Echinococcosis: Control and Prevention

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Abstract

Human cystic echinococcosis (CE) has been eliminated or significantly reduced as a public health problem in several previously highly endemic regions. This has been achieved by the long-term application of prevention and control measures primarily targeted to deworming dogs, health education, meat inspection, and effective surveillance in livestock and human populations. Human CE, however, remains a serious neglected zoonotic disease in many resource-poor pastoral regions. The incidence of human alveolar echinococcosis (AE) has increased in continental Europe and is a major public health problem in parts of Eurasia. Better understanding of wildlife ecology for fox and small mammal hosts has enabled targeted anthelmintic baiting of fox populations and development of spatially explicit models to predict population dynamics for key intermediate host species and human AE risk in endemic landscapes. Challenges that remain for echinococcosis control include effective intervention in resource-poor communities, better availability of surveillance tools, optimal application of livestock vaccination, and management and ecology of dog and wildlife host populations.

1. INTRODUCTION

By the mid 19th century the aetiology of human cystic hydatidosis and colloid 'carcinoma' were recognized to be of helminthic parasitic origin caused by a cestode(s) (see Chapter 1). However, whether both diseases were caused by different forms of *Echinococcus granulosus* or by two separate species was not fully confirmed until the life cycle biology and pathology of *Echinococcus multilocularis* in wild mammals was determined in the 1950s (Rausch and Schiller, 1951; Vogel, 1955). In contrast, the life cycle of *E. granulosus* in domestic mammals was already delineated in 1863 after experimental infection studies by Von Siebold and Naunyn (see Grove, 1990). Furthermore, the public health importance of CE (hydatidosis) in continental Europe and Iceland in the mid 19th century was significant enough for hydatid disease control recommendations to be published in 1854 and 1863 (Grove, 1990). This was followed by an ultimately successful long-term national health education programme against CE in Iceland (1863–90) (Craig and Larrieu, 2006). The earliest control programme for human alveolar echinococcosis (AE) occurred on Reuben Island in northwest Japan from the 1940s when the fox population was deliberately eliminated to eradicate transmission (Ito et al., 2003a). Currently (2016) both Iceland and Reuben Island (Japan) remain free from echinococcosis and still maintain strict controls on dog registrations and/or movement.

Despite several highly successful hydatid control programmes from the 1960s, primarily in regions with relatively well-developed agricultural sectors (e.g., New Zealand, Tasmania, Cyprus, Chile), human CE remains a significant public health problem in the early 21st century over large pastoral areas in South America, North Africa, Eastern Europe, the Middle East, Central Asia, Russia and China (WHO/OIE, 2001; Alvares Rojas et al., 2014). Total numbers of human cases are >>1 million with an associated significant high disease burden (Budke et al., 2006). The highest burden of human CE occurs over a large more or less contiguous transmission zone from North Africa, Near East, Middle East, Central Asia, eastern Russia and western China (Budke et al., 2006; Craig et al., 2007a). Over this endemic zone, however, only a few CE control programmes are currently active (e.g., western China) or planned (e.g., Tunisia) (WHO, 2010a).

At least 18 echinococcosis control programmes to reduce human CE incidence, have been implemented in different world regions since the 1960s, of which 3 were at national level (New Zealand, Cyprus, Uruguay) and the others at provincial level (Table 1). In all of those programmes the key element or control tool initially or eventually applied was the supervised dosing of owned dogs with a praziquantel(PZQ)-based anthelmintic at a frequency of 4–8 times per year (Gemmell et al., 2001; Craig and Larrieu, 2006; Lembo et al., 2013). Five island-based CE control programmes, including Iceland (from 1863), New Zealand, Tasmania, Cyprus and the Falkland Islands (Las Malvinas), were highly successful in eliminating human CE as a public health problem, with all immediately or eventually applying dog-targeted interventions (including culling, purgation and/or anthelmintic treatments) (Gemmell and Roberts, 1998; Economides et al., 1998; Craig and Larrieu, 2006). By contrast several continental-based CE

Table 1 Summary of control programmes for cystic echinococcosis

Program	Period	Option Auth.	Screen	Pre	~10y	~20y	Final status 2015	References
Iceland	1863–1960	2 (Gov)	Humans	22%		No new	Eliminated	Dungal (1957)
New Zealand	(1939 start) 1959–2002	(2) 5 (hon) (MoA)	Humans[a]	4.5	3.2	0.7/0	Elimination declared 2002	Gemmell (1990) and Craig and Larrieu (2006)
			Sheep (%)	48	0.4–15.6	<0.001		
			Dogs (%)	37	<5	<0.002		
Tasmania	1965–96	3 (MoA)	Humans	>90	28 cases	0	Elimination declared 1996 (reemerging?)	Beard et al. (2001) and Jenkins et al. (2014)
			Sheep	52	8.7	<0.002		
			Dogs	12.7	0.8	0.06		
Cyprus	1971–85	4 (MoA)	Humans	12.9	0	8ˆ	Reemerged (ˆN.Cyprus)	Economides and Christofi (2000) and Christofi et al. (2002)
			Sheep	66	0.9	0.014		
			Dogs	6.8	0.02	2.6		
Falkland Is. (Malvinas)	1965–2010	(3) 5 (MoA)	Humans	55		0	Near elimination	Christofi et al. (2002) and Lembo et al. (2013)
			Sheep	59	1.8	0.16		
			Dogs	?	1.7ˆ	<0.01^ (coproag.)		
Sanpete Utah, USA	1971–81	3 (RI) (State)	Humans	3.7		0 new	Near elimination	Loveless et al. (1978) and Andersen et al. (1981)
			Sheep	7.1	2.8	0		
			Dogs	28.3	9.8	0		
Neuquen Argentina	(1970 start) 1995–2004	(3), 5 (MoH)	Humans	22.1		6.2–28	Continued transmission	Larrieu and Zanini (2012) and Larrieu et al. (2004a,b)
			Sheep	76	26.1	2.1		
			Dogs	28	3	1.2		
Rio Negro Argentina	1980–2003	(3),5 (6) (MoH)	Humans	5.6	1.8	0.3	Continued low transmission (ˆ7.8 in <3y old sheep)	Larrieu and Zanini (2012), Larrieu et al. (2000a)
			Sheep	61	2.9	20ˆ		
			Dogs	41.2	18	5.2		

(*Continued*)

Table 1 Summary of control programmes for cystic echinococcosis—cont'd

Program	Period	Option Auth.	Screen	Pre	~10y	~20y	Final status 2015	References
Uruguay	(1965 start)	(3), 5	Humans	12.4	6.5		Continued	Larrieu and Zanini, 2012
	1994–2002	(hon)	Sheep	41	9	7.6	transmission	and Cabrera et al.
		(MoH)	Dogs	10.1	0.7			(2002a,b)
Chile XII	1979–97	5	Humans	80	20		Reemergence	Craig and Larrieu (2006),
		(MoA)	Sheep	60	25	5–7		Larrieu and Zanini
			Dogs	71	5	0.3		(2012), and Vidal et al. (1994)
Rio Grande	1983–2000	5	Humans[b]	1.7			Continued	Larrieu and Zanini (2012)
Brazil		(MoA)	Sheep	26		3	transmission	and Farias et al. (2004)
			Dogs	28.3	9	25		
Powys	1983–89	5	Humans	3.9	2.3	0 < 15y	Reemergence	Palmer et al. (1996) and
Wales			Sheep	23.5	10.5		In dogs	Buishi et al. (2005b)
			Dogs	4–25	0	9		
Turkana	1983–2000	(4), 5	Humans[b]	9	7	3	Continued	Macpherson and Wachira
Kenya		(NGO)	Goats	2–30	2.5[b]	1.8[b]	transmission	(1997), Njeroge et al.
			Dogs	63	27	31ˆ	(ˆcoproag.)	(2000) and Buishi et al. 2006
La Rioja	1987–2000	(4),5	Humans	19	4	2.46	Continued low	Jimenez et al. (2002) and
Spain		(MoH)	Sheep	82.3	20		transmission	Carmena et al. (2008)
			Dogs	7	0.2			
Sardinia	1987–2000	(2), 5	Humans	16	9.8		Continued	Craig and Larrieu, 2006
		(RI)	Sheep	85	87		transmission	and Conchedda et al.
			Dogs	24	25			(2002)
Hutubi	1987–90	5	Humans	43.8			Ongoing	Andersen et al. (1991) and
China		(RI)	Sheep	88.8	5.6	4.7	national prog	Zhang et al. (2009b)
		(MoA)	Dogs	18.5	0			

Datangma China	2000–2005	5, (6) (NGO)	Humans[b]	1–2.6		Ongoing national prog (ˆcoproag.)	Heath et al. (2006)and Yang et al. (2009)
			Yak		38		
			Dogs	50ˆ	17ˆ		
Shiqu China	2006-Current	5 (MoH)	Humans[b]	3.3		Ongoing (ˆcoproag.)	Wang et al. (2008) and Moss et al. (2013)
			Sheep	>50			
			Dogs	8 (21ˆ)			

2, main Option applied (see Table 2 for definitions); *(2)*, previous Option used; *Auth.*, Authority responsible; *hon*, Honorary Commission; *MoH*, Ministry of Health; *MoA*, Ministry of Agriculture; *NGO*, Non Government Organization; *RI*, Research Institute.

[a]Incidence – cases per 100,000.

[b]Ultrasound prevalence %

Modified from Craig, P.S., Larrieu, E., 2006. Control of cystic echinococcosis/hydatidosis: 1863–2002. Adv. Parasitol. 61, 443–508; Larrieu, E., Zanini, F., 2012. Critical analysis of cystic echinococcosis control programs and praziquantel use in South America, 1974–2010. Rev. Panam. Salud Publica 31, 81–87.

control programmes ranged from highly successful (e.g., Region XII, Chile; Rio Negro, Argentina; La Rioja, Spain), eventually successful (e.g., Uruguay) to more limited impact (e.g., Turkana, Kenya; mid-Wales, UK) (Craig and Larrieu, 2006) (Table 1).

Modern control of *E. multilocularis* transmission in wildlife cycles is much more difficult to implement compared to *E.granulosus* in its domestic animal cycles because it requires targeted anthelmintics to the fox population. Distribution of baits containing PZQ in endemic areas can have a significant impact on vulpine prevalence, but logistics, cost and sustainability are difficult to maintain over long periods and over large geographic areas (Hegglin and Deplazes, 2013). Where domestic dogs have an important role in zoonotic risk for human AE, frequent deworming of owned dogs should be implemented for public health reasons (Rausch et al., 1990; Wang et al., 2014).

A critical aspect of echinococcosis control has been the appropriate surveillance of both human CE or AE disease incidence or prevalence, livestock prevalence for CE and canine or vulpine echinococcosis prevalence. Without adequate surveillance data at baseline and at quarterly or annual periods post intervention, the impact of control measures will be difficult or impossible to assess and thus justify ongoing expenditure to maintain costly interventions.

Since the 1970s new tools and approaches have become available to assist in planning and implementation of interventions and surveillance strategies. These include an excellent antiworm drug (PZQ) for dogs and foxes (baits); use of portable ultrasound for human screening (CE and/or AE) within endemic communities; a highly effective vaccine (EG95) to prevent ovine echinococcosis; a laboratory-based test [coproantigen enzyme-linked immunosorbent assays (ELISA)] to replace the arecoline purgation test in dogs and to test fox scats; computer-based modelling of cost-benefit for interventions; and transmission dynamics and predictive modelling for intervention combinations (Torgerson and Heath, 2003; Craig et al., 2007b). The reasons for success in some CE control programmes and variable impacts for others are important issues that have been discussed (e.g., Gemmell, 1990; Craig and Larrieu, 2006) but received only little critical analysis (Larrieu and Zanini, 2012; Lightowlers, 2012).

1.1 Basis for prevention and control

The life cycle biology of all taeniid cestodes, including *Echinococcus* spp., has evolved through predator–prey transmission between carnivore and herbivore mammalian hosts. Though similar in this respect *Echinococcus granulosus senso lato* and *E. multilocularis* differ in utilization of intermediate hosts, i.e., ungulate versus rodent/small mammals respectively. Transmission of *E. granulosus s.l.* is now primarily represented globally by cycles between dogs and domestic livestock, while *E. multilocularis* transmission occurs primarily within wildlife cycles between fox definitive and rodent intermediate hosts. From a control perspective the main target for intervention of both *Echinococcus* species is the definitive host (dogs or foxes) with the aim to reduce or eliminate adult worm burdens. The anticestode drug PZQ provides an excellent cestocidal deworming tool for dogs and foxes but the logistics of regular mass treatment are challenging. Dogs are also an excellent host for *E. multilocularis* and as such may increase zoonotic risk. Targeting intermediate hosts for CE control may be undertaken through classical meat inspection at slaughter but also using an infection preventive vaccine (EG95). There are currently no usable vaccines for definitive hosts. In contrast control measures directed against small mammals would not usually be considered economic or ecologically sound. Treatment of human CE and AE cases may be a public health priority but will not directly affect transmission because humans are almost always 'dead-end' hosts. Health education has the potential to reduce risky behaviour of humans, for example, unhygienic slaughter and dog contact, but education is also probably more important for community acceptance and voluntary participation in long-term hydatid-control programmes.

