Hydatid disease – still a global problem

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Hydatid disease (cystic echinococcosis) remains highly prevalent and a serious cause of human morbidity and mortality in many parts of the world. While there are some regions where the disease has been controlled, most efforts to control transmission of the parasite have had limited success. Recent genetic data indicate that *Echinococcus granulosus*, which was formally thought to be a single species, comprises a number of distinct species. The vast majority of human infections are caused by the most common genotype which is generally transmitted by sheep and goats. Renewed hope for effective control of the parasite's transmission has followed the development of the EG95 vaccine that can be used to reduce infection levels in livestock animals thereby reducing the reliance of control measures on interventions in dogs.

Along with rabbits, foxes and numerous noxious weeds, one of the unintended gifts that Europeans gave to Australia in the early days of the nascent nation was *Echinococcus granulosus*, contained within the organs of imported sheep[1]. The parasite found its new home very much to its liking, not only becoming highly prevalent in sheep but also establishing itself in wildlife populations such that much of the transmission that occurs nowadays in Australia is sylvatic[1,2].

Until recently four species of *Echinococcus* parasite were considered to infect humans. The genetically polymorphic species *E. granulosus* is responsible for the vast majority of human infections; is the only species that is distributed globally and the only species endemic in Australia. *E. granulosus* has a two-host life cycle, with dogs and other canids acting as definitive hosts, harbouring the small tapeworm in the intestine. Parasite eggs are released in the dog's faeces and, should these be eaten by a suitable species of intermediate host, the parasite establishes in the tissues as a larval stage forming a cyst. The life cycle is complete when infected tissues of the intermediate hosts are ingested by a dog and the parasite matures into the sexually reproducing adult tapeworm. Infection in the intermediate hosts has long been known as hydatid disease; the term cystic echinococcosis is now coming into common usage also. Many different herbivorous mammalian species have been described as intermediate hosts for *E. granulosus*, including domesticated sheep, goats, cattle, buffaloes, pigs, camelids, cervids and horses.

Hydatid disease in humans manifests as fluid-filled cysts, most commonly occurring in the liver and lung, but also occasionally occurring in any tissue site including the heart, brain or bone. The symptoms and other medical sequelae of hydatid disease depend on many factors including the number, location and size of the cysts. For a proportion of patients, infection can be treated effectively with benzimidazole drugs; however, for the majority of cases chemotherapy has little or no effect on the parasite. Some cases of infection in the liver can be treated effectively via percutaneous surgical procedures; however, surgical resection remains the mainstay for treatment. One interesting discovery arising from decades of monitoring of asymptomatic hydatid patients in the Rio Negro province of Argentina has been that more than 20% of patients with simple, viable hydatid cysts were observed to have their cysts undergo total involution over a five-year period in which no intervention was undertaken[3]. Watch and wait is now the recommended procedure. The personal cost of hydatid disease for many individual patients is enormous. Frequently patients undergo multiple rounds of surgery. The global burden arising from of *E. granulosus* infections has been

estimated to be in excess of 1–3 million DALYs lost annually and financial losses of $2 billion annually[4]. The infection continues to be highly prevalent in many parts of the world and may be increasing in prevalence in some areas[5].

From the earliest times of scientific study, it was realised that *E. granulosus* showed a high degree of morphological variability and differences in host specificity. Analysis of DNA sequence variability identified a number of genetic types and although there was initially confusion about the validity of some of the genotypes that were described, and their host associations, it is now becoming accepted that there are several different genotypes among what had been referred to as *E. granulosus* and that differences in relation to some of these genotypes warrant delineation as separate species[6]. Genotyping of hydatid cysts from human cases has identified that the genotype most commonly infecting sheep, *E. granulosus sensu strictu,* is responsible for the vast majority of human infections and that the only other genotype to cause a significant number of human cases is *E. canadensis* G6/7, which is transmitted commonly by camels and pigs acting as intermediate hosts.

Recognition that hydatid disease was a major cause of human mortality in Iceland in the 1800s led to a control program being established in 1863 by a Danish veterinarian, Harald Krabbe, based mostly on public education[7]. During the 1950s and 1960s, interest in hydatid disease control was heightened. Informal hydatid control activities became widespread in New Zealand after 1947 leading to a formal government-supported control campaign from 1959. Some 43 years after the initiation of the formal cystic echinococcosis control campaign, New Zealand declared provisional freedom from hydatid disease in September 2002[8]. Encouraged by the control activities in New Zealand, hydatid control was instigated in Tasmania, leading to the declaration of provisional freedom from *E. granulosus* in February 1996[9]. Numerous other hydatid control activities have been initiated in countries or regions of the world, but most have had limited success[10]. Certain peculiarities of the social situation in Iceland contributed to the success of that campaign whereas public education has not been successful elsewhere[11]. The campaigns undertaken in New Zealand and Tasmania were advantaged by having continuous government support, adequate funding, no wildlife reservoir and being undertaken in island situations.

