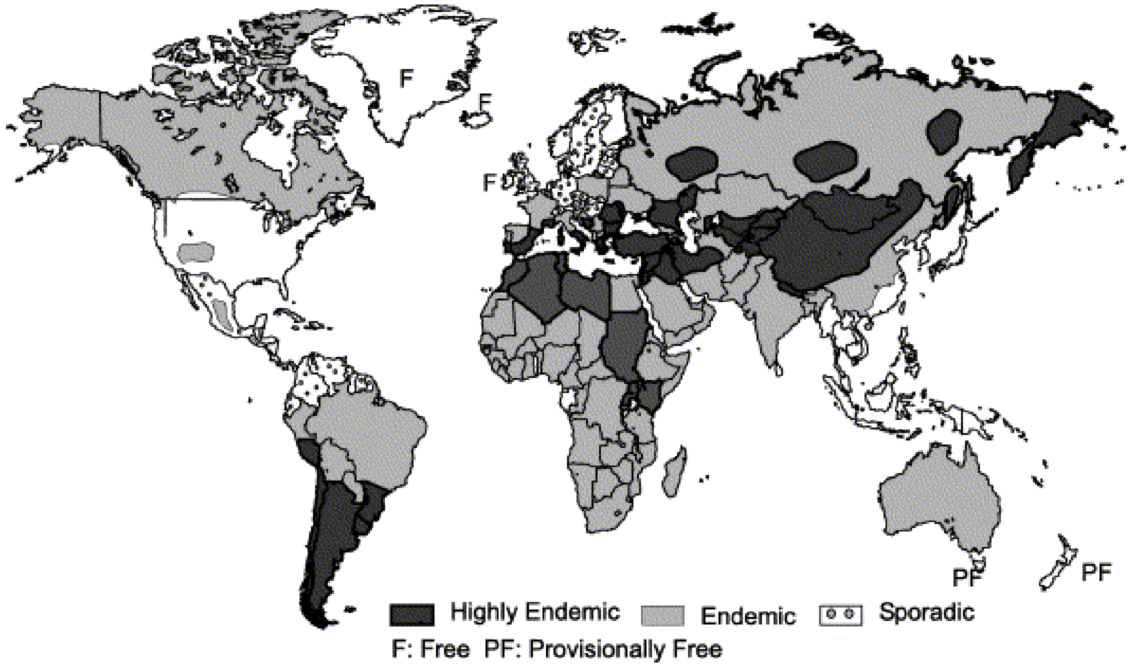

Figure 1.1. Approximate geographical distribution of the zoonotic strains of *E. granulosus*. Adapted from Eckert et al., 2000 and Eckert et al., 2001. © Institute für Parasitologie, Universität Zürich.

The most frequent strain associated with human CE appears to be the common sheep strain (G1). Although in some locations strains such as the Tasmanian sheep strain (G2), camel strain (G6), pig strain (G7/G9) and cervid strain (G8) occur in a significant number of cases. The cattle strain (G5) has been implicated in some cases of human CE (Thompson and McManus, 2002).

The proposed *Echinococcus equinus* (or *E. granulosus* strain G4) does not appear to be zoonotic and the only intermediate hosts reported to date are equines. Furthermore, the parasite is widespread in Ireland (Hatch, 1970) but zoonotic strains of *E. granulosus* are absent and no autochthonous cases of CE have been reported. *E. equinus* was recognized as distinct from the sheep strain and promoted to a subspecies (*E. granulosus equinus*) by Williams and Sweatman (1963). Rausch (1967) dismissed this as the sheep and horse strain exist sympatrically. However, the epidemiological evidence, particularly host specificity, supports a separate taxonomic status. Recent molecular evidence, which implies that *E. granulosus* (G4) strain is at least as distinct from the sheep strain (G1) as either is from *E. multilocularis*, strongly supports the taxonomic status as the separate species *E. equinus* (Le et al., 2002; McManus, 2002; Thompson and McManus, 2002). The parasite seems to have the dog as the only known definitive host and equine species as its intermediate host. Geographically it is present in many areas where *E. granulosus* is found. The cycle of *E. equinus* appears to be maintained by the feeding of horse offal to dogs. In the UK and Ireland, this is typically by the feeding of material from horses to foxhounds.

Echinococcus vogeli and *E. oligarthus* have been occasionally reported as causing a polycystic type of human hydatid disease in Latin America. Little is known about the epidemiology and the transmission to man in the handful of cases reported (Rausch and D'Alessandro, 2002).

Echinococcus multilocularis, commonly known as the fox tapeworm, can be found in areas of central and northern Europe, northern Asia, and parts of North America (Figure 1.2). It has also been proposed that *E. multilocularis* may be in parts of northern Africa, but currently there is not enough information to substantiate this claim (Schantz et al., 1995). The life cycle of *E. multilocularis* is primarily sylvatic. The red fox (*Vulpes vulpes*) is the most well known host but the arctic fox (*Alopex lagopus*), the coyote (*Canis latrans*), the wolf (*Canis lupus*), the raccoon-dog (*Nyctereutes procyanoides*), the sand fox (*Vulpes corsac*), and the Tibetan fox (*Vulpes ferrilata*) are all known definitive hosts, depending on geographic location. Other canids (including domestic dogs), and occasionally felids, can also be definitive hosts if they become infected through the ingestion of an intermediate host harboring an infective metacestode. The principal intermediate hosts include rodents of the family *Arvicolidae*, with a number of reports of infection in the *Sciuridae*, *Cricetidae, Dipodidae* and *Muridae*; some of which may be important locally. Lagomorphs of the family *Ochotonidae* are frequently infected in parts of China. There have been occasional reports of infections in insectivores such as the *Soricidae* and *Talpida.*

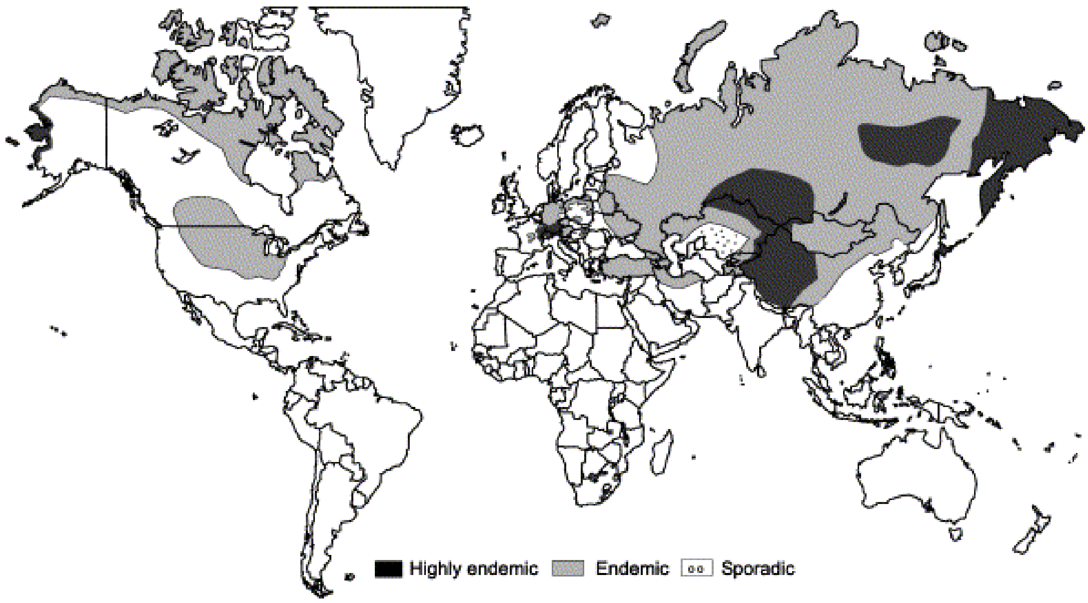

Figure 1.2. Approximate geographical distribution of *E. multilocularis*. Adapted from Eckert et al., 2000 and Eckert et al., 2001. © Institute für Parasitologie, Universität Zürich.

1.4. Clinical aspects

In the definitive host, adult *Echinococcus* penetrate deeply between the villi into the crypts of Lieberkuhn. Despite this intimate host parasite relationship there are few if any lesions. Consequently, there appears to be no ill effect on the definitive host even in the presence of very heavy infections.

In the intermediate host, hydatid cysts have been found in a large variety of mammalian species and often grow slowly, sometimes taking several years to develop. Cysts most frequently affect the liver and lungs but they can also develop in other internal organs including the central nervous system. The cysts vary greatly in size and shape and may be present in large numbers in one organ. The location of cysts and cyst morphology not only depends on host factors but also on the strain or species of *Echinococcus* involved. Hydatid cysts frequently remain asymptomatic for the life span of the host. However, in man symptoms can be severe and it is reasonable to assume that in at least a proportion of infected animals some clinical signs may arise.

Sheep and goats are typically infected with multiple, pleomorphic *E. granulosus* cysts mainly localised in the liver and lungs. Anaphylaxis has been induced experimentally in sheep although sudden death in sheep or other animals has not been recorded (Eckert et al., 2001). In cattle, cysts are often multiple and unilocular with the liver and lungs most frequently infected. If cattle are infected with the cattle strain the predominant location is the lungs. In horses, cysts typically grow slowly in the liver and even long-lived cysts may remain small and asymptomatic (Roneus et al., 1982). Even though large cysts frequently remain asymptomatic (Thompson and Smyth, 1975), clinical manifestations have been recorded. In one case reported in Switzerland a nine-year-old Irish horse presented with massive liver enlargement, increased levels of liver enzymes, liver dysfunction, obstructive lung disease, intermittent colic, anorexia and emaciation. This horse was heavily infected with several hundred hepatic and pulmonary cysts ranging from 1 to 3 cm in diameter (Hermann et al., 1988). In pigs the liver is most commonly infected, although cysts can be found in any organ.

Perhaps the most important effect of echinococcosis in domestic livestock is the potential economic impact of the infection. Whilst clinical symptomatology may be relatively unusual, there are reports of decrease in feed conversion ratios, lowering of milk production in lactating animals, decreases in reproduction rates and decreases in the value of wool or hides from infected animals (Kenzhebaev, 1985; Polydorou, 1981; Ramazanov, 1982). These effects have been analysed economically (Torgerson et al., 2000; Torgerson et al., 2001; Torgerson and Dowling, 2001), and it is possible that in some societies the economic effects of infection in domestic stock may be the most important economic effect costing the livestock industries millions of dollars in endemic areas.

In wildlife, the predilection site of the cysts may render the host more susceptible to predation. In the moose in Canada, hydatid cysts frequently occur in the lungs, and those animals most heavily infected are caught more frequently by timber wolves and are often the first to be shot by hunters (Ran and Canon, 1979). Likewise, heavily infected wallabies in Australia may be more susceptible to predation by dingoes due to compromised lung function (Jenkins and Morris, 1995).

The effects of *E. multilocularis* on the intermediate host tends to be more profound due to the tumour-like proliferation of the metacestode. In the comparatively short-lived natural intermediate hosts, to which the parasite is well adapted, metacestodes develop rapidly and death often occurs, usually around 5 months after infection. Clinical and pathological changes in experimentally infected rodents include enlargement of the abdomen, increase in body weight due to the proliferating metacestode, weakness, apathy, anorexia, ascites and finally death. Upon post-mortem examination, infiltration of the liver, peritoneal cavity, other abdominal organs, and the lungs may be evident.

Domestic and wild pigs, dogs, monkeys and some other animal species have been described as aberrant hosts for *E. multilocularis* (Deplazes and Eckert, 2001). Among these hosts, horses and swine appear to be the least susceptible with the development of small lesions, typically only 1–20 mm in diameter, as well as suppressed development of the metacestode tissue (Eckert, 1996; Ohbayashi, 1996). Dogs with metacestode infection of the liver and or peritoneum presented with abdominal enlargement, ascites, and hyper-γ-globulinaemia (Haller et al., 1998). Recently, concurrent infection of the dog as both the definitive and the intermediate host has been recorded. Infected simians may show clinical signs such as emaciation, inappetence, and jaundice. In one example, a 10–20 cm diameter lesion was found in the liver of a naturally infected orangutan in a Japanese zoo (Taniyama et al., 1996).

1.5. Human echinococcosis

Human echinococcosis results when man ingests eggs, which have been shed in the faeces of the definitive host. The initial phase of CE is asymptomatic with small well-encapsulated cysts. After an undefined period of several months to years, the infection may become symptomatic as a space-occupying lesion. However, 60% of infections will remain asymptomatic (Pawlowski et al., 2001). The liver is the most common organ involved, usually with over two thirds of cysts. The lungs are infected in about 20% of cases, with other organ involvement accounting for less than 10% of cases. The treatment options for CE include surgical removal of the lesions and in many parts of the world CE is the most common reason for abdominal surgery. Surgery has a success rate of up to 90% (Pawlowski et al., 2001). An alternative to surgery is the

PAIR technique (Puncture-Aspiration-Injection-Reaspiration), (World Health Organization, 1996). Chemotherapy, using benzimidazoles, has also been used with some success. In calcified cysts, there is an indication for a wait and see approach to treatment.

Alveolar echinococcosis (AE), due to the metacestode stage of *E. multilocularis*, is an often-fatal condition if untreated. The cyst is multivesicular and highly infiltrative locally. The primary site of metacestode development is almost exclusively the liver. Secondary metastasis may form in a variety of adjacent or distant organs in longer standing cases, making surgical management difficult. Patients present with cholestatic jaundice and/or epigastric pain, fatigue, weight loss, hepatomegally or abnormal routine laboratory findings (Pawlowski et al., 2001). Treatment options include partial and radical surgical resection for localized lesions in combination with long-term chemotherapy using benzimidazoles. In rare cases, liver transplantation has been undertaken.

Human infections with *E. vogeli* and *E. oligathus* results in polycystic echinococcosis. Relatively few cases have been described and they were all in Latin America. In 80% of cases the lesions involved the liver; the rest were located in the lung or single organ sites (D'Alessandro, 1997). The most common clinical presentation includes liver masses, enlarged abdomen, abdominal pain, weight loss and fever. In about 25% of cases there are signs of biliary hypertension and biliary obstruction. From the limited numbers of cases that have been reported the fatality rate is at least 26%. *Echinococcus equinus* (*E. granulosus* strain G4) appears to be non-pathogenic to man.

1.6. Epidemiology and transmission to man

Echinococcus granulosus has both sylvatic cycles, often involving wild carnivores and ungulates; and domestic cycles, usually involving dogs and farm livestock. It is the latter transmission cycle that is the most common and poses the greatest threat to human health. The highest incidence rates in man are often seen in areas where there is a close association with man and domestic livestock, often using dogs as working dogs. A common source of infection for dogs is offal from infected sheep, which often harbour the zoonotic G1 strain responsible for many cases of human CE. The resultant high infection levels in these dogs then pose a risk to human contacts. The potential for domestic transmission of *E. granulosus* is highest in poor countries where the level of education may be low, veterinary services inadequate and there is the widespread practice of home slaughtering. In such circumstances, the rates of infection in dogs can reach between 20% and 50% with perhaps an excess of 50% of the sheep population being infected. The risks associated with infection are illustrated by the deteriorating situation in Central Asia. Prior to the break up of the Soviet Union, CE in man was at relatively low levels. However, following independence of the Central Asian republics there was widespread structural and economic reform. This resulted in privatisation of farms, abandonment of centralised meat processing facilities and a return to small subsistence-type agricultural practices. Veterinary services also collapsed due to a lack of government funding. This has resulted in an epidemic of human CE, with the annual incidence of surgical cases reported by hospitals in excess of 4–5 times the number reported prior to 1991 (Torgerson et al., 2002a; Torgerson et al., 2002b; Torgerson et al., 2003a) (Figure 1.3). A similar pattern is also emerging in other former communist countries like Bulgaria (Todorov and Boeva, 1999).

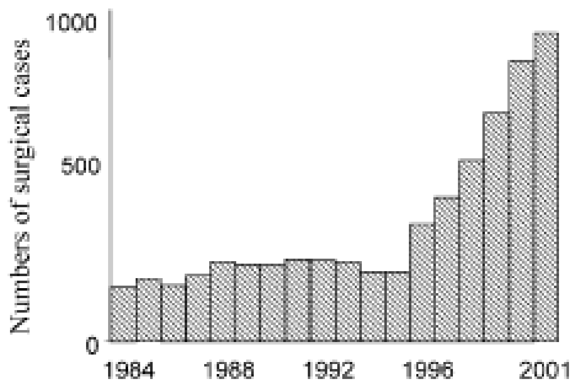

Figure 1.3. Change in the numbers of surgical cases of CE in Kazakhstan between 1984 and 2001. Adapted from Torgerson et al. (2002a) with additional data.

Nevertheless, providing resources are available, a dramatic reduction in prevalence and even eradication is possible. This is due mainly to the factors that affect the transmission dynamics. The parasite has a relatively low biotic potential, and density dependent constraints may only act at the level of the definitive hosts (Gemmell, 1990; Lahmar et al., 2001; Torgerson, 2003a; Torgerson et al., 2003b). In Iceland, Tasmania, New Zealand and Southern Cyprus control has been highly successful and eradication or near eradication has been achieved. However, these are island nations. In continental countries, eradication would be harder to achieve because of the potential for reintroduction from neighbouring countries and the presence of sylvatic cycles. Nevertheless, control is possible such that the parasite can be maintained at low levels.

In endemic areas a considerable proportion of horses can be infected with *E. equinus* (Thompson and Smyth, 1975). Interestingly, this parasite is widespread in Ireland where zoonotic strains of *E. granulosus* are absent. However, the sheep strain of *E. granulosus* is highly endemic in some parts of Wales in the UK, and the reasons why *E. equinus* has managed to establish in Ireland but not *E. granulosus*, despite the free movement of animals between the UK and Ireland is not known. It is possible that this is due to the relatively low sheep population and density of sheep that has, until relatively recently, existed in Ireland. This would lower the probability of transmission and thus make establishment difficult. In contrast in Wales, the sheep population has always been at a high density. If this hypothesis is correct, then there will be an increasing risk of introduction of *E. granulosus* into Ireland as there has been a large increase in the sheep population over the last 20 years to avail of EU subsidies.

Human AE remains a sporadic human disease over much of the northern hemisphere. The majority of cases are a result of environmental contamination with infected fox faeces and subsequent transmission to humans. In the central European endemic area, the red fox (*Vulpes vulpes*) is likely to be responsible for most of the environmental contamination with *E. multilocularis* eggs (Eckert and Deplazes, 1999). In addition to the prevalent sylvatic life-cycle, a semi-domestic life-cycle has developed in some areas of the world. One of the first known examples of this phenomenon was on St. Lawrence Island off the Alaskan coast where, in the 1950s, a cycle between dogs and voles was discovered (Schantz et al., 1995). Later, stray dogs on the Japanese islands of Reubun and Hokkaido also tested positive for *E. multilocularis*, with a prevalence rate of 1.6% on Reuben Island (Yamashita, 1973) and 2% on Hokkaido Island (Iida, 1969). More recently, a cycle involving dogs and rodent species has been encountered in the Sichuan and Gansu provinces of China, where in one study 6 out of 58 dogs were found to be positive on post-mortem examination (Craig et al., 1992). Felids have also been shown capable of acting as aberrant definitive hosts for *E. multilocularis* with a low or negligible egg excretion rate (Petavy et al., 2000). It has been estimated that prevalence rates in cats in Europe range from 0% to 5.5% (Eckert, 1998).

The existence of this semi-domestic cycle may have resulted in a relatively high prevalence rate of human AE in some communities. In Gansu Province in China there are communities where the ultrasound prevalence rate reaches 5% (Craig et al., 1992) and similar rates have also been detected in Sichuan Province (Wang et al., 2001). Presently active epidemiological research is being undertaken in this region and it seems likely that there may be direct transmission from domestic and stray dogs to the human population. Preliminary unpublished results suggest a prevalence rate of *E. multilocularis* in dogs of as much as 30%. In the pastoral Tibetan communities of Sichuan it is possible that dogs are becoming infected by scavenging rodents in the montane treeless steppe region and subsequently transmitting the disease by close contact with the local human communities.

In Europe, *E. multilocularis* is being found in new regions previously thought to be free from the parasite (Figure 1.4). Presently, it is not certain if this is due to improvements in diagnosis or a recent extension of the parasite's range (Romig For EurEchinoReg, 2002). There has been a drastic increase in the fox population density and an increase in the prevalence of infection in previously endemic areas recorded in the last 10 years. Likewise, there appears to have been an increase in the prevalence in intermediate hosts (Romig et al., 1999). This increase in parasite density could have increased the risk for man of exposure to *E. multilocularis* and subsequent development of AE. The reasons for the increase in fox numbers are not known. However, fox mortality due to rabies has been reduced to virtually zero (Thulke et al., 1998), and the increase in the fox population is associated with the implementation of the rabies immunization campaign. However, similar increases in fox populations have also occurred in the UK where rabies is absent indicating that additional factors are important. In particular, foxes have become increasingly adapted to urban habitats and this may account for a significant part of the population increase (Deplazes et al., 2002).

Figure 1.4. The geographical range of *E. multilocularis* in Europe recognized in 1990 ▬ and 2000 ▭ . Data from Eckert et al. (2000) and Romig For EurEchinoReg (2002).© Institüte für Parasitologie, Universität Zürich.

The only known final host of *E. vogeli* is the bush dog (*Speothus venaticus*) whose distribution includes all the tropical sylvatic areas of South America except Chile, Argentina and Uruguay. The cestode has also been found on one occasion in a domestic dog. In addition, it has been possible to experimentally infect domestic dogs (Rausch and D'Alessandro, 2002). The natural hosts, bush dogs, are timid and elusive and may play little role in infecting man. However, paccas, the typical intermediate host, are widely hunted for food with the aid of dogs, which are often rewarded by being fed the viscera. *Echinococcus oligathus* has been recorded naturally in 6 species of felids that occur in Central and South America. Experimentally the domestic cat has also been infected. Only three cases of echinococcosis due to *E. oligathus* have been confirmed in man (Rausch and D'Alessandro, 2002) and it is not known how these individuals became infected.

There is evidence of indirect transmission of echinococcosis to man through, for example, contaminated food or water supplies rather than with direct contact with dogs (Carmona et al., 1998; Dowling et al., 2000; Larieu et al., 2000; Torgerson et al., 2003a). Furthermore, there is also epidemiological and experimental evidence that taeniid eggs can be transmitted considerable distances by mechanical carriers such as insects or birds (Gemmell, 1990; Torgerson et al., 1995).

1.7. Diagnosis

In the intermediate host, the presence of *E. granulosus* has usually been detected at post-mortem by examination of the viscera. This can provide important epidemiological data, which can be used to define the likely infection pressure (Cabrera et al., 1996; Ming et al., 1992; Torgerson et al., 1998). The main disadvantage of this approach is that a slaughterhouse sample is potentially biased. In Kenya ultrasound detected hydatid cysts in sheep and goats with a sensitivity and specificity of 54% and 97%, respectively (Sage et al., 1998). Ultrasound has also been used in horses (Hermann et al., 1988). Currently, there is no suitably sensitive and specific serological test available for individual diagnosis in livestock species (Eckert et al., 2001). Nevertheless, serum antibody activity is used for detecting infection at the herd or flock level. This may be useful in hydatid screening programmes, particularly, when cysts may be too small to easily identify at necropsy. Antibodies that react against hydatid cyst fluid antigen can be detected from 4 weeks after exposure, and greater than 90% sensitivity using antigen B enriched hydatid fluid extracts have been recorded. However, there are cross reactivity problems with *Taenia hydatigena*, *T. ovis* and *Fasciola hepatica* (Eckert et al., 2001). When conducting surveillance work, it is very important to also record the age structure of the intermediate host population as the numbers of hydatid cysts increase with age due to the lack of naturally induced protective immunity (Roberts et al., 1986); a high abundance or prevalence of infection in young livestock would be considered of much greater significance than a similar level in older stock.

The diagnosis of *E. multilocularis* in intermediate and aberrant hosts should be based on several criteria. These consist of the use of macroscopic and histological examinations, including the morphology and size of hooks on the protoscolices. In very small lesions additional techniques may be necessary such as immunohistology with monoclonal antibodies, DNA-hybridisation or PCR techniques (Eckert et al., 2001). In living animals such as dogs or monkeys, ultrasound examination of the abdominal organs is indicated with specific antibody detection (Deplazes and Eckert, 2001).

The most reliable means of diagnosis of *Echinococcus* in the definitive host is by necropsy, as the worm burden can be estimated and parasites collected for identification (Eckert, 1997). Straightforward coprological examination may reveal the presence of taeniid eggs, but will not distinguish infection with *Echinococcus* spp. and *Taenia* spp. The parasympathomimetic drug arecoline when given to dogs causes purgation of the entire intestinal contents. The drug also paralyses tapeworms which can then be collected and identified. This is an unpleasant technique but remains the only quantitative technique that can be used in the living dog and continues to play an important role in epidemiological studies (Torgerson et al., 2003b). However, the technique is time consuming, can be hazardous to the operator and occasionally produces severe reactions in the dogs. Also, not every dog will purge, and a significant number of carriers are not detected (Schantz et al., 1995). Consequently immunological and molecular approaches have been developed.

The detection of parasite-specific antigens in faecal samples is perhaps one of the most useful ways for collecting prevalence data in large surveys. The test is based on a parasite-specific layer of capture IgG antibodies which retains antigens from faecal supernatants. These coproantigen ELISAs report sensitivities of up to 93% and specificities of up to 99%. Tests have been developed for the detection of *E. granulosus* (Allan et al., 1992; Deplazes et al., 1992) and *E. multilocularis* (Deplazes et al., 1999). Discrimination between *E. granulosus* and *E. multilocularis* infections is difficult and the detection of very low burdens of less than 20 parasites may also be problematical. Longitudinal studies have demonstrated that coproantigen production can be detected in faeces within 10–20 days of infection, some 1–4 weeks prior to eggs appearing in the faeces (Allan et al., 1992; Deplazes et al., 1992; Jenkins et al., 2000; Malgor et al., 1997). Once the worms are expelled, coproantigen levels drop rapidly and become negative within 3–4 days. The *E. granulosus* coproantigen ELISAs have been used in a number of studies in the Middle East, Wales, Southern and Eastern Europe, and South America (reviewed by Fraser et al., 2002). Likewise, coproantigen ELISAs have been used for the surveillance of *E. multilocularis* in Japan and Europe.