2. TARGETS, OPTIONS AND TOOLS FOR CONTROL OF *ECHINOCOCCUS GRANULOSUS*

At any one time transmission of *E. granulosus* is dependent on presence of viable parasite stages in dogs or other canids (adult tapeworms), domestic ungulates or wild herbivores (metacestodes) and the environment (eggs). As stated, human infections with the metacestode (CE) do not normally contribute to active transmission (because it requires a dog to ingest hydatid cysts). Removal or reduction in worm biomass in definitive hosts (usually dogs) will have the greatest and quickest effect to reduce active transmission because egg production will decrease rapidly and thus infection pressure to livestock. This will also importantly reduce the direct zoonotic risk from dogs within endemic communities. Targeting livestock to prevent infection (anti-oncosphere vaccination) or to kill hydatid cysts (anthelmintics) could also be effective especially in conjunction with slaughter inspection (liver/lungs condemnation) and husbandry practices that reduce numbers of older sheep (have the greatest viable metacestode burden). Simulation models for combined deworming of dogs and vaccination of sheep indicate improved efficacy (Torgerson and Heath, 2003; Lightowlers, 2012). Community knowledge about the life cycle of *Echinococcus* and risks of infection from dogs should also be beneficial in relation to preventative behavioural changes (e.g., not to feed dogs raw offal). Where hydatid control measures can be integrated with the control of other zoonotic diseases or public health programmes (i.e., 'One Health'' approaches), this is expected to be more efficient and cost-effective (Narrod et al., 2012), although so far there are few examples of this regarding CE (Zinsstag et al., 2006; Rabinowitz et al., 2013).

2.1 Control approaches, options and phases for cystic echinococcosis control

The control measures formulated in the 1860s (Krabbe, 1864) to reduce the transmission of *E. granulosus* between dogs and sheep are still valid today. The four key components were:

- prevent dogs getting access to offal,
- treat dogs with a dewormer,
- meat inspection and offal disposal, no home slaughter,
- health education about hygiene and dog contact.

These control directives were applied nationally in Iceland from 1863, and were supported in the early 20th century by a change in sheep husbandry in Iceland towards marketing fat lambs rather than sheep production for milk and cheese, so that human CE cases significantly reduced within 30 years and transmission was eliminated from Iceland after ∼100 years (Dungal, 1957; Grove, 1990; Craig and Larrieu, 2006). Between the 1950s and 1970s another four island hydatid control programmes were initiated (i.e., New Zealand, Tasmania, Falkland Islands, Cyprus) and were all ultimately highly successful (Gemmell, 1978; Gemmell and Roberts, 1998). They all targeted dogs in vertical programmes to varying degrees, but with some differences. For example, annual arecoline testing of dogs followed by euthanasia (Cyprus) or by enforced quarantine (Tasmania) of positive animals, or the supervised six weekly dosing of dogs with PZQ (New Zealand, Falkland Islands). From the 1980s the use of regular PZQ dosing of dogs was also the key intervention tool in several continental hydatid control programmes in

South America (Argentina, Uruguay, Chile, Brazil), in Europe (Wales, Spain), in East Africa (Kenya), and in Asia (China, Kyrgyzstan).

From these programmes, but especially the Island-based schemes, a list of five 'control options' for CE was considered by Gemmell (1978), then formulated by Gemmell and Lawson (1986) and further extended to include potential livestock vaccination, i.e., an 'Option 6' (Craig and Larrieu, 2006) (Table 2). Option 5 that is based on the regular dosing of owned dogs with PZQ, has been the preferred option, since the drug became readily available in the 1980s to enable a 'fast-track' approach (Gemmell and Roberts, 1998). The challenge for control authorities was and is the existing infrastructure capability, available veterinary-related manpower, effective outreach to access all owned dogs (4–8 times per year) in target rural communities in often remote resource-poor areas, and that the communities are furthermore compliant with the control scheme. The lack of obvious clinical signs of infection with *E. granulosus* in both livestock and dogs, coupled with the relatively low direct economic impact in livestock, means that there is often little priority especially for poor livestock keepers within endemic communities, and also low priority for animal health sectors biased towards more economic problems in livestock (Craig et al., 2007a).

In common with some other neglected zoonotic diseases (NZDs) the complication with CE is that it is foremost a public health problem rather than an animal health problem. Thus consideration for control is a human health priority and although a ministry of health can collect hospital data (i.e., surgical cases per 100,000 year), it relies on cooperation with the veterinary sector (e.g., Ministry of Agriculture) to deliver control measures and also to undertake domestic animal surveillance (WHO, 2010a,b). Intersectoral cooperation that is beneficial is frequently difficult to initiate and sustain (Gemmell, 1978; Marcotty et al., 2013). Hydatid control schemes/programmes have been delivered by a ministry of agriculture (e.g., Tasmania; Region XII, Chile), a department of veterinary services (e.g., Cyprus), a ministry of health (e.g., Rio Negro, Argentina; western China), an honorary commission (e.g., New Zealand; Uruguay), or a nongovernment organization (e.g., Turkana, Kenya). In all cases some degree of cooperation between the veterinary and medical sectors was required to make a decision to initiate planning for hydatid control and to then collect animal and public health surveillance data respectively. Table 3 lists the phases of control that could be considered: planning phase, attack phase, consolidation phase and maintenance of elimination (Gemmell et al., 1986b, 2001; Gemmell and Roberts, 1998).

Table 2 Options considered for control of cystic echinococcosis

Option	Main components	Period required	Examples	References
1	Decision not to proceed	Planning only		Gemmell and Roberts (1998)
2	Horizontal measures, health education, upgrade of abattoirs, changes in husbandry	>50 years	Iceland (from 1863) New Zealand (before 1959)	Dungal (1957) Gemmell (1990)
3	Arecoline testing, quarantine, health education	10–20 years	Tasmania (1965–96) Utah (1971–81) Uruguay (before 1994)	Beard et al. (2001) Andersen et al. (1981) Gemmell et al. (2001)
4	Dog population control and euthanasia arecoline testing	10 years	Cyprus (1971–85)	Gemmell et al. (2001)
5	PZQ dosing dogs (4–8 x p.a), meat inspection, health education	<10 –>20 years	New Zealand (from 1960) Chile XII (1979–97) Rio Negro (1980–2003) La Rioja (1987–2000) Mid-Wales (1983–89)	Economides et al. (1998) Gemmell and Schantz (1997) Larrieu et al. (2000a) Jimenez et al. (2002) Palmer et al. (1996)
6	PZQ dosing dogs (2 x p.a), livestock vaccine, health education	? <10 years	Datangma (2000–05) Rio Negro (2010–15)	Heath et al. (2006) Larrieu et al. (2015)

PZQ, praziquantel; *p.a.*, per annum.
After Gemmell, M.A., Roberts, M.G., Beard, T.C., Campano Diaz, S., Lawson, J.R., Nonnemaker, J.M., 2001. Chapter 6: control of echinococcosis, In: Eckert, J., Gemmell, M.A., Meslin, F.X., Pawlowski, Z.S. (Eds.), WHO/OIE Manual on Echinococcosis in Humans and Animals : A Public Health Problem of Global Concern. WHO/OIE, Paris, France; Craig, P.S., Larrieu, E., 2006. Control of cystic echinococcosis/hydatidosis: 1863–2002. Adv. Parasitol. 61, 443–508.

Table 3 Phases considered for cystic echinococcosis control programmes

Phase	Period/start	Key elements
Planning	1–5 years before start	Decide on Option (1–6) and approach, cost-benefit analysis, burden of human disease, funding sources and expectation for 5–10 years, identify control authority, integrated measures, select intervention region and communities, applied research needs, participatory planning, outreach ability, transport, quality of baseline data (humans, livestock, dogs), surveillance options, registration of households and dogs, stray dog issues, select staff required, training, health education aspects, medical support treatment and follow-up of CE cases, intersector cooperation. May also consider a pilot scheme.
Attack	1–5 years, 5–10 years, >10 years	Intervention/control measures applied, specified dosing frequency (PZQ, arecoline) minimum 2–4 p.a for PZQ, dog population control, setting-specific health education, slaughter inspection and condemnation, use of livestock vaccine, husbandry aspects, age-specific surveillance data for humans and livestock, arecoline or coproantigen testing of dogs.
Consolidation	Year 8–10, or >10 years after start	Attack phase ceased, transfer to surveillance with infected livestock trace-back, application of quarantine on positive properties, possible reintroduction of dog-dosing measures, provision or voluntary purchase of PZQ for dog owners, use of sentinel livestock, possible legislation against home–slaughter and animal movement, incorporation of EG95 into routine vaccine schedules. This phase may need to be permanent.

(*Continued*)

Table 3 Phases considered for cystic echinococcosis control programmes—cont'd

Phase	Period/start	Key elements
Maintenance	20 to >30 years after start	A permanent phase applied when control activities stopped and when elimination is close or been declared, maintain vigilance by meat inspection (identify small lesions) and hospital records (for children), trace-back when required, movement controls (licence or passport) on dogs especially for islands. Definitions used for elimination.

See reviews Gemmell, M.A., Schantz, P.M., 1997. Formulating policies for control of *Echinococcus granulosus*: an overview of planning, implementation and evaluation. In: Andersen, F.L., Ouhelli, H., Kachani, M. (Eds.), Compendium on *Cystic Echinococcosis* in Africa and in Middle Eastern Countries with Special Reference to Morocco. Brigham Young University Print Services, Provo, Utah, USA. pp. 329–345; Gemmell, M.A., Roberts, M.G., Beard, T.C., Campano Diaz, S., Lawson, J.R., Nonnemaker, J.M., 2001. Chapter 6: control of echinococcosis, In: Eckert, J., Gemmell, M.A., Meslin, F.X., Pawlowski, Z.S. (Eds.), WHO/OIE Manual on Echinococcosis in Humans and Animals : A Public Health Problem of Global Concern. WHO/OIE, Paris, France; Lembo, T., Craig, P.S., Miles, M.A., Hampson, K.R., Meslin, F.X., 2013. Zoonoses prevention, control, and elimination in dogs, In: Macpherson, C.N.L., Meslin, F.X., Wandeler, A.I. (Eds.), Dogs, Zoonoses and Public Health. CABI, Wallingford, UK, pp. 205–258.

2.1.1 Definitions of control

To establish whether a reduction in pathogen transmission has been achieved as a result of a purposeful control campaign, the concepts of 'control', 'elimination' and 'eradication' require consideration (Gemmell, 1986; Molyneux, 2006).

For echinococcosis, the elimination of human CE disease is the ultimate goal, i.e., no human cases in a defined geographic region. However, because CE patients may have a long asymptomatic period, cases will continue to appear in older age groups (e.g., >40-years-old) long after elimination has been declared. This was the situation in Iceland, New Zealand and Tasmania, wherein CE cases in older age groups continued to occur some years after elimination was considered to have occurred (Craig and Larrieu, 2006; Moro and Schantz, 2006a,b; O'Hern and Cooley, 2013). Elimination of infection or transmission, as opposed to disease in humans, is more difficult because it requires that there is no infection in domestic animals (dogs and livestock) and possibly wildlife hosts, however, that may be the ultimate aim of an echinococcosis control programme. For example, provisional elimination of *E. granulosus* transmission was declared in Tasmania in 1996, a total of 32 years after the start of a hydatid control programme

(Jenkins, 2005), and in 2002 in New Zealand 43 years after implementation of a vertical control programme (Pharo, 2002). However, in Tasmania infection in cattle and dogs was detected after 2006, suggesting some transmission of *E. granulosus* between dogs and cattle and/or possibly also involving hunting dogs and wild herbivores (Jenkins et al., 2014). No new human CE cases have been reported in Iceland since the 1960s nor on the Falkland Islands (Malvinas) since 1992 after the start of control programmes respectively in 1863 and 1977 (Lembo et al., 2013).

Pathogen eradication has been defined as the worldwide reduction to zero cases, for example, as in the case of smallpox or the potential near-future eradication of human dracunculiasis (Molyneux, 2006). For zoonotic diseases, such as echinococcosis, with animal host reservoirs this would be virtually impossible to achieve unless within restricted geographic areas such as islands. For most echinococcosis control programmes in continental regions, successful 'control' will usually be considered to be a significant reduction in the incidence, prevalence and morbidity of human CE to some low level. In other words, to eliminate CE as a public health problem, or effectively converting a region of high CE endemic status to one of sporadic CE disease status, and possibly eventual elimination altogether of human disease was achieved in New Zealand and the Falkland Islands.

Following an 'attack' phase characterized, for example, by 5–10 years of regular dosing of owned dogs, and improved husbandry and slaughter practices, as well as health education, the conversion of a hydatid programme to a 'consolidation' phase characterized by surveillance and trace back, can occur when an acceptable level of transmission reduction has occurred (Heath et al., 2006). This could be when there are no new human CE cases under 10–15 years of age (hospital records or ultrasound screening data), when ovine CE prevalence is <0.1% in sheep less than 3-year-old (abattoir records) and when prevalence of canine echinococcosis is < 0.01% (arecoline or coproantigen data) (WHO, 2011).

2.2 Targetting dogs for control of *Echinococcus granulosus*

Since the domestic dog was identified as the main definitive host of *E. granulosus* by the early 1860s, it became clear that reduction/elimination of dog populations and/or more acceptably treating dogs with a dewormer or anthelmintic, could break the life cycle of the parasite and reduce human exposure (Gemmell, 1990; Grove, 1990). The three main approaches involving targeting dogs have been: (1) use of arecoline salts to purge dogs; (2) use of PZQ as an anthelmintic; (3) dog population management.