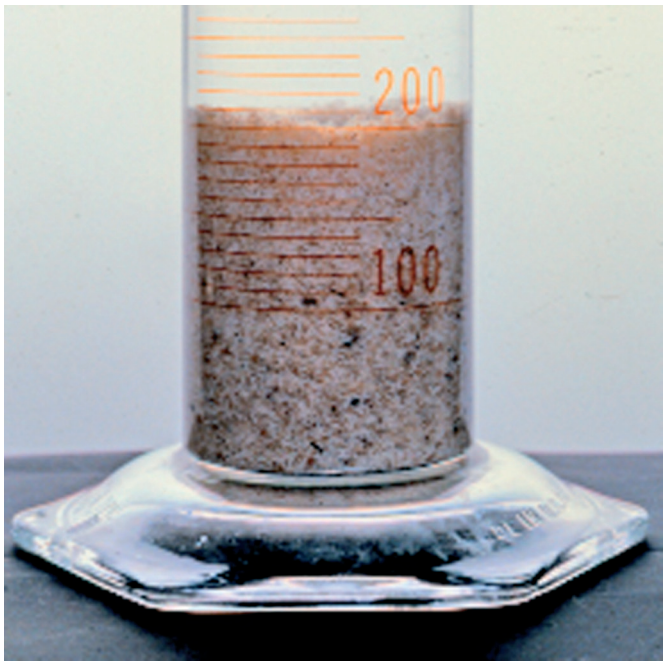

Figure 1. *Echinococcus granulosus* adult worms recovered from the small intestine of a naturally infected dingo from the Kosciuszko National Park. More than 300,000 mature worms were present in this one animal and heavy infections are common in wild dogs and dingoes in eastern Australia. Sylvatic transmission of the parasite on the Australian mainland is likely to hamper chances for elimination of locally acquired hydatid disease from eastern Australia.

The hydatid control programs in New Zealand and Tasmania relied heavily on treatment of dogs to remove *E. granulosus* infections, other dog control initiatives and care not to feed dogs with untreated offal. Dog control has also been effective in a limited number of other places; for example, in the Greek-controlled areas of Cyprus dog control was brought about by euthanasia, mostly by shooting, of 82,984 dogs[12]. In the year 1971 alone, 27,552 dogs were destroyed, equating to 75 dogs every day. However, in many other parts of the world where hydatid disease remains highly prevalent, it is virtually impossible to control dogs. Social and political factors are such that even unowned, semi-wild dogs are protected by the community which will resist strongly either dog euthanasia or even sterilisation. Other factors that have contributed to a limited effectiveness of many attempts to control *E. granulosus* are the long duration required by campaigns that rely on dog control and the need to treat dogs with anthelmintic frequently so that they cannot become infected with gravid worms[11].

There is renewed hope for reducing human cystic echinococcosis following the development of an effective vaccine that can greatly reduce infections in animal intermediate hosts[13,14]. Early data from use of the vaccine against naturally acquired infections indicate that it can be used to reduce disease transmission[15]. Mathematical modelling suggests that application of the vaccine in livestock together with a limited (twice yearly) treatment of dogs with anthelmintic would bring about a high level of control of *E. granulosus* within five to seven years[16]. Efforts

are now under way to undertake carefully controlled studies to gather solid scientific evidence to determine whether this control scenario would be as effective as the model predicts. If it is effective, it would provide a blueprint for renewed control programs and a reduction in the global burden of human cystic echinococcosis.

From an Australian perspective, much of the transmission of *E. granulosus* that now occurs on the continent occurs through the sylvatic cycle involving wild dogs, dingoes and macropod marsupials, mostly in the mountainous areas along the eastern coast[1]. While the EG95 vaccine can protect macropods against *E. granulosus* infection[17] and control of echinococcosis is feasible in wild canids[18], it seems unlikely that the extent of the problem in Australia would lead to wide-scale control activities in wild animals unless specific genera are threatened with extinction due to hydatid disease.

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Biographies

Drs Lightowlers and **Jenkins** began their work on hydatids at the same time and in the same place. Having completed a PhD in immunology at the University of Western Australia and a three-year post-doctoral fellowship at the Institute of Medical and Veterinary Science in Adelaide, Dr Lightowlers joined Mike Rickard's research group at the University of Melbourne, arriving in March 1981. He set about investigating antibody responses to hydatids in sheep and vaccination against *Taenia taeniaeformis* infection in mice. Within a month of Lightowlers' arrival in Melbourne, a new PhD student arrived in the same lab to begin thesis studies on antibody responses to tapeworm infections in dogs. Prior to his arrival in Melbourne, Jenkins had completed an MSc in immunology at the University of London and a stint as research officer on an ADAB (now AusAid) project in Jakarta, Indonesia. The next few years took Lightowlers and Jenkins on numerous hydatid-related field trips, wherein they minimised the cost burden of their activities on their meagre research funds by camping and living off the land. Jenkins went on to work on hydatids in Kenya and later led hydatid control activities in southern NSW and the ACT. His research interests also include dingo biology and hydatid transmission through wildlife. He is currently Senior Research Fellow in the School of Animal and Veterinary Sciences, Charles Sturt University. Dr Lightowlers remained in Melbourne, where he works in the Faculty of Veterinary Science, and concentrated his activities in the area of vaccination. He and his research group are currently involved in field trials of recombinant vaccines for prevention of transmission of both the hydatid parasite and also a related parasite that causes neurocysticercosis. Lightowlers and Jenkins continue their now >30-year collaboration on hydatids, having a number of current projects together related to anthelmintic treatment of hydatid infection in sheep, and vaccination.