Other techniques with greater specificity would be useful when the prevalence rate in the dog population is relatively low (Christofi et al., 2002) and for discriminating dogs with positive taeniid egg counts. A PCR has been developed for detecting *E. multilocularis*-specific DNA (Dinkel et al., 1998; Mathis et al., 1996) and is presently being developed for the detection of *E. granulosus* DNA (Cabrera et al., 2002a). Although this technique is sensitive enough to detect parasite-specific DNA from a very small number of eggs, it is not quantitative and is not suitable for large scale screening of samples; an important consideration in the design of control and surveillance systems. Thus, PCR based techniques are well suited as confirmatory tools once preliminary screening has been completed. In particular, positive predictive values for the coproantigen test become poor when the prevalence is very low. In such a scenario, coproantigen positive dogs could then be screened with a PCR based technique to distinguish between true and false positive results.

There is recent evidence that there are significant variations of parasite burdens with the age of the definitive host. Lahmar et al. (2001) and Torgerson et al. (2003b) have demonstrated that young dogs are likely to have the highest burdens of *E. granulosus* in highly endemic regions. Likewise, Hofer et al. (2000) demonstrated that young foxes had significantly higher mean burdens of *E. multilocularis* than older foxes. The suggestion has been made that this may be due to host protective immunity and the relatively short life-span of the parasite compared to that of the host. Therefore, the age structure of the definitive host population should also be considered when designing surveillance or epidemiological studies.

1.8. Control

Control of CE has always involved a combination of routine anthelmintic treatment of dogs, control and reduction of stray dog populations, supervision of the slaughter of livestock and subsequent disposal of offal, and education of the public. The prepatent period of *E. granulosus* is approximately 6 weeks and hence this has usually been the recommended treatment interval. Praziquantel is currently the most effective anthelmintic available for this purpose. Mathematical models have been developed to describe the transmission dynamics (reviewed by Gemmell, 1990) and more recently to simulate control options (Torgerson, 2002a). Although six-weekly anthelmintic treatment is highly effective, it is expensive in terms of manpower and logistics, and therefore, less suitable for use in poor countries. Simulation models suggest it may be possible to lengthen the interval between anthelmintic treatments to at least 3 months and still reduce prevalence rates in dogs and livestock to less than 1% within 10–15 years (Torgerson, 2003a). This idea has been supported by field studies in Uruguay (Cabrera et al., 2002b) and New Zealand (Gemmell, 1990). The lengthening of the treatment intervals to beyond the prepatent period can work because the mean time to reinfection is often considerably longer than six weeks. New intervention strategies are also being developed. One of the most promising is the development of a vaccine in sheep, which in trials has demonstrated close to 100% protection (Lightowlers et al., 1996; Lightowlers et al., 1999). Widespread vaccination of sheep would prevent the transmission of the parasite to dogs, but would not have an immediate effect as it only prevents new infections and does not eliminate cysts already present. Thus, it would take a number of years before all the previously infected sheep were removed from the population. Therefore, it would be pertinent to combine vaccination with anthelmintic prophylaxis in dogs to prevent or lower transmission to man from the start of the control programme.

One major obstacle to any programme is the capture rate of either host in the life-cycle. Studies in China have suggested that the capture rate in dogs is little more than 50–60% of the population (Fen-Jie, 1993). Thus, a considerable proportion of dogs escape anthelmintic treatment and undermine attempts at control. This is due, *inter alia*, to the large population of stray dogs that is often present in endemic areas and vigorous attempts to reduce the stray dog population should be an integral part of a control strategy. Nevertheless, the uncertainty in the treatment rate can be modelled stochastically (Torgerson, 2003a) and a probability distribution of the outcome of intervention determined with likely best and worst-case scenarios. Vaccination of sheep can also be included in the model. For example, routine three-month anthelmintic treatment gives very good long-term results providing at least 75% of the dog population (including strays) is treated. Six-monthly anthelmintic treatment only reduces the levels of echinococcosis substantially if the treatment rate is well in excess of 90%, which is unlikely to occur in practice. Providing at least 75% of sheep are vaccinated, echinococcosis will be reduced considerably, but not for several years after implementation. However, lowering the flock immunity to 60% results in a significant risk of failure. Nevertheless, if control consists of a combination of vaccination and routine anthelmintic treatment, the model suggests a high probability of success even if anthelmintic treatment is only given every 6 months to 60% of dogs with as few as 60% of sheep vaccinated. This illustrates the cumulative effect of controlling the parasite at more than one point in its life cycle and may indicate the most promising means of control, particularly in a low income country (Figure 1.5) where control of CE presents the greatest challenges. In such countries, CE is at its most intensely endemic, resources are scarce and continual reintroduction from sylvatic cycles or neighbouring countries are constant threats. In this respect, economic analysis should be an important priority (Torgerson, 2003b; Torgerson and Dowling, 2001; Torgerson et al., 2000; Torgerson et al., 2001) to develop the most cost-effective means of control. Thus, economic models that define the cost of the disease can be combined with the simulation models summarised above. This would predict the results of intervention strategies to determine the most cost effective use of resources to lower the incidence in man and the prevalence in domestic animals.

The only other species of *Echinococcus* for which control has been attempted is *E. multilocularis*. The control of this parasite is more problematical than *E. granulosus* because of the mainly sylvatic cycle of the parasite. However, the use of aircraft to distribute baits in Germany (20 baits per km^2, each containing 50 mg of praziquantel) has reduced the prevalence of the parasite in rural foxes (Eckert et al., 2000; Romig et al., 1999; Schelling et al., 1997). Furthermore, a five-year dog- and fox-culling programme appears to have eliminated the parasite from Reuben Island, Japan (Craig et al., 1996).

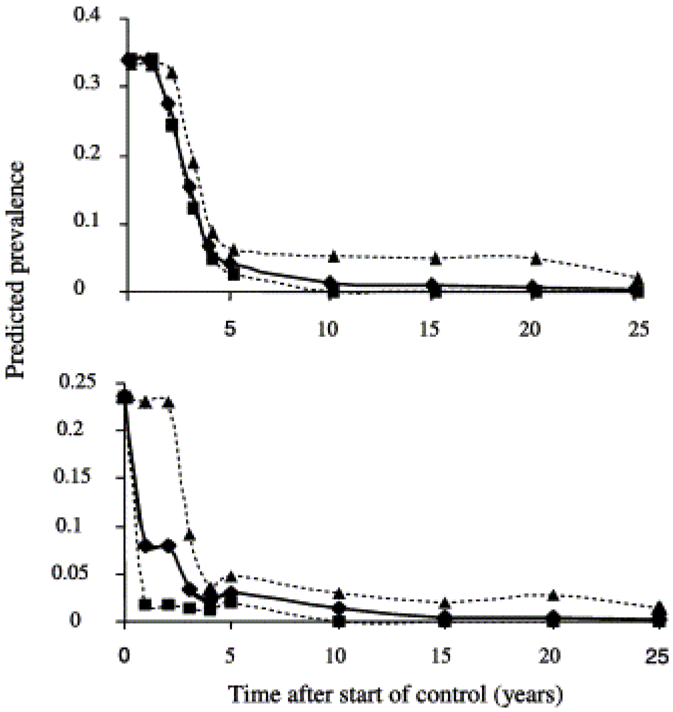

Figure 1.5. Predicted response of echinococcosis to control measures of a combination of vaccination of lambs and 6-monthly anthelmintic treatment in Kazakhstan. Top changes in prevalence in sheep, bottom changes in prevalence of farm dogs. — Most likely scenario with ··· 95% confidence limits. Present data indicates that initial prevalence in dogs is 0.23 and that in sheep of 0.34.

1.9. Conclusions

Despite the large efforts that have been put into the research and control of echinococcosis, it still remains a disease of worldwide significance. In some areas of the world, CE caused by *E. granulosus* is a re-emerging disease in places where it was previously at low levels. There are also disturbing trends in the distribution of *E. multilocularis* with an increased detection rate in Europe and a number of intensely infected communities in China. If this deteriorating trend is to be stopped then additional efforts are needed to control these diseases.

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Chapter 2

Objectives and Study Design

2.1. Project objectives

1. Collect purgation samples from dogs of Shiqu County, Sichuan Province, P.R. China to evaluate *Echinococcus* spp. prevalence and abundance.

2. Utilize univariate and multivariate logistic regression to evaluate a questionnaire for risk factors associated with canine echinococcosis.

3. Fit purgation data to transmission dynamics models and determine values for infection pressure, acquisition of immunity, and loss of immunity utilizing Bayesian, maximum likelihood, and resampling techniques.

4. Determine whether an abundance model assuming the presence or absence of acquired immunity is the best fit for *E. granulosus* and *E. multilocularis* purgation data.

5. Evaluate quality of life of individuals with abdominal echinococcosis compared to an age and gender cross-matched population using the SF-12 v2 quality of life survey.

6. Determine number of disability adjusted life years (DALYs) lost due to *Echinococcus* spp. infection in Shiqu County utilizing Monte-Carlo resampling techniques.

7. Evaluate the economic losses associated with *Echinococcus* spp. infection in Shiqu County and the potential outcome of a proposed control program based on the anthelmintic treatment of dogs, plus vaccination of sheep and goats, in terms of economic savings and cost per DALY averted.

2.2. Study location

This study took place during 2002 – 2003 in Shiqu (Serxu) County, Sichuan Province, People's Republic of China. Shiqu County is in a region known as the Tibetan plateau and is situated at an altitude of approximately 4200 meters above sea level (Figure 2.1). The county belongs to Sichuan Province, which is located in western China, and has a total population of more than 84 million. The province is ethnically diverse with members of the Han, Yi, Tibetan, Qiang, Mongolian, Lisu, Manchu, Naxi, Bai, Bouyei, Dai, Miao, and Tujla ethnic groups all present in various degrees. The Tibetans of Sichuan Province live primarily in the Garze (Ganzi) and Ngawa Tibetan Autonomous Prefectures and the Muli Tibetan Autonomous County in Liangshan Prefecture. Shiqu County is part of the Garze Tibetan Autonomous Prefecture and has a population of 63,000 and an area of 20,477 square kilometers (Sichuan Statistical Yearbook, 2002).

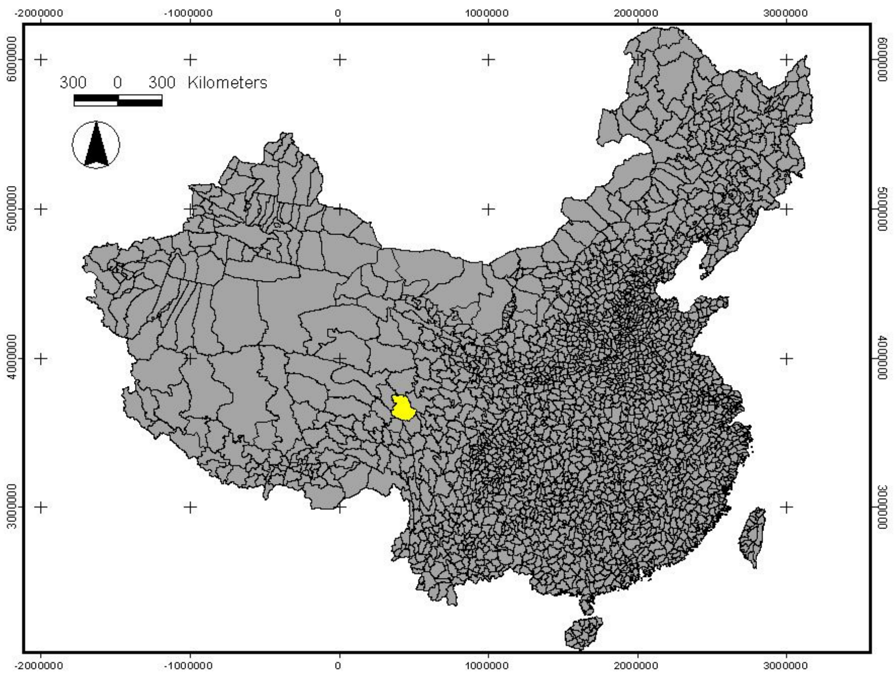

Figure 2.1. Map of China, with Shiqu County indicated in yellow.

Shiqu County is culturally Tibetan and has a population composed primarily of transhumant yak herdsmen, who move their yaks between winter pasturelands, often associated with fixed settlements, and higher altitude summer pasturelands not associated with fixed settlements. Hygiene and sanitation conditions, in the region, are extremely poor. In addition, inhabitants live in close quarters with both owned and stray domestic dogs. Even though the numerous stray dogs can be vicious, villagers will not destroy them or let outsiders destroy them due to their strong Buddhist religious beliefs. Poor socioeconomic and hygiene conditions, in addition to a close relationship with dogs, lead to an extremely high *Echinococcus* spp. prevalence in the current human population.

2.3. Methodology

2.3.1. Purgation using arecoline hydrobromide

Only dogs that were owned and could be tied were purged during this study. This limitation was due to the necessity of monitoring the dog after administration of the purgative agent, as well as a need to contain the dog while it purged so as to not risk extensive environmental contamination with potentially zoonotic parasites. Individual dogs were purged using the parasympathomimetic drug arecoline hydrobromide (Boehringer Ingelheim) at a dose rate of 7 mg/kg. The drug was administered in a small dough ball made of tsampa (barley flour mixed with water), which is the staple diet of the Tibetan people. Tsampa was chosen as the principle mode of drug delivery because it is a food that the dogs are accustomed to receiving, it is easily moldable in order to enclose the drug, and it was readily available. Once a dog had purged, which often took up to 1.5 hours due to the mode of delivery, the fecal material was collected in a leak-proof container and the ground, where the feces were collected, was decontaminated as well as possible. Inhabitants of the area were instructed to stay away from the purge site and special emphasis was placed on the importance of keeping small children away from the dog and the area.

2.3.2. Sample processing

After samples were collected, the fecal material was placed in either 10% formal saline or 85% ethanol, depending on availability. Samples were evaluated using a black-based pan so that the parasites could be more easily identified against a dark background. A small quantity of fecal material was added to the pan followed by copious amounts of water. The feces were washed numerous times, until the water in the pan was almost clear. All parasites detected were counted, collected in 10% formal saline or 85% ethanol, and recorded. Personnel associated with the samples donned biohazard suits, latex gloves, masks, and boot covers. Parasite samples were then taken to the Institute of Parasitology, University of Zürich, Switzerland for microscopic examination and confirmation of morphological identification.

2.3.3. Risk factor questionnaire

At the time of purgation, dog owners were asked to complete a questionnaire that focused on possible risk factors for acquiring human and canine echinococcosis. Questionnaires were written in both English and Mandarin Chinese and administered orally to participants in the local Tibetan dialect (Appendix A). The questionnaire was designed so that the answer to most questions could simply be circled, thereby eliminating some degree of translation-based uncertainty. At this time, a brief description of the life cycles of *Echinococcus* spp. was given to the dog owners as well as a description of the disease in humans. Information obtained from the questionnaires was inputted into an EpiInfo 2000 version 3 database (CDC, Atlanta GA) and subsequent logistic regression analysis performed using the same program in order to determine risk factors for canine echinococcosis.

2.3.4. Statistical evaluation and modeling

Statistical methods utilized for this study included use of various mathematical distributions, with special emphasis given to the negative binomial distribution as a model of aggregated parasite counts. Other statistical methods employed included the use of Bayesian priors, maximum likelihood, and Monte Carlo resampling techniques. Statistical analysis was performed using Excel (Microsoft, Redmond, WA) spreadsheets with the additional statistical power of the Excel add-in PopTools

(CSIRO, Australia). Transmission models, based on parasite abundance and prevalence in dogs, were used to determine parameters representing infection pressure, acquisition of immunity, and loss of immunity, with these parameters then incorporated into a proposed control program for the region.

2.3.5. SF-12 v2 quality of life survey

A Tibetan language version of the short form 12 version 2 (SF-12 v2) health survey (QualityMetric, Inc., Lincoln, RI) was utilized to assess quality of life variations between individuals diagnosed, via abdominal ultrasound, with echinococcosis and an age and gender cross-matched population from the same area (Appendices B,C). The SF-12 v2 is a condensed version of the SF-36 survey, which has become a standard tool over the years. The information obtained via this health survey was utilized to justify the addition of morbidity associated cost estimates into an economics based model.

2.3.6. Human screening and burden of disease

Human screening, via abdominal ultrasound evaluation, was performed on 3135 voluntary self-selected individuals in Shiqu County using a portable ultrasound machine (SSC218, ALOKA Medical Equipment, Shanghai, P.R. China). Diagnosis of alveolar echinococcosis (AE) and cystic echinococcosis (CE) was made based on ultrasound characteristics as recommended by the WHO-IWGE Ultrasound Classification scheme (Vuitton and Pawlowski, 2001; WHO Informal Working Group, 2003). Human AE and CE prevalences were determined and adjusted according to the current age and gender structure of Shiqu County. The burden of disease associated with echinococcosis was calculated, utilizing disability adjusted life years (DALYs), with Monte-Carlo techniques used to model uncertainty in prevalence estimates and disability weights.

2.3.7. Economic evaluation and control recommendations

Human losses, associated with treatment costs and loss of income due to morbidity and mortality owing to human AE and CE, in addition to production losses in sheep, goats, and yaks due to *E. granulosus* infection were evaluated for Shiqu County. A control scheme consisting of biannual owned dog deworming and stray dog baiting with the anthelmintic praziquantel, in addition to sheep and goat vaccination, was recommended based on the current prevalence of infection in dogs as well as infection pressure to the dog definitive host as predicted by transmission models. The proposed control program was then costed and amount spent per DALY averted, in addition to livestock associated savings, calculated.

2.4. Ethical considerations

Ethical approval for all work carried out within China was obtained from the Medical Sciences Expert Consultant Committee, Sichuan Provincial Health Bureau, Sichuan Province, P.R. China.

2.4.1. Human ethical considerations

All human participants, who were diagnosed with echinococcosis via abdominal ultrasonography, were supplied free of charge with a five month supply of the anthelmintic albendazole in addition to being notified of their surgical options. An attempt was made, at the time of screening, to familiarize the participant with the disease and its route of transmission in the hope that improved hygiene will also aid in the decrease of human echinococcosis in the region.

2.4.2. Animal welfare considerations

Dogs that were given the parasympathomimetic purgative agent arecoline hydrobromide were monitored for several hours after the administration of the drug, with atropine kept on hand in case of a severe adverse reaction. Arecoline was always administered with caution in order to protect both the definitive host and the administrator of the drug. The most common clinical signs associated with toxicity are vomiting and excessive salivation. A more severe clinical manifestation is cardiac collapse, which can be treated with the administration of atropine sulfate at a dose of 0.3 to 0.4 mg in accordance with the size of the dog. It is also not advisable to administer the drug to pregnant bitches or very young or very old dogs, which was taken into consideration when performing this study. Administration of arecoline has also been known to result in intestinal perforation after a piece of bone or other sharp object was propelled through the intestinal wall due to intense intestinal contractions. Previous studies have shown, however, that the dog fatality rate associated with the use of the purgative is very low, with arecoline being widely used as an anthelmintic in the 1950s and 1960s. Gregory (1978) reported that toxicity occurred in approximately 5 dogs per 1000 dosed and death resulted in about 1 in 9,500 dogs dosed at a rate of 3.25 mg/kg. No dog died as a result of this study, with the most common side affect being vomition.

2.5. References

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Chapter 3

A canine purgation study and risk factor analysis for echinococcosis in a high endemic region of the Tibetan plateau

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3.1. Abstract

The Tibetan plateau of western China has been shown to have a very high prevalence of human cystic echinococcosis (CE) caused by *Echinococcus granulosus* and human alveolar echinococcosis (AE) caused by *Echinococcus multilocularis*. The domestic dog is suspected to be the primary definitive host for the transmission of both *E. granulosus* and *E. multilocularis* to humans in this locality. A purgation study of 371 dogs in Shiqu County, Sichuan Province during 2002 – 2003 resulted in an *E. multilocularis* prevalence of 12% and an *E. granulosus* prevalence of 8%. These crude prevalences were then adjusted, based on the known sensitivity of arecoline purgation for the detection of *E. granulosus* and a suggested sensitivity for the detection of *E. multilocularis*. In addition, it was assumed that some immature parasites of either species could be misidentified morphologically and wrongly assigned. This resulted in credible true prevalence intervals of between 13 – 33% for *E. multilocularis* and 8 – 19% for *E. granulosus*. Prevalences of other intestinal helminthes found on purgation were: *Taenia* spp. 31%, *Dipylidium caninum* 1%, and ascarids 8%. Risk factors associated with the acquisition of canine echinococcosis were evaluated based on responses to a questionnaire administered to dog owners. Male dogs were more likely to be infected with *Echinococcus* spp. than female dogs ($P < 0.05$) and dogs allowed to roam were more likely to be infected with *E. multilocularis* ($P < 0.05$).

3.2. Introduction

Echinococcus granulosus and *Echinococcus multilocularis* are the cestode species responsible for human cystic echinococcosis (CE) and human alveolar echinococcosis (AE), respectively. Shiqu County in Sichuan Province, People's Republic of China has been found to harbor one of the highest prevalences of CE and AE ever recorded (Budke et al., 2004). It is speculated that domestic dog is the primary definitive host for both *E. granulosus* and *E. multilocularis* transmission to humans in this region (Wang et al., 2001). The inhabitants of Shiqu County are primarily herdsmen of the Tibetan ethnic group. Due to their physical environment, socio-economic situation, and religious beliefs they live in conditions with a poor standard of hygiene and have a close relationship with their livestock (yak, sheep, and goats) and dogs. Deworming of dogs is not widely performed due to a lack of knowledge of canine intestinal parasites as well as an inability and/or unwillingness to pay for anthelmintics. Herdsmen, in this locality, usually have traditional areas, based on village membership, where they maintain yaks in the summer and the winter. In the winter, often at a time prescribed by the local government, livestock are taken to lower altitude winter pastureland where people normally live in fixed settlements consisting of mud-brick houses. During the spring, yaks are taken to summer pastureland where there are no permanent settlements. Owned dogs, in this region, are valued based on their aggressiveness and kept primarily to guard personal property and livestock. Women are responsible for the feeding and general care of the dog unless there are no females in the household. Feeding of raw offal to dogs is a rule rather than an exception as is permitting stray dogs to roam in the vicinity. Strong Buddhist beliefs do not allow for the elimination of stray dogs and many strays are actually fed and "adopted" by households or monasteries. Since there are very few abattoir facilities in the area, most slaughtering and carcass disposal is performed at home. Screening, via abdominal ultrasound, for the identification of human echinococcosis has been carried out previously in western Sichuan Province (Wang et al., 2001; Budke et al, 2004). However, no extensive studies of infection in the owned dog definitive host have been previously conducted.

3.3. Materials and methods

Arecoline hydrobromide purgation. During the Spring of 2002 and the Spring and Autumn of 2003, the parasympathomimetic purgative agent arecoline hydrobromide (Boehringer Ingelheim) was used to collect intestinal parasites from 371 owned dogs in Shiqu County. Dogs were administered 7 mg/kg arecoline hydrobromide in a food-ball after obtaining owner consent and explaining potential side effects of treatment. Purged material was collected in leak-proof bags and saturated in either 10% formal saline or 85% ethanol until examination of the material could be conducted. After purgation, the site was buried and dog owners were instructed to interact with their dog using caution due to the potential presence of zoonotic parasites. Purged samples were taken to the Sichuan Institute of Parasitic Diseases (SIPD) in Chengdu, Sichuan Province, P.R. China where helminthes were removed, counted, and placed in 10% formal saline or 85% ethanol depending on the preservative agent originally used for the sample. Parasitic material was later transported to the Institute of Parasitology, University of Zürich for further speciation based on microscopic examination.

Analysis. All data was entered into an Excel spreadsheet (Microsoft, Redmond, WA) where prevalence and abundance were calculated. Exact 95% binomial confidence intervals were assigned to prevalence calculations and 95% negative binomial confidence intervals were assigned to abundance data utilizing the likelihood profile tool of the Excel add-on PopTools (CSIRO, Australia) (Torgerson et al., 2003a). True prevalence estimates of *E. granulosus* and *E. multilocularis* were determined based on the suggested sensitivity and specificity of arecoline hydrobromide purgation.

Specificity of purgation has been reported to be 100%. This is likely to be true at the genus level, but since both *E. granulosus* and *E. multilocularis* are present in the region, it was assumed that some misidentification could take place especially in regards to immature worms. Therefore, the specificity of *E. granulosus* detection on purgation was based on the portion of the *E. granulosus* lifespan spent in the immature stage (approximately 15%) (Thompson, 1995). The assumption was made that about one half of the immature worms would be misidentified resulting in a specificity of approximately 92%. Specificity of purgation of *E. multilocularis* was determined in a similar manner to *E. granulosus*, with 17% of the adult worm lifespan in the immature stage (Eckert, 1998). Assuming that one half of the immature worms would be misidentified, this leads to a specificity of approximately 92%. Crude prevalences of *E. granulosus* and *E. multilocularis* were then modeled as binomial distributions, with each value in the distributions having a 92% chance of being correct and an 8% chance of being misidentified. Since the only real possibility for misidentification of *E. granulosus* or *E. multilocularis* is with the other species, lost specificity for the diagnosis of one worm was allocated to the other species and vice versa. The random variable generator function of PopTools was utilized to produce the data sets which were then resampled 10,000 times using the same program.

Schantz (1997) reported that of 46 true *E. granulosus* positive dogs identified on postmortem examination, 30 animals produced a positive purge following a single treatment with arecoline. This was used as the basis of a beta distribution to model the true sensitivity of arecoline purgation of *E. granulosus*, with parameters 31 and 17. The random variable generator function of PopTools was used to produce the distribution, which was then resampled 10,000 times. Each iteration was used to calculate the true prevalence based on the observed prevalence and the specificity. Based on results of the only known published study where *E. multilocularis* was found on purgation of dogs, a distribution was assigned to the sensitivity of *E. multilocularis* purgation (Stefanic et al., 2004). In this study, 131 dogs were purged with 4 positively identified as *E. multilocularis* on purgation. In addition, PCR was able to identify a further two *E. multilocularis* positive dogs resulting in an estimated sensitivity of 67%. A total of 6 dogs found to be *Echinococcus* spp. purge positive were not picked up on PCR analysis. The species of these worms where, however, not reported. In order to set the lower and upper limits of the sensitivity distribution, minimum and maximum true positive and purge positive estimates were determined. This resulted in a minimum of 6 and a maximum of 12 true positive cases and a minimum of 4 and a maximum of 10 purge positive cases, with the assumption being made that there were no true positive cases that were negative on both PCR and purgation. Based on these finding, a minimum of 33% (4/12) and a maximum of 83% (10/12) was used for specificity calculations. A triangular distribution was then assigned to the specificity of *E. multilocularis* purgation with an average of 67%, a minimum of 33%, and a maximum of 83%. A triangular distribution is a continuous distribution that is typically used to describe an outcome based on knowledge of the minimum and maximum values and an inspired guess of what the modal value may be. The random number generator function of PopTools was employed to produce the distribution, which was then resampled 10,000 times and each iteration used to calculate a true prevalence.