2.2.1 Arecoline purgation

In 1890 Iceland passed a nationwide law to control dogs by taxation and to enforce treatment with a dewormer. Initially an extract of kamala fruit (*Mallotus philippinensis*) was used as a dewormer but was quickly replaced by a more effective purgative based on extracts of areca nut (*Areca catechu*). A synthetic derivative arecoline hydrobromide (from 1924) was used in dogs at 2–5 mg/kg as a single dose (or with a second follow-up dose), to paralyze tapeworms (*Echinococcus, Taenia* spp and other cestode genera) and to dislodge them through involuntary intestinal smooth muscle contractions by acting on the host parasympathetic nervous system. This resulted in purgation of contents of the intestinal tract including any helminth parasites (Gemmell, 1973; Craig, 1997; WHO/OIE, 2001). Arecoline is not helminthicidal and therefore purged worms are still alive, as will be any tapeworms that still remain attached to the small intestine. Thus a purged dog could still have a small biomass of viable *Echinococcus* worms. However, the potential diagnostic application of arecoline purgation (arecoline testing) was clear and in that regard it has been used successfully as a surveillance tool in several hydatid control programmes from the 1960s and 1990s (see Section 3.2).

Arecoline purgation was employed as both a crude dewormer and a diagnostic test in a number of early hydatid control programmes including: Iceland (from 1890), New Zealand (from 1938), Tasmania (from 1964), Uruguay (from 1965), Neuquen (from 1970) and Cyprus (from 1971) (Gemmell, 1978; Craig and Larrieu, 2006). The two great advantages of arecoline purgation were firstly its 'on-site' educational value to enable dog owners to observe whether their dogs were infected with tapeworms (especially the common large *Taenia* spp), and secondly that purgation should be 100% specific for *E. granulosus s.l.* (i.e., where *E. multilocularis* is not coendemic). However, the logistics of mass arecoline purgation of owned dog populations is very demanding and requires good organization, rural population compliance, timed notice of treatment schedules, trained manpower, purge inspection/analysis ability and biohazard containment in the field (Cabrera et al., 2002b). The sensitivity of single dose arecoline for eliminating *E. granulosus* from infected dogs ranges from 40 to 75% (usually within 30–120 min in dogs starved for 12 h) and therefore a number of dogs will not purge properly or fail to purge. In addition, owner compliance may not be guaranteed because of distressed animals. Since the late 1970s the anthelmintic drug PZQ has been the drug of choice to deworm dogs in *Echinococcus* control programmes (see later). However, arecoline purgation remains a useful surveillance test for canine echinococcosis when other diagnostic tests are not available and when epidemiological data are required that include mean worm burdens (Ziadinov et al., 2008; Craig et al., 2015).

2.2.2 Praziquantel dosing

The discovery of PZQ in 1972 (by the companies Merck and Bayer) was probably the most important advance for control of echinococcosis since the determination of the life cycle of *E. granulosus* more than 100 years earlier. PZQ (isoquinolone-pyrazine) was found to be highly effective against trematodes and cestodes, including *Echinococcus* and *Taenia* spp.at a dose range of 2–5 mg/kg (Gemmell and Johnstone, 1981). The first use of PZQ for mass treatment of canine echinococcosis began in the late 1970s as six to eight weekly dosing campaigns in the New Zealand Hydatid Control Programme and for hydatid disease control in the Falkland Islands and from the early 1980s in southern Chile (Region XII) and Argentina (Rio Negro) (Craig and Larrieu, 2006). Other successful applications of PZQ dosing of dogs for control of hydatidosis were reported in northern Spain (La Rioja) from 1987 (dosing frequency 6 weekly then 16 weekly from 1993) (Jimenez et al., 2002) and in Uruguay from 1992 again with a target of 6 weekly dosing frequency (Cabrera et al., 1996). From 2006 PZQ manufactured in China was used for an ambitious monthly dosing programme for canine echinococcosis to control transmission in northwest Sichuan Province, then control was expanded in 2010 to include six other provincial regions of western China (WHO, 2011). Application of regular supervised PZQ dosing for hydatid control in remote-settled communities (Larrieu and Zanini, 2012) and in nomadic or semi-nomadic pastoral communities is probably the most challenging (Macpherson and Wachira, 1997; Heath et al., 2006; Huang et al., 2008; Lembo et al., 2013).

PZQ is normally given to dogs orally in tablet form at a dose of 5 mg/kg, though lower doses have been used, as have biscuit (Chi, 1993) and injectable formulations. Its efficacy is >99% against *E. granulosus s.l.* and also for *E. multilocularis* but has no residual effect and is not ovicidal. Treated dogs should ideally be restrained before and after dosing, and as a precaution against environmental contamination any voided faecal matter must be buried or burnt.

The selected frequency for dosing dogs with PZQ is an important aspect of echinococcosis control programmes from perspectives of transmission potential, natural reinfection rates and the logistics, sustainability and cost of application. The prepatent period of *E. granulosus* sensu stricto in dogs (i.e., time from ingestion of protoscoleces in hydatid cysts to egg production by adult worms) is between 42 and 45 days. Thus a six weekly (42 days) dosing frequency would be expected to prevent egg output if all dogs were successfully treated. In reality maintaining a supervised six weekly PZQ dosing programme for >90% of owned dogs in a given region is extremely demanding and costly and especially for resource-poor remote rural areas. Furthermore, dosing all dogs eight times per year may not always be feasible or affordable over the lengthy time periods (5–10 years) required to have a significant impact on transmission. This aspect is one reason why successful long-term hydatid control programmes have tended to be initiated in the richer and better developed agricultural sectors, for example, as occurred in New Zealand, Spain, Argentina and Chile.

Reduction of a PZQ dosing frequency to less than eight times per year has been considered and applied, for example, in the consolidation phase of hydatid control in Chile where prevalence of echinococcosis in dogs and sheep had dropped significantly (Vidal et al., 1994; Gemmell and Schantz, 1997). A lower frequency of dosing may also be selected for other nonscientific reasons, e.g., because of lack of veterinary technicians, difficult outreach, seasonal restrictions, lack of funding and/or change of public health priorities (Craig and Larrieu, 2006). In the western China Echinococcosis Control Programme (from 2006–7) the intended targeted dog-dosing frequency was monthly, however, this is very difficult to achieve especially in scattered semi-nomadic remote communities (e.g., Tibetans, Mongolians, Kazakhs). An independent evaluation of canine echinococcosis was undertaken in northwest China in an area of a control zone that covered Hobukesar Mongol Autonomous County in northwest Xinjiang, and was subject to monthly dosing (van Kesteren et al., 2015). These authors, however, found that 36.8% of dog owners had never dosed their dogs and only 22% of dogs were reportedly dosed within the six week period prior to dog testing by coproantigen ELISA.

Optimization of a PZQ-based dosing programme for canine echinococcosis could also be informed by exposure data about the natural reinfection rate of owned dogs in the target intervention zone (Larrieu and Zanini, 2012; Lembo et al., 2013). Such data, however, are difficult to collect and ideally should be determined in the planning phase of hydatid control (Gemmell et al., 2001). Nevertheless dog reinfection data have been examined for cohorts of owned dogs that were followed up in several endemic regions where hydatid control was already in place, for example, in Rio Negro, Argentina (Larrieu et al., 2000a) and Shiqu county, China (Moss et al., 2013). Reinfection studies were also undertaken prior to a planned change of intervention in Uruguay from arecoline purgation to emphasis on PZQ dosing (Cabrera et al., 1996). In those studies dog cohorts (>300 dogs per cohort, prevalences at baseline 13.2–42%) were tested using arecoline purge or coproantigen ELISA then treated once with PZQ and followed up at 2, 3–4 and 8–9 months posttreatment (Lembo et al., 2013). Canine echinococcosis prevalences had returned to an equivalent of 50–100% of pretreatment levels by 8–9 months later, and by 11–41% as a proportion of baseline levels after 3–4 months posttreatment when actual prevalences ranged from 2.2% to 6.7% (Table 4). These three different natural reinfection studies suggest that a minimum dog-dosing frequency for PZQ should be every three months, i.e., four times per year, which has also been recommended by WHO (WHO/OIE, 2001; WHO, 2011).

Computer-based models of *E. granulosus* transmission dynamics, though theoretical, can be informative for consideration of minimum dog-dosing frequencies, especially when multiple interventions are applied, for example, the inclusion of the EG95 vaccine for ovine echinococcosis (Torgerson and Heath, 2003; Huang et al., 2011).

2.2.3 Dog population management

The domestic dog is the most important definitive host for *E. granulosus s.s.* and dog ownership and contact are key risk factors for human CE in rural endemic areas (Otero-Abad and Torgerson, 2013; Wang et al., 2014; Craig et al., 2015). Presence of free-roaming owned, community-owned and/or stray dogs in urban or periurban areas may also be a risk factor for human

Table 4 Reinfection studies in dogs from natural exposure to *E.granulosus* after a single PZQ dose

Region	N dogs	Prev. % Day 0	2 months	3–4 months	8–9 months	References
Rio Negro (Argentina)	476	42[a]	3.5	6.7	21.3	Larrieu et al. (2000b)
Florida (Uruguay)	303	13.2[a]	0	5.4	18.6	Cabrera et al. (1996)
Shiqu (China)	329	19.5[b]	9.3	2.2	14.1	Moss et al. (2013)

[a]Arecoline test.
[b]coproELISA.

CE. For example, as was observed for community-owned dogs in central Kathmandu, Nepal (Baronet et al., 1994), or for abattoir dogs in Lima, Peru (Reyes et al., 2012). Therefore managing dog populations to reduce their numbers could in theory help to reduce transmission, especially in conjunction with other measures such as dosing dogs and stricter livestock slaughter practices. Culling dog numbers was recommended in Iceland by Krabbe in the 1860s but not generally accepted, rather in Iceland a law was passed in 1890 to keep dogs outside city boundaries and to treat them with areca extract (Grove, 1990). By contrast, in Cyprus in the early 1970s arecoline purge positive dogs and free-roaming dogs were euthanized by the government veterinary services as part of a hydatid control programme that was highly effective (Economides et al., 1998). Unwanted dogs were also culled as part of a control scheme in Hutubi county northwest China (Zhang et al., 2009b). In the La Rioja hydatid control programme in Spain, stray and uncontrolled dogs were impounded then euthanized, and a sample of animals necropsied annually to provide surveillance prevalence data on canine echinococcosis (Jimenez et al., 2002).

There are, however, significant problems of ethics and logistics as well as availability of humane means to reduce numbers of unwanted dogs (Kachani and Heath, 2014). One feature of most rural endemic areas is that local veterinary, agricultural or municipal authorities do not know the size of owned or stray domestic dog populations because they are not livestock in the economic sense and thus of low priority (Craig et al., 2007a). In the planning phase prior to implementing hydatid control measures, the owned dog population needs to be enumerated and animals registered by household or family group. In addition the size and location of stray dog populations should be determined. One difficulty is that so-called 'stray' populations may include unowned (free-roaming) dogs, but also free-roaming dogs that are family-owned or community-owned (Baronet et al., 1994; Kachani and Heath, 2014; Wang et al., 2014). Failure to adequately include stray dogs in an echinococcosis control campaign may cause problems of intervention efficacy and even premature termination or failure (Conchedda et al., 2002; Jimenez et al., 2002). The average number of owned dogs per household varies in pastoral regions as does the average owned dog turnover rate. In pastoral communities of northwest Sichuan Province and Xinjiang (China), the mean number of dogs per family was 0.86–1.34 (Wang et al., 2006a; Zhang et al., 2009b); 1.8 per household in Morocco (Ouhelli et al., 1997) and 2.2 dogs per household in Limari Province, Chile (Acosta-Jammet et al., 2014).

Attempts to reduce dog populations by culling may not always have a significant impact on dog population densities (WHO, 2011) especially where a canid vaccine is available for other diseases, e.g., rabies and distemper viruses (Lembo et al., 2013). There is no vaccine for canine echinococcosis reinforcing a view that culling dog populations has a role in hydatid control. If dog culling is to be considered in relation to hydatid control there should be general community approval and participatory planning, also cooperation between veterinary and municipality sectors. The latter sector often already has responsibility for culling stray dogs and may respond after public concern, for example, in relation to dog-bites. Culling measures that may be acceptable include barbiturate/anaesthetic overdose, gassing, free bullet or captive-bolt (Kachani and Heath, 2014). Where possible and affordable nonlethal measures should also be considered and these include fertility control by spaying or castration (Macpherson and Wachira, 1997; Economides et al., 2002; Larrieu and Zanini, 2012) or immunocontraception (van Johanssen and Penrith, 2009; Lembo et al., 2013). As mentioned, impounding stray dogs may have public appeal but often is not feasible or affordable especially in resource-poor areas. Dosing stray dog populations with PZQ directly (costly) or in baits (sustainable?) may be factored into a control programme, but will be more difficult and expensive to include. For example, in Tibetan communities in Shiqu county (Sichuan, China) 2500 owned dogs were registered versus an estimated 4400 nonregistered unowned 'community' dogs (Budke et al., 2005b).

2.2.4 Vaccination of definitive hosts of Echinococcus granulosus

Pet and shepherd dogs play a major role in transmission of *E. granulosus* to humans. Dogs are few in number compared to the number of intermediate hosts, and they are often relatively easy to secure to have them vaccinated.

Ample evidence exists for the existence of protective immune responses against hymenolepid cestodes (reviewed by Ito and Smyth, 1987). Adult *E. granulosus* are certainly immunogenic in their hosts (Jenkins and Rickard, 1986), but there is little evidence to support the existence of immunologically mediated protective immune responses against the adult tapeworm. What evidence does exist that indicates the degree of immunity acquired following an initial infection is inconsistent and incomplete, if it exists at all (reviewed by Lightowlers, 1990). In a series of trials undertaken by Gemmell et al. (1986a), 16 dogs were given 8 or 9 repeated rounds of *E. granulosus* infection and treatment, and the number, size and fecundity of the worms developing after each infection were assessed. The results were very variable both among dogs as well as for individual dogs. Five of the animals appeared to show no diminution in the number or development of tapeworms over the course of the repeated infections. None of the dogs developed a clear level of immunity to the establishment of infection, however, some animals showed a decline in the size and fecundity of worms developing as the number of repeated infections increased. Gemmell et al. interpreted their data to predict that most animals would become resistant by the 12th challenge infection, although this has never been actually demonstrated. One remarkable aspect of the work published by Gemmell et al. is that, while Michael Gemmell had extensive experience working with *E. granulosus* in dogs, possibly more experience than any other person before or since, the variability of the 'takes' of infection between different animals given the same batch of protoscolesces was extraordinarily high. This highlights one of the particular difficulties working with experimental infections in dogs with *E. granulosus* and emphasizes a special need for caution when interpreting the results of challenge infections in dogs because of the high level of variability in the course of infections even in naive animals.

Attempts to induce protection against *E. granulosus* by vaccination with nonliving antigen preparations have seen inconsistent results. Turner et al. (1936) were able to induce partial resistance to *E. granulosus* infection in dogs following immunizations with antigens derived from hydatid cysts. Gemmell (1962) found that worms developing in dogs vaccinated with freeze-dried preparations of either adult tapeworm tissue or scolices were almost always less developed than were the worms in unvaccinated dogs. Herd et al. (1975) described the results of a trial involving two groups of dogs; one group of six animals was vaccinated with antigens secreted in in vitro culture by 33–39 day old *E. granulosus* tapeworms that were maintained in culture for 6–10 days. Five control animals received immunizations with adjuvant alone. The number of worms establishing following a challenge infection was not significantly affected, however, there was a decrease in the proportion of mature worms containing eggs in the vaccinated animals compared with the controls. Vaccination appeared to have caused an arrested, or delayed, development of the worms. A follow-up experiment involving two groups of 10 dogs was unable to repeat the same vaccine-associated effect, with several of the control animals showing what appeared to be the same type of arrested/delayed development (Herd, 1977). These data serve to further emphasize the need for caution in interpretation of data from *E. granulosus* challenge trials undertaken in dogs. Gemmell et al. (1986a) also observed retarded growth of the whole worm population in some previously naive dogs following an experimental infection with *E. granulosus*.

Zhang et al. (2006) described an antifecundity effect in dogs vaccinated with recombinant antigens. In two experiments, they observed a very high level of protection (97–100%) in terms of suppression of worm growth and, especially, of egg development and embryogenesis. The potential significance of their finding as a potential new tool for control of CE was subsequently highlighted in a review publication (Zhang and McManus, 2008).

E. granulosus worms develop in a relatively synchronous manner following an experimental infection and after shedding a gravid proglottid, appear immature while a new gravid proglottid develops over a period of about 10 days (Heath and Lawrence, 1991). Studies that have described an antifecundity effect in vaccinated dogs have not considered that the effect could potentially have been the result of precocious development stimulated in the vaccinated animals, rather than retarded development. None of the investigations discussed above that described antifecundity effects included data on the examination the dogs' faeces prior to necropsy. Had this been undertaken, it would have indicated or excluded precocious development of worms. There is also no information to indicate whether worms that appeared to be developing relatively slow would progress over subsequent days into fully gravid worms. This information would be vital to the interpretation of any antifecundity effect of vaccination as having a potential use in controlling *E. granulosus* transmission, especially since most studies have failed to detect any effect of vaccination on the numbers of worms establishing.

Petavy et al. (2008) described the use of *Salmonella* vaccine vectors expressing two different proteins of *E. granulosus* and the use of these live, attenuated organisms to immunize dogs against a subsequent challenge infection with the parasite. The paper described a reduced number of *E. granulosus* worms developing in the vaccinated animals. Due to the small sample size used by Petavy et al., there is some controversy as to whether the modest effects that were claimed were statistically significant (Torgerson, 2008). There have been no follow-up publications on this vaccine since the initial publication.

The most impressive results that have been obtained in vaccination against *E. granulosus* infection in dogs were those described by Zhang et al. (2006) in which vaccinated dogs were found to have almost no mature worms at all, while control animals were all infected with large numbers of mature worms. It is now a decade since these data were presented and no follow-up data have been fully published. Conference proceedings presented by Dr Zhang et al. have indicated that they have been unable to replicate the statistically significant effects previously attributed to the recombinant antigens and, indeed, saw the same comprehensive antifecundity effect in a control group of dogs vaccinated with adjuvant alone (Zhang et al., 2009a).

In conclusion, there appears to be little cause for optimism for the development of an effective vaccine for dogs, with most studies beset by the occurrence of unreliable, nonspecific and unrepeatable effects.

2.3 Targetting livestock for cystic echinococcosis control

2.3.1 Slaughter inspection

Ideally, all agricultural animals that are potential intermediate hosts for *E. granulosus* should be inspected at slaughter. Organs containing hydatid cysts should be removed, condemned and destroyed in a manner that prevents consumption by dogs. Preferably it should be a legal requirement that all livestock should be slaughtered in an abattoir under veterinary control.

A major problem in highly endemic areas of echinococcosis is the clandestine slaughter of livestock resulting in offal being available for consumption by dogs. In many low-income countries where there is livestock pastoralism, organized slaughter facilities may be inadequate or nonexistent with little or no veterinary supervision of slaughter. This combined with lack of knowledge by livestock owners promotes conditions for transmission to dogs. This is well-illustrated in countries of the former Soviet Union where organized slaughter facilities were abandoned when livestock farms were privatized. This resulted in a substantial epidemic of CE across central Asia, the Caucasus and parts of eastern Europe (Torgerson, 2013).

In many upper income countries the incidence of cestode zoonoses has declined with the development of hygienic supervised slaughter facilities. For example, EU Regulation (EC) No 853/2004 (EUR-Lex - f84002 - EN - EUR-Lex, n.d.) laying down specific hygiene rules for food of animal origin states that in most cases meat for human consumption must be from animals slaughtered in an approved slaughterhouse where there is veterinary supervised postmortem inspection. However, such strict regulations are no guarantee that transmission of echinococcosis will be prevented. Italy, for example, has one of the highest incidences of human CE in the European

Union with over 1000 cases treated surgically each year (Brundu et al., 2014). This indicates that there must be infected offal that remains available to dogs despite these regulations being in place. In contrast in Tunisia 80% of butcher's shops slaughter animals and sell the resultant meat and only 13% of butchers had any understanding of the transmission of echinococcosis. Dogs were seen close to 52% of these butcher's shops (Besbes et al., 2003). This well illustrates that illegal slaughtering has an important impact on the transmission of CE. Access to slaughtered animals by dogs is demonstrated by a study from Uganda. Dogs with access to slaughter facilities had a higher prevalence of *E. granulosus* infection. However, if meat inspection was practised at the slaughter facility there was a lower prevalence of infection in the local dog population compared to where there was no meat inspection (Oba et al., 2016).

Also of importance is natural mortality of livestock and the resulting carcasses being available for consumption by dogs. For example, in some areas of the Tibetan plateau there may be a 20% mortality of yaks in the spring. Following recovery of the skin, the dead yaks are discarded and subsequently scavenged by dogs and other carnivores (Hu et al., 2013). This is likely to be a major contributing factor to the transmission of CE in Tibetan communities.

2.3.2 Vaccination of livestock intermediate hosts

Theoretically at least, it would be possible to consider vaccination of humans living in endemic areas for the prevention of CE. However, there is relatively little transmission of *E. granulosus* in the developed world, with the most highly endemic areas being in developing countries. For this reason there is a lack of commercial incentive for the development of a human vaccine and the investment of many hundreds of million dollars that are required to produce, trial and license a new human vaccine. Vaccination of animals to break the parasite's life cycle offers a more practical alternative. Domestic dogs and livestock animals both offer potentially valuable targets for vaccination against *E. granulosus*.

In contrast to the definitive hosts of taeniid cestode parasites, there is ample evidence about the existence of immunologically mediated immunity against infection in the parasites' intermediate hosts, including for *E. granulosus* (Rickard and Williams, 1982). Protective antigens have been identified, produced using recombinant techniques and developed into highly effective vaccines for several species of *Taenia* and for *E. granulosus* (Lightowlers, 2006).

Sheep infected with *E. granulosus* show a resistance to reinfection and there is cross-immunity between the different cestode species infecting sheep (Gemmell, 1966; Heath et al., 1979). Heath et al. (1981) discovered that sheep could be protected against an experimental challenge infection with *E. granulosus* by previous injection of *E. granulosus* oncospheres, or by vaccination with the products of oncospheres secreted in in vitro culture (Osborn and Heath, 1982). The protective oncosphere components were identified (Heath and Lawrence, 1996) and one protective antigen, designated EG95, was cloned from oncosphere mRNA by Lightowlers et al. (1996). The vaccine has proven to be reliable and effective in experimental trials carried out in New Zealand, Australia, China, Argentina, Chile, Romania and Iran (Lightowlers et al., 1999; Heath et al., 2003; Lightowlers, 2006, 2012).

Larrieu et al. (2013, 2015) undertook a field trial of the vaccine in a remote region of Rio Negro Province of Argentina. Despite the difficulties of working in the region and a large proportion of the animals not receiving their full vaccination compliment, a significant reduction in *E. granulosus* infection was observed in 5-year-old animals vaccinated initially as lambs. To minimize the number of interventions required to be undertaken in the animals, lambs were vaccinated with two injections approximately one month apart and a single subsequent booster injection was given when the animals were approximately 1 year of age. This regime appears to have been sufficient to induce protection lasting until the animals were assessed for infection, at 5 years of age (Larrieu et al., 2015).

Mathematical modelling of various *E. granulosus* control options (Torgerson and Heath, 2003) suggests that a combination of vaccination with EG95 together with 6-monthly treatment of dogs with PZQ would provide an effective strategy for achieving a rapid and high level of control of CE transmission.

The EG95 vaccine has been registered for use in China for some years, although there has been no full publication of data relating to the use or effectiveness of the vaccine manufactured in China. The EG95 vaccine is also registered for use in Argentina. To this time the only published descriptions of the use of EG95 in Argentina have involved vaccine provision at no cost and produced at the University of Melbourne. The Argentine company Tecnovax has recently supplied commercially-produced EG95 vaccine to CE control projects being undertaken in sheep in Chile, however, the high price that was charged for the vaccine (US$ 1.8–1.9 per dose) raises concern. Most countries in which CE is highly endemic are poor countries and often it is the poorer livestock keepers in these countries that are associated with the highest levels of CE transmission. In order to maximize the potential for EG95 to reduce CE transmission in such circumstances, the vaccine must be made available at a minimum cost. Ideally, it could be incorporated in other, commercially important vaccines such as clostridial vaccines, at little or no additional cost to the livestock owner.

2.3.3 Hydatid anthelmintics for livestock

Benzimidazole-based chemotherapy used frequently for medical treatment of CE in humans involves patients taking the drug on a daily basis over extended periods (Brunetti and Junghanss, 2009). Such treatments are not suitable for routine treatment of CE in livestock animals. If a practical and effective drug treatment could be developed for livestock animals that involved a single treatment, or a small number of anthelmintic treatments, which rendered CE cysts either non-viable or at least, non-fertile, this would provide a significant advance for the control of CE transmission.

Several studies have investigated the effects of various anthelmintic treatments on hydatid cysts in naturally infected animals (Heath and Lawrence, 1978; Gemmell et al., 1981; Schantz et al., 1982; Morris et al., 1985, 1990; Blanton et al., 1998). The primary emphasis of many of these studies was to use hydatid disease in sheep (and goats in one study) as models for testing chemotherapy regimens that could be suitable for use in humans. Many studies found that chemotherapy regimens in which animals received drug doses at daily or weekly intervals over an extended period did achieve the death of cysts, however, this is of limited significance in relation to the control of CE transmission. Heath and Lawrence (1978) and Gemmell et al. (1981) investigated the use of mebendazole or PZQ specifically for the purpose of treating infections in sheep and included either single treatments or relatively short treatment regimes. However, neither was able to demonstrate any adverse effect on cysts.

Several, more recent attempts to treat CE cysts in sheep have met with partial success (Dueger et al., 1999; Mitrea et al., 2007; Gavidia et al., 2009, 2010), although all have involved multiple treatments of the animals at weekly or more frequent intervals. The most effective treatment identified to date, daily dosing at 30 mg of oxfendazole per kg, was found to be unacceptably toxic, resulting in a 24% death rate for treated sheep (Dueger et al., 1999). At this time there is no effective, practical method available for chemotherapy of CE in livestock animals that could be implemented as part of a CE control programme.