The 10,000 new observed prevalence data sets, based on an approximate 92% specificity for arecoline purgation, were then divided by the 10,000 data sets for sensitivity and the upper and lower 2.5 percentiles calculated to arrive at 95% credible true prevalence intervals for *E. granulosus* and *E. multilocularis*. No data is available that would indicate the sensitivity of arecoline purgation for the other helminthes detected, therefore, no adjustments were made to their purgation based prevalences. In order to investigate if there was any association between the burdens of different parasite species, and hence evidence for similar transmission mechanisms, log (n+1) transformed burdens of each parasite were correlated against the burdens of each other species or group detected to construct a correlation matrix.

Risk factor questionnaire. A twenty-eight question survey, written in both English and Mandarin Chinese, was administered orally to dog owners willing to participate in the purgation study. One questionnaire was filled out for each dog being tested. The first set of questions included general information about the dog owner such as name, village name, and occupation. The next set focused on the dog being tested and included age, gender, name, and a brief physical description. Questions about the feeding habits of the dog, human interaction with the dog, history of fox hunting, and whether or not there were stray dogs in the area were asked. Information on livestock ownership, water source, and any previously diagnosed cases of human echinococcosis in the household was also obtained. The questionnaire concluded with questions that evaluated the participant's knowledge of echinococcosis and its acquisition. Questions were designed so that the majority of responses could either be circled or answered in only a few words in order to minimize any misunderstandings during translation. All questionnaires were identified by the date, a unique numerical identifier, and GPS coordinates. After the questionnaire was completed, information regarding the *Echinococcus* spp. life cycles and mode of transmission to humans was provided to the participant.

Dogs were identified as being infected with *Echinococcus* if adult *Echinococcus* spp. were found upon purgation. Information obtained from the questionnaire was inputted into an Epi Info 2000 version 3 database (CDC, Atlanta, GA) and univariate and multivariate logistic regression performed utilizing the same program. A total of 371 questionnaires were evaluated for risk factors associated with echinococcosis in owned dogs. All dogs infected with *Echinococcus* spp. were first evaluated together. Dogs diagnosed with *E. granulosus* infection were then separated from those diagnosed with *E. multilocularis*, with dogs having a dual infection evaluated in both analyses.

3.4. Results

Purgation of 371 dogs in Shiqu County during 2002-2003 resulted in an overall *E. multilocularis* prevalence of 12% and an overall *E. granulosus* prevalence of 8% (Table 3.1). Credible true prevalence intervals were calculated to be 13 – 33% for *E. multilocularis* and 8 – 19% for *E. granulosus*. The prevalences of other intestinal helminthes found on purgation were: *Taenia* spp. 31%, *Dipylidium caninum* 1%, and ascarids 8% (Table 3.1). Mean abundance (the mean number of parasites per host) of *E. granulosus* was 80 worms and mean abundance of *E. multilocularis* was 131 worms (Table 3.1). Mean intensity of infection (the mean number of parasites per infected host) with *E. granulosus* was 959 worms, with a mean intensity of 1084 worms for *E. multilocularis* infection. A correlation matrix of parasite burdens of the various species or group found on purgation indicated weak yet significant correlations between *E. multilocularis* and *Taenia* spp., *E. multilocularis* and *D. caninum*, *E. granulosus* and *Taenia* spp., *Taenia* spp. and *D. caninum*, and *Taenia* spp. and ascarids (Table 3.2).

Table 3.1. Purgation results for dogs (n = 371) in Shiqu County, Sichuan Province, P.R. China (2002-2003). Crude prevalence represents actual prevalence found upon arecoline purgation, while adjusted prevalence represents prevalence after purgation sensitivity and specificity have been taken into account.

Parasite	**Prevalence (%)**	**Confidence limits or credibility interval**	**Mean abundance**	**Confidence limits[c]**
E. granulosus				
Crude	8.35	5.75 – 11.65[a]	80	32.60 – 288.96
Adjusted	12.7	8.3 – 18.8[b]		
E. multilocularis				
Crude	12.13	8.99 – 15.89[a]	131	61.58 – 362.44
Adjusted	19.7	13.4 – 32.7[b]		
Taenia spp.	31.00	26.32 – 35.98[a]	1.32	1.016 – 1.7506
D. caninum	1.08	0.29 – 2.74[a]	0.0189	0.00517 – 0.10485
Ascarids	7.55	5.07 – 10.72[a]	0.124	0.0794 – 0.19636

[a] Exact binomial 95% confidence limits
[b] Credibility interval based on assumptions on the sensitivity and specificity of arecoline purgation
[c] Negative binomial 95% confidence limits

Table 3.2. Correlation matrix for log-transformed parasite abundance.

	E. multilocularis	*E. granulosus*	*Taenia* spp.	*D. caninum*	Ascarids
E. multilocularis		-0.034	**0.166**	**0.114**	0.049
E. granulosus	-0.034		**0.240**	-0.025	0.026
Taeniia spp.	**0.166**	**0.240**		**0.137**	**0.177**
D. caninum	**0.114**	-0.025	**0.137**		0.021
Ascarids	0.049	0.026	**0.177**	0.021	

* correlation coefficients in bold are considered significant at the 95% confidence level.

Questionnaires (n = 371) were evaluated for risk factors associated with the acquisition of *Echinococcus* spp. infection in dogs. Univariate analysis demonstrated that a dog being male ($P < 0.05$) was a significant risk factor for canine *Echinococcus* spp. infection (Table 3.3). Having a dog over 3 years of age (mean age of tested dogs = 4.1 years), not keeping a dog tied all of the time, yak ownership, sheep and/or goat ownership, and having a dog who is known to eat small mammals were not found to be significant risk factors for *Echinococcus* spp. infection in owned dogs ($P > 0.05$).

Multivariate logistic regression also indicated that a dog being male was a significant risk factor for infection with *Echinococcus* spp. (P < 0.05) (Table 3.4). Univariate analysis indicated that not having a dog tied all of the time versus keeping a dog tied all of the time was a significant risk factor for *E. multilocularis* infection (P < 0.05) (Table 3.5), with multivariate analysis confirming the finding (Table 3.6). The same factors were evaluated for *E. granulosus* infection in dogs, with none found to be significant risks for infection on univariate or multivariate logistic regression analysis (data not shown).

Table 3.3. Univariate analysis for possible variables associated with the acquisition of canine *Echinococcus* spp. infection (n = 371).

Variable	Odds Ratio	95% confidence interval	*P*-value
Dog is tied all of the time (dichotomous)	0.6730	0.3753 – 1.2069	0.1838
Household has yaks (dichotomous)	1.7840	0.6726 – 4.7320	0.2448
Household has sheep/goats (dichotomous)	1.5182	0.8910 – 2.5868	0.1247
Dog has been seen eating small mammals (dichotomous)	0.9662	0.5797 – 1.6103	0.8950
Dog is >3 years of age (dichotomous)	0.8557	0.5135 – 1.4260	0.5499
Dog is male (dichotomous)	2.5252	1.1041 – 5.7754	**0.0282**

Table 3.4. Multivariate analysis of possible risk factors for acquisition of canine *Echinococcus* spp. infection (n = 371).

Variable	Odds Ratio (95% CI)	Regression Coefficient	S.E.	*P*-value
Dog is tied all of the time (dichotomous)	0.6755 (0.3743 – 1.2190)	-0.3924	0.3012	0.1928
Household has yaks (dichotomous)	1.4700 (0.5393 – 4.0069)	0.3852	0.5116	0.4515
Household has sheep/goats (dichotomous)	1.3692 (0.7906 – 2.3711)	0.3142	0.2802	0.2622
Dog is male (dichotomous)	2.4554 (1.0684 – 5.6431)	0.8983	0.4246	**0.0344**

* Variables with P < 0.25 on univariate analysis were included in multivariate analysis

Table 3.5. Univariate analysis for possible variables associated with the acquisition of canine *E. multilocularis* infection (*n* = 371).

Variable	Odds Ratio	95% confidence interval	*P*-value
Dog is tied all of the time (dichotomous)	0.3770	0.1630 – 0.8721	**0.0226**
Household has yaks (dichotomous)	1.2328	0.4166 – 3.6480	0.7053
Household has sheep/ goats (dichotomous)	1.4546	0.7609 – 2.7807	0.2570
Dog has been seen eating small mammals (dichotomous)	1.2267	0.6574 – 2.2889	0.5209
Dog is >3 years of age (dichotomous)	1.0981	0.5886 – 2.0484	0.7687
Dog is male (dichotomous)	1.9542	0.7415 – 5.1500	0.1754

Table 3.6. Multivariate analysis of possible risk factors for acquisition of canine *E. multilocularis* infection (n = 371).

Variable	Odds Ratio (95% CI)	Regression Coefficient	S.E.	*P*-value
Dog is tied all of the time (dichotomous)	0.3693 (0.1593 – 0.8558)	-0.9962	0.4288	**0.0202**
Dog is male (dichotomous)	2.0350 (0.7683 – 5.3903)	0.7105	0.4970	0.1528

* Variables with $P < 0.25$ on univariate analysis were included in multivariate analysis

3.5. Discussion

E. granulosus and *E. multilocularis* purgation based prevalences in owned dogs from Shiqu County are grounds for concern in regards to transmission to humans, especially in light of the high AE and CE levels reported in abdominal ultrasound screened humans from the same county (Budke et al., 2004). In addition, intestinal parasite prevalence based on purgation is most likely an underestimate of true prevalence. Distributions were, therefore, utilized to encompass what is known about the sensitivity and specificity of purgation based on data currently available, with both the prevalences found on purgation and the prevalences adjusted for the sensitivity and specificity of arecoline purgation reported here. Sensitivity of arecoline hydrobromide purgation of *E. granulosus* was found to be 65% after a single dose of arecoline in a study where 118 dogs were purged and subsequently euthanized and necropsied (Schantz, 1997). In regards to *E. multilocularis*, one previous study reported detecting *E. multilocularis* using arecoline to purge dogs, however, information on sensitivity of purgation for detecting *E. multilocularis* is lacking (Stefanic et al., 2004). Sensitivity estimates for *E. multilocularis* purgation are based on purge results in comparison to PCR findings which, in contrast to necropsy, is not considered a gold standard test. Therefore, a triangular distribution was utilized to model this uncertainty. Specificity was also adjusted for the Shiqu County study based on the premise that since both *E. granulosus* and *E. multilocularis* are present at the study site, some degree of misidentification could occur, especially in regards to immature worms.

Although all associations between parasite burdens identified in this study are weak, the strongest was found between *E. granulosus* and *Taenia* spp. This makes sense in regards to the common mode of transmission between *E. granulosus* and those *Taenia* spp. that utilize a livestock intermediate host. These findings may indicate that the same livestock are commonly infected with both *E. granulosus* and *Taenia* spp. or that certain dogs have more access to infected livestock and thus tend to acquire parasites transmitted from these animals. Further speciation will, however, enable differentiation of taeniids that use small mammal intermediate hosts from those that use livestock. Other weak, yet significant, correlations were found between *Taenia* spp. and all other parasites evaluated and between *D. caninum* and *E. multilocularis*. *Taenia* spp. association with *E. multilocularis* can be due to common intermediate hosts of *E. multilocularis* and some *Taenia* spp. The association between *Taenia* spp. and ascarids can also be attributed, to some extent, to similar means of transmission (from intermediate or paratenic hosts, respectively). Correlations between *D. caninum* and both *Taenia* spp. and *E. multilocularis* must be addressed with the most skepticism since *D. caninum* was found in very few tested dogs and the mode of transmission is different for *D. caninum* compared to the other parasites evaluated. One possible explanation is higher susceptibility in certain hosts to multiple parasitism, but in this study there is very little evidence to support this theory.

The significant risk factor, for owned dog *Echinococcus* spp. infection, of a dog being male may indicate that male dogs are more likely to maintain territory and hunt compared to female dogs. This can be compared to the situation of foxes in

Switzerland where male foxes and especially sub-adult male foxes have been shown to carry the majority of the *E. multilocularis* biomass and are known to travel further than their age-matched female counterparts (Hofer et al., 2000). A higher risk in male dogs does not appear to be associated with male dogs being tied less than female dogs, with no significant difference found between the prevalence of tied male versus that of tied female dogs ($P > 0.05$). A dog being male does appear to have a non-significant impact for both *E. granulosus* and *E. multilocularis*, however, when evaluated independently their P values were both greater than the statistically significant cut-off point 0.05 being used here. The significant risk factor, for *E. multilocularis* infection in owned dogs, of not having the dog tied all of the time indicates that these dogs have an increased opportunity to hunt and, therefore, have more access to infected small mammal intermediate hosts. Risk factor analysis for human CE and AE is not a new method and has been performed in multiple countries and regions (Carmona et al., 1998; Dowling and Torgerson, 2000; Dowling et al., 2000; Craig et al., 2000; Yamamoto et al., 2001; Torgerson et al., 2003b). Risk factors associated with canine echinococcosis have not, however, been previously evaluated. Looking at potential factors associated with the acquisition of *Echinococcus* spp. by the definitive host allows for a more current picture of the situation versus evaluation of human cases, which may have been acquired up to ten years prior to the survey.

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Chapter 4

Modeling the transmission of *Echinococcus granulosus* and *Echinococcus multilocularis* in dogs for a high endemic region of the Tibetan plateau

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4.1. Abstract

Echinococcus granulosus and *Echinococcus multilocularis* abundance and prevalence data, for domestic dogs of Shiqu County, Sichuan Province, P.R. China, were fitted to mathematical models to evaluate transmission parameters. Abundance models, assuming the presence and absence of immunity, were fit for both *E. granulosus* and *E. multilocularis* using Bayesian priors, maximum likelihood, and Monte Carlo sampling techniques. When the models were compared, using the likelihood ratio test for nested models, the model assuming the presence of immunity was the best fit for *E. granulosus* infection, with a purgation based prevalence of 8% (true prevalence interval of 8% - 19% based on the sensitivity of purgation) and a mean abundance of 80 parasites per dog, with an average infection pressure of 560 parasites per year. In contrast, the model assuming the absence of immunity was the best fit for *E. multilocularis* infection, with a purgation based prevalence of 12% (true prevalence interval of 13% - 33% based on the sensitivity of purgation) and a mean abundance of 131 parasites per dog, with an average infection pressure of 334 or 533 parasites per year assuming a 5 or 3 month parasite life expectancy respectively. The prevalence data for both parasites was then fit to a set of differential equations modeling the transition between infection states in order to determine number of infectious insults per year. Infection pressure was 0.21, with a 95% credibility interval of 0.12 – 0.41, infections per year for *E. granulosus* and 0.52, with a 95% credibility interval of 0.29 – 0.77, infections per year for *E. multilocularis* assuming a 5 month parasite lifespan or 0.85, with a 95% credibility interval of 0.47 – 1.25 infections per year, assuming a 3 month *E. multilocularis* lifespan in dogs.

4.2. Introduction

Echinococcus granulosus and *Echinococcus multilocularis* are considered two of the most pathogenic helminthes known to man, causing human cystic and alveolar echinococcosis respectively. Shiqu County, located on the Tibetan plateau of western Sichuan Province, People's Republic of China has been shown to have a high prevalence of both *E. granulosus* and *E. multilocularis* in humans and dogs (Wang et al., 2001; Wang et al., 2004; Budke et al., 2004; Budke et al., 2005). A dog purgation study performed in Shiqu County during 2002 – 2003 allowed for the collection of baseline prevalence and abundance data for *Echinococcus* spp. from this region. Crude prevalence, based on purgation, was found to be 8% for *E. granulosus* and 12% for *E. multilocularis*. Prevalence adjusted for the sensitivity and specificity of arecoline hydrobromide purgation resulted in a true prevalence, 95% credibility interval, of 8% - 19% for *E. granulosus* and 13% - 33% for *E. multilocularis* (Budke et al., 2005). Reporting prevalence and abundance is quite informative, however, it does not provide an adequate description of the parameters influencing the transmission of these two parasite species in this location.

Mathematical models, maximum likelihood techniques, and the use of Bayesian priors are becoming important tools to aid in the evaluation of parameters such as infection pressure, parasite death rate, acquisition of immunity, and loss of immunity (Torgerson and Heath, 2003; Torgerson et al., 2003; Basanez et al., 2004). Parasite-induced host immunity is an important density dependent constraint in the transmission of parasites and, therefore, an understanding of its magnitude is crucial as it may affect control strategies (Anderson and May, 1985). Presence or absence of immunity, in the dog definitive host, continues to be a subject of much debate, with past studies such as Roberts et al. (1986) and Ming et al. (1992) indicating a lack of parasite-induced host immunity in dogs infected with *E. granulosus*. Other studies, however, such as Lahmar et al. (2001) and Torgerson et al. (2003) suggest that acquired immunity in the dog definitive host is possible in high prevalence areas. Unlike *E. granulosus*, *E. multilocularis* infection in the domestic dog has been evaluated on a much more limited scale (Rausch et al., 1990). In addition, whereas modeling *E. multilocularis* transmission dynamics in the fox definitive host is becoming more commonplace (Roberts and Aubert, 1995; Hansen et al. 2003; Ishikawa et al., 2003), modeling *E. multilocularis* in the dog definitive host has not previously been reported. Studies carried out in Gansu and Sichuan provinces of western China have, however, stressed the importance of the domestic dog in association with the acquisition of human alveolar echinococcosis, with speculation of the occurrence of a semi-domestic (or synanthropic) cycle operating in these regions (Craig et al., 2000; Wang et al., 2001). Understanding the transmission dynamics of these two parasite species and how they coexist will not only enable a better comprehension of the transmission dynamics within and the interplay between the two cycles, as well as possible risk of transmission to man, but will also allow for the development of an efficient control strategy. This study, therefore, attempts to quantify infection pressure and immunity-based parameters in order to help attain this goal in reference to the study region.

4.3. Materials and methods

Study area. During 2002 – 2003, a total of 371 owned dogs were purged in Shiqu County, Sichuan Province, P.R. China using 7 mg/ kg arecoline hydrobromide and the resulting material screened for intestinal helminthes as described in Budke et al. (2005). An owner's questionnaire accompanied each participating dog, so that information regarding the age of the animal was available for analysis. Dogs were sampled from numerous small villages in Shiqu County, however, due to the uniformity in cultural environment, as well as the variability in number of dogs tested per individual village, they were treated as a single group for analysis purposes.

Abundance based models. Mean abundance of *E. granulosus* and *E. multilocularis* adults in purged dogs was determined. This was accomplished by finding the parameters that gave the best maximum likelihood estimation (MLE) fit, assuming a negative binomial distribution, using the Excel (Microsoft, Redmond, WA) add-in Solver. A likelihood profile and 95% confidence interval, along with a probability density for the parameters given the data and model, were determined using the likelihood profile function of the Excel add-in PopTools (CSIRO, Australia). The data was then fit to the abundance models developed by Roberts et al. (1986) and refined by Torgerson et al. (2003), where h is the infection pressure in terms of parasites per year, μ is the rate of parasite loss ($1/\mu$ is the mean survival time of the parasite), a is a parameter influencing the rate at which immunity is acquired, and γ is the loss of immunity. Models assuming both presence and absence of acquired immunity were evaluated, assuming a constant infection pressure.

Torgerson et al. (2003) reported that the variation of the abundance (m) of *E. granulosus* with age of dogs (t) can be modeled as:

$$m = \frac{ah^2}{(\gamma + ah)(\mu - \gamma - ah)}\left[\exp - \{(\gamma + ah)\,t\} - \exp - \{\mu\, t\}\right] + \frac{\gamma h}{\mu\,(\gamma + ah)}\left[1 - \exp - \{\mu\, t\}\right]$$

When there is no parasite-induced host immunity (i.e. $a = 0$) this is equivalent to:

$$m = \frac{h}{\mu}\left[1 - \exp - \{\mu\, t\}\right]$$

The above models were fitted to the data for the variation of *E. granulosus* and *E. multilocularis* with age using a negative binomial likelihood function in order to give the probability of the number of parasites (s) for each observation (o_i) given the mean (M) predicted by the abundance model either with or without immunity

$$Pr\{o_i = s\} = \frac{\Gamma(k+s)}{\Gamma(k)\,s!}\left(\frac{M}{k+M}\right)^s\left(\frac{k}{k+M}\right)^k$$

where Γ represents the gamma distribution and k is the negative binomial constant. Likewise, the negative binomial distribution was used to model the uncertainty of the point estimate of the mean abundance, given the data, for individual groups of dogs.

A Bayesian sampling-resampling technique was utilized to obtain the mean values and 95% credibility intervals for the parameters h, a, γ, and μ (Smith and Gelfand, 1992). Since Bayesian priors allow for the use of previously acquired information, it often results in narrowed credibility intervals for the unknown parameters. Bayes' theorem can be written as:

$$\Pr\{H_i | \text{data}\} = \frac{\mathcal{L}\{\text{data}|\text{H}_\text{i}\}\text{Prior}\{\text{H}_\text{i}\}}{\sum_\text{j} \mathcal{L}\{\text{data}|\text{H}_\text{j}\}\text{Prior}\{\text{H}_\text{j}\}}$$

where the probability of the hypothesis (H_i) given the data equals the joint probability of the data and the hypothesis over the sum of such joint probabilities, summed over all possible hypotheses. In the sampling-resampling approach to Bayesian modeling employed here, we are using a Monte-Carlo form of integration where we draw a random value for each parameter from its prior distribution and calculate the likelihood for the chosen combination. Repeating this process 10,000 times approximates integration over the prior ranges of the parameters (Smith and Gelfand, 1992).

A normal Bayesian prior distribution for μ, with a mean of 1.1 and a standard deviation of 0.2, was assigned and used in the abundance model for *E. granulosus*, assuming immunity (Torgerson et al., 2003). The value assigned to μ was based on knowledge of the *E. granulosus* lifespan of approximately 10 months, as determined by Aminjanov (1975), and is the same value used previously by Torgerson et al. (2003). A macro was written in Excel to sample across the prior distribution 10,000 times and recalculate each parameter of the model based on the designated value of μ and the maximized (log) likelihood function, assuming negative binomial errors, using the Excel add-in Solver. Bayesian 95% credibility intervals were then obtained as percentiles of the posterior distribution. This method was then implemented for the *E. granulosus* model assuming the absence of immunity, using the same prior distribution for μ. The same methods were applied to *E. multilocularis*, however, μ was assigned a normal distribution with a mean of 2.4 and standard deviation of 0.5 based on the parasite's shorter lifespan of approximately 5 months (Eckert, 1998). An *E. multilocularis* lifespan of 3 months was also modeled based on a recent experimental infection study in the dog definitive host (Kapel et al., unpublished data). Therefore, a distribution for μ, with a mean of 4.0 and a standard deviation of 0.8 was also used, with standard deviation assumed to be similar in proportion to the standard deviation in the μ estimate for *E. granulosus*.

Outcomes of the abundance models, assuming the presence and absence of immunity, were then compared, for each parasite, using the likelihood ratio test (LRT) for nested models. This is a statistical test of the goodness-of-fit between two models, one of which collapses down into the other when a certain parameter or parameters are set to 0. This statistic follows a chi-squared distribution, with degrees of freedom equal to the number of additional parameters in the more complex model (Hilborn and Mangel, 1997). In this case, the number of degrees of freedom would equal 1 since the parameter γ also disappears when a is set to 0.

Prevalence based models. Prevalence data for both *E. granulosus* and *E. multilocularis* were fitted to the differential equations (Roberts et al., 1986):

$$\frac{dY}{dt} = -[\gamma + \mu]Y + \alpha\beta S$$

and

$$\frac{dX}{dt} = -[\beta + \mu]X + \beta[1-\alpha]S + \gamma Y$$

using the ordinary differential equation (ODE) function of PopTools. In the above equations, Y is the proportion of animals infected, but immune to further infection, and X is the proportion of animals infected, but not immune to reinfection, with age (t) in years. Therefore, prevalence = X + Y, assuming a constant infection pressure. The parameter β represents infection pressure in terms of number of infectious insults per year, μ is the rate of parasite loss ($1/\mu$ is the mean survival time of the parasite), α indicates the acquisition of immunity although it is not the same rate parameter as a used in the abundance based model, and γ indicates the loss of immunity, with susceptibility (S) at age t represented as (Roberts et al., 1986):

$$S(t) = \frac{1}{\gamma + \alpha\beta}\left[\gamma + \alpha\beta \exp\{-(\gamma + \alpha\beta)t\}\right]$$

Dogs with *E. granulosus* adults found on purgation were assigned a value of 1, indicating that they were positive. Prevalence (P) for each age group of dogs was then adjusted to take into account the sensitivity of arecoline purgation, with specificity assumed to be 100% and sensitivity (Se) assumed constant across age groups. Apparent prevalence (AP) = Se*P, therefore, P = AP/Se. A beta distribution was assigned to each age of dog, based on the number positive by purgation and the total number tested in the designated age group. A random variable was generated from this distribution and divided by a random variable generated from a beta distribution modeling the sensitivity of arecoline purgation. The distribution was based on a study by Schantz (1997) reporting that of 46 true *E. granulosus* positive dogs identified on necropsy, 30 animals produced a positive purge following a single dose of arecoline, indicating a sensitivity of approximately 65%. The value obtained from the division of the values generated from the two distributions represented the posterior distribution of the prevalence expressed as the expected number of positive cases for that age category. Actual number of cases was then subtracted from this number and converted to a percentage, which was then applied to the negative dogs based on a binomial distribution. For each of 10,000 iterations, dogs designated positive were assigned a value of 1, with positive dogs summed for each age group and an adjusted prevalence determined. Mean adjusted prevalence was then assigned to each age group (1 year to 15 years).

The parameters β, α, γ, and μ were then assigned prior distributions. For *E. granulosus*, β was assigned a uniform distribution between 0 and 5, α was assigned a uniform distribution between 0 and 1, γ was assigned a uniform distribution between 0 and 1, and μ was assigned a normal distribution with a mean of 1.1 and a standard deviation of 0.2. Uniform distributions for β, α, and γ were utilized due to a lack of prior knowledge about the parameters, whereas, μ was modeled as a normal distribution around a mean of 1.1 based on knowledge of the *E. granulosus* expected lifespan as determined by Aminjanov (1975). A macro was written in Excel to randomly sample across the prior distribution 10,000 times. Model predicted and mean adjusted prevalence were then compared using a binomial likelihood function and Bayesian 95% credibility intervals obtained as percentiles of the posterior distribution. The same methods were applied to *E. multilocularis*, however, μ was assigned a normal distribution with a mean of 2.4 and standard deviation of 0.5 (Eckert, 1998) for an estimated lifespan of 5 months and a mean of 4.0 and a standard deviation of 0.8 for an estimated lifespan of 3 months (Kapel et al., unpublished data).

4.4. Results

Abundance based models. Mean abundance and 95% confidence interval (CI) of *E. granulosus* in purged dogs was 80 (32 - 289) worms, with a negative binomial constant (*k*) value and 95% CI of 0.0096 (0.0065 - 0.014). Mean abundance and 95% CI of *E. multilocularis* in purged dogs was 131 (62 - 357) worms, with a *k* value and 95% CI of 0.014 (0.0065 - 0.019). A breakdown of mean abundance by age, with 95% negative binomial confidence limits, can be found in Table 4.1. The likelihood ratio test indicated that the abundance model, assuming the absence of immunity, was the best fit for *E. multilocularis* data ($P < 0.05$) and the model assuming the presence of acquired immunity was the best fit for *E. granulosus* data ($P < 0.05$). Comparison of *Echinococcus granulosus* and *Echinococcus multilocularis* mean abundance for ages 0 to 5 years and 6 to 15 years, with 95% negative binomial confidence bands, can be found in Figure 4.1. Best fit values for h, a, and γ, with their 95% creditability intervals were, h = 560 (495 – 681), $a = 1.44\text{x}10^{-3}$ ($1.08\text{x}10^{-3}$ – $2.30\text{x}10^{-3}$), and γ = $5.50\text{x}10^{-5}$ ($3.03\text{x}10^{-5}$ – $7.50\text{x}10^{-5}$) for *E. granulosus* and h = 334 (221 – 452) for *E. multilocularis* assuming a 5 month parasite lifespan and h = 533 (340 – 731) assuming a 3 month parasite lifespan (Table 4.2).

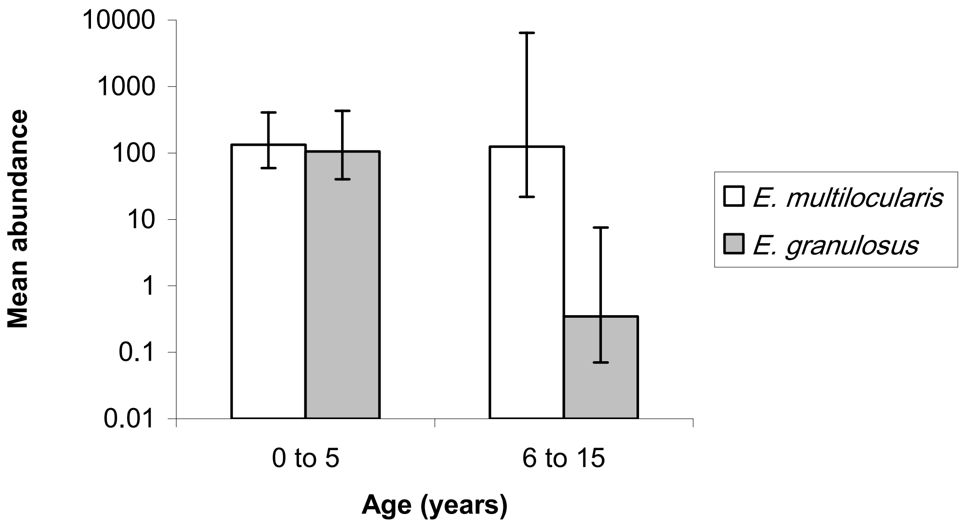

Figure 4.1. Comparison of *Echinococcus granulosus* and *Echinococcus multilocularis* mean abundance, with 95% negative binomial confidence intervals, for dogs aged 0 to 5 years and 6 to 15 years in Shiqu County. The Y-axis (but not the data) has been log-transformed to better illustrate the 95% confidence intervals.

Table 4.1. Mean abundance of *Echinococcus granulosus* (*E.g.*) and *Echinococcus multilocularis* (*E.m.*) by age, with 95% negative binomial confidence intervals, for dogs of Shiqu County.

Age (years)	Number in age group	Mean abundance of *E.g.* per age group	Mean abundance of *E.m.* per age group
≤ 1	48	418 (53 – >1000)	437 (44 – >1000)
2	63	6 (1 – 273)	63 (14 - >1000)
3	77	45 (10 – 987)	70 (17 – 968)
4	51	14 (2 – 799)	128 (32 – >1000)
5	42	121 (14 – >1000)	15 (3– 383)
6	21	0	12 (1 – >1000)
7	19	0.2 (0.01 – >1000)	526 (7 – >1000)
8	13	0	43 (3 – >1000)
>8	37	1 (0.12 – 56)	12 (1 – >1000)

Table 4.2. Abundance model parameters for *Echinococcus granulosus* and *Echinococcus multilocularis* in dogs of Shiqu County.

Parasite	Parameter	Posterior Mean	95% credibility interval
E. granulosus	h	560	495 – 681
	a	1.44×10^{-3}	1.08×10^{-3} – 2.30×10^{-3}
	γ	5.50×10^{-5}	3.03×10^{-5} – 7.5×10^{-5}
E. multilocularis	[a] h	334	221 – 452
	[b] h	533	340 – 731

[a] Assuming a 5 month *E. multilocularis* lifespan in dogs
[b] Assuming a 3 month *E. multilocularis* lifespan in dogs

Prevalence based models. A breakdown by age of *E. granulosus* and *E. multilocularis* purgation prevalence and adjusted prevalence, based on the sensitivity of arecoline purgation, in domestic dogs of Shiqu County can be found in Table 4.3. Prevalence data input into the differential equations describing transition between infectious states for *E. granulosus* and *E. multilocularis* resulted in a mean infection pressure (β) and 95% credibility interval of 0.21 (0.12 – 0.41) infectious insults per year for *E. granulosus* and 0.52 (0.29 - 0.77) infectious insults per year for *E. multilocularis*, based on a 5 month parasite lifespan, or 0.85 (0.47 – 1.25) infectious insults per year, based on a 3 month parasite lifespan. This equates to an average of one infection with *E. granulosus* every 4.8 years and one infection with *E. multilocularis* every 1.9 years, assuming a 5 month parasite lifespan, or one infection with *E. multilocularis* every 1.2 years, assuming a 3 month parasite lifespan. The value for the α parameter, with 95% credibility interval, for *E. granulosus* was 0.76 (0.087 – 0.98) and the value for the γ parameter, with 95% credibility interval, was 0.18 (0.005 – 0.94). For *E. multilocularis*, α was not found to be significant from 0, which is consistent with the results obtained from the abundance based model.

Table 4.3. Crude and adjusted prevalence by age for dogs infected with *Echinococcus granulosus* (*E.g.*) and *Echinococcus multilocularis* (*E.m.*) in Shiqu County.

Age (years)	Number in age group	Purgation prevalence of *E.g.* per age group (crude)	Arecoline sensitivity adjusted 95% credibility intervals for *E.g.* prevalence	Purgation prevalence of *E.m.* per age group (crude)	Arecoline sensitivity adjusted 95% credibility intervals for *E.m.* prevalence
≤ 1	48	10.4%	5.4% - 32.6%	8.3%	3.5% - 28.2%
2	63	8.0%	3.9% - 25.1%	12.7%	8.9% - 35.0%
3	77	10.4%	7.1% - 29.2%	13.0%	10.0% - 34.7%
4	51	9.8%	4.9% - 30.4%	19.6%	15.2% - 50.3%
5	42	9.5%	4.1% - 31.7%	14.3%	8.3% - 41.7%
6	21	0%	0% - 13.5%	9.5%	1.9% - 39.3%
7	19	5.3%	0.25% - 28.4%	5.3%	0.25% - 28.4%
8	13	0%	0 % - 21.3%	15.4%	3.1% - 59.9%
9	11	18.2%	3.9% - 70.6%	0%	0% - 23.84%
10	17	0%	0% -16.5%	5.9%	0.24% - 32.4%
>10	9	11.1%	2.8% - 43.4%	11.1%	2.8% - 43.4%

4.5. Discussion

A set of age stratified prevalence and abundance data, for *E. granulosus* and *E. multilocularis*, has been fitted to models in order to gain a better understanding of the prevailing infection pressure and the likelihood of parasite-induced host immunity in response to infection. For analysis purposes, calculations were performed under the assumption that infection pressure remains constant across all age categories. The prevalence based models, for the studied owned dog population, suggested a mean of 0.21 infections per year for *E. granulosus* and 0.52 infections per year for *E. multilocularis*, assuming a 5 month parasite lifespan, or 0.85 infections per year, assuming a 3 month parasite lifespan. Likewise, the abundance based models indicated the infection pressure was a mean of 560 parasites for *E. granulosus* and 334 parasites for *E. multilocularis*, assuming a 5 month parasite lifespan, or 533 parasites, assuming a 3 month lifespan. Given the assumptions of this model, the best fit of the data suggests that *E. granulosus* stimulated immunity in the dog at the present infection pressure, however, *E. multilocularis* did not. This is well illustrated by the fact that very few *E. granulosus* were recovered in dogs over 5 years of age, but substantial numbers of *E. multilocularis* were obtained (Table 4.1, Figure 4.1).

Indications of acquired immunity for *E. granulosus* in the dog is consistent with experimental studies. Heath and Lawrence (1991) indicated that dogs could develop a degree of immunity after being given a large infection of protoscoleces, with egg release completely suppressed after an initial release of eggs. In addition, it was shown by Deplazes et al. (1994) that dogs demonstrated significant cellular and humoral immune responses to protoscolex or adult worm antigens 35 days after experimental infection with *E. granulosus*. A further study by Moreno et al. (2004) suggests that increased levels of parasite-specific IgE and local IgA, after dogs were experimentally infected with *E. granulosus*, may be related with protection against a challenge with *E. granulosus*. In addition, experimental infections by Gemmell et al. (1986) found increased resistance to reinfection in dogs following multiple experimental exposures to protoscoleces.

Torgerson et al. (2003) evaluated *E. granulosus* abundance in domestic dogs from lower prevalence villages (mean prevalence of 5.8%) versus dogs from higher prevalence farms (mean prevalence of 23%) in Kazakhstan. The same abundance model, as described in this paper, indicated the presence of immunity in farm dogs, but not in village dogs. Such a change in the distribution of parasites under higher infection pressure is a classic indication of the presence of parasite-induced host immunity (Anderson and May, 1985). When these findings are compared to the dogs tested in Shiqu County, one sees that the Shiqu County dogs lie somewhere between the farm and village dogs of Kazakhstan in regards to *E. granulosus* prevalence and infection pressure. Therefore, the Kazakhstan farm dogs, with a higher infection pressure, go from susceptible to immune status at a faster rate than the Shiqu County dogs, whilst in the Kazakhstan village dogs there appears to have been insufficient exposure to stimulate immunity. The lower levels of infection in older animals could be interpreted as age resistance, as suggested by Lübke (1973), or as age-related decrease in infection pressure. However, if either of these hypotheses is correct, the Kazakhstan study would have shown a similar decrease in both the older farm and village dogs (Torgerson et al., 2003).

The models suggest that there is insufficient evidence of parasite-induced acquired immunity for infection with *E. multilocularis* at a prevalence of 13 - 33%. There is the possibility that cross-reactivity between *E. granulosus* and *E. multilocularis* may occur. However, if this were the case, one might expect to find a lower level of *E. multilocularis* in older dogs as they will have also been exposed to *E. granulosus*. Another possible explanation is that a difference in immunological response to *E. granulosus* versus *E. multilocularis* may be present due to the preference of *E. granulosus* for the anterior quarter of the small intestine and the preference of *E. multilocularis* for the posterior region of the small intestine (Thompson and Eckert, 1983). Dogs may also have a different immunological response to *E. multilocularis* compared to the parasite's more usual hosts, foxes. In the latter hosts, there is some evidence of lower parasite burdens in old foxes compared to young foxes. A study in Zürich, Switzerland found 85% of the *E. multilocularis* biomass in subadult foxes (Hofer et al., 2000). Alternatively, it may be that the infection pressure in this population of dogs is insufficient to stimulate protective immunity against reinfection or that seasonality is affecting *E. multilocularis*-induced immunity and/or transmission dynamics. However, due of the remoteness of the study location and the difficulty in planning data gathering expeditions, it was not possible to design a study taking this factor into account.

Use of Bayesian techniques is becoming more commonplace in the field of parasitology (Basanez et al., 2004). Thus, prior information on relevant parameters can be exploited and improve the precision of results. For the transmission models used in this study, a normal distribution was utilized to model the prior distribution of μ for *E. granulosus*, based on the known lifespan of the parasite of approximately 10 months (Aminajanov, 1975). This is the same distribution used by Torgerson et al. (2003) for investigation of the transmission dynamics of *E. granulosus* in dogs of rural Kazakhstan. A normal distribution was also utilized to model the parameter μ for *E. multilocularis* based on the parasite's documented lifespan of approximately 5 months (Eckert, 1998) as well as a lifespan of 3 months, which has been recently proposed after experimental infection studies in dogs (Kapel et al., unpublished data).

The Shiqu County findings of an average of one infectious insult every 4.8 years for *E. granulosus* in owned dogs can also be compared to past studies where this parameter was determined. A Chinese study performed by Ming et al. (1992) indicated an average of one infection every 2.2 years when dogs were infected at a prevalence of 38.1%, whereas a Tunisian study performed by Lahmar et al. (2001), and reanalyzed in Torgerson and Heath (2003), indicated an average of one infection every 1.47 years, with an overall prevalence of 27%. The Shiqu County findings are, therefore, reasonable when the lower prevalence (true prevalence credibility interval of 8% - 19%) is taken into account. The higher infection pressure, for *E. multilocularis* infection, of an average of one infectious insult every 1.2 years or every 1.9 years, depending on whether a 3 month or 5 month parasite lifespan is used, is also realistic due to the shorter parasite lifespan as well as the higher infection prevalence (true prevalence credibility interval of 13 - 33%). However, no pre-existing analysis of *E. multilocularis* in domestic dogs is known to the authors.

The determined negative binomial constant (k) value for *E. granulosus* infection of dogs in Shiqu County, in reference to parasite prevalence, is also in line with previously determined estimates (Torgerson and Heath, 2004) (Table 4.4). The k parameter is an indicator of the degree of parasite aggregation. As k goes towards infinity, the distribution becomes Poisson or random. In contrast, as k tends towards 0, the parasite population becomes ever more aggregated, with the limit being when the entire parasite population is present in a single animal. The low *k* values that were associated with the mean abundance in these studied dogs indicate that the parasite population was highly over-dispersed with a few dogs carrying extremely high parasite burdens. It is these dogs that may represent the greatest public health threat as they will be responsible for the majority of the environmental contamination.

Table 4.4. Negative binomial constant (*k*) values and their accompanying *Echinococcus granulosus* prevalences for various reported dog studies compared to findings for *E. granulosus* (*E.g.*) and *Echinococcus multilocularis* (*E.m.*) for Shiqu County (bold).

Location	Prevalence	*k*	Reference
China	0.381	0.0571	Ming et al. (1992)
[a]Iran	0.272	0.041	Eslami and Hossein (1998)
Tunisia	0.270	0.0232	Lahmar et al. (2001)
Kazakhstan (farm dogs)	0.231	0.0270	Torgerson et al. (2003)
Uruguay	0.197	0.080	Parada et al. (1995)
[a]Jordan	0.138	0.0217	El-Shehabi et al. (2000)
Shiqu County (*E.m.*)	**0.13 – 0.33**	**0.014**	
Shiqu County (*E.g.*)	**0.08 – 0.19**	**0.0095**	
[a]Uruguay	0.076	0.014	Gasser et al. (1994)
Kazakhstan (village dogs)	0.058	0.00736	Torgerson et al. (2003)
[a]U.K. (Wales)	0.047	0.011	Jones and Walters (1992)

[a] *k* calculated by Torgerson and Heath (2003).

Negative binomial constant values have not been reported previously for *E. multilocularis*, however, the value found here is realistic when considering prevalence and what is known from past studies dealing with *E. granulosus* infection in the dog. By using the negative binomial distribution, the heterogeneity of parasites within the host population has been incorporated into the model analysis. This is illustrated by the wide confidence intervals for abundance estimates of individual age classes (Table 4.1). Likewise, this heterogeneity was incorporated in all calculations of parameter estimates. The reason for this aggregation may be variations in host resistance, but more likely, in the case of *Echinococcus* spp., it is the highly aggregated nature of infectious insults due to asexual reproduction in the intermediate host (Galvani, 2003). Thus, a single small mammal infected with a metacestode of *E. multilocularis* may contain many thousands of protoscolices, resulting in a high intensity of infection in dogs that happen to consume such small mammals (Schmitt et al., 1997). Likewise, because of the low prevalence rate generally seen in small mammals in endemic areas, dogs will escape infection on the majority of occasions they consume a small mammal (Hofer et al., 2000). Although there may be spatial variations in the environment, which may affect infection pressure, spatial resolution of such heterogeneities at this scale is likely to be difficult due to the confounding effect of the aggregated distribution in the definitive host, which is a known natural phenomenon (Morgan et al., 2004). This is particularly true for a dog population that is freely allowed to roam within and between villages.

In conclusion, it is the hope that this study will act as a baseline for future investigations looking at the role of and transmission dynamics associated with domestic dogs in the transmission of *E. multilocularis* in certain high endemic regions such as Shiqu County. In addition, findings from this survey may result in more precise recommendations for the implementation of a control program, for this region, based on the anthelmintic treatment of dogs.

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4.6. References

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Chapter 5

Use of disability adjusted life years in the estimation of the disease burden of echinococcosis for a high endemic region of the Tibetan Plateau

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5.1. Abstract

Shiqu County, located on the Tibetan plateau of western China, has an extremely high prevalence of both human alveolar echinococcosis (AE), and cystic echinococcosis (CE). The short form 12 version 2 quality of life survey, which was used to evaluate the extent to which morbidity associated with echinococcosis should be accounted, verified that there was a significant reduction in the mean health scores in all categories for individuals diagnosed with abdominal echinococcosis compared with an age and sex cross-matched population. Results of a larger ultrasound survey, which screened 3135 subjects, demonstrated that the prevalence rates of AE and CE were both approximately 6% with a combined prevalence rate of 11.4%. Prevalence rates adjusted for the age and sex structure of Shiqu County were 4.6% for AE and 4.9% for CE with an estimated overall adjusted prevalence rate of 9.5%. The burden of disease associated with echinococcosis was calculated using disability adjusted life years (DALYs) based on these estimated prevalence rates. Monte-Carlo techniques were used to model the uncertainty in the prevalence estimates and the disability weights. Using these methods, we estimated that the total numbers of DALYs lost due echinococcosis was 50,933 (95% confidence interval [CI] = 41,995–61,026). The DALYs lost consisted of approximately 32,978 (95% CI = 25,019–42,422) due to AE and 17,955 (95% CI = 14,268–22,128) due to CE and suggests an average of approximately 0.81 DALY lost per person. This study has clearly shown that the impact of DALYs lost due to echinococcosis, in terms of medical treatment costs, lost income, and physical and social suffering, is likely to be substantial in this highly endemic region of China.

5.2. Introduction

Human cystic echinococcosis (CE) and alveolar echinococcosis (AE) are caused by the larval stage of the taeniid tapeworms *Echinococcus granulosus* and *E. multilocularis*, respectively, and are among the most deadly helminth diseases known to humans. Cystic echinococcosis produces space-occupying lesions, usually in the liver or lungs, whereas AE results in highly infiltrative lesions of the liver and may give rise to metastases (Ammann et al., 1996). Expenses and loss of health and vitality associated with *Echinococcus* infection can become a significant burden not only for the affected individual and his or her family, but also for the community as a whole. The Tibetan plateau region of western China has been found to have one of the highest prevalences of both human CE and AE in the world (Wang et al., 2001).

Potential impact of the disease on afflicted individuals must be taken into consideration when constructing a disability adjusted life year (DALY) estimate. A health survey is a useful tool with which to evaluate the physical and mental health state of a person with, in this instance, echinococcosis compared with a control population. Two previous studies suggested that patients surgically treated for CE had a significant decrease in the quality of life (Torgerson et al., 2001; Torgerson and Dowling, 2001). Subjects presenting for treatment have also been reported as having a substantially higher rate of unemployment (Torgerson et al., 2003). However, to evaluate the societal burden of disease it is important to understand the effect that CE and AE have on previously undiagnosed individuals. The short-form 12 (SF-12) version 2 health survey is a generic measure of general health and well-being that can be used to evaluate the extent to which morbidity, associated with echinococcosis, should be accounted (Ware et al., 2002). Therefore, the quality of life of individuals who were found to be abdominal ultrasound positive for either AE or CE on a cross-sectional study of the population of Shiqu County (Sichuan Province, People's Republic of China) was compared with negative individuals using this instrument. It is essential to know such information about the morbidity effects of echinococcosis before the numbers of DALYs lost due to the disease can be estimated.

DALYs were first constructed for the Global Burden of Disease Study, which was developed to attempt to quantify the worldwide burden of disease attributed to 107 causes by sex and age (Murray, 1994; Murray and Lopez, 1996). This technique considers the impact of both premature mortality and morbidity caused by a disease state and can then be used to evaluate the economic impact of the disease on the community as well as the potential cost-effectiveness of intervention strategies. Human echinococcosis was not evaluated in the Global Burden of Disease Study (Murray, 1994; Murray and Lopez, 1996). Therefore, DALYs have been constructed for both AE and CE and applied to a region of the Tibetan plateau (Shiqu County, Sichuan Province).

5.3. Materials and Methods

The SF-12 version 2 health survey. The SF-12 version 2 health survey (QualityMetric, Inc., Lincoln, RI) was used in this study due to its brevity and ease of use. Eight domains, or scales, of health are assessed in the survey: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. These domains were chosen from among 40 recommended in the Medical Outcomes Study and are considered among the most frequently measured health concepts (Stewart and Ware, 1992). In addition, two component scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) were evaluated. The translation of the American English version of the SF-12 version 2 into Tibetan was undertaken according to the International Quality of Life Assessment protocol, which involved forward and backward translation and testing on a small pilot study (Bullinger et al., 1998). In addition, appropriate wording substitutions were made that embodied similar concepts and health requirement levels, but were more familiar to the survey subjects (Wagner et al., 1998). Scoring of the SF-12 version 2 health survey was undertaken in accordance with standard procedures (Ware et al., 2002).

Subjects. From 2001 to 2003, 3,135 subjects were examined using abdominal ultrasound as part of an echinococcosis screening and epidemiologic survey for Shiqu County, which has an estimated population of 63,000 (Sichuan Statistical Yearbook, 2002). Prevalence estimates and an age profile, of the screened population, were calculated from the results of the ultrasound survey. The age profile of the screened population was then compared with the most recent census of the population of Shiqu County and an adjusted number of cases, expected from the 3,135 subjects if they had the same age profile as the total population, was calculated (The Editorial Commission of the Shiqu County Record, 2000). The adjusted prevalence for echinococcosis was then determined accordingly. Consent was obtained from all participants and individuals shown to be echinococcosis positive, based on World Health Organization diagnostic criteria, were provided free of charge with albendazole tablets as well as informed of their surgical options (WHO Informal Working Group, 2003; Pawlowski et al., 2001). Ethical approval for all work carried out in China was obtained from the Medical Sciences Expert Consultant Committee, Sichuan Provincial Health Bureau, Sichuan Province (People's Republic of China). During April 2003, the Tibetan version of the SF-12 version 2 health survey was administered to ultrasound survey participants with the assistance of local government and health officials. Since up to 75% of inhabitants of the Tibetan plateau are illiterate, the Tibetan questionnaire was administered orally to those partaking in the survey. There were 39 individuals, identified as being echinococcosis positive via abdominal ultrasound, who consented to participate in the study. A cross-matched population (n = 39) based on age and sex, drawn from those testing ultrasound negative, was then administered the survey and the results compared with those of the ultrasound-positive subjects. Results from the Tibetan plateau echinococcosis survey were also evaluated against the standardized 1998 United States norm (Ware et al., 2002). All comparisons were made using a Student's *t*-test.

Construction of DALYs. The use of DALYs is an attempt to quantify the burden of a disease, in this case echinococcosis, for Shiqu County (Sichuan Province, People's Republic of China). The basic formula for DALYs lost by an individual is as follows

$$-\left[\frac{DCe^{-\beta a}}{(\beta+r)^2}\left[e^{-(\beta+r)(L)}\left(1+(\beta+r)(L+a)\right)-\left(1+(\beta+r)a\right)\right]\right]$$

where, r is a discount rate, β is an age-weighting parameter, C is an age-weighting correction constant, D is a disability weight, a is the age of the individual at diagnosis, and L is the time lost to disability or premature mortality (Murray, 1994). Parameter values used were r = 3%, β = 0.04, and C = 0.16243 (Murray, 1994; Murray and Lopez, 1996). Disability weights (D), derived for AE and CE, were based on values for liver cancer obtained from the original Global Burden of Disease Study as well as from the Dutch Disability Weight Group, which produced a set of disability weights for use in a western European context (Stouthard et al., 2000). Liver cancer was chosen for this purpose since, like echinococcosis, it causes a space-occupying mass and often results in similar clinical symptoms (Table 5.1).

Table 5.1. Comparison of the presenting clinical signs of alveolar echinococcosis (AE) and cystic echinococcosis (CE) of the liver with hepatocellular carcinoma (HCC)

Presenting clinical signs	**Jaundice**	**Hepatomegaly**	**Mass-related pain**	**Lung involvement**	**Asymptomatic***	**Reference**
HCC (n = 336)	42.6%	83.9%	56%	3.2%	2.1%	Sithinamsuwan et al., 2000
AE (n = 30)	43%	23%	20%	3%	7%	Vuitton et al., 1996
AE (n = 76)	25%	14%	25%	7%	14%	Vuitton et al., 1996
AE (n = 33)	21%	76%	60%	9%	–	Wilson and Rausch, 1980
CE (n = 59)	7%	5%	42%	9%	36%	Schaefer and Khan, 1991

* These cases were found incidentally in patients without clinical signs (diagnosed by chance at necropsy, laparotomy, or during ultrasound examination for other reasons such as pregnancy). Other categories were diagnosed clinically and confirmed radiologically.