2.3.4 Livestock management

It is well established that in endemic areas of echinococcosis, the prevalence and abundance of hydatid cysts increase with the age of the livestock. This has been shown for a number of species including sheep and goats (Gemmell, 1990; Ming et al., 1992; Cabrera et al., 1995; Torgerson et al., 1998), cattle (Torgerson et al., 2003a,b; Lahmar et al., 2013), camels (Lahmar et al., 2013, 2004) and donkeys (Mukbel et al., 2000; Lahmar et al., 2014). In addition the cyst size and fertility increase with the age of animal (Torgerson et al., 2009). This means that most of the infective parasite biomass is in the oldest animals in the population and it is these animals that pose the greatest risk of infection to dogs. This is a particular issue if meat is not the primary product as animals specifically bred for meat production are often slaughtered young. In Tibetan communities there is a religious prohibition to killing animals and most stock are kept for wool or milk and thus some animals reach considerable longevity before dying of natural causes. In India cattle and buffalo appear to have the highest prevalence of echinococcosis amongst domestic animals (Pednekar et al., 2009) and are kept for dairy as beef is not eaten mainly by the Hindu communities. In Uttar Pradesh buffaloes have been reported to have a prevalence of 36% with a cyst fertility rate of 15% compared to a prevalence in 2% sheep and goats with a fertility rate of just 2% (Irshadullah et al., 1989). India has a high burden of CE, possibly second only to China (Torgerson et al., 2015).

This age-related abundance of infection could potentially be exploited. In a study in Kyrgyzstan, it was shown that old sheep (≥4 years) had 80% of the protoscoleces but represented just 28% of sheep presenting for slaughter (Torgerson et al., 2009). These observations on the dynamics of the infective biomass in intermediates hosts suggest that management of the livestock population by removing old animals (such as through culling) would lead to a massive and rapid reduction in the infection pressure to dogs and could be a powerful tool to control CE. This has not yet been attempted in practise.

2.4 Modelling transmission of *Echinococcus granulosus*

2.4.1 Transmission dynamics

Mathematical models of the life cycle were first developed by Roberts and co workers and by Harris and co workers in the 1980s (Harris et al., 1980; Roberts et al., 1986). The model developed by Roberts et al. has now been applied and developed further in various definitive and intermediate host populations (Gemmell, 1990; Ming et al., 1992; Cabrera et al., 1995; Torgerson et al., 1998, 2003a,b; Torgerson and Heath, 2003; Torgerson, 2006a). This model has both quantitative and qualitative forms and models the changes in parasite abundance and prevalence with age in either intermediate or definitive hosts. Important parameters include the death rate of the parasite, the possibility of acquisition of parasite-induced immunity and the prevailing infection pressure or exposure rate. In the intermediate host the numbers of cysts in infected animals increase with age (which is a proxy for time) and the prevalence approaches an asymptote of one in the oldest animals. This appears to hold true for every intermediate host investigated including sheep, goats, cattle, camels and donkeys (Gemmell, 1990; Ming et al., 1992; Cabrera et al., 1995; Torgerson et al., 1998, 2003a,b; Mukbel et al., 2000; Lahmar et al., 2004, 2013, 2014). This model, therefore, provides a straightforward means to estimating the infection pressure to a group of animals. Representative groups of animals from each age group are necropsied, their cysts counted and the data fitted to the model. Knowledge of the infection pressure to the intermediate hosts can give a strong indication of the force of control efforts needed to control and eventually eliminate the parasite. The model also shows that it is essential to record the ages of animals during surveillance studies. If only young sheep, perhaps, slaughtered in an abattoir close to a city are used it can give a mistaken impression of a low prevalence of echinococcosis in the sheep population.

The model has also been applied in dog populations using arecoline surveillance or necropsy data (Lahmar et al., 2001; Torgerson et al., 2003a,b; Budke et al., 2005b). In dogs the model can estimate reinfection rates (number of exposures per year) that would be useful when deciding the frequency of anthelmintic treatment of dogs during a control programme. The model also indicates the possibility that there is parasite-induced protective immunity in dogs against reinfection as old animals often have lower parasite abundances than young animals. However, this might also be explained by different behaviours in young and old dogs resulting in differences in infection pressure to the two age groups. Mathematical analysis of data sets suggests that there is difficulty in differentiating between the two scenarios (Torgerson, 2006b). This is arguably an important question to answer as good herd immunity in dogs could pave the way for future vaccine development. However, experimental vaccine studies in dogs have so far been unconvincing with regard to possible vaccine development (Torgerson, 2009) (see section 2.2.4).

2.4.2 Optimizing interventions

Having fitted suitable surveillance data from definitive and intermediate hosts to the model and obtaining estimates of the infection pressure or frequency of infection, it is then possible to model the possible outcomes of a control intervention (Torgerson, 2003). Using PZQ to treat dogs can be modelled, for example, as decreasing the life expectancy of the parasite or the use of the sheep vaccine might be modelled as a decrease in infection pressure to dogs. This is reviewed in Torgerson and Budke (2003) and Torgerson and Heath (2003). This model has suggested that, in most instances, treatment of dogs every 3 months with PZQ will effectively control echinococcosis provided the majority of dogs are treated. If sheep are also vaccinated, it may be possible to reduce treatment frequency to every six months.

The model has also been developed further to model the infectious biomass in sheep – that is in terms of protoscoleces per sheep rather than abundance or prevalence of cysts (Torgerson et al., 2009). Using a data set in Kyrgyzstan where the prevalence in sheep is approximately 64%, it demonstrated that 80% of the infectious biomass was in sheep $\geq$4 years of age, although these animals were just 28% of animals slaughtered. This, therefore, provided a rationale that targeted control or culling of old sheep could be a potentially effective way of immediately substantially reducing infection pressure to dogs and shorten the time period to control.

2.5 Health education

Health education can play a vital role in reducing transmission of echinococcosis to humans. The first successful elimination campaign of *E. granulosus* was undertaken in Iceland. Initially the programme relied heavily on education. In 1864 a 16-page booklet was published in Icelandic, emphasizing the need to destroy cysts and cleaning dogs of tapeworms using areca extracts. This was delivered free of charge to every household. There was a scarcity of books in Icelandic so the booklet was read, possibly by everyone as the population was highly literate (Beard, 1973). The prevalence of CE in the Icelandic population, as shown by autopsy was over 20% in the latter part of the 19th century. But by the middle of the 20th century the parasite had been eliminated (Beard, 1973). The situation in Iceland was, perhaps, the ideal and unique because the population was literate and highly receptive to educational messages.

Echinococcosis is often highly endemic in underdeveloped or resource-poor communities where education is inadequate and there are high levels of illiteracy (Ito et al., 2003b). In an endemic area of Morocco only 50% of people have heard of the disease, and of those, only 21% were aware of the role of dogs in disease transmission (El Berbri et al., 2015). Likewise in an endemic area of Turkey, 84% of the population had no knowledge of the disease (Ertabaklar et al., 2012). In Tunisia, the highest incidence of human CE was found in areas with the lowest rates of literacy (Chahed et al., 2010). Even medical professionals may have poor knowledge of the disease. In both urban and rural health facilities in Tanzania, only a few practitioners were observed to have the correct knowledge on the transmission of echinococcosis (John et al., 2008).

Other than in Iceland the potential benefits of education have been demonstrated in several epidemiological studies. In the Kyrgyz republic it has also been shown that dogs from households where there was some knowledge of echinococcosis had a lower coproantigen positivity than those from households with no knowledge (Mastin et al., 2015). A similar phenomenon has also been observed amongst the Turkana in northern Kenya (Buishi et al., 2006) and in Libya (Buishi et al., 2005a). However, introducing educational materials into the population can be a challenge where there are low levels of literacy. For example, on the Tibetan plateau education of dog owners and their children about hydatid control was only partly achieved during a 5 year period and was hampered by a high proportion of illiteracy with few children going to school. Eventually a laminated colour page illustrated by cartoons was distributed to most households (Heath et al., 2006). By contrast in New Zealand nearly 30 years of specific health education failed to significantly impact on human or animal infection rates (Gemmell et al., 2001).

Echinococcosis is also a food-borne disease with transmission to humans by contaminated vegetables (Torgerson et al., 2015). Thus in endemic areas, it is essential that dogs are kept off kitchen gardens and fresh produce is well washed to avoid infection of humans by this indirect route. Studies by (Shaikenov et al., 2004) found 5 of 120 soil samples taken from gardens of rural homesteads in southern Kazakhstan were contaminated with *E. granulosus* (G1 strain) eggs.

2.6 Integrated control for cystic echinococcosis

A number of successful CE control programmes have relied heavily on a single tool, such as education in Iceland (Beard, 1973), or through dog control and treatment as in New Zealand (Gemmell, 1990), Cyprus (Economides and Christofi, 2000) and Tasmania (Jenkins, 2005). Whilst they have been successful, they have often required several decades of sustained effort to bring about effective control and elimination. They are also costly and require a high compliance rate to be successful and there may be difficulty in treating stray dogs. Integrated control uses not only anthelmintic treatment of dogs and dog population control, but also incorporates other control methods such as the use of the EG95 livestock vaccine, education and the control of slaughter of domestic animals. It may also be extended to include the control of other zoonoses or animal diseases such as vaccination of dogs against rabies or vaccination of sheep against brucellosis; both brucellosis and rabies often occur in *Echinococcus*-endemic regions.

Modelling has suggested that the use of both livestock vaccination and treatment of dogs could reduce the frequency of anthelmintic treatment of dogs that is required whilst still achieving effective control (Torgerson and Heath, 2003). Thus such a programme might consist of vaccination of all young animals (twice), one annual booster immunization of all previously vaccinated livestock and six-monthly treatment of all dogs with PZQ. This would save considerable amounts of resources in terms of logistics and costs. The effectiveness is, at least in theory, because there is intervention in both life cycle hosts that has a potentiating effect and thus means compliance rates can be lower to result in effective control. Although the vaccine is now being assessed and used in China, Argentina and Chile and likely to be used elsewhere, there are, to date, no data to confirm the theoretical results of modelling.

If this integrated vaccination of sheep and anthelmintic treatment of dogs was further combined with education and improvement of slaughter facilities, control of CE would be further facilitated. Improvement of slaughter facilities ensures that animals are slaughtered under veterinary supervision, and this should improve the safe disposal of offal to interrupt the disease cycle. Slaughterhouses provide opportunities for surveillance of echinococcosis and other diseases; however, such facilities are found in only a few endemic areas. Modern slaughterhouses are usually expensive, but building low-cost concrete-slab buildings in remote areas is a viable alternative (WHO, 2011). Educational materials should be produced and distributed to the population. These materials should be easy to understand, particularly since there may be a high level of illiteracy, and they should be culturally relevant to the target population (e.g., Heath et al., 2006).

Finally the culling and hence safe removal of old and likely infected livestock animals from the population should be considered. As discussed above this would have the advantage of immediately reducing the infection pressure to dogs considerably.

3. SURVEILLANCE FOR *ECHINOCOCCUS GRANULOSUS*

3.1 Surveillance of cystic echinococcosis in humans

Surveillance in humans is critical for a decision to embark on a CE control programme and also to inform the public and the control authority about the progress of control. Surgical and medical treatment data have been the key to measuring the public health impact and burden of CE disease in endemic communities (Schantz, 1997; WHO/OIE, 2001; Budke et al., 2006). In addition, community screening using ultrasound scanners for abdominal CE case finding has more recently been adopted to provide epidemiological and surveillance data (Macpherson et al., 2003). Serological surveys have a more limited use in surveillance and should not be used as a primary screening tool.

3.1.1 Hospital records

Annual incidence per 100,000 population is the most commonly used index for the frequency rate of human CE at district, provincial or national level. Such hospital data are usually based on surgical case rates (primarily abdominal and thoracic) but should also include cases treated medically (i.e., by benzimidazole chemotherapy), and also those CE cases that are confirmed but not treated (i.e., under 'watch and wait' management). Age-specific incidence especially for the <15 years group can provide the most relevant 'recent' data (as opposed to old cases contracted preintervention) in relation to efficacy of an extended hydatid control programme. Hospital-based retrospective and prospective data sets can indicate the success of control measures or conversely the failure or poor efficacy of interventions, though that may not be very clear until 5–10 years after the start of a CE control programme. Hospital records may not, however, be accurate for the total number of CE cases treated because of poor access to affordable treatment, underreporting, case spread over separate surgical specialities, misdiagnosis and poor record keeping (Craig et al., 2007a). Furthermore, asymptomatic cases may not be identified and thus not treated, unless after accidental detection, and thus are usually not recorded.

3.1.2 Active mass screening for human cystic echinococcosis

Active screening via radiographic surveys (ultrasound, X-ray) should provide a more accurate measure of total CE cases at community level and include known cases, new cases and asymptomatic cases. This then will provide a community cross-sectional prevalence (%) rather than incidence rate per year, but could also be used in longitudinal studies when communities are screened annually or multiannually. Age-specific ultrasound prevalences again can be extremely useful in the assessment of the impact of interventions associated with a CE control programme, for example, as shown in Rio Negro, Argentina (Frider et al., 2001) and in Turkana, Kenya (Macpherson and Wachira, 1997). One problem is that although the majority of human CE cases are hepatic, around 10% will be pulmonary and thus not detected in routine ultrasound screening. The parallel use of mobile X-ray units is thus required, but that has only been applied in relatively few screening programmes (e.g., Schantz et al., 2003). Where accurate livestock slaughter data are difficult or impossible to collect, such as in many underdeveloped pastoral regions, then age-specific human CE ultrasound prevalences can provide alternative data to measure control efficacy (Macpherson et al., 1984; Larrieu et al, 2004b; Heath et al., 2006).

Serological-based screening for human CE has been applied in epidemiological settings (see review by Rogan and Craig, 2002), but sensitivity and specificity are not sufficiently robust to warrant sero-testing as a primary screening method. A positive serological result alone is not a diagnosis of CE. Supportive or confirmative use of hydatid serology in conjunction with ultrasound-based screening can have a potentially useful role (e.g., Feng et al., 2010), but even then care is required for interpretation of sero-positive but image-negative persons.

3.2 Surveillance for *Echinococcus granulosus* in dogs

The major hydatid control programmes over the period 1960s—2000s used annual ovine CE prevalence together with annual human CE incidence rates as the primary surveillance data. In addition, for owned dog populations, annual or multiannual arecoline purge data was used for surveillance of canine echinococcosis in almost all programmes including New Zealand, Tasmania, Uruguay and Welsh programmes (Craig and Larrieu, 2006). Necropsy data for unwanted and stray dogs were utilized in the hydatid control schemes in Cyprus and La Rioja (Spain) (Economides et al., 1998; Jimenez et al., 2002). With the advent of coproantigen ELISAs in the 1990s, laboratory testing of dog faeces was possible on a large scale and coprotests were used for surveillance in Wales (Buishi et al., 2005b) and Cyprus (Christofi et al., 2002) after main intervention measures had ceased. Copro-ELISA is currently employed as the main screening test for canine echinococcosis in the Rio Negro (Argentina) (Larrieu et al., 2000a; Morel et al., 2013) and west China (WHO, 2011) hydatid control programmes.

Coproantigen ELISA has effectively replaced arecoline testing as the main screening test for dogs in current hydatid programmes (WHO, 2011; Craig et al., 2015). In addition, the advent of copro-PCR tests from the early 2000s (Abbasi et al., 2003) has provided a valuable tool for the species-specific confirmation of *E. granulosus* infection in dogs for both epidemiological and surveillance studies (reviewed by Craig et al., 2015).

3.2.1 Necropsy of dogs

Necropsy examination of the entire length of the dog small intestine for the presence of *Echinococcus* tapeworms is the gold-standard for detection of canine echinococcosis (Craig, 1997; WHO/OIE, 2001). The obvious drawback for necropsy is that it requires dogs to be euthanized, which may not be acceptable or feasible and might lose support of community participation in hydatid control programmes (Kachani and Heath, 2014). Dogs that might be available for euthanasia are usually either unwanted owned dogs (e.g., old, sick, dangerous) or unowned stray dogs in a district or municipality (e.g., nuisance scavenging, aggressive packs, via rabies control) (see Section 4.1.3). Stray dogs may have a higher or lower exposure risk for *Echinococcus* compared to owned dogs (primary target for surveillance), and thus may not be the most representative sample for canine echinococcosis surveillance. Necropsy data from unwanted or stray dogs has been used to assess prevalence of canine echinocococcosis, for example, in the La Rioja (Spain) hydatid control programme (Jimenez et al., 2002), and for validation of coproantigen-based surveillance of dogs in a hydatid control zone in northwest Xinjiang, China (van Kesteren et al., 2015).

Biohazard considerations are required for necropsy in the field or in a laboratory, and an experienced person is needed to undertake necropsy probably also with supporting technical assistance. Adult *E. granulosus* (3—7 mm) occur in the upper duodenum starting close to the stomach and usually are attached over the first third of the small intestine in dogs. The sedimentation and counting technique (SCT) is the most sensitive technique and thus the most accurate for detection and counting worms (WHO/OIE, 2001). Other postmortem techniques include the more practical field applicable direct examination method wherein short lengths of fresh gut are incubated in warm saline to detach worms, which can be examined/counted in the sediment (Craig et al., 2015). Under low magnification (e.g., hand-lens or low-power microscopy) the characteristic morphology of *E. granulosus s.l.* should be confirmed. In coendemic areas where dogs may be exposed to both *E. granulosus s.l.* and *E. multilocularis* then differential morphology (position of genital pore, uterus form) of *Echinococcus* worms will be required (Craig et al., 2015).

3.2.2 Arecoline testing for canine echinococcosis

Areca nut extract or the synthetic compound arecoline hydrobromide has been used as an intestinal purgative since the late 19th – early 20th Centuries, effectively both as a crude dewormer (Section 3.1.1) and also for premortem detection of *E. granulosus* in dogs. From the 1960s it was the primary tool for surveillance of canine echinococcosis in hydatid control programmes (Gemmell, 1978). Tens of thousands of rural-owned dogs were screened over 10–20 years using arecoline purgation in all the five 'Island' hydatid programmes (i.e., Iceland, New Zealand, Tasmania, Falkland Islands, Cyprus) (Section 6.1.1) and among others Regions XI and XII in Chile, Neuquen and Rio Negro (Argentina), and Uruguay programmes (Craig and Larrieu, 2006). Arecoline testing still remains useful because of its very high specificity especially in relation to transmission studies and epidemiological studies or precontrol baseline investigations (e.g., Hoida et al., 1998; Budke et al., 2005c; Ziadinov et al., 2008; van Kesteren et al., 2013).

The major drawback with arecoline testing of dogs is the difficult logistics and organization needed to undertake purging on the large scale required for surveillance of a hydatid control programme. Tied dogs usually purge within 30–60min but some take longer, others fail to purge, while some react toxically or become dehydrated from arecoline salts. The sensitivity of arecoline purgation after a single oral dose (2 mg/kg) varies from 40% to around 75% (Lahmar et al., 2007). Microscopic examination of boiled or formalin-fixed purges in the laboratory will usually have greater sensitivity compared to diagnosis in the field (Craig et al., 1995; Gemmell and Schantz, 1997), and greater species specificity in areas coendemic for *E. multilocularis* (Budke et al., 2005c). The potential health educational value of purgation for the dog owners is often significant and beneficial, after owners observe the biohazard clothing and strict conditions undertaken by dosing staff, and intact moving tapeworms (especially the large common *Taenia* spp) voided by treated dogs (Gemmell, 1990; Farias et al., 2004). Detection of *Taenia hydatigena* after arecoline testing has been used in hydatid control surveillance as an indicator of dog access to offal and thus 'flags-up' risk behaviour for transmission of echinococcosis (Economides and Christofi, 2002).

3.2.3 Coproantigen tests for canine echinococcosis

The possibility for detection of specific taeniid tapeworm antigens in canid faecal supernatants (coproantigens) was considered in the 1960s (Babos and

Nemeth, 1962) and more intensively investigated as a diagnostic approach for taeniid cestodes, using capture antibodies in ELISAs, from the late 1980s (Allan and Craig, 1989) and for experimental and natural infections of canine echinococcosis in the early 1990s (Allan et al., 1992; Deplazes et al., 1992). Coproantigen ELISAs that utilize anti-*Echinococcus* progottid somatic (Allan et al., 1992; Pierangeli et al., 2010) or ES (Deplazes et al., 1992; Malgor et al., 1997) capture antibodies purified from rabbit hyperimmune antisera appear to be relatively robust with good genus specificity for *Echinococcus* spp usually >90% and sensitivities >70% (Allan and Craig, 2006; Carmena et al., 2006). Anti-*Echinococcus* monoclonal antibodies have potential advantages over polyclonals (Casaravila et al., 2005; Morel et al., 2013) especially in relation to reagent batch and test standardization, though specificity may not be significantly better, nor detection of low worm burdens. *Echinococcus* worm burdens below 50–100 worms may result in some false negatives, and infections due to *T.hydatigena* have been reported to result in some false positives (Allan et al., 1992; Malgor et al., 1997; Morel et al., 2013). It is important to assess a given coproantigen ELISA (including commercial kits) against a panel of faecal samples from dogs with parasitologically confirmed monospecific infections (i.e., necropsy or arecoline purge of experimental or natural infections) including *E. granulosus* or *Taenia* spp., so that the test parameters are determined prior to local application (Morel et al., 2013; Huang et al., 2013; Craig et al., 2015).

Overall the levels of test sensitivity and specificity of coproantigen ELISAs achieved by independent groups (see review by Craig et al., 2015) are at least comparable to arecoline purgation and thus has lead to recommendations that copro-ELISA has the potential to replace arecoline testing as a diagnostic test for canine echinococcosis (Craig et al., 1995; Gemmell and Schantz, 1997; Guarnera et al., 2000; WHO/OIE, 2001; Lopera et al., 2003; Pierangeli et al., 2010; Lembo et al., 2013; Morel et al., 2013).

3.2.3.1 Coproantigen screening in cystic echinococcosis control programmes

Coproantigen ELISAs have now been employed in several hydatid intervention/control programmes to determine baseline levels of canine echinococcosis and/or for surveillance in place of (previous use) arecoline testing.

In mid-Wales (UK) arecoline testing was initially used to determine precontrol levels (prevalence 4.6–25%) of canine echinococcosis in farm dogs prior to 1983 (Craig and Larrieu, 2006) before a supervised six weekly

PZQ dosing programme was implemented over a 6-year-period (1983–89). A coproantigen ELISA developed in 1992 (Allan et al., 1992) was subsequently used in 1993 to screen a sample of farm dogs in the Welsh intervention zone, and recorded 0% copro-positives versus 2.4–9.2% in neighbouring nonintervention zones (Palmer et al., 1996). Dog-dosing measures were terminated in 1989 for economic reasons, and subsequent follow-up copro-ELISA surveys in 2002 and 2008 recorded 8.5% and 10.6% copro-prevalences in farm dogs in the intervention zone (Buishi et al., 2005b; Mastin et al., 2011). In 2010–11, three monthly PZQ dosing (i.e., four times per year) was reintroduced in the original intervention zone for a pilot period of one year only. Coproantigen testing indicated that after 3–4 months copro-prevalence in farm dogs had reduced in the intervention zone from 8.8% to 1.9% and further to 0% in the last quarter, i.e., 12 months after the first dosing round. However, copro-prevalence in farm dogs started to rebound in the following 12 months after dosing had stopped (Lembo et al., 2013).

In Cyprus after the highly successful hydatid control programme in the 1970s (elimination declared in 1985), most of the island was under a maintenance phase of control based on CE surveillance (abattoirs, hospitals). In addition, over the period 1997–2000 more than 6500 owned dogs were screened using coproantigen ELISA, of which 2.8% were copro-positive and treated with PZQ (Christofi et al., 2002).

On the Falkland Islands (Malvinas), since the late 1970s there has been an ongoing government-managed PZQ dosing programme (currently by owners) for all dogs (estimated 900–1000). In 1992–3 coproantigen testing of 464 dogs on the Islands detected 1.7% copro-positives (Reichel et al., 1996). Further testing (n = 563 dogs) in 2010 indicated that coproantigen prevalence had reduced to <0.1% (Lembo et al., 2013). This low coproantigen prevalence in dogs, coupled with very low ovine CE prevalence (<0.02%) suggested that transmission of *E. granulosus* is close to elimination from the Islands and is not now a public health problem (last human case 1992). Thus dog dosing could be made voluntary and a decision made to transfer to a permanent consolidation phase with sole reliance on abattoir surveillance, farm trace-back, quarantine measures and targeted dosing of dogs (S. Pointing, personal communication).

Hydatid disease control in several provinces in the Patagonia region of Argentina has been ongoing since the 1970s, and coproantigen ELISA has been applied to screen dogs in the Rio Negro and Neuquen programmes. In the latter, coproantigen prevalence was 12.4% (n = 403 dogs) compared to 3.7% based on arecoline testing. An 'in house' coproELISA was used with 93.6% sensitivity and 88.5% specificity (Pierangeli et al., 2010). CoproELISA was used as a farm dog surveillance test to compare sheep ranches in hydatid control zones in Patagonia, which indicated district copro-prevalences from 2.9% (Rio Negro) to 13.9% (Tierra del Fuego), and overall 7.3% of 352 farms sampled in Neuquen had a copro-positive dog (Cavagion et al., 2005). In Rio Grande do Sul, the main CE endemic region of south Brazil where hydatid control was considered, a coproELISA baseline prevalence of 27.7% was obtained, which reduced to 0% copro-prevalence 30 days after PZQ dosing. However, 4 months posttreatment copro-prevalence was 47.4%, which suggested to the authors (despite a small sample size) that dosing frequency should be every 30 days (Farias et al., 2004).

An investigation of canine echinococcosis using a coproELISA was undertaken in 2002 in the remote northwest Turkana district of Kenya 5 years after the effective dismantling of a hydatid control programme which ran from 1983 to 1997 (Macpherson and Wachira, 1997). In the intervention zone, 29% of owned dogs were copro-positive, and furthermore 33% of necropsied unwanted dogs were infected (Buishi et al., 2006). Clearly transmission to dogs was still occurring, however, mean worm intensity was 53 worms per dog in the intervention area compared to 1416 worms per dog in an area not covered in the previous control programme. This suggested that the intensity of transmission had remained low in the intervention zone (Buishi et al., 2006). This result also indicated the usefulness of *Echinococcus* worm burden estimates, which can only be obtained from necropsy or arecoline purgation studies.