Life expectancy was based on the Japanese estimated life span, which is one of the longest known, and was used to standardize DALYs lost in accordance with the Global Burden of Disease Study (Murray, 1994). A life expectancy of 82.50 years was, therefore, chosen for females and 80.0 years was chosen for males. A model life-table, West Level 26, was used to estimate expected longevity for each age, with a Chinese life-table used for comparison (Murray, 1994; Lopez et al., 2000). The general DALY formula was used in the construction of DALYs specific for AE and CE. The DALYs were constructed on the premise of solely chemotherapeutic therapy because this is the most common treatment modality for the region and in nearly all cases the only treatment currently available.

Analysis. A DALY for AE was developed with disability outcomes divided into five components (cured, improved, stable, worse, or death) based on the health survey as well as findings from past studies in which albendazole was used as the sole treatment of human AE (Table 5.2). To model uncertainty, Monte Carlo techniques were used using Pop-Tools software (Commonwealth Scientific and Industrial Research Organization, Sydney, Australia). From published data (Table 5.2), the results of chemotherapeutic treatment of 103 AE patients were used to construct a multinomial distribution for the likely outcome of treatment. Of these 103 subjects, there was an approximate probability of 4% of cure resulting from calcification and regression of the lesions. Patients in this category were assigned a disability weight of 0.200 (Dutch weight for clinically disease free cancer) for five years. A probability of approximately 27% was given for having mild disease (improved) with disability weight 0.200 (Dutch weight for clinically disease free cancer), a probability of approximately 41% was given for having disease equated to a disability weight of 0.239 (stable) (the Global Burden of Disease weight for pre-terminal liver cancer), and a probability of approximately 22% was given for severe disease equating to a disability weight 0.809 (worse) (the Global Burden of Disease weight for terminal liver cancer). Patients assigned to these three disease states were provided with a disability weight until the end of their expected lifespan based on a trinomial distribution. In addition, approximately 6% of the patients were assigned the outcome of eventual death, which equates to a disability weight of 0.809 for 10 years followed by death. Using these probabilities, subjects from a population of 103 were repeatedly and randomly assigned to these five groups with the above probabilities to model the uncertainty associated with the results from a sample size of 103. Thus for AE, the proportion a_{AE} assigned to the cure category varied as a_{AE} x 103 ~ multinomial (103, 0.04), the proportion b_{AE} with disability weight 0.200 varied as b_{AE} x 103 ~ multinomial (103, 0.27), the proportion c_{AE} with disability weight 0.239 varied as c_{AE} x 103 ~ multinomial (103, 0.41), the proportion d_{AE} with disability weight 0.809 varied as d_{AE} x 103 ~ multinomial (103, 0.22), and the proportion e_{AE} assigned death in 10 years varied as e_{AE} x 103 ~ multinomial (103, 0.06), where $a_{\mathrm{AE}} + b_{\mathrm{AE}} + c_{\mathrm{AE}} + d_{\mathrm{AE}} + e_{\mathrm{AE}} \equiv 1$.

Table 5.2. Outcomes due to treatment of alveolar echinococcosis with albendazole

Number in study	Cured	Improved	Stable	Worse	Death	Reference
5	0	1 (20%)	2 (40%)	1 (20%)	1 (20%)	Wen et al., 1994
11	2 (18%)	0	5 (46%)	3 (27%)	1 (9%)	Liang et al., 1997
35	2 (6%)	4 (11%)	25 (72%)	4 (11%)	0	Horton, 1989
37	0	11 (30%)	10 (27%)	12 (32%)	4 (11%)	Ammann et al., 1994
15	1 (7%)	12 (80%)	0	2 (13%)	0	Liu et al., 1991

Disability weights for CE were assigned in a similar manner based on the results of albendazole treatment of 547 patients from past studies (Table 5.3). There were no fatalities reported in these studies due, in part, to the absence of long-term follow-up. Therefore, an approximate 1% fatality rate was assigned to account for cases that will likely progress. Therefore, the proportion a_{CE} assigned to the cure category varied as a_{CE} x 547 ~ multinomial (547, 0.47), the proportion b_{CE} with disability weight 0.200 varied as b_{CE} x 547 ~ multinomial (547, 0.35), the proportion c_{CE} with disability weight 0.239 varied as c_{CE} x 547 ~ multinomial (547, 0.13), the proportion c_{CE} with disability weight 0.809 varied as d_{CE} x 547 ~ multinomial (547, 0.04), and the proportion d_{CE} assigned to death in 10 years varied as e_{CE} x 547 ~ multinomial (547, 0.01), where $a_{CE} + b_{CE} + c_{CE} + d_{CE} + e_{CE} \equiv 1$.

Table 5.3. Outcomes due to treatment of cystic echinococcosis with albendazole

Number in study	Cured	Improved	Stable	Worse	Death	Reference
58	14 (24%)	29 (50%)	15 (26%)	0	0	Wen et al., 1994
253	72 (28%)	129 (51%)	46 (18%)	6 (3%)	0	Horton, 1989
59	50 (85%)	5 (8%)	1 (2%)	3 (5%)	0	Chai et al., 2002
118	97 (82%)	6 (5%)	0	15 (13%)	0	Chai et al., 2002
59	25 (42%)	25 (42%)	9 (16%)	0	0	Nahmias et al., 1994

A uniform distribution was used to subtract between 0 and 5 years from the age of abdominal ultrasound diagnosis to model the age of onset of morbidity rather than the age of detection provided by the ultrasound diagnosis. The uncertainty of the point prevalence estimates was modeled using a binomial distribution. Thus, the prevalence rate P_{AE} in the general population for AE was modeled as P_{AE} x N_t ~ binomial (N_t, N_{AE}/N_t), where N_t is the sample size that undertook ultrasound examination and N_{AE} were the adjusted number positive for AE. The prevalence rate P_{ACE} of abdominal CE was modeled as P_{ACE} x N_t ~ binomial (N_t, N_{ACE}/N_t), where N_{ACE} is the adjusted number that were positive for CE on abdominal ultrasound. In both cases of AE and CE, Nt = 3,135 (see above). In addition, past studies have indicated that only approximately 75% of CE cysts are located in the liver, with a substantial proportion of cases suffering from pulmonary echinococcosis, which cannot be diagnosed with ultrasound techniques (Menghebat et al., 1993). Therefore, to account for pulmonary and other cases of non-diagnosed CE, the prevalence of CE for the improved/stable/worse category was modeled as: $P_{CE} = P_{CE}$ x Γ, where $\Gamma \sim$ uniform (1.17, 1.33).

A spreadsheet model incorporating the DALY formula was constructed in Excel® (Microsoft, Redmond, WA). Monte Carlo routines were implemented to re-sample across the distributions 10,000 times to account for variability in disability weight and prevalence estimates. Individuals diagnosed with both AE and CE were categorized as having AE for analysis purposes. Disability weight assignment was assumed to be age independent since there is no evidence to suggest disparity in clinical presentation dependent on age of onset. Since the prevalence of AE and CE vary at the township level, an average was taken for the entire county and the age and sex distribution of patients identified in this study was applied at the county level.

5.4. Results

The 39 questionnaires for echinococcosis-positive participants were completed in their entirety except for one missing response for each of the following questions: 3a, 3b, 4a, 4b, 5, 6a, 6b, and 6c. There were no missing responses for the control group. Of the 39 positive individuals, 26 (67%) were female and 13 (33%) were male. Patient ages ranged from 8 to 80 years. Of the females, 60% were less than 41 years of age and 39% of males were less than 41 years of age. Patients with CE made up 51% of the echinococcosis-positive group and patients with AE made up the other 49%. If an individual did not answer a question, the domain the question contributed to was not included in analysis for that person. Based on comparison of mean scores for the Shiqu County control group and the United States norms, it was decided that the echinococcosis-negative group from Shiqu County was a better indicator of the standard to which echinococcosis-positive patients in the area should be compared. The CE-positive individuals were compared with AE-positive individuals for all eight domains of health. No significant difference was found ($P > 0.05$) between the two groups for any of the domains tested and it was, therefore, decided to combine the CE-positive and AE-positive persons into a single echinococcosis-positive group for further analysis.

Individuals with a positive diagnosis of *E. multilocularis* or *E. granulosus* infection had a significantly lower mean score for all eight areas of health (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) and the two component scores (PCS and MCS) compared with the cross-matched population from the same region ($P < 0.05$) (Figure 5.1). Males and females from Shiqu County were compared with an analysis for sex bias. Scores in all areas were within one standard error for both the control group and the echinococcosis-positive group. When echinococcosis-negative males were compared with echinococcosis-positive males, the control group scored higher in all categories ($P < 0.05$) except social functioning. Echinococcosis-negative females scored significantly higher than echinococcosis-positive females in all categories ($P < 0.05$). Individuals less than 41 years of age were compared with individuals greater than 40 years of age. When control groups and echinococcosis-positive groups were evaluated, it was shown that the older group, on average, scored the same or lower than the younger age group in all areas except for the vitality domain for the control group and the mental health domain for the echinococcosis-positive group. The only categories showing a significant difference, however, were bodily pain and role-emotional for the control group. Due to the findings of the SF-12 version 2 health survey, it was confirmed that human echinococcosis was associated with a decrease in the overall quality of life.

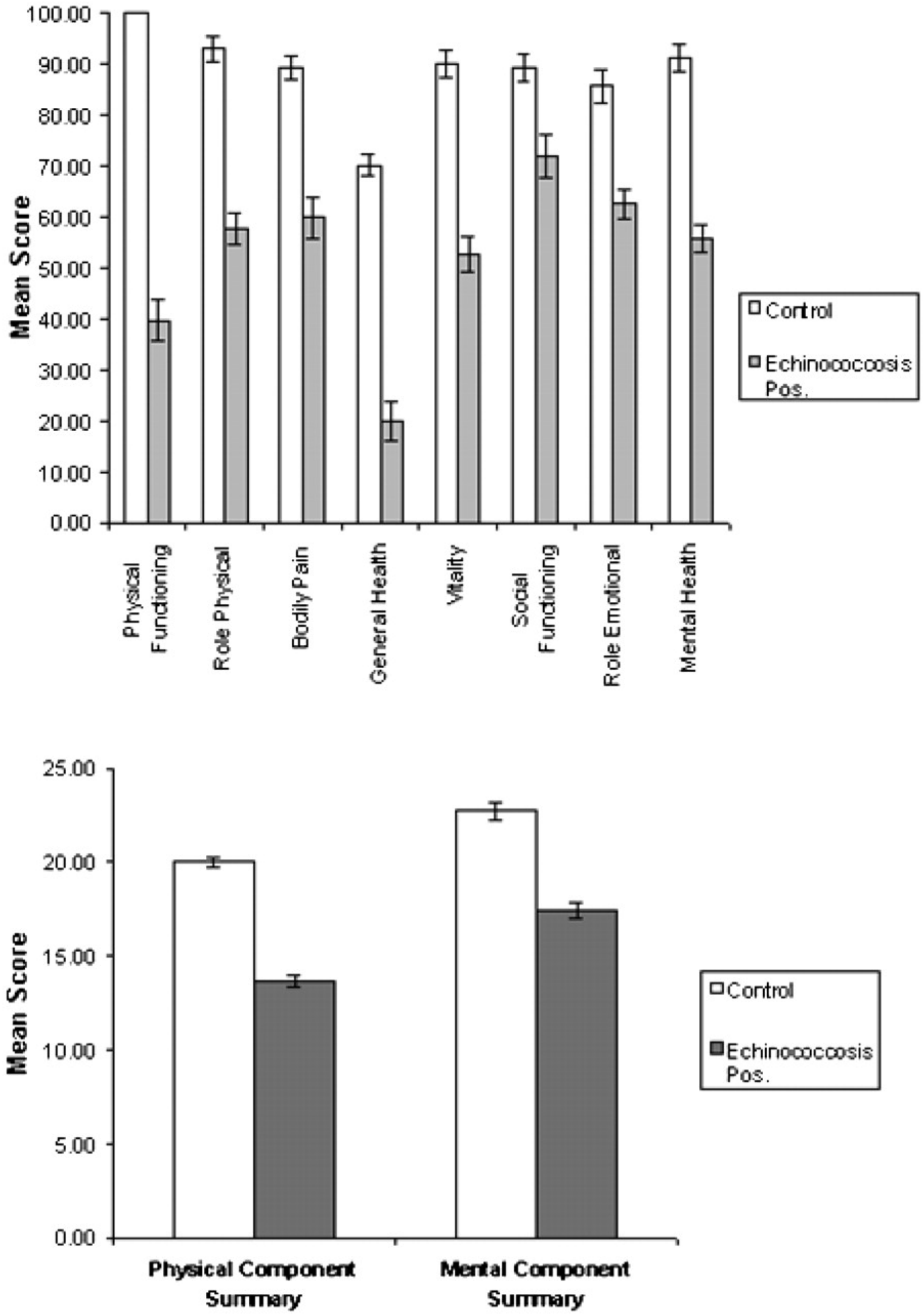
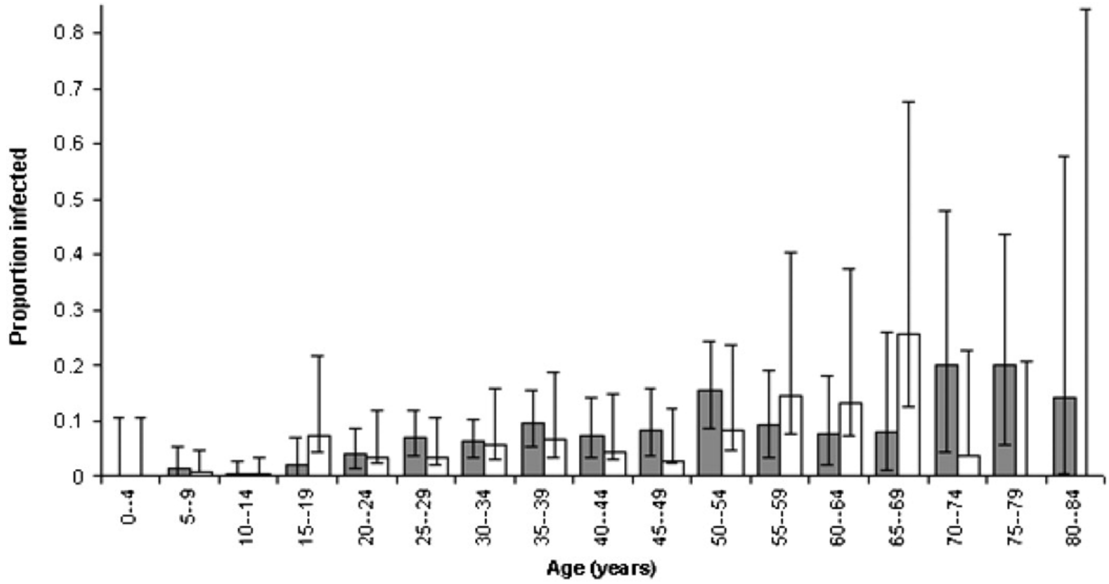


Figure 5.1. Mean Health Scores from the short form 12 version 2 health survey for echinococcosis-positive (Pos.) patients versus a control group from Shiqu County, Sichuan Province, People's Republic of China. Error bars show the standard error of the mean.

Of the 3,135 subjects examined with abdominal ultrasound, 178 cases were positive for CE (5.68%) and 180 cases (5.74%) were positive for AE (Figure 5.2). The distribution by age and sex of the screened population and total population is shown in Figure 5.3, with the total proportion of the screened population infected given in Figure 5.2. The estimated total adjusted prevalence was 4.6% for AE and 4.9% for CE, with an overall adjusted prevalence rate of 9.5%. Using the estimated adjusted variation of prevalence with age in Shiqu County and the West Level 26 life table, we estimated an echinococcosis burden of disease estimate of 50,933 (95% confidence interval [CI] = 41,995–61,026) DALYs lost for the region (Figure 5.4). Alveolar echinococcosis contributed 32,978 (95% CI = 25,019–42,422) DALYs and CE contributed 17,955 (95% CI = 14,268–22,128) DALYs to the total value. This represents a loss of approximately 0.81 DALY per resident of Shiqu County due to echinococcosis or approximately 0.085 per person per 1% prevalence. When the data were fit to a Chinese life-table with a life expectancy of 68.85 years for males and 72.99 years for females, the total estimated DALYs lost for Shiqu county was 49,601 (95% CI = 40,781–59,446) (Figure 5.4).



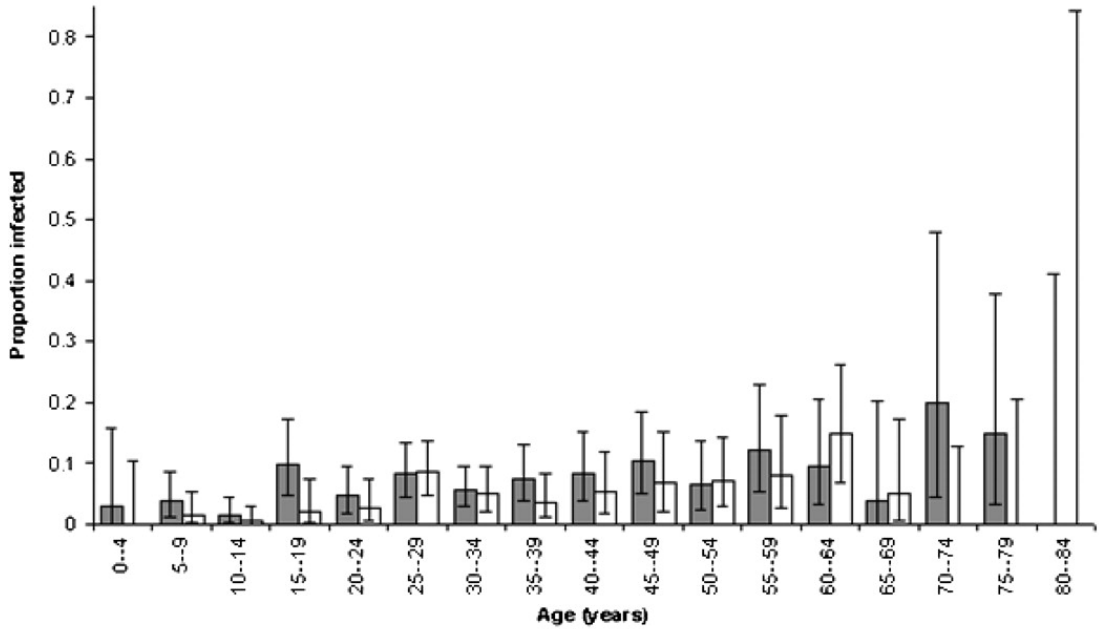
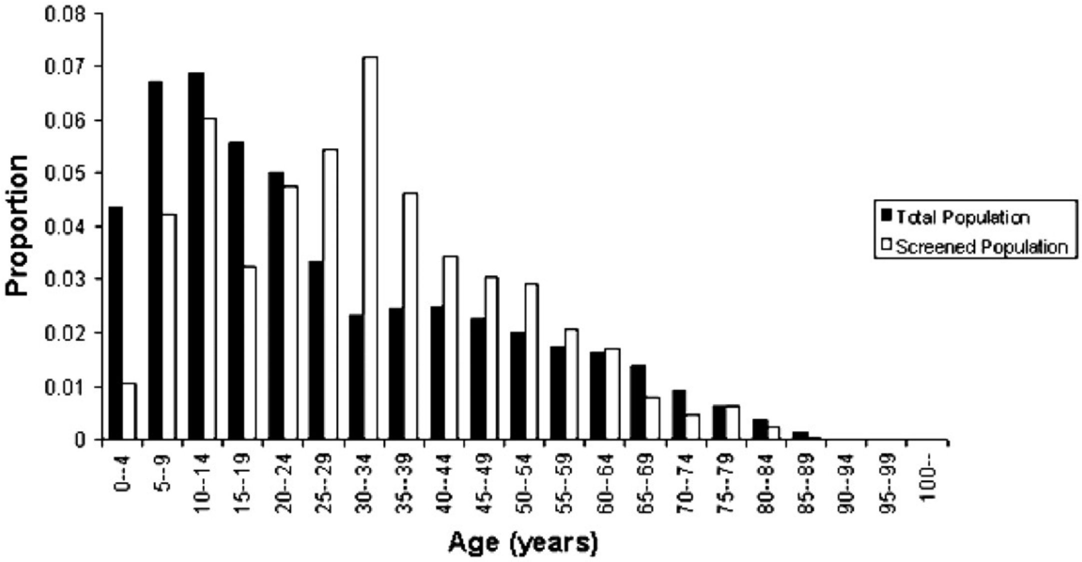


Figure 5.2. Proportion of the screened population infected by age and sex (Shiqu County, Sichuan Province, People's Republic of China). The upper graph represents cases of alveolar echinococcosis (with 95% exact binomial confidence limits) and the lower graph represents cases of cystic echinococcosis (with 95% exact binomial confidence limits). Females are represented in gray and males are represented in white.



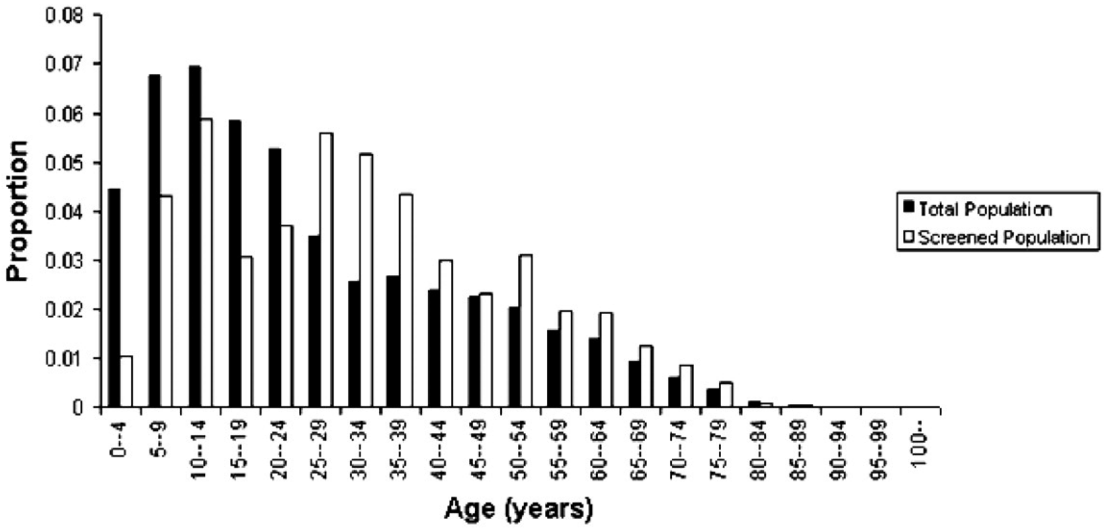
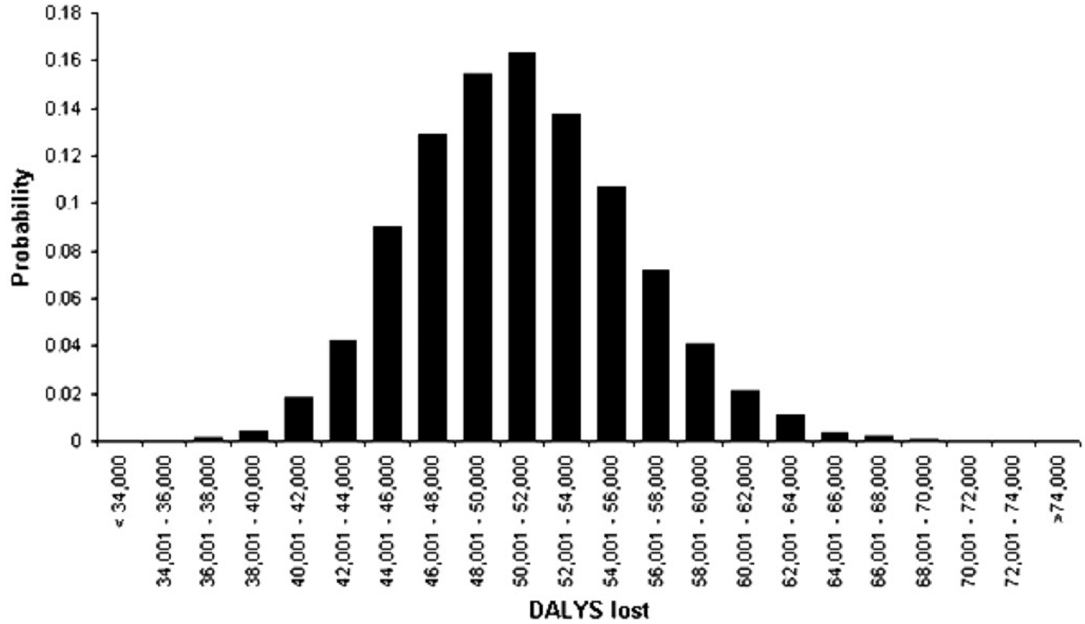


Figure 5.3. Distribution by age and sex of the screened population of Shiqu County, Sichuan Province, People's Republic of China versus the total population. The upper graph represents females and the bottom graph represents males.



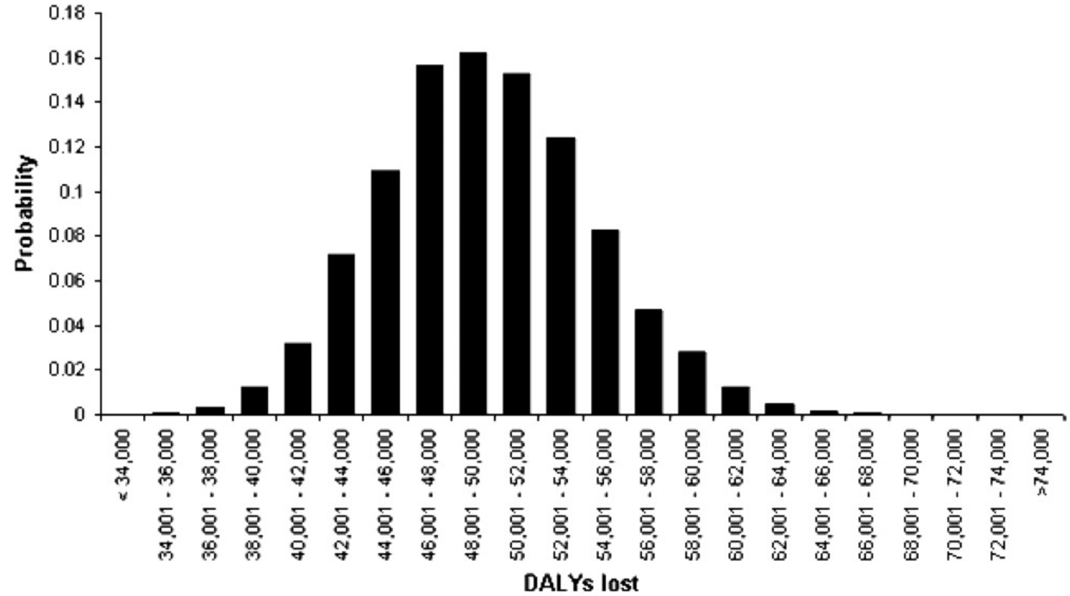


Figure 5.4. Frequency distribution of likely disability adjusted life years (DALYs) lost due to echinococcosis in Shiqu County, Sichuan Province, People's Republic of China using a Japanese life-table (**upper graph**) and a Chinese life-table (**lower graph**).

5.5. Discussion

Since disability weights have never before been assigned to human *Echinococcus* infection, it was therefore necessary to apply weights using the resources available to this study. A health survey was decided upon as one of the most attainable ways of showing a decrease in overall health of individuals with echinococcosis compared with the population norm. The SF-36 health survey has been used to indicate differences in health status between echinococcosis-positive individuals compared with a local cross-matched population (Torgerson et al., 2001; Torgerson and Dowling, 2001). In Jordan, individuals treated for CE scored significantly lower in the role physical and bodily pain categories, which was used as a justification for including morbidity costs in an economic model for the same region (Torgerson et al., 2001). A similar study conducted in Wales showed a reduction in quality of life of individuals treated surgically for CE (Torgerson and Dowling, 2001). In contrast to the Shiqu County study, the Jordanian and Welsh participants had been treated for and were aware of their condition and its potential outcome. The physical impact of abdominal surgery may also have contributed to these patients' overall change in quality of life (Nguyen et al., 2001). In contrast, the Shiqu County study allows for a pre-treatment evaluation of the association of morbidity with the condition itself. The SF-12 version 2 health survey results for this study confirm that morbidity associated with echinococcosis needs to be considered, but do not prove that echinococcosis caused the decrease in the recorded quality of life. It is possible that subjects with a low quality of life are more susceptible to infection.

DALYs were decided upon as the most suitable measure of disease burden for this study, even though there has been controversy over the appropriateness of their use in the past (Anand and Hanson, 1997; Koch, 2000). One issue is the use of a single life table, based on the Japanese life span, being used over a vast range of populations where life expectancy may not be as high. In this study, using a Chinese life table resulted in a 2.6% decrease in the total number of DALYs lost due to echinococcosis. Another criticism directed at the DALY is that it assigns global disability rates without allowing for cultural or socioeconomic differentiation between tested populations (Allotey et al., 2003). The DALY, therefore, most likely undervalues the true disability caused by diseases and disabilities in developing countries. Others have argued that the DALY devalues the life of a disabled person and that age-weighting also devalues the lives of individuals on an un-grounded basis (Anand and Hanson, 1997; Rock, 2000). Even with these acknowledged obstacles, the DALY is still widely used and is generally acknowledged as one of the best ways in which to quantify an estimated measurement of morbidity and mortality from a given disease for a given population.

Deciding whether to incorporate mortality and cure into the DALY was another complexity, seeing that length of illness associated with AE and CE is extremely variable depending on location of the lesion or lesions as well as the rate at which the cyst grows or metastasizes. Without the benefit of surgical or chemotherapeutic treatment, the maximum life expectancy, after the time of diagnosis, for an AE patient is approximately 15 years (Wilson et al., 1992; Ammann and Eckert, 1995). In contrast, CE patients have the potential to live an extended period of time, with one case study reporting a patient who lived with latent CE for 53 years (Spruance, 1974). The mortality rate for untreated CE, however, is not known although operative fatality is estimated at approximately 2% or less (Ammann and Eckert, 1996). Long-term fatality rates associated with CE and AE treated solely with albendazole also remain unknown since chemotherapy with benzimidazoles is still a relatively recent development. In addition, spontaneous calcification of lesions and cure as well as albendazole associated calcification and cure of both CE and AE have been reported and, therefore, included in the DALY estimation (WHO Informal Working Group, 2003; Rausch et al., 1987; Gottstein and Hempill, 1997).

Distribution of disability weights, consequently, proved to be challenging due to the varying clinical outcomes of the diseases, as well as the fact that methods used for assigning these weights in the past remain quite vague (Murray and Lopez, 1996). Disability weights for AE and CE were, therefore, assigned based on preceding articles reporting success and failure of treatment exclusively with albendazole. These reports were used only as a guideline, however, since many patients in these studies were deemed unlikely surgical candidates. In addition, previously reported studies have only followed patients for a short period of time and true disease-related death rates for these patients are likely to be greatly underestimated. The closest disease state for which a DALY was constructed for the Global Burden of Disease Study was liver cancer. Values for various stages of liver cancer were taken from both the Global

Burden Disease Study as well as from the Dutch Disability Weight Group and applied to AE and CE. Although echinococcosis is a more chronic disease, the similar clinical symptoms justifies using these weights. However, echinococcosis would have fewer DALYs lost if compared with a population with a similar incidence of liver cancer due to the longer life expectancy of individuals with echinococcosis.

Assigning disability weights for AE and CE was also complex due to the large number of possible outcomes both with and without treatment as well as a wide range of primary lesion sites for CE. Not all CE cases become symptomatic and spontaneous cure has been reported due to calcification of the cyst, rupture of the cyst into the bile duct or bronchial tree with subsequent expulsion of the cyst material, or via collapse and resolution of the cyst (Ammann and Eckert, 1996). In addition, CE cases with pulmonary cysts, which cannot be diagnosed via ultrasound, need to be taken into account (Menghebat et al., 1993; Al-Qaoud et al., 2003). This is especially true for high altitude areas, such as the Tibetan plateau, where lung-associated disease could be more clinically severe. Therefore, even when taking into account pulmonary CE, the estimated DALYs lost remains a conservative estimate. Unlike most studies that have calculated the burden of other diseases, this report has attempted to take into account the uncertainty surrounding the data used to estimate disability weights and the prevalence rates of the diseases. By modeling this uncertainty using Monte-Carlo techniques, the construction of a probability density for the total number of DALYs lost has been achieved. Therefore, the assumptions described in this report are accounted for in the results given the uncertainty in the parameters. Such a stochastic approach is more useful than a deterministic approach calculating a single value for a point estimate because it gives an idea of the accuracy of the estimate of DALYs lost. The information obtained can then be used to assess the cost effectiveness of designing public health programs to control echinococcosis and to assess the risk of a poor return of DALYs saved for investment in such control programs.

The number of DALYs lost due to echinococcosis in this region is very high especially when acknowledging the potential undervaluation of DALYs in less developed parts of the world, such as the Tibetan plateau. The DALYs lost due to echinococcosis in Shiqu County is approximately 0.81 per person and compares unfavorably to the average DALY lost of 0.18 from the general Chinese population due to all disabilities evaluated combined, communicable and noncommunicable (Murray, 1994). Findings for Shiqu County are, however, not typical for China. Shiqu County and its surrounding counties are especially prone to a high prevalence of echinococcosis due to the poor socioeconomic situation, local religious beliefs and customs, and the animal husbandry practices of the region (Wang et al., 2001). Poor hygiene in addition to a close relationship with dogs, which have ready access to small mammals as well as offal from yaks, sheep, and goats helps contribute to the high prevalence of disease in humans. This study has clearly shown that the impact of DALYs lost due to echinococcosis, in terms of medical treatment costs, lost income, and physical and social suffering, is likely to be substantial. In addition, control options need to be considered to most efficiently decrease the incidence of AE and CE in the local population as well as decrease economic losses from *E. granulosus* infection in sheep, goats, and yaks. These issues will be addressed in a future publication.

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Chapter 6

Economic effects of echinococcosis on a highly endemic region of the Tibetan plateau

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6.1. Abstract

This paper attempts to quantify the economic losses due to *Echinococcus multilocularis* and *Echinococcus granulosus* in Shiqu County, Sichuan, P.R. China as well as illustrate the cost effectiveness of dog anthelmintic prophylaxis combined with a sheep and goat vaccination program in terms of DALYs saved. Human losses, associated with treatment costs and loss of income due to morbidity and mortality, in addition to production losses in livestock due to *E. granulosus* infection, were evaluated. Annual combined human and animal losses (+/- 95% CI) is estimated to reach U.S.$218,676 (U.S.$189,850 – 247,871) if only liver related losses in sheep, goats, and yaks are taken into account. This equates to approximately U.S.$3.47 per person annually or 1.4% of *per capita* GDP. Total annual losses can, however, reach close to U.S.$1,000,000 if additional livestock production losses are assumed. Eventual prevention of 65% to 95% of annual losses due to CE is suggested with the proposed biannual dog anthelmintic prophylaxis and sheep and goat vaccination program. Prevention of 9% to 50% of human AE associated losses is suggested based on stochastic models for the current epidemiological situation. The median estimated cost of the program would be approximately $56,000 per annum, which is a fraction of the estimated combined livestock and human financial losses due to the disease. Overall cost for the proposed control program is within the World Health Organization's second most cost-effective band of less than U.S.$150 per DALY averted, however, cost per DALY averted would be less than U.S.$25 dollars for the human health sector if cost-sharing was implemented between the public health and agricultural sectors based on proportional benefit from control.

6.2. Introduction

Alveolar echinococcosis (AE) and cystic echinococcosis (CE), caused by accidental ingestion of eggs from the cestodes *Echinococcus multilocularis* and *Echinococcus granulosus* respectively, result in morbidity and mortality in affected individuals. In addition, infection with these parasites also results in economic losses on the household, community, and national levels. The People's Republic of China is a country with a population of over one billion, 84 million of which live in Sichuan Province. China is a developing country with a lower-middle income and an average 2001 GDP per head of $935 (purchasing power parity GDP *per capita* of U.S.$4,300) (Sichuan Statistical Yearbook, 2002). Average 2001 *per capita* GDP for Shiqu County, Sichuan Province, P.R. China, however, was much lower at U.S.$238 (purchasing power parity *per capita* GDP of U.S.$1095) (Table 6.1) (Sichuan Statistical Yearbook, 2002). With such a low income, costs associated with echinococcosis can become a great burden not only for the affected individual and his or her family, but also for the community as a whole. Shiqu County, with an estimated prevalence rate of 4.6% and 4.9% for human AE and human CE respectively, has one of the highest levels of human echinococcosis ever recorded (Budke et al., 2004). With a population of 63,000, Shiqu County has been shown to loose approximately 50,000 lifetime prevalence disability adjusted life years (DALYs) or 1100 DALYs per year due to human echinococcosis, resulting in a loss of 0.81 DALY per individual (Budke et al., 2004).

Table 6.1. Population indicators for AE and CE in Shiqu County.

Item	Value	Source
Population of Shiqu County	63,000	2002 Sichuan Statistical Yearbook
Per capita GDP for Shiqu County (PPP *per capita* GDP)	U.S.$238 ($1095)	2002 Sichuan Statistical Yearbook
*Abdominal ultrasound prevalence for AE	4.6%	Budke et al., 2004
*Abdominal ultrasound prevalence for CE	4.9%	Budke et al., 2004
Estimated number of undiagnosed cases	5627	Budke et al., 2004
Average age of diagnosis (years)	35	Budke et al., 2004

* 3135 individuals ultrasounded

In addition to DALYs lost, quantifiable financial costs associated with human echinococcosis can be attributed to diagnostic procedures, surgical and/or chemotherapeutic treatment, hospitalization, and economic losses accrued during the convalescent period. Medical costs associated with the surgical treatment of echinococcosis can be expensive in the context of local *per capita* GDP and travel to one of the larger cities in the region for surgery, namely Kanding, Chengdu or Xining, is in itself too expensive for most Tibetan herdsmen. Therefore, sole chemotherapeutic treatment with albendazole continues to be the most available and least costly means of therapy for the inhabitants of Shiqu County.

Economic losses due to lost income during illness, treatment, and the convalescent period must be taken into account as should mortality related loss of income. In addition, economic and social losses associated with undiagnosed and, therefore, untreated cases need to be considered. Animal production losses must also be evaluated in the case of cystic echinococcosis. These include losses from infected sheep, goat, and yak livers as well as decreased hide value, carcass weight, and reproduction. Currently, the vast majority of expenses attributable to both human echinococcosis and production losses, due to livestock infected with *E. granulosus*, are being absorbed by the local community. This includes infected individuals who have to pay for treatment and lose money due to lost work as well as local herdsmen who must absorb the costs of decreased livestock production. Due to the public health threat from the local infected dog population, as well as the impact on the local economy, it is suggested here that a publicly funded control program be implemented for this region, with the cost of said program shared between the public health and agricultural sectors. The most economically and logistically feasible way to decrease the incidence of human echinococcosis in the Shiqu County region is the practice of deworming local dogs combined with a sheep and goat vaccination program (Heath et al., 2003). Praziquantel is inexpensive, if purchased in bulk for a control program, and requires limited effort and technical skill to distribute. A livestock vaccination program would help to decrease *E. granulosus* prevalence, even though it would not effect the transmission of *E. multilocularis*. The addition of an education program would also be beneficial through decreasing the amount of raw offal fed to dogs (Torgerson, 2003).

Mathematical models have suggested that a combined dog deworming and sheep and goat vaccination program would be most effective in substantially reducing the prevalence of cystic echinococcosis in animals (Torgerson, 2003). This information is further supported by large scale vaccination field trials in Xinjiang (Hutubi County) and Sichuan (Ganzi County), P.R. China (Heath et al., 2003). In addition, a study performed in Shiqu County examining the transmission dynamics of *E. granulosus* and *E. multilocularis* in owned dogs, indicated a mean infection pressure of one infectious insult every 4.8 years for *E. granulosus* and one infectious insult every 1.9 years for *E. multilocularis*, assuming a 5 month *E. multilocularis* lifespan or once every 1.2 years, assuming a 3 month *E. multilocularis* lifespan, which has recently been suggested by experimental infection in dogs (Kapel, C.M.O. and others, unpublished data) (Budke et al., in press). This indicates that deworming once every 6 months should help control both *E. granulosus* and *E. multilocularis* if sufficient coverage is obtained and the number of susceptible individuals in the population is somewhat greater than the current number of cases. A more intensive deworming program (e.g. monthly or 6 weekly) was considered for the Shiqu County area, but was judged impractical due to the pastoral lifestyle of the local inhabitants. The addition of a stray dog baiting program at the same time as owned dog deworming is, however, proposed. Cost-benefit analysis was used, along with DALYs lost, to determine costs per DALY saved if the proposed control program was implemented. Findings were then evaluated to see whether the proposed control plan was within the World Health Organization’s criteria for a cost effective strategy.

6.3. Materials and methods

Human treatment costs. Medical costs, for the study area, have been associated with sole chemotherapeutic therapy. Chemotherapy alone, using albendazole, is estimated at U.S.$86.98 for one year of treatment (Qiu Jiamin, personal communication). Prevalences of 4.6% for human AE and 4.9% for human CE were based on the results of abdominal ultrasound screening performed on 3135 individuals in Shiqu County during 2001-2003 and then extrapolated to the population of the entire county after being adjusted for age and gender bias (Budke et al., 2004).

Income losses. Based on findings from the SF-12 v2 quality of life survey, subjects diagnosed with echinococcosis had a significantly decreased quality of life for all areas tested, including physical functioning (Budke et al., 2004). Such a decrease in quality of life is likely to affect the ability to work and hence generate income. Therefore, a case control study of individuals with echinococcosis was undertaken on the same population as previously described. Ethical approval for all work carried out within China was obtained from the Medical Sciences Expert Consultant Committee, Sichuan Provincial Health Bureau, Sichuan Province, P.R. China. Questions relating to income were used to categorize adult subjects into 4 income brackets: < U.S.$120 per annum, U.S.$121-U.S.$241 per annum, U.S.$242-U.S.$362 per annum and >U.S.$362 per annum.

Analysis of human-associated losses. The proportions of adult subjects in each income bracket with and without echinococcosis were compared using the chi-squared test. Significant differences were utilized to estimate income losses for affected individuals and this data used for further analysis. A spreadsheet model was then constructed in Excel (Microsoft, Redmond WA). Variables affecting human economic losses, due to treatment costs and income losses, were randomly varied along their distributions and summed using Monte Carlo techniques in order to model outcome uncertainty. Overall, 10,000 simulations were performed.

Monte Carlo resampling techniques were again employed to assign clinical severity and income loss to human echinococcosis cases. AE and CE cases where assigned a clinical severity outcome according to a multinomial distribution based on literature values of cases treated solely with albendazole (Budke et al., 2004). A multinomial distribution is an extension of the binomial distribution when there are more than 2 possible outcomes for each iteration. Individuals in each category were then assigned a reduction of income based on projected severity of disease. The various categories were assigned a reduction in *per capita* GDP at a level of 2% for 5 years, 5% for 46 years (average estimated lifespan at time of diagnosis), 10% for 46 years, 25% for 46 years, 50% for 5 years followed by 100% for 41 years, or 100% for 46 years indicating death. Undiagnosed cases, based on extrapolation of the ultrasound positive cases to the entire population of Shiqu County and corrected for age and gender bias, were also allocated a loss of income. A uniform distribution of 0% to 5% loss of income was applied to undiagnosed CE cases, which is comparable to losses assumed in past studies (Torgerson et al., 2000; Torgerson et al., 2001). Due to the increased clinical severity associated with AE, a 0% to 10% loss of income was assigned to undiagnosed AE cases. Loss of income for undiagnosed cases was applied until the end of the expected lifespan based on the West Level 26 life table used to calculate DALYs lost for this population (Budke et al., 2004). A 3% annual discount rate was applied to all income calculations (World Bank, 1993). All distributions were sampled across 10,000 times and mean and 95% confidence intervals obtained for losses.

Analysis of livestock-associated losses. Livestock numbers for Shiqu County were derived from 1997 published statistics, with population size assumed to be normally distributed (Editorial Commission of the Shiqu County Record, 2000). Previous studies provided a baseline for *E. granulosus* prevalence in the various livestock intermediate hosts. Prevalence values were taken from the most comprehensive *E. granulosus* intermediate host study, which was performed during the 1980s. During this study, 7874 animals (3645 yaks, 4104 sheep, 125 goats) were examined in Shiqu County with an infection rate of 49.9% for yaks, 81.7% for sheep, and 40.8% for goats (Shi, 1997). Beta distributions were then used to model uncertainty in the prevalence estimates. Values for livestock related products were determined for the region based on local market conditions or extrapolated from other studies (Tables 6.2, 6.3, 6.4). Log-normal distributions were applied to losses associated with liver condemnation, decreased carcass weight, and decreased number of young born to infected sheep and goats. A log-normal distribution was chosen since the values for each are most likely skewed towards the lower end of the distribution and cannot be less than 0. This is due to the fact that the majority of infected animals will be lightly to moderately infected with only a few in the highly infected range. A log-normal distribution was also applied to decreased hide value in sheep and liver condemnation and decreased carcass weight and hide value in yaks. A uniform distribution of 1% to 5% decrease in calves born to infected female yaks was applied. A uniform distribution allows for an equal probability of occurrence over the entire distribution. This type of distribution was chosen since there is no prior information on how *Echinococcus* infection affects reproduction in yaks, yet some decrease is being presumed since the phenomena has been suggested in sheep and goats (Kenzhebaev, 1985). Overall annual losses were estimated for liver associated losses alone as well as for livestock associated losses with and without decreased reproduction, carcass weight, and hide value in yaks due to the lack of data on the effect of *E. granulosus* infection in yaks. Monte-Carlo resampling techniques were utilized across the distributions 10,000 times and a mean and 95% credibility interval determined. All computations were performed using an Excel (Microsoft, Redmond, WA) spreadsheet along with the statistical add-in PopTools (CSIRO, Australia).

Table 6.2. Sheep production factors for Shiqu County (costs in U.S. dollars)

Factor	Value	Information source
Sheep population of Ganzi Prefecture	900,500	2002 Sichuan Statistical Yearbook
Sheep population of Shiqu County	259,659	Shiqu County Record 1997
Average number of lambs born per ewe per year	1	Yin niu township government (personal communication)
Average price for an adult sheep	Male- $36.24 Female- $30.20	Yin niu township government (personal communication)
Price of an edible liver lost	♣$2.31	
Price for a hide (including wool)	♣$1.32	
Average age at slaughter	4 years	Yin niu township government (personal communication)
Reduction in carcass weight of infected sheep	2.5%	Polydorou, 1981
Reduction in hide value of infected sheep	20 %	Kenzhebaev, 1985
Reduction in lambs born to infected ewes	11%	Kenzhebaev, 1985
Prevalence of infection in adult sheep at slaughter	81.7%	Shi, 1997

♣ assume proportional to costs in Jordan (Torgerson et al., 2001)

Table 6.3. Goat production factors for Shiqu County (costs in U.S. dollars).

Factor	Value	Information source
Goat population of Ganzi Prefecture	657,900	2002 Sichuan Statistical Yearbook
Goat population of Shiqu County	48,852	Shiqu County Record 1997
Average number of kids born per nanny per year	1	Yin niu township government (personal communication)
Average price for an adult goat	Male- $19.33 Female- $14.50	Yin niu township government (personal communication)
Price of an edible liver lost	♣$1.17	
Average age at slaughter	4 years	Yin niu township government (personal communication)
Reduction in carcass weight of infected goats	2.5%	Polydorou, 1981
Reduction in kids born to infected nannies	11%	Kenzhebaev, 1985
Prevalence of infection of goats at slaughter	40.8%	Shi, 1997

♣ assume proportional to costs in Jordan (Torgerson et al., 2001)

Table 6.4. Yak production factors for Shiqu County (costs in U.S. dollars).

Factor	Value	Information source
Yak population of Ganzi Prefecture	2,820,400	2002 Sichuan Statistical Yearbook
Yak population of Shiqu County	300,012	Shiqu County Record 1997
Average number of young born per female yak per year	1	Yin niu township government (personal communication)
Average price for an adult yak	Male- $217.44 Female- $138.92	Yin niu township government (personal communication)
Price of an edible liver lost	♦$2.31	
Price for a hide	♣$7.28	
Average age at slaughter	6 years	Yin niu township government (personal communication)
Reduction in carcass weight of infected yaks	2.5%	Polydorou, 1981
Reduction in young born to infected female yaks	11%	Kenzhebaev, 1985
Prevalence of infection at slaughter	49.9%	Shi, 1997

♣ assume proportional to costs in Jordan (Torgerson et al., 2001)

♦ edible portion of liver lost assumed to be the same as for sheep

Control costs. The proposed control strategy is based on anthelmintic prophylaxis of owned dogs and the distribution of baits for stray dogs living near settlements two times per year in addition to a sheep and goat vaccination program. Number of family members per household and number of dogs per family were based on questionnaires administered to dog owners in Shiqu County during 2002-2003. Hence, an estimate of the total owned dog population was calculated. In addition, the stray dog population was estimated using a uniform distribution of 1 dog per every 5 households to 1 dog per every 2 households. Control costs for Shiqu County were estimated based on deworming a normally distributed population of dogs with praziquantel two times a year at 1 RMB ($0.12) per dog per visit. Costs of veterinary services for the administration of the anthelmintic was estimated at 1 RMB ($0.12) per household two times a year. Baiting costs for stray dogs was based on a cost of 2 RMB ($0.24) per bait, including the cost of making the bait, and a bait distribution cost of 1.0 RMB ($0.12) per bait, which includes all transport and labor costs associated with bait distribution. Praziquantel and veterinary costs were established on previously reported estimates for the region and bait distribution costs are reasonable based on local wages (Heath et al., 2003). Sheep and goat vaccination was modeled on a vaccination program assuming three inoculations per animal over a five year period (Heath et al., 2003). Cost of vaccination for a single animal was assumed to be 1 RMB ($0.12) per inoculation and 1 RMB ($0.12) for veterinary services (Heath et al., 2003).

Costs / benefits. Complete eradication of both *E. granulosus* and *E. multilocularis* is extremely unlikely due the near impossibility of attaining 100% compliance as well as the continued maintenance of *E. multilocularis* in a wildlife cycle. In light of past control studies, a mean compliance rate of 75% is a more attainable goal for a rural area such as Shiqu County (Fen-Jie, 1993). Due to the variation in life cycles and parasite life expectancy, a single control program will effect amount of control obtained for each parasite differently. Mathematical models for *E. granulosus* have indicated the possibility of an over 90% decrease in intermediate host prevalence within 10 years and near complete eradication of the parasite in 15 to 20 years, assuming a biannual dog deworming scheme together with a sheep and goat vaccination program, with an average compliance of 75% (Torgerson, 2003). A conservative estimate of a long-term (e.g. 20 years) *E. granulosus* control program, based on two times per year owned dog deworming and stray dog baiting plus sheep and goat vaccination, was estimated at a mean of approximately 80% reduction in intermediate host prevalence, with a minimum level of 65% and a maximum estimate of approximately 95% reduction. These values were then utilized in a cost-benefit analysis.