In northern Ganze Tibetan Autonomous Prefecture (Sichuan Province, China) a 5 year (2000–05) echinococcosis pilot control programme incorporated six monthly PZQ dosing of owned dogs and applied a coproantigen ELISA for canine surveillance. Copro-prevalence in owned dogs reduced from a precontrol baseline of 50% to 17% after 5 years (Heath et al., 2006; Yang et al., 2009). This high altitude remote area was difficult to reach more than twice per year mainly because of seasonal limitations; however, the coproantigen results suggested that a more intensive dosing pressure would be required together with removal or dosing of the large stray dog population (Heath et al., 2006). Since 2006–07 a national echinococcosis control programme has been rolled out across western China (including Ganze) with target monthly dog dosing and the coproantigen testing of dogs as a key surveillance tool (Huang et al., 2013). In a remote Mongolian autonomous county (Hobukesar) in northern Xinjiang (China) also subject to this national programme, an independent evaluation of dog treatment and surveillance, gave a copro-prevalence range of 15–70% over six communities investigated by van Kesteren et al. (2015). Furthermore, household questionnaire data indicated significant variation in dog-dosing practice and supervisory visits by veterinary auxillaries (van Kesteren et al., 2015).

These few examples indicate the potential usefulness of coproantigen surveillance in connection with hydatid control programmes; however, limitations include test availability (especially commercial kits), variable test sensitivity and specificity and lack of indication for worm burdens.

3.2.4 Copro-PCR tests for canine echinococcosis

The application of the polymerase chain reaction to amplify *Echinococcus* spp DNA extracted from adult worms, egg concentrates, or whole faecal extracts, provided for the first time the potential for laboratory-based antemortem species-specific identification of canine or vulpine echinococcosis (Bretagne et al., 1993; Mathis et al., 1996; Cabrera et al., 2002a). The development of a copro-PCR test for the detection of *E. granulosus s.l.* DNA directly in canid faecal samples that gave 100% specificity versus *E. multilocularis* and *Taenia* spp (Abbasi et al., 2003), provided the potential to equal or improve the parasitological specificity of arecoline testing. PCR testing for canine echinococcosis has been applied in CE endemic areas (*E. granulosus s.l.*) and in CE/AE coendemic areas (i.e., both *E. granulosus* and *E. multilocularis* transmission) in Kazakhstan (Stefanic et al., 2004), western China (Moss et al., 2013) and Kyrgyzstan (van Kesteren et al., 2013). The sensitivity for *E. granulosus* egg-equivalent detection ranged from one to four eggs per gram of faeces (Abassi et al., 2003; Boufana et al., 2013) and DNA was detectable in faeces from prepatent infections with *E. granulosus* by 21–25 days post infection (Lahmar et al., 2007).

At least 10 copro-PCRs had been published by 2015 for detection of *E. granulosus s.l.* infection in dogs by targeting various genes or repeat elements (i.e., *cox1, 12sRNA, NAD1, EgG1HaeIII*) that are specific for *E. granulosus s.l.* but varied in test genotypic specificity (reviewed by Craig et al., 2015). In the absence, or more likely unwillingness, to undertake necropsy or purgation of dogs in endemic areas for baseline studies and surveillance, then PCR should provide the only unequivocal method for specific confirmation of *E. granulosus* infection via DNA detection. However, PCR is a relatively complex and expensive procedure requiring good laboratory facilities, and therefore has to date had limited routine application in hydatid control programmes. Therefore copro-PCR in current form, or the lower-tech loop-mediated isothermal amplification methods (Salant et al., 2012; Ni et al., 2014), is not yet recommended as a primary screening tool for canine echinococcosis. The ability of copro-PCR, however, to confirm infection by screening a proportion of dogs (e.g., coproantigen positives) can provide supporting data and confidence in the specificity of epidemiological and surveillance data for canine echinococcosis especially in low CE endemic or reemerging transmission areas (Jenkins et al., 2014) or coendemic areas (Stefanic et al., 2004; Boufana et al., 2013).

3.3 Surveillance for cystic echinococcosis in livestock

3.3.1 Meat inspection

Surveillance in abattoirs provides a valuable opportunity for surveillance in livestock, regardless of species of interest. Ideally, for surveillance purposes livers and lungs presented at the abattoir should be visually inspected for larger cysts and palpated for smaller cysts. It may be necessary to slice the liver to enumerate cysts especially in young animals. Both prevalence and abundance of hydatid cysts increases with age (Gemmell, 1990) and so it is essential to record the ages of the animals during any surveillance study. Studies that primarily inspect young animals such as 1-year-old lambs that are slaughtered for meat will underestimate the prevalence of CE and the results of such studies should be adjusted accordingly. Likewise in any longitudinal study to monitor a control programme, for example, similar age groups of animals must be compared at different time points.

3.3.2 Serology for cystic echinococcosis in livestock

Serology as a clinical diagnostic test for CE in humans is highly effective, with most patients infected with viable cysts being unequivocally positive in different types of test and using a variety of *E. granulosus* antigens (Kagan, 1968; Manzano-Roman et al., 2015). Many publications have investigated serological tests for diagnosis of CE in animals, particularly sheep. The results of these studies have been variable; some publications have described high levels of sensitivity and specificity for the tests that were developed (reviewed by Lightowlers, 1990; Craig et al., 2015). These publications must, however, be interpreted with caution.

Humans are relatively rarely infected with cestode parasites. A relatively small number of cestode species are known to infect humans. The situation with livestock animals is very different, especially for sheep and goats. Infections with cestode parasites other than *E. granulosus* are virtually ubiquitous in sheep and goats, especially *T. hydatigena*, but also other cestode infections are common (*Monezia, Taenia ovis, Taenia multiceps*). There is substantial evidence for antigenic cross-reactivity between the different taeniid species (Yong et al., 1978; Yong and Heath, 1979; Rickard and Williams, 1982; Gemmell et al., 1986a,b; Lightowlers et al., 1993). Possible infections with, or exposure to, cestode species other than *E. granulosus* are vital factors that must be taken into account in any evaluation of serological tests for CE in livestock. Another critical aspect is the age of the animals that are being compared with respect to their responses in serological tests for CE. Livestock animals are likely to accumulate exposure to cestode parasites over their lifespan and potentially have an increased 'background' reaction in serological tests. It is insufficient to compare samples from *E. granulosus* infected animals and uninfected animals or animals infected with other cestode parasites without also taking into account the age of the animals. For example, comparison of samples from aged sheep infected with *E. granulosus* with samples from lambs infected with *T. hydatigena* would not provide a reliable measure of the specificity of a test.

Few studies have taken these factors into account in their descriptions of serological tests for CE in livestock animals. An ideal comparison is the level of serological reactivity in *E. granulosus* infected animals and noninfected animals of the same age and derived from the same flock. When such comparisons have been made, or when comparisons have been made using sera from sheep experimentally infected with various cestodes, high levels of positive responses have typically been seen in animals which have had no *E. granulosus* infection (Lightowlers et al., 1984; Yong et al., 1984; Dueger et al., 2003).

An exhaustive investigation was undertaken of serological reactivity to various *E. granulosus* antigen preparations by Lightowlers et al. (1984) involving sheep serum samples from *E. granulosus* infected and uninfected sheep from the same flock, animals with heavy, large fertile hydatid cysts, and mature sheep from an island where dogs are never present. Differences in the average reactivity of the groups of sera in ELISA were evident between infected flocks and uninfected flocks, however, it was not possible to diagnose reliably the presence of CE on an individual animal basis, even in cases of very heavily infected animals.

Data from serial bleeds of sheep experimentally infected with *E. granulosus* indicate unequivocally that they do respond to the infection, producing specific antibody (Yong and Heath, 1979; Conder et al., 1980; Yong et al., 1984). The level (titre) and frequency of detectable responses (sensitivity), however, seem substantially different to the titres commonly detected in humans undergoing serological diagnosis for CE. This lead Lightowlers et al. (1986) to investigate the hypothesis that *E. granulosus*–infected sheep may develop a degree of nonresponsiveness to hydatid antigens. A small amount to cyst fluid from the animals' own hydatid cysts was released into the peritoneal cavity at laparotomy. Classic, high-level, anamnestic antibody responses were elicited, indicating that the animals were both primed to respond to hydatid antigens and were not suppressed in their ability to respond, at least insofar as it involved exposure to antigen via this route.

In conclusion, there is currently no serological method that can be used to reliably and specifically diagnose hydatid infection in livestock animals.

3.3.3 Ultrasound for cystic echinococcosis detection in sheep and goats

CE in livestock animals is essentially asymptomatic and therefore premortem clinical diagnosis is not possible. Serological tests remain unusable for routine practical application (see Section 3.3.2). Radiographic methods for cyst imaging, especially portable ultrasound scanners, offer a more practical and reliable approach for the potential premortem diagnosis of CE in small ruminants (see review Craig et al., 2015). Two large studies in 300 Kenyan sheep/goats (Sage et al., 1998) and 120 sheep in Sardinia (Dore et al., 2014) that were scanned then inspected postmortem, indicated that identification of CE–infected sheep or goats was possible in standing animals with sensitivities of 54.4% and 88.7% in respective studies. The calculated specificity for CE was higher (97.6%) in the Kenyan study than in the Sardinian assessment (75.9%), but that might reflect the higher resolution transducer and imager used in the more recent Sardinian study (Dore et al., 2014). The main cause of false positive images in both studies was the presence of cysts of *T. hydatigena,* which had also been noted in another study (Maxson et al., 1996). Certainly the few studies, published on the application of ultrasound for CE diagnosis in sheep and goats, suggest that this approach has good potential and is overall more reliable than current serological tests. In underdeveloped endemic regions where it is difficult or impossible to use meat-inspection data for CE surveillance, then mass ultrasound scanning in live sheep or goats may offer a reasonable alternative.

3.3.4 Sentinel animals

Few, if any, studies have deliberately distributed *known* noninfected animals to act as sentinels for transmission of *E. granulosus*. Logically, all newborn livestock are effectively sentinels by which continuing transmission can be determined. Lloyd et al. (1991, 1998) described the use of sentinel lambs in mid-Wales for monitoring transmission of *E. granulosus*. The lambs were purchased from their farm of origin and slaughtered at the time of the researchers' choosing. This method may provide a greater assurance that animals would be available for assessment when they were needed, rather than relying on farmers' agreeing to sell animals for necropsy without their having been a preexisting arrangement. In the Welsh study, 6% of sentinel lambs became infected with *E. granulosus* within 19 months of exposure in an intervention area previously under a six weekly dog-dosing regime (Lloyd et al., 1991, 1998). Another study in Uruguay observed that sentinel lambs were not infected at postmortem when six weekly dog dosing was used, but 4–18% of lambs were infected when the dog-dosing frequency was reduced to 12–16 week intervals (Cabrera et al., 2002b).

4. CRITICAL APPRAISAL OF CYSTIC ECHINOCOCCOSIS CONTROL PROGRAMMES

4.1 Successful hydatid control programmes

Since the first hydatid control programme was implemented in Iceland in the 1860 s at least 18 other intervention programmes have been undertaken in different world regions to reduce the transmission of *E. granulosus* and to try and reduce or eliminate human CE as a public health problem. Many of these programmes have already been reviewed elsewhere (Gemmell, 1978, 1990; Gemmell and Schantz, 1997; Economides et al., 1998; Gemmell and Roberts, 1998; Gemmell et al., 2001; Craig and Larrieu, 2006; Larrieu and Zanini, 2012; Lightowlers, 2012).

The ultimately successful control programme in Iceland lasted >100 years and eliminated transmission from the island by the 1950s–60s. However, incidence of human CE in the <40 year age group had already fallen significantly by the decade 1890–1900 (Beard et al., 2001). This was in many ways a unique situation where a small, highly literate population responded positively to health education messages and legislation to stop home slaughter, reduce dog contacts and accept annual arecoline treatment of dogs; in addition a national change in sheep husbandry from milk and wool production to marketing fat lamb, helped to reduce the parasite reservoir of ovine echinococcosis (Dungal, 1957; Craig and Larrieu, 2006). The Icelandic success against hydatidosis influenced New Zealand to begin a health education progamme from 1938 to 1958, which also included free provision of arecoline to dog owners, and legislation making it illegal to feed dogs raw offal. In contrast to Iceland, however, surveillance data from hospitals and abattoirs indicated no reduction in transmission of CE after 20 years of a hydatid educational campaign (Gemmell, 1990). Other health education campaigns that similarly included encouragement of owners to dose dogs, did not appear to have any significant effect on transmission of *E. granulosus* in mid-Wales (after 1989) nor in Sardinia (1969–90) (Craig and Larrieu, 2006).

Replacing long-term horizontal programmes, (where emphasis was on education, abattoir upgrades, meat inspection and dog management), with faster-track vertical programmes based on regular dog dosing (once PZQ became readily available in the late 1970s–early 1980s) was the key to potential success for the majority of hydatid control programmes. Reduction in the adult worm biomass in rural dog populations would relatively rapidly reduce infective pressure to sheep (and other livestock) and humans. Presence of hydatid cysts in older sheep (>5 years) would require application of dog dosing in an attack phase for >5 years and probably 5–10 years. Key aspects of dog dosing with PZQ for a successful outcome were:

- determination of number of owned dogs (registration),
- provide supervised dosing at a frequency of 4–8 times per year,
- dose at least 90% of registered dogs and
- maintain dosing pressure for 5–10 years.