The proposed intervention strategy will have less effect on *E. multilocularis* because the parasite is only being controlled at one point in the life cycle, i.e. the definitive host. In addition, the parasite has a shorter life expectancy and is maintained in a wildlife cycle (Deplazes and Eckert, 2001). More probable is the establishment of a new equilibrium, with a lower prevalence in the dog population and human cases reported at a lower incidence level. Pre-control abundance θ in the dog definitive host in the absence of parasite-induced immunity can be modeled as:

$$\theta = \frac{h}{\mu}\left(1-\exp\{-\mu t\}\right) \quad (1)$$

where h is the prevailing infection pressure in number of parasites per year, t is the dog's age, and μ is the rate of loss of infection ($1/\mu$ = parasite lifespan) (Roberts et al., 1986). In this case, time t is modeled as the average age of the dogs from this population (4.5 years) (Budke et al., 2005). The same equation can be used to estimate the average abundance of *E. multilocularis* in dogs that become infected over the 6 month period between anthelmintic treatments. Upon treatment with praziquantal, all parasites will be removed from the dogs. By making the conservative assumption that all infections in dogs are transmitted as a spill-over from the fox-small mammal lifecycle, the same equation can be used as the infection pressure remains unchanged. The prevalence 6 months after treatment can be calculated by equation (1) using the steady state infection pressure and making t = 0.5. Thus θ', the new mean abundance of *E. multilocularis* in the dog population, can be estimated by finding the solution of:

$$\theta' = \frac{1}{0.5-0}\int_{0}^{0.5}\left[\frac{h}{\mu}(1-\exp\{-ut\})\,dt\right] \quad (2)$$

which is the mean value of equation 1 between 0 and 6 months. In order to model uncertainty in the estimates of parameters μ and h, the parameters were assigned distributions based on abundance models applied to data from dogs of this region (Budke et al., in press). Therefore, μ is modeled as a normal distribution with a mean of 2.4 and a standard deviation of 0.5, with a corresponding normally distributed h with a mean of 334 and standard deviation of 60. The parameter μ was also modeled as a normal distribution with a mean of 4 and a standard deviation of 0.8, with a corresponding normally distributed h with a mean of 533 and standard deviation of 100 (Budke et al., in press). Both sets of values were used in order to model *E. multilocularis* lifespan in the dog at 5 months and at 3 months, with values for h determined by abundance data for the area (Budke et al., in press). This function was then weighted according to a uniformly distributed compliance rate with a mean of 75% and lower and upper limits of 60% and 90% respectively. Post-control abundance was estimated as post-control abundance, assuming 100% compliance, multiplied by the compliance distribution with a mean of 75% and added to pre-control abundance multiplied by one minus the compliance rate.

Change in human incidence of AE was then modeled taking into account the number of susceptible individuals in the population and the number of current cases. A simple model can be derived to model the numbers of human cases N as a function of the abundance in dogs θ:

$$\frac{dN}{d\theta} = \eta(S - N)$$

where S is the numbers of susceptible individuals and η is a transmission parameter which encompasses the contact rate between parasite and humans as well as factors affecting the viability of the free living eggs in the environment. The parameter θ is the mean abundance of parasites in the dog population. From this it can be shown:

$$N = S(1 - \exp\{-\eta\theta\}) \qquad (3)$$

The number of potentially susceptible people in a population of 63,000 was modeled as a log normal distribution with a mean of 3000 and a standard deviation of 5000, which was then shifted to the right by 3000 and maximum number of susceptibles truncated at the population size of 63,000. This was to model possible numbers of susceptibles from an estimated minimum of approximately 5% of the population (5% were found to be abdominal ultrasound positive upon screening) up to a maximum of the total population (Budke et al., 2004). However, this distribution will skew the numbers of cases towards the lower limit as it is possible that a high proportion of susceptibles are already infected due to the local conditions of severe and widespread poverty combined with the population living in conditions of poor hygiene and in intimate association with the dog population. The number of current cases in the population was modeled as a beta distribution based on 180 AE positives out of 3135 abdominal ultrasound screened individuals and multiplied by a correction factor for age and gender structure of the Shiqu County population (Budke et al., 2004). The transmission parameter η can be calculated for each value of N, S and θ drawn from the prior distributions. This value is used on each occasion to estimate the numbers of new cases N' assuming that:

$$N' = S(1 - \exp\{-\eta\theta'\})$$

The prior distributions were sampled 10,000 times, with the model recalculating the posterior value of N' on each occasion. The upper 97.5% and lower 2.5% values of N' were used to calculate the 95% confidence interval for the number of new cases. These values were then used in a cost-benefit analysis for the reduction in human disease.

6.4. Results

Human costs. Evaluation of income levels of abdominal ultrasound participants indicated that individuals diagnosed with AE or CE were significantly more likely ($P < 0.05$) to be in a lower income bracket than those individuals testing abdominal ultrasound negative for echinococcosis (Table 6.5). Total cost for the current population is estimated at U.S.$1,507,224 (U.S.$525,737 – 2,496,698), with a per capita lifetime cost of U.S.$23.94 (U.S.$8.30 – 39.38) and an annual cost of U.S.$32,788 (U.S.$11,120 – 54,215), equating to a loss of approximately 0.2% of *per capita* GDP each year.

Table 6.5. Income levels for participants in the Shiqu County abdominal ultrasound study for echinococcosis (income in U.S. dollars).

Annual income	Control group (%)	*CE positive (%)	*AE positive (%)
< $120	47%	50%	52%
$121 - $241	30%	35%	40%
$242 – $362	9%	12%	5%
> $362	14%	2%	3%

*$P < 0.05$

Livestock costs. Annual estimated livestock related losses, with 95% confidence intervals, associated with *Echinococcus granulosus* infection are found in Table 6.6. Losses due to infected livers alone equates to U.S.$185,635 (U.S.$167,793 – 205, 389) per year. Total losses associated with discarded livers, decreased reproduction, and decreased carcass weight in sheep, goats, and yak in addition to decreased value of sheep and yak hides is U.S.$903,649 (U.S.$717,158 – 1,113,354) annually. When losses due to decreased calf production, losses in carcass weight of yaks, and decreases in the value of yak hides were subtracted from this value, annual losses resulted in U.S.$449,189 (U.S.$444,275 – 559,131). Annual combined human and animal losses due to echinococcosis is U.S.$218,676 (U.S.$189,850 – 247,871), when only liver associated losses in livestock are assumed. This equates to approximately U.S.$3.47 per person annually or 1.4% of *per capita* GDP. A loss of U.S.$532,249 (U.S.$472,112 – 595,561) was estimated assuming the only loss in yaks is due to discarded liver, resulting in a loss of U.S.$8.44 per individual annually or a 3.5% loss of *per capita* GDP. The worse case scenario would include losses associated with discarded livers, decreased reproduction, and decreased carcass weight in sheep, goats, and yaks in addition to decreased value of sheep and yak hides, which when added to human losses would result in U.S.$936,408 (U.S.$746,807 – 1,148,242) annually.

Table 6.6. Annual economic losses associated with livestock due to *Echinococcus granulosus* (in U.S. dollars).

Factor	Median (95% CI)
Losses due to discarded sheep, goat, and yak liver	185,635 (167,793 – 205,389
Losses due to decreased sheep, goat, and yak carcass weight	144,841 (129,920 – 161,597)
Losses in lamb, kid, and calf production	522,306 (345,331 – 722,132)
Reduction in sheep fleece	13,976 (12,094 – 16,019
Reduction in yak hide	36,286 (31,387 – 41,841)
Total costs (excluding losses in calf production, yak carcass weight, and yak hide)	499,189 (444,275 – 559,131)
Total costs (including losses in calf production, yak carcass weight, and yak hide)	903,649 (717,158 – 1,113,354)

Costs of control. The population of Shiqu County was found to have an average of five members and two dogs per household, equating to approximately 25,196 (21,720 – 28,851) owned dogs. In addition, the stray dog population was estimated at 4,409 (2,616 – 6,205). The annual cost of deworming the entire predicted owned dog population biannually is U.S.$9,073 (U.S.$8,044 – 10,163). Costs required to distribute baits equal in number to the projected stray dog population biannually is estimated at U.S.$3,160 (U.S.$1,881 – 4,463). Annual cost of a sheep and goat vaccination program is estimated at U.S.$44,478 (U.S.$40,811 – 48,115). A control program combining dog deworming and sheep and goat vaccination, leads to an annual estimated total cost of U.S.$56,458 (U.S.$52,458 – 60,865).

Costs / benefits. An 80% long term post-control reduction in human and livestock CE incidence, with a minimum level of 65% and a maximum estimate of approximately 95%, is being assumed based on mathematical models of control intervention. A post-control decrease in human incidence of AE, with a mean of 31% and a 95% confidence interval between 13% and 50%, was estimated based on a 5 month lifespan for *E. multilocularis* in the dog definitive host. A 21% decrease in human incidence, with a 95% confidence interval of 9% to 38%, was predicted using a 3 month *E. multilocularis* lifespan in the dog definitive host. Potential economic benefits assuming prevention of AE (assuming a 5 month lifespan) and CE associated human losses in addition to liver associated losses due to *E. granulosus*, livestock losses with only liver associated losses in yaks, and all livestock losses due to discarded livers, decreased reproduction, and decreased carcass weight in sheep, goats, and yaks in addition to decreased value of sheep and yak hides can be found in Table 6.7. Economic benefits, assuming a 3 month *E. multilocularis* lifespan in the dog definitive host, are not shown since the difference between the use of a 5 month versus a 3 month lifespan results in less than a U.S.$3,000 per year difference for any category.

If cost-sharing is implemented between the public health sector, responsible for human associated losses, and the agricultural sector, responsible for livestock associated losses, cost to each sector would be more manageable. For example, if benefits are based on the most conservative estimate of solely liver associated livestock losses, the public health sector would be expected to pay an average of U.S.$5,364 per year. The livestock sector would then be responsible for the remaining U.S$51,094 annually, resulting in a cost-benefit ratio of approximately 1:3.

Table 6.7. Cost-benefit analysis for prevention of *Echinococcus granulosus* and *Echinococcus multilocularis* human and livestock associated losses, assuming an *E. multilocularis* lifespan of 5 months.

Associated livestock losses	**Reduction in Incidence**	**Median and 95% confidence intervals for overall benefit (in U.S.$)**
Liver only	*65% CE + 13%AE	74,106 (59,615 – 89,473)
Liver only	*95% CE + 50% AE	141,309 (118,657 – 164,977)
Total losses (excluding losses in calf production, carcass weight, and yak hide)	*65% CE + 13%AE	278,292 (240,829 – 318,249)
Total losses (excluding losses in calf production, carcass weight, and yak hide)	*95% CE + 50% AE	439,734 (384,342 – 498,447)
Total costs (including losses in calf production, carcass weight, and yak hide)	*65% CE + 13%AE	541,692 (419,513 – 677,198)
Total costs (including losses in calf production, carcass weight, and yak hide)	*95% CE + 50% AE	824,704 (644,793 – 1,022,429)

* reduction in CE takes into account both human and livestock associated losses

Cost per DALY averted. Assuming that an average of 80% of DALYs due to CE are averted and 31% of DALYs due to AE are averted (based on an average *E. multilocularis* lifespan of 5 months), with the proposed dog deworming and sheep and goat vaccination program, the cost per DALY saved is U.S.$106.88 (U.S.$88.63 – 127.99). If an average of 80% of CE DALYs and 21% of AE DALYS (based on an average *E. multilocularis* lifespan on 3 months) are averted, the cost per DALY saved is U.S.$123.46 (U.S.$102.29 – 148.15). Lower and upper limits respectively of number of potential DALYs saved, assuming a 3 month *E. multilocularis* lifespan, result in 65% of CE DALYs being averted and 9% of AE DALYS being averted, resulting in a cost of U.S.$179.75 (U.S.$147.50 – 217.76) per DALY saved and 95% of CE DALYs and 38% of AE DALYS being averted resulting in a cost per DALY saved of U.S.$88.81 (U.S.$73.63 – 106.42). Lower and upper limits of potential DALYs averted, assuming a 5 month *E. multilocularis* lifespan, results in a lower limit of 65% of CE DALYS being averted and 13% of AE DALYs being averted, resulting in a cost of U.S.$164.77 (U.S.$136.00 – 198.22) per DALY saved and an upper limit of 95% of CE DALYS being averted and 50% of AE DALYs being averted resulting in a cost of U.S.$78.35 (U.S.$65.02 – 93.93) per DALY saved.

However, if cost-sharing was implemented between the public health and agricultural sectors proportional to each sector's overall benefit, assuming the suggested control program and livestock losses due to the most conservative estimate of liver associated losses only, the cost per DALY averted attributable to the public health sector, assuming a 3 month *E. multilocularis* lifespan, would be U.S.$11.73 (U.S.$9.72 – 14.07). If a 5 month *E. multilocularis* lifespan is assumed, the cost to the public health sector is estimated at U.S.$10.15 (U.S.$8.42 – 12.15) per DALY averted.

6.5. Discussion

Economic losses associated with decreased income levels for individuals diagnosed with AE or CE can be justified based on past studies (Heath et al., 2003; Torgerson et al., 2001; Baitursinov et al., 2004). In addition, a lower average income was found in individuals diagnosed with echinococcosis compared to a control population during an abdominal ultrasound study performed on 3135 individuals in Shiqu County during 2001-2003. Based on this case control study, the 0% to 5% loss of income assumed for CE cases is most likely a conservative estimate. The question does arise, however, of whether a lower income and, therefore, a possible decrease in hygiene leads to an increased chance of contracting echinococcosis or if clinical problems associated with echinococcosis lead to a decrease in income. Either way, there does appear to be an association between a decreased income level and *Echinococcus* infection. This finding is consistent with the results of a study in Kyrgystan which demonstrated higher unemployment levels in individuals diagnosed with cystic echinococcosis (Torgerson et al., 2003). Income loss, for this region, was extrapolated to the end of the expected lifespan for most infected individuals since, unlike in developed countries, all population members contribute to family income, primarily livestock rearing and digging for medicinal herbs, for the vast majority of their lives. This is, however, most likely an underestimate since mortality due to undiagnosed echinococcosis would shorten lifespan and result in a total loss of income from the time of death until the end of the expected lifespan.

In regards to the economic impact of echinococcosis due to losses in domesticated livestock, very little is known of the impact of *E. granulosus* infection in yaks. Therefore, calculations were performed with and without losses due to decreased reproduction, carcass weight, and hide value. Studies on the production impact of echinococcosis in yaks will need to be performed in order to narrow the estimated economic losses in these animal populations. In addition to sensitivity analysis on the contribution of infected yaks to overall livestock losses, Monte-Carlo techniques were utilized by varying parameter values across distributions in order to show variability in economic losses. Overall economic impact of echinococcosis on the population of Shiqu County is severe, especially in light of the low economic status of the region. An annual loss of at least 1.4% of *per capita* GDP, due to echinococcosis, compares unfavorably to studies performed in Jordan and Uruguay, which indicated a loss of 0.074% and 0.058% of annual *per capita* GDP respectively due to *E. granulosus* infection (Torgerson et al., 2000; Torgerson et al., 2001). This comparison is not, however, optimal since whole country losses for Jordan and Uruguay, which include substantial urbanized areas, are being compared to a remote rural area of the Tibetan plateau. A better comparison would be between rural areas of Jordan and Uruguay, which are more likely to be poorer than the overall country averages, and the Shiqu

County study area. In this case, proportion of annual GDP lost due to echinococcosis would be higher for Jordan and Uruguay than the original studies suggested.

Due to the severity of echinococcosis infection, a control program aimed at anthelmintic prophylaxis of dogs and vaccination of sheep and goats would have a beneficial result even if a relatively small percentage of human and livestock cases could be avoided. In addition, because of the large impact that *E. granulosus* has on the domestic livestock industry, which results in the majority of economic losses, the control program suggested here would be beneficial even without taking into account benefits due to the prevention of human AE. Therefore, in essence, all savings in terms of AE can be considered an added benefit of the control program. In Shiqu County, the definitive host assumed to have the most impact on *Echinococcus* spp. transmission to humans is the domestic dog. Past studies have emphasized the need for the destruction of stray dogs in order to truly effect the transmission of *Echinococcus* spp. (Polydorou, 1992). In the case of the Tibetan plateau, this control method was considered, however, it has not been implemented due to the strong religious beliefs of the people of this region. In addition, expanding the proposed vaccination program to include yaks was considered, however, studies have shown that the yak (*Bos grunniens*) most likely is not an adequate host for *E. granulosus* due to arrested metacestode development in this species (Xiao et al., 2003). Therefore, vaccination of yaks is not necessary to control echinococcosis in this district.

Deworming of the wildlife definitive hosts of *E. multilocularis*, in this case the Red fox (*Vulpes vulpes*) and Tibetan fox (*Vulpes ferrilata*), through the use of baits is not a viable option due to the large geographic area and the substantial funding necessary to implement such a program. Some baits distributed for stray dogs will most likely be consumed by foxes, however, the vast majority of the wildlife hosts will not be reached. Controlling the infection in domestic dogs will alleviate the pressure on humans in the area, but will not eliminate the principle cycle of *E. multilocularis* since small mammals will continue to be infected by wild canids. Another concern, when dealing with a cycle maintained in a wildlife population, is that any cessation of the control program would likely result in an eventual return to previous prevalence levels. Therefore, a control program would have to be a permanent commitment for the community and eventual dismantling would not be an option. *E. multilocularis* lifespans of both 5 months and 3 months were used in analysis based on the 5 month lifespan reported in the fox and newly reported information citing a 3 month lifespan in experimentally infected dogs (Deplazes and Eckert, 2001; Kapel, C.M.O. and others, unpublished data).

The role of resistance to *E. multilocularis* in the human host is currently under study. Preliminary research has shown possible genetically based mechanisms of susceptibility/resistance including the influence of the HLA B8, DR3, DQ2 haplotype (Godot et al., 2000a; Godot et al., 2000b). If genetic susceptibility plays a large role in the acquisition of human AE, control programs could have very different outcomes for different human populations. For example, if the population has low numbers of susceptible individuals, a control program may have a more limited effect on decreasing local human incidence. This can be explained by the fact that the infection pressure and transmission rate is high enough to result in most of the susceptibles being infected. Thus, a decrease in infection pressure could have a relatively limited effect on the number of cases because of the non linear relationship between infection pressure and cases described by equation (3). This hypothesis has been suggested to explain increasing prevalence in the fox definitive host in Switzerland, which has yet to lead to a significant increase in human incidence (Gottstein et al., 2001). However, the genetic susceptibility of a population is currently not a measurable variable. Therefore, a log normal distribution has been used in the analysis for Shiqu County data in order to explore various degrees of potential susceptibility in the population.
The most well known *E. multilocularis* control program, where domestic dogs played an important role in the cycle, occurred on St. Lawrence Island, Alaska in the 1970s and 1980s. In this region, prevalence rates of *E. multilocularis* in dogs ranged from 0-25% depending on location (Rausch et al., 1990). This can be compared to preliminary findings for Shiqu County indicating an overall *E. multilocularis* prevalence of between 13% and 33% (Budke et al., 2005). On St. Lawrence Island, the control program consisted of monthly dosing of village dogs with the anthelmintic praziquantel with a capture rate of approximately 90%. Examination of the northern vole (*Microtus oeconomus*), which acted as the primary intermediate host, was used as an index for the parasite in the environment. Over the ten-year control program, the prevalence of *E. multilocularis* in the village vole population was reduced from approximately 29% to 3%. Overall prevalence in Shiqu County dogs is comparable to

St. Lawrence Island, therefore, a biannual deworming scheme, versus the monthly deworming program on St. Lawrence Island, can be predicted to have a significantly more limited impact assuming all other variables are similar and this is confirmed in the model predictions. In Shiqu County, deworming would also have to be carefully timed with the movement of the herdsmen and their dogs between summer and winter pastures and the impact of a nomadic lifestyle on *Echinococcus* transmission further investigated. In addition, it is not known to what extent dogs in Shiqu County are actively involved in the transmission cycle and hence infecting small mammals, or if they are primarily acting as a dead end host from spill-over from the fox-small mammal cycle. If the former, then the regular deworming of dogs will have a greater impact on the reduction of AE compared to the latter situation.

Previous studies have also evaluated possible control programs geared towards the eradication or decreased prevalence of *E. granulosus* (Torgerson, 2003; Lawson et al., 1988). Since the use of vaccination against *E. granulosus* in livestock is still in its infancy, however, there are few case studies looking at long term impact of a control plan incorporating vaccination. One example of an *E. granulosus* control program was carried out in La Rioja, Spain and consisted of deworming herding dogs with praziquantel every 6 weeks and non-herding dogs with praziquantel every 4 months, with questionable compliance, in addition to an education program and culling of stray dogs. At the end of the 14 year program, the prevalence in dogs had dropped from 7.0% to 0.2% (97.2% reduction), the prevalence in sheep had declined from 82.3% to 20.3% (75.4% reduction), and the rate of diagnosis of new human cases had dropped by 78.9% (Jimenez et al., 2002). Preliminary *E. granulosus* prevalence rates for Shiqu County of 8% to 19% in dogs and 81.9% in sheep make it a comparable initial situation (Budke et al., 2005). Complete eradication of *E. granulosus* in Shiqu County would, however, be very difficult due to the continental situation and thus immigration of infected animals into the area. Therefore, sporadic cases in humans would likely still occur even after near eradication and a long-term surveillance program would need to be maintained.

Utilizing the above-mentioned *E. multilocularis* and *E. granulosus* control programs as a measuring stick for past programs' success, in addition to work done with mathematical models, it can be anticipated that a two times per year dog deworming scheme in conjunction with a sheep and goat vaccination program, assuming a compliance of approximately 75%, should decrease prevalence in the intermediate hosts, dog definitive host, and human aberrant host by 65% to 95% for *E. granulosus* (Torgerson, 2003). There is a greater number of unknown factors associated with how a dog deworming program will affect *E. multilocularis* incidence. However, based on the infection pressure calculated from mathematical models, a decrease in human incidence of between 9% and 38% or between 13% and 50% is suggested, depending on the lifespan of *E. multilocularis* utilized (Budke et al., in press). The large number of DALYs lost annually and per population, along with the economic impact associated with the disease in humans and livestock, makes echinococcosis a parasitic disease worth careful consideration. Assuming either 80% of DALYs due to CE and 21% of DALYs due to AE are averted or 80% of DALYs due to CE and 31% of DALYs due to AE are averted, the cost per DALY saved remains firmly within the World Health Organization's second most cost-effective band of less than U.S.$150 per DALY saved if one organization or sector was wholly responsible for control costs (TDR/Gen 1996: 96.1). Cost per DALY averted is, however, quite deceptive since large monetary savings of up to U.S.$800,000, due primarily to savings in livestock production factors, pay for the program. If, however, cost-sharing was implemented between the public health and agricultural sectors or between the public and private sectors, cost per DALY attributable to each sector would be far lower. For example, if responsibility for control costs were divided proportionally between the public health sector (human health related benefits) and the agricultural sector (livestock associated benefits) the cost to the health sector would fall within the World Health Organization's most cost-effective band of less than U.S.$25 per DALY averted. This paper has shown that by putting a limited amount of funding into a dog deworming and sheep and goat vaccination program, a large savings in human health and monetary losses due to both human morbidity and mortality as well as losses in livestock production can potentially be obtained.

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Chapter 7

General Discussion and Conclusions

7.1. General overview

This study has endeavored to take a multifaceted approach to the epidemiology of *Echinococcus granulosus* and *Echinococcus multilocularis* for a highly endemic region of the Tibetan plateau. Subject areas broached included field-based parasitology, risk factor analysis, mathematical modeling of transmission dynamics, use of health indicators such as the SF-12 v2 health survey and the disability adjusted life year (DALY), economic analysis of both human and livestock associated losses, and control program recommendation. Evaluating and incorporating the findings from these different areas has enabled a better understanding of the human health, social, and economic impact of echinococcosis on a rural Tibetan community. It is the hope that these insights will aid in the control of echinococcosis in this region as well as help to improve the quality of life of the local inhabitants.

7. 2. *Echinococcus* fieldwork: past, present, and future

The use of arecoline hydrobromide purgation to determine *Echinococcus granulosus* prevalence and abundance in domestic dogs has a long history in areas such as New Zealand, Europe, and Africa (Gemmel, 1973; Jones and Walters, 1992; Macpherson et al., 1986). Shiqu County, Sichuan Province, People's Republic of China was, however, the first location where arecoline purgation was used to intentionally recover *E. multilocularis* from domestic dogs. Newer molecular methods, for example, the detection of copro-antigens via ELISA tests and copro-PCR, are becoming increasingly commonplace and more widely used in *Echinococcus* based epidemiological surveys (Abbasi et al., 2003; Dinkel et al., 1998; Mathis et al., 1996; Stefanic et al., 2004). These tests are tremendously useful, however, they are unable to provide important abundance information that only purgation and necropsy can supply. Because the study represented in the previous chapters was interested in evaluating parameters dependent on age-related abundance in the dog, it was necessary to use a method that allowed for the ability to perform worm counts. Necropsy was not an option for stray dogs, due to the strong religious beliefs of the people of the communities being studied, and obviously was not an acceptable practice in regards to owned dogs. Therefore, arecoline purgation is still the best non-lethal way to obtain parasite abundance data in a field setting. The method is not, however, perfect and its shortcomings in terms of sensitivity must be acknowledged.

This can, nevertheless, be overcome as shown in Chapter 3 by the use of Bayesian and resampling methods to determine true prevalence based on estimated sensitivity and specificity of purgation using arecoline hydrobromide. Due to new and improving molecular based diagnostic techniques, the future may not hold as large a role for dog purgation in epidemiological studies as it has in the past, however, until there is a new way to evaluate abundance of infection in a non-lethal manner it will continue to have a place in field-based *Echinococcus* research.

Purgation results indicated that both *E. granulosus* and *E. multilocularis* were highly aggregated within the dog definitive host, which is comparable with past findings for *E. granulosus* infection (Table 4.4). True prevalence of *E. granulosus* for dogs in Shiqu County was found to have a 95% credibility interval of 8 – 19%, with a 95% credibility interval for *E. multilocularis* prevalence of 13 – 33%. High prevalence in domestic dogs represents a large means for environmental contamination with *Echinococcus* spp. eggs as well as a great potential for individuals to come into contact with an infected dog.

7.3. Risk factor analysis

Risk factor analysis using logistic regression techniques is an epidemiological staple in regards to public health program implementation and evaluation. The use of a questionnaire to obtain input on potential risk factors in Shiqu County did have its difficulties in reference to cultural and language barriers, however, it was overall a successful and useful endeavor (Appendix A). The primary interest for this study's risk factor survey, versus other projects looking at risk factors for echinococcosis, was that this study focused on factors associated with the acquisition of the parasite in the dog definitive host rather than in the human accidental host. It is the hope that by evaluating risks for acquisition of the parasite in the definitive host (i.e. the current cycle) it will allow for a more targeted control program, rather than making recommendations based on risk factors for human disease that could have been acquired up to 10 years prior to the survey.

Logistic regression indicated that male dogs were more likely to be infected with *Echinococcus* spp. than female dogs ($P < 0.05$) and dogs allowed to roam were more likely to be infected with *E. multilocularis* ($P < 0.05$). Both of these findings are reasonable considering the mode of transmission to the definitive host and indicate the potential of increased opportunity to hunt. These finding can then be used when recommending a control program.

7.4. Transmission dynamics and mathematical modeling

The study described in Chapter 4 was the first time that transmission dynamics models were fitted to *E. multilocularis* abundance and prevalence data from the domestic dog definitive host and was the first time transmission models were fit to *Echinococcus* spp. for western Sichuan Province. The equations used to model parasite transmission allowed for the estimation of infection pressure in terms of number of parasites acquired (h), infection pressure in terms of number of infectious insults per year (β), parasite lifespan (μ), acquisition of immunity (α), and loss of immunity (γ). In addition, the negative binomial aggregation constant (k) was determined for both *E. granulosus* and *E. multilocularis* abundance. Acquired immunity remains a much debated topic in terms of *Echinococcus* spp. infection in the definitive host. The findings presented in Chapter 4 indicate that there appears to be acquired immunity for *E. granulosus* infection in the dog definitive host at the level of infection pressure present in the study area (true prevalence interval of 8% – 19% based on the sensitivity of purgation) assuming a constant infection pressure. In contrast, no statistical difference was found between the abundance model assuming the presence of immunity and the abundance model assuming the absence of acquired immunity for *E. multilocularis*, with a true prevalence interval of 13 – 33% based on the sensitivity of purgation. This may be due to the fact that there is not acquired immunity in dogs infected with *E. multilocularis* or it may mean that the infection pressure in the study region was simply not high enough to result in immunity. Further studies evaluating the domestic dog's role in the *E. multilocularis* lifecycle will need to be performed in order to answer this question.

When dog data for Shiqu County was applied to the prevalence model, infection pressure for *E. granulosus* was determined to have a mean and 95% credibility interval of 0.208 (0.118 – 0.412) infections per year and infection pressure for *E. multilocularis* was determined to have a mean and 95% credibility interval of 0.515

(0.291 – 0.773) infections per year assuming a 5 month parasite lifespan or 0.853 (0.468 – 1.25) infections per year assuming a 3 month parasite lifespan. Infection pressure in terms of number of parasites per year (h) resulted in a mean and 95% credibility interval of 560 (495 – 681) parasites for *E. granulosus* and 334 (221 – 452) parasites for *E. multilocularis* assuming a 5 month parasite lifespan or 533 (340 – 731) parasites assuming a 3 month parasite lifespan. Knowledge of the parasites' life cycle parameters, in addition to the way in which acquired immunity does or does not play a role in the region, is valuable in aiding in the development and implementation of the most efficient and cost effective program for the area under study.

7.5. The SF-12 v2 quality of life survey

To the author's knowledge, this was the first time that the short form 12 version 2 (SF-12 v2) health survey was utilized to evaluate the quality of life associated with echinococcosis, as well as the first time that the SF-12 v2 survey was translated into the Tibetan language. Findings confirmed a lower quality of life in patients diagnosed via abdominal ultrasound compared to an age and gender cross-matched population, indicating that there was a significant degree of morbidity in echinococcosis patients even before they felt the need to seek medical assistance. Information acquired from the use of the SF-12 v2 quality of life survey was extremely useful when performing both burden of disease and human health-associated economic loss assessment for the Shiqu County community.

7.6. The use of disability adjusted life years (DALYs)

The study represented in Chapter 5 was the first time that disability adjusted life years (DALYs) have been used to describe the burden of disease associated with human echinococcosis. In addition to being a new disease topic for assessment, methodology to arrive at the findings had to be approached in a very different way than those afflictions evaluated for the large Global Burden of Disease Study (Murray and Lopez, 1996). Disability weights based on other afflictions with similar clinical signs as well as literature based outcomes of treatment with albendazole were utilized. In addition, Monte Carlo methods were implemented in order to account for uncertainty due to disease prevalence being estimated by an abdominal ultrasound based study and then extrapolated to the larger population of Shiqu County, Sichuan Province, People's Republic of China. The use of traditionally obtained, let alone uniquely determined, DALYs is still a topic of much debate amongst health policy planners. DALYs have had there critics over the years, some of them being extremely vocal in their dislike for any technique which they believe puts a number value on the worth of a person's life (Anand and Hanson, 1997; Koch, 2000; Rock, 2000). Until a better method is found, however, DALYs continue to be a standard in the study of disease burden and used as a measure of the economic efficiency of a control program.

Due to the severe clinical nature of human echinococcosis and especially alveolar echinococcosis, as well as the high prevalence of infection in the studied community, approximately 50,000 lifetime prevalence DALYs were estimated to be lost from the current Shiqu County population. This represents 0.81 DALY lost per individual in the community. Although these numbers are only based on a small-scale abdominal ultrasound study, it is the hope that such a high figure will bring notice to the severity of this condition and the impact being made on the people of the Tibetan plateau of western Sichuan Province.

7.7. *Echinococcus* economics and control

Economic evaluation of human and livestock losses, due to *Echinococcus granulosus*, has been performed previously for numerous countries (Torgerson et al., 2000; Torgerson and Dowling, 2001; Torgerson et al., 2001). The study represented in Chapter 6 was, however, the first time economic losses associated with both *E. granulosus* and *E. multilocularis* have been evaluated together for a community. In addition, Monte Carlo techniques were utilized to resample over various distributions assigned to parameters associated with human and livestock losses. Using resampling techniques allows for the production of distributions for various losses and, therefore, results in a more realistic estimate of potential losses than a point estimate. A dual parasite approach to control was also evaluated and the difficulties associated with dealing with both a domestic and wildlife cycle discussed. Biannual domestic dog deworming plus a sheep and goat vaccination program was proposed based on past studies, mathematical models, and average number of infectious insults per year derived from transmission models applied to this population (Rausch et al., 1990;

Jimenez et al., 2002; Torgerson, 2003; Budke et al., in press). Findings from this study provided a first glimpse of potential economic losses due to *Echinococcus* spp. infection in the Shiqu County region as well as how much the community could expect to save if the suggested control program was implemented. In general, this information, along with the estimated number of DALYs lost for the same county, provides a multidimensional view of the health, social, and economic problems facing this area in regards to human and animal echinococcosis.

In order to perform future economic analysis of echinococcosis in this area, an evaluation of the effects of *E. granulosus* infection in the yak should be performed. A study of this kind has never been done and would be very beneficial in helping to gauge more precisely the economic impact of infection in this species. Economic evaluation of the impact of *E. granulosus* infection in sheep and goats has been performed, however, a more standardized study would be immensely beneficial due to the worldwide distribution of this parasite (Kenzhebaev, 1985; Polydorou, 1981).

7.8. Conclusions and recommendations

Results from the dog purgation and human abdominal ultrasound aspects of this study indicate an extremely high prevalence of *E. granulosus* and *E. multilocularis* in both the dog definitive host and humans. These findings stress the urgency for control program implementation and increased human and livestock monitoring for echinococcosis in the study area. A biannual anthelmintic treatment program for both owned and stray dogs, in addition to a sheep and goat vaccination plan, is proposed with careful monitoring especially in terms of how the *E. multilocularis* cycle is affected. Additional studies looking at the domestic dog's role in *E. multilocularis* transmission is also required to see if their position is just as a conduit host between the wildlife cycle and man, or if they are actually playing a key role in maintaining the cycle as was seen on St Lawrence Island, Alaska (Rausch et al., 1990). A further enquiry would be whether the semi-nomadic lifestyle of some of the local inhabitants and their dogs, who move between winter and summer pastures, affects transmission of *E. multilocularis* and if so how could a control program be catered to take advantage of this fact. Investigation of this aspect would, however, require strategic timing of sample collection, which would be difficult to orchestrate due to logistical difficulties associated with reaching the study site during certain seasons.

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Appendix A

Shiqu County dog questionnaire

China: Surveillance Data for *Echinococcus* spp.
中国：关于有腔棘球涤虫的调查数据

Date 日期_______________

Grid point 坐标点_________________

全球定位系统坐标：
GPS X ________________

GPS Y ________________

General Information 常规信息

1. Village name 村庄名称__________________

2. Household name 户主姓名_____________________

3. Are you nomadic? (please circle one)
   您是牧民吗？（请选择右边的一项）
   No 不是
   Yes- herdsman 是---放牧
   Yes- dig herbs 是---采药
   Yes- hunter 是---狩猎

4. Number of years at current location __________
   请填写您在这个地区居住的时间为（年）

5. What is your occupation? _________________
   请填写您在这里所从事的职业

6. Do you or have you ever hunted fox (explain) ________________________
   请叙述您以前猎捕狐狸的一些情况

Dog Information 关于狗的信息

7. Length of dog ownership (years) ______________
   请填写您驯养这只狗的时间（年）

8. Number of dogs currently owned _______________
   请填写您家里所养狗的总数

9. Name of dog ___________________
   这只狗的名字是

10. General description of dog ____________________
请您对这只狗进行概括的描述

11. Age of dog (years) ________________
这只狗的年龄是

12. Sex of dog (please circle one) Male 公
请选择这只狗的性别 Female 母

13. Does your dog eat raw meat? (please circle one) Yes-frequently是—经常
请选择这只狗是否吃未经过烧煮的肉 Yes- occasionally 是—有时候
No 不

14. Has the dog been seen eating rodents? (please circle one)Yes-frequently 是—经常
您的狗吃其他啮齿类的动物吗？ Yes- occasionally 是—有时候
No 不

15. Is the dog tied? (please circle one) Never- 从来没有
您绑住您的狗吗？ Yes- all of the time 是—总是
Yes- during the day only 是—只有白天
Yes- at night only 是—只有夜里

16. Who cares for the dog? _______________________
请填写您家里经常照顾狗的人是

17. Do you use dog feces as fertilizer (please circle one) Yes 是的
您用狗的粪便做肥料吗？ No 不是
Don’t have a garden
我家里没有（菜，花）园

18. Are there stray dogs in the area (please circle one) Yes 有 __________
在附近有没有发现野狗 No 没有

19. Do you play with or pet your dog (please circle one) Yes 是的
您和您的狗一起玩耍吗？ No 不是

Livestock Information 关于牲畜的信息

20. Do you own yaks? (please circle one) Yes 有 ___________
您有牦牛吗？ No 没有

21. Do you own sheep or goats? (please circle one) Yes 有 ___________
您有绵羊或者山羊吗？ No 没有

Water Source 水源

22. What is your primary water source
您家里所使用的水源是
(please circle one)
（请选择）

central supply 集中提供
tap in the house 家用自来水
tap in the street 自来水（公共场所）
pump in the yard 院子里的水泵
tank filled from truck 供水车中的水箱
carried from river 河水
carried from stream 泉水
from a well 井水

Human Hydatid Disease 包虫病

23. Number of family members ultrasounded _________
请填写您家里有几位成员进行过超声波检查

24. Presence of positive cases (please circle one)
检查结果是否有人感染

Yes 有
No 没有

If yes, please fill out the following (noting how disease was confirmed and location of lesion): 如果有请指出是下列哪项（说明：疾病是由什么方式检查出来以及伤口的位置）

Male- AE confirmed 男—AE 检查

Male- CE confirmed 男—CE 检查

Male- hydatid disease suspected 男—怀疑感染包虫病

Female- AE confirmed 女—AE 检查

Female- CE confirmed 女—CE 检查

Female- hydatid disease suspected 女—怀疑感染包虫病

25. How long ago was the most recent case diagnosed (in years)? ___________
请填写您上次检查的时间（几年以前）

26. Was surgery performed on this case? ____________
请填写您以前是否针对这种疾病进行了外科手术

Knowledge of Hydatid Disease 对于包虫病的认识

27. Correct description of hydatid disease (please circle one) Yes 能
您是否能对包虫病进行正确的描述 No 不能

28. Correct transmission knowledge (please circle one) Yes 能
您是否能把包虫病的知识传达给其他人 No 不能

Samples and Findings 采样以及发现

Sample collected (please circle one) feces (ground)粪便（地面）
所采集的样品 feces (loop)粪便（采样仪器）
purged sample 使用泄药采集的样品
necropsy 尸体检验时采集的样品

Echinococcus multilocularis found (number) ___________
发现多腔棘球涤虫的数目

Echinococcus granulosus found (number) ___________
发现颗粒状棘球涤虫的数目

ELISA (please circle one) positive 阳性
Negative 阴性

PCR (please circle one) positive 阳性 Em / Eg
negative 阴性

Other parasites found (please specify) _________________________
其它寄生虫病例

Where samples kept from this animal (please specify) __________________
寄生虫感染的位置

Appendix B

SF-12 v2 quality of life survey: American English version

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
b Climbing several flights of stairs	☐ 1	☐ 2	☐ 3

3. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
b Were limited in the kind of work or other activities	☐1	☐2	☐3	☐4	☐5

4. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
b Did work or other activities less carefully than usual	☐1	☐2	☐3	☐4	☐5

5. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

6. **These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>...**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting friends, relatives, etc.)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Appendix C

SF-12 v2 quality of life survey: Tibetan version

(༡)

ཁྱེད་རང་གི་འཁྲོད་བསྟེན་དང་བདེ་ཐང་།

ཞིབ་འཇུག་འདིའི་ནང་ཁྱེད་རང་གི་འཁྲོད་བསྟེན་སྐོར་ལྟ་ཚུལ་ག་རེ་ཡོད་མེད་འདྲི་བ་བྱེད་ཀྱི་ཡོད། གནས་ཚུལ་འདིས་ཁྱེད་རང་ནས་རང་ཉིད་ཐོག་ཚོར་བ་ག་འདྲ་ཡོད་མེད་དང་། ནམ་རྒྱུན་བྱེད་སྒོ་ཁག་ཡག་པོས་ག་འདྲ་བྱེད་ཐུབ་ཀྱི་ཡོད་མེད་ཞིབ་འཇུག་བྱེད་རྒྱུར་ཕན་ཐོགས་ཡོད། ཞིབ་ཚིག་ཐོ་འདིར་ལེན་འདེབས་ཆ་ཚང་གནང་ཐུགས་རྗེ་ཆེ་ཞུ་རྒྱུ་ཡིན།

གནམ་གསལ་འདྲི་བ་རྣམས་ལ་ལེན་འདེབས་ཀྱི་འགྲེལ་བཤད་ཡག་བོད་རྒྱབ་ཐུབ་པའི་སྒོང་ཆ་གྲུ་བཞི་མ་གཅིག་གི་ནང་ལ་ཀྲུར་རྟགས་རྒྱབ་རོགས་གནང་།

༡ སྤྱིར་བཏང་བྱས་ན་ཁྱེད་རང་ནས་རང་གི་འཁྲོད་བསྟེན་སྐོར་ལབ་ན།

ཤིན་ཏུ་ཡག་པོ།	ཡག་པོ་ཞེ་དྲག	ཡག་པོ།	འབྲིང་།	ཞན་པོ།
▽	▽	▽	▽	▽
□	□	□	□	□

(༢)

༢ གནམ་གསལ་འདྲི་བ་ཁག་ནི། ཉི་མ་གཅིག་ནང་ཁྱེད་རང་གིས་བྱེད་སྤྱོད་པའི་བྱེད་སྒོ་ཁག་གི་སྐོར་ཡིན། ཏེད་སྐབས་འདིའི་ཚོའི་ཐོག་ལ་ཁྱེད་རང་གི་འཁྲོད་བསྟེན་གྱིས་འགོག་རྐྱེན་ག་ཚོད་བཟོ་གི་འདུག འགོག་རྐྱེན་བཟོ་གི་ཡོད་ན་ག་ཚོད།

	འགོག་རྐྱེན་ཞེ་དྲག	འགོག་རྐྱེན་ཉུང་ཙམ།	འགོག་རྐྱེན་བཟོ་གི་མི་འདུག
	▽	▽	▽
ཉུང་ལས་འཕྲིང་ཙམ་བྱེད་སྐབས།			
དཔེར་ན་རྒྱ་སྒོག་དཔོར་འཛིན། གད་ཕྱིས་རྒྱབ་པ།			
སྟངས་འཛུ་རྒྱག་པ།	□	□	□
རི་འཛེགས་བྱེད་པ།	□	□	□

༣

༣ འདས་པའི་བདུན་ཕྲག་བཞིའི་ནང་ལ། ཁྱེད་རང་གི་གཟུགས་པོའི་འཕྲོད་བསྟེན་གྱིས་རྐྱེན་བྱས་ནས་ཁྱེད་རང་གི་ལས་ཀའི་ཐོག་དང་ཡང་ན་དུས་རྒྱུན་བྱེད་སྒོའི་ཐོག་ལ་ག་ཚམ་གསལ་དཀའ་ངལ་དུས་ཡུན་རིང་ལོས་ག་ཚོད་བཟོས་སོང་།

	དུས་ཚོད་ག་དུས་ཡིན་ནའི།	དུས་ཚོད་མང་ཆེ་བ།	དུས་ཚོད་ཁ་ཤས་ལ།	དུས་ཚོད་ཉུང་ཉུང་རེད།	ཚོན་ནས་འགོག་རྐྱེན་མ་བྱུང་།
ཁྱེད་རང་གི་འདོད་པ་ལྟར་					
ལས་སྤྱོད་བསྒྲུབ་པ་					
ལས་དོན་གང་ཞིག་ཐོག་གམ					
ཡང་ན་དུས་རྒྱུན་བྱེད་སྒོ་ཁག					
ལ་འགོག་རྐྱེན་དུས་ཡུན					
རིང་ལོས་བཟོས་སོང་།					

༤

༡ འདས་པའི་བདུན་ཕྲག་བཞིའི་ནང་ལ་སེམས་ཀྱི་དཀའ་ངལ་དཔེར་ན་སེམས་དམའ་ཞུམ་པ་ཡང་ན་རི་འཁྲུག་བྱས་པའི་རྐྱེན་བྱས་ནས་ཁྱེད་རང་གི་ལས་ཀ་འམ་ཡང་ན་དུས་རྒྱུན་བྱེད་སྒོའི་ཐོག་ག་ཚམ་གསལ་དཀའ་ངལ་དུས་ཡུན་རིང་ལོས་ག་ཚོད་བཟོས་སོང་

	དུས་ཚོད་ག་དུས་ཡིན་ནའི།	དུས་ཚོད་མང་ཆེ་བ།	དུས་ཚོད་ཁ་ཤས་ལ།	དུས་ཚོད་ཉུང་ཉུང་རེད།	ཚོན་ནས་འགོག་རྐྱེན་མ་བྱུང་།
ཁྱེད་རང་གི་འདོད་པ་ལྟར་					
ལས་སྤྱོད་བསྒྲུབ་པ་					
ལས་དོན་གང་ཞིག་ཐོག་གམ					
ཡང་ན་དུས་རྒྱུན་བྱེད་སྒོ་ཁག་ལ					
གཞན་པ་ཟབ་བྱེད་རྒྱུ་ནམ					
རྒྱུན་ལས་སྤྱོད་པ།					

(༥)

༥ འདས་པའི་བདུན་ཕྲག་བཞིའི་ནང་ལ་ཟུག་ཟེར་གྱིས་རྐྱེན་པས་ཁྱེད་རང་གི་སྤྱིར་བཏང་ལས་ཀར་འགོག་རྐྱེན་ག་ཚོད་བཟོས་སོང་།

རྒྱ་བ་ནས་བཟོས་མས་སོང་།	ཏོག་ཙམ་བཟོས་སོང་།	གང་ཙམ།	ག་ཆེན།	ཞེ་དྲག་བཟོས་སོང་།
▽	▽	▽	▽	▽
□	□	□	□	□

(༦)

༦ འདྲི་བ་འདི་ཚོ་ནི་ཁྱེད་རང་རང་ཉིད་སྐོར་ཚོར་སྣང་དང་བདུན་ཕྲག་བཞིའི་ནང་གང་ཅིའི་ཐོག་གནས་སྟངས་ག་འདྲ་བྱུང་མེད་སྐོར་ཡིན། འདྲི་བ་སོ་སོ་ལ་ལེན་རྒྱབ་སྐབས་ཚོར་སྣང་གང་བྱུང་བ་དེ་རང་གཞི་བཞག་ནས་གནང་རོགས། འདས་པའི་བདུན་ཕྲག་བཞིའི་ནང་ལ་ གཤམ་གསལ་ཚོར་སྣང་ཐོག་དུས་ཡུན་རིང་ལོས་ག་ཚོད་བཏང་དགོས་བྱུང་སོང་།

	དུས་ཚོད་གཏན་ཡུལ་བཞིན་ནང་ནས།	དུས་ཚོད་མང་ཆེ་བ།	དུས་ཚོད་ཁ་ཤས་ལ།	དུས་ཚོད་ཉུང་ཉུང་རེ།	ཚོད་ནས་འགོག་ཅིག་མ་བྱུང་།
	▽	▽	▽	▽	▽
ཁྱེད་རང་ནམ་ཞི་འདུལ་གྱི་ཚོར་སྣང་	□	□	□	□	□
ཁྱེད་རང་ནུས་ཤུགས་ཞེ་དྲག་ཡོད་པའི་ཚོར་སྣང་	□	□	□	□	□
ཁྱེད་རང་ནམ་སེམས་ཕམ་པ་དང་དམའ་ཕབ་པའི་ཚོར་སྣང་	□	□	□	□	□

②

༢ འདས་པའི་བདུན་ཕྲག་བཞིའི་ནང་གཟུགས་བབ་འཕྲོད་བསྟེན་དང་སེམས་ཚོར་ནང་གི་དཀའ་ངལ་གྱིས
རྐྱེན་པས་སྤྱི་ཚོགས་ལས་དོན་དཔེར་ན་གྲོགས་པོ་ཡང་ན་སྤུན་མཆེད་ཐུག་འཕྲད་སོགས་ལ་འགོག་རྐྱེན་
དུས་ཚོད་རིང་ཡོས་བཟོས་སོང་།

དུས་ཚོད་ག་དུས་ཡིན་ནའང་།	དུས་ཚོད་མང་ཆེ་བ།	དུས་ཚོད་ཁ་ཤས་ལ།	དུས་ཚོད་ཉུང་ཉུང་རེད།	ནམ་ཡང་འགོག་རྐྱེན་མ་བྱུང་།
▽	▽	▽	▽	▽
☐	☐	☐	☐	☐

ཐུགས་རྗེ་ཆེ།

Date ______________

Village Name ________________

Name ______________________

Sex : F M (circle one)

Age ________

Diagnosis: Negative AE CE Mixed (circle one)

If positive, is this the initial diagnosis? Yes No _______ (date)

Has individual ever received treatment for echinococcosis?
No Yes __________________ (circle one)

Curriculum Vitae

Christine M. Budke

EDUCATION

9/02-11/04 – University of Basel, Basel, Switzerland – PhD (Epidemiology)
6/01-9/02 – University College Dublin, Dublin, Ireland – first year of PhD studies
9/97-6/01 – Purdue University School of Veterinary Medicine, West Lafayette, IN- DVM
9/91-6/95 – Colgate University, Hamilton, NY – BA (Biology)
9/87-8/91 – The Wellington School, Columbus, OH

PROFESSIONAL TRAINING

5/01-6/01 – Veterinary externship, Southeastern Cooperative Wildlife Disease Study, Athens, GA
10/00-12/00 – Veterinary preceptorship, The National Aquarium, Baltimore, MD
6/00-7/00 – Statistical analysis training externship, Faculty of Veterinary Medicine, University College Dublin, Dublin, Ireland
5/00-6/00 – Parasitology fieldwork externship, Institute of Zoology, Almaty, Kazakhstan
7/99-7/99 – Parados Game Ranch wildlife veterinary medicine course, Nelspruit, S. Africa
6/99-7/99 – AQUAMED, Louisiana State University, Baton Rouge, LA
6/94-8/94 – Summer internship, The Ohio State University Dept. of Pathology, Columbus, OH

WORK/VOLUNTEER EXPERIENCE

6/01-12/04 – Member of the TRANSECH research project: Collaborative project to evaluate the transmission of *Echinococcus multilocularis* on the Tibetan plateau.

7/95-8/97 – Veterinary assistant/kennel worker: Employed as a veterinary assistant and a kennel worker at a four veterinarian practice. – The Animal Care Center at Sawmill, Columbus, OH.

6/96-8/97 – Volunteer wildlife rehabilitator: The Ohio Wildlife Center, Columbus, OH.

HONORS/AWARDS

1998 – Geraldine R. Dodge Foundation Summer Grant for Veterinary Students, project title: “A situational analysis for the improvement of the management and veterinary medical treatment of water buffalo in the Nile Delta region of Egypt”

PROFESSIONAL AFFILIATIONS/MEMBERSHIPS

American Society of Tropical Medicine and Hygiene- (2004-present)
Royal College of Veterinary Surgeons- (2002-present)
Wildlife Disease Association- (2002-present)
British Society for Parasitology- (2002-present)
Irish Society for Parasitology- (2001-present)
American Veterinary Medical Association- (2001-present)

CONFERENCES ATTENDED

Echinococcosis in Central Asia- oral presentation (Sholpan-Alta, Kyrgystan 2004)
XXIst International Conference of Hydatidology- oral presentation (Nairobi, Kenya 2004)
SGTP/SSMPT/SSTMP joint annual meeting- poster presentation (Basel, Switzerland 2003)
Irish Society for Parasitology Annual Conference (Dublin, Ireland 2002)
Central Veterinary Conference (Kansas City, MO 2002)
British Society for Parasitology Spring Meeting (Salford, UK 2002)
Irish Society for Parasitology Annual Conference (Dublin, Ireland 2001)
American Association of Zoo Veterinarians Annual Conference (Columbus, OH 1999)
American Veterinary Medical Association National Conference (Baltimore, MD 1998)
Marine Mammal Welfare Forum (Chicago, IL 1998)
Geraldine R. Dodge Foundation Summer Grants for Veterinary Students presentations (West Lafayette, IN 1998)

During my studies I have attended lectures and courses by the following lecturers:

E. Adams, N. Alexander, H. Babad, S. Cousens, P. Deplazes, J. Edmunds, A. Ferketich, A. Foss, N. Gay, A. Hall, R. Hayes, A. Hofman, E. Lasaffre, D. Little, A. Mathis, E. Massad, A. Sharma, A. Sutton, M. Tanner, P.R. Torgerson, P. Vickerman, E. Vynnycky, R. White, B. Zaba, J. Zinsstag

Publications

Budke, **C.M.**, Qiu, J., Wang, Q., Torgerson, P.R., in press. Economic effects of echinococcosis on a highly endemic region of the Tibetan plateau. Am. J. Trop. Med. Hyg.

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