When the above dog-directed measures were applied successfully by a government control authority with a good infrastructure, that included surveillance in sheep, dogs and humans, then prevalence of ovine and canine echinococcosis declined within 5 years and human CE rates within 10 years (Gemmell et al., 2001; Craig and Larrieu, 2006; Larrieu and Zanini, 2012).

4.1.1 Island programmes: New Zealand, Tasmania

In the first half of the 20th century human hydatidosis (CE) was recognized as a major public health problem in rural communities in New Zealand and Tasmania (an island state of Australia) (Lightowlers, 2012). Both territories began vertical-directed control programmes that targeted owned dogs from 1959 to 1964 respectively. The New Zealand programme was initially funded by a dog tax collected by a National Hydatids Council, then after 1991 through the Ministry of Agriculture. The Tasmania programme was funded and implemented from the beginning via the Department of

Agriculture. Both programmes used mass testing of dogs with arecoline, but in New Zealand (from 1978), PZQ was in addition employed to dose dogs at a frequency of 8 times per year (i.e., approximately every six weeks). In Tasmania by contrast, annual arecoline testing of dogs on farms by mobile units was maintained for 11 years (without the use of PZQ) in conjunction with strict quarantine measures for positive farms. Transmission was considered to have almost ceased in Tasmania within 10 years (McConnell and Green, 1979). In contrast, the attack phase in New Zealand using PZQ with centralized testing of purges, lasted 32 years. There were no human CE cases under 20 years of age in Tasmania after 1976, prevalence ovine CE had dropped from 52% to 3.4% by 1978 and dog prevalence to 0.06% by 1985 (Beard et al., 2001).

Tasmania declared the state was provisionally free of hydatidosis in 1996, which is 32 years after the start of the control programme; New Zealand declared itself free of hydatidosis in 2002, a 43 year period after the start (Pharo, 2002; Jenkins, 2005). The Tasmanian hydatid control programme had a shorter attack phase and was very cost-effective utilizing only 0.5% of the state health budget. Part of the success in Tasmania was participation and support of rural communities and the efficient organization of control under the Department of Agriculture, in particular the use of mobile dog testing units for farm outreach and the strict use of enforced quarantine. The examples of hydatid control undertaken by New Zealand and Tasmania were very successful, with the latter declaring elimination of human CE as a public health problem in less than 20 years from initiation. Other hydatid programmes were influenced by the ultimate success of these two Australasian examples (Lightowlers, 2012). What is the current status of transmission in these two regions 15–20 years after declaration of freedom from hydatidosis? Both regions operated effective consolidation phases comprising largely meat inspection and trace-back after control measures had ceased. In New Zealand small lesions in slaughtered livestock were subject to histological examination to rule out CE, while in Tasmania PCR has been employed to confirm lesion identity. In both regions the only human CE cases that occurred postcontrol were in the >40 years age group and thus probably were infected prior to the termination of control measures (O'Hearn and Cooley, 2013). However, complete elimination of *E. granulosus* transmission has probably either not occurred or has reemerged in Tasmania as evidenced by the finding of CE in cattle born on the island and the occurrence of *Echinococcus* PCR-DNA positives in local farm dogs (Jenkins et al., 2014).

4.1.2 Island programmes: Falkland Islands, Cyprus

The incidence of human CE in the small population on the Falkland Islands (Las Malvinas) between 1965 and 1975 was equivalent to 55 per 100,000 per annum (Craig and Larrieu, 2006). Six weekly dog dosing with PZQ was introduced by the Department of Agriculture in 1977. Initially dosing was supervised, then dog owners were expected to dose their dogs with the drug provided free. Surveillance of ovine CE in Stanley abattoir in 1993 indicated a reduction from a precontrol baseline of 59% to 0.16% (Reichel et al., 1996). No preintervention baseline data for canine echinococcosis were available, but coproantigen ELISA indicated 1.7% copro-prevalence in 1993 (Reichel et al., 1996), which had further reduced to <0.1% by 2010 (Lembo et al., 2013). In 2015 dog owners were still expected (via government information and local meetings) to dose their dogs every six weeks with PZQ provided by the Department of Agriculture. In addition an active farm trace-back system was operated, from the single abattoir, to identify and quarantine farms when any hydatid positive sheep were identified by inspection and PCR testing (Lembo et al., 2013). There have been no human CE cases on the Falklands except in the elderly. The Department of Agriculture considers echinococcosis transmission to be on the verge of elimination, however, sporadic occurrence of positive animals (sheep and dogs) persists in isolated farms as well as the continued occurrence of *T. hydatigena* cysts in sheep that indicated probable lack of compliance by owners in relation to dog dosing (S. Pointing, personal communication).

In Cyprus prior to 1971, baseline data on hydatidosis/echinococcosis indicated a human CE incidence of 12.9 per 100,000 per annum, ovine CE prevalence was between 25 and 80% and arecoline purge prevalence of canine echinococcosis was 14% (Economides et al., 1998). Hydatid control was implemented in 1971 by the Department of Veterinary Services (under the Ministry of Agriculture) and largely focussed on active culling of stray dogs, euthanasia for arecoline-positive owned dogs (3 monthly testing) and strict livestock slaughter controls (Polydorou, 1993). Between 1971 and 1985 more than 85,000 dogs were killed. Dog prevalence reduced to 0.75% by 1977 and in 1984–85 none of 36,000 dogs were found infected by arecoline testing. There were no human cases diagnosed in the <20 years age group and hydatid eradication was claimed in 1985 (Polydorou, 1993). Sporadic transmission, however, reemerged between 1993 and 1996 in livestock in 21% of villages and 0.6% of dogs were arecoline test positive in the government controlled area (GCA) of the island (excludes Turkish occupied Northern Cyprus); furthermore, 2.8% of dogs were coproantigen positive in the period 1997–2000 (Christofi et al., 2002). Control measures were reapplied in the GCA in the mid-1990s which included PZQ dosing of dogs 2–3 times per year, stray dog management (no culling), movement control of livestock and prosecution for illegal slaughtering. Strict quarantine of *Echinococcus*-positive properties was implemented until there was a minimum of 3 years absence of *Echinococcus* or *T.hydatigena* cysts at livestock slaughter inspection (Economides and Christofi, 2002).

4.1.3 South American control programmes: Chile, Argentina, Uruguay

Human CE has been recognized since the mid-20th century as an important public health problem in at least five countries of South America, i.e., Argentina, Chile, Uruguay, Peru and Brazil, with an estimated 2000 cases annually across this region (Larrieu et al., 2004a). Ultrasound mass screening studies in the 1980s and 1990s indicated human CE prevalence in communities ranged from 1.6 to >14% (Moro and Schantz, 2006b). During the period 1970s–90s several vertical control programmes for CE were implemented in Uruguay (nationally) and in regions of the other four countries listed previously. The New Zealand and Tasmania successes were used as models for the South American programmes initially using arecoline then replaced by PZQ as the key dog treatment tool. The aim was to dose dogs eight times per year for at least 5 years in conjunction with health education and appropriate animal and human surveillance (Larrieu and Zanini, 2012). These hydatid control schemes were, however, organized under different authorities, i.e., the Department of Health in Argentina (Neuquen, Rio Negro, Tierra del Fuego) and Peru, the Ministry of Agriculture in Chile (Regions XI and XII) and an honorary hydatid commission in Uruguay. Greatest impacts, as measured by reductions in human incidence or prevalence and sheep and dog prevalences, occurred in Rio Negro (1980–2003), Chile Region XII (1982–97) and Uruguay (1990–2007) (Craig and Larrieu, 2006; Larrieu and Zanini, 2012) (Table 1).

4.1.3.1 Region XII, Chile

In Chile in 1979 the government's Ministerio de Agricultura y Servicio Agricola y Ganadero (SAG) introduced a vertical hydatid control programme for Region XII in the highly endemic south of the country. The main tool in the attack phase was six weekly (eight times per year) supervised dosing of farm dogs with PZQ, which had a significant impact in animal hosts within

5 years. Ovine CE prevalence declined from >60% to 25% and canine echinococcosis from 70% to 5% by 1984. Human CE incidence reduced from >40 per 100,000 to 1.8 per 100,000 per year by 1992 (Gemmell and Roberts, 1998; Craig and Larrieu, 2006). In 1984 dog owners were expected to dose dogs four times per year and the other four times to be carried out by veterinarians. In 1987–88 the dog-dosing frequency was reduced to two times per year to further save costs, however, ovine CE prevalence had plateaued at 5–7% (Vidal et al., 1994; Gemmell and Schantz, 1997). In response SAG reintroduced eight times per year dog dosing in 1991, which drove ovine CE prevalence close to zero by 1994 (Gemmell and Schantz, 1997; Craig and Larrieu, 2006). The transition to a consolidation phase occurred in 1998, which then placed emphasis on voluntary dog dosing and surveillance, however, indications of reemergence of echinococcosis were observed in Region XII by 2002 in sheep and dogs (Alvarez, 2002; Larrieu and Zanini, 2012).

4.1.3.2 Rio Negro, Argentina

The Rio Negro CE control programme in Argentina was launched in 1980 under the Ministry of Health (Provincial Council of Public Health and Department of Zoonoses). Provincial incidence of human CE was 73 per 100,000, and in children 50 per 100,000 (Larrieu et al., 2000a). Health workers were responsible for home visits, distributing PZQ pills to owners and checking on dog-dosing compliance and frequency, while veterinarians undertook surveillance aspects in dogs and sheep. Dogs were dosed four times per year under owner responsibility. Arecoline purge prevalence in dogs was reduced from a 41% baseline in 1980 to 5% by 2008–10. Ovine CE prevalence reduced from 61% to 2.9% by 1998. Importantly, within 12 years of the start of interventions, CE incidence in children (<13 years of age) reduced to below 20 per 100,000; furthermore, CE ultrasound prevalence in children <15 yrs reduced from 5.6% to 0.3% by 2008–10 (Frider et al., 2001; Larrieu et al., 2000a; Larrieu and Zanini, 2012).

The control measures for both the Region XII (Chile) and the Rio Negro (Argentina) hydatid control programmes were applied continuously for more than 15 years in remote resource-poor rural communities. The key measure was dosing dogs with PZQ 4–8 times per year by dedicated technical teams or by effective owner compliance. With upgrade of abattoirs and meat inspection training, surveillance in sheep was able to be efficiently undertaken to provide key surveillance data to monitor progress. CE incidence or prevalence rates in children <15 years indicated that transmission to humans had reduced significantly in both regions within 10 years (Larrieu et al., 2004b). Both programmes were managed under existing government authorities (Agriculture or Public Health) with good outreach and community acceptance and were also cost-effective, e.g., Rio Negro programme cost US$ 41,000 per annum, which included veterinary and medical costs (Larrieu et al., 2000a). Both programmes transferred from attack to consolidation phases with emphasis on owners to dose dogs and surveillance, abattoir surveillance and trace-back. However, dismantling of the vertical programme (Region XII, Chile) and handover of dosing to farm owners (also in Rio Negro) lead to probable reemergence in Region XII and persistence of low level transmission in Rio Negro (Larrieu and Zanini, 2012).

4.1.3.3 Uruguay

Uruguay was the only country in South America to implement a hydatid control programme at national level. Similar to New Zealand (pre-1990) a national commission against hydatidosis was created in 1965 and funded by a dog tax (Comision Honoraria de Lucha Contra la Hidatidosis). Initially, sheep farm owners were provided with arecoline and expected to treat their own dogs, then later dosing was done by mobile arecoline teams but they probably only covered about 50–60% of rural dogs (Craig et al., 1995). Between 1972 and 85 ovine CE prevalence had not reduced significantly from precontrol baseline of 40–65% and national human incidence was 12.4 per 100,000. In 1992 the programme was relaunched by the Honorary Hydatid Commission under the Ministry of Health, using an enlarged technical team to dose dogs monthly with PZQ, so that by 1995, 90% of farms were being included nationally (Larrieu and Zanini, 2012). Within 5 years (1997) arecoline surveillance indicated a reduced prevalence (0.7%) of canine echinococcosis, and within 10 years ovine CE was <5% in lambs, while incidence of human CE fell to 6.5 per 100,000 (Cabrera et al., 2002b). Thus Uruguay was able to convert a largely unsuccessful control programme, based on a combination of Option 2 (health education) and Option 3 (arecoline testing) type intervention to an effective Option five type intervention scheme based on supervised frequent dog dosing with PZQ. By 2006–07 the Uruguay programme was merged with a new National Commission for Zoonoses under the Ministry of Health and hydatid control moved into a consolidation phase with emphasis on continued monthly dosing, surveillance and dog population management (Larrieu and Zanini, 2012). Coproantigen ELISA was employed to test dogs and also mass castration and spaying schemes were introduced across the country. Between 2008 and 2013 coproantigen prevalence decreased from 10.2% to 3.4% in rural settlements, and human ultrasound prevalence of CE from 6.5% to 2% with only two CE cases less than 20-year-old (Irabedra et al., 2016).

4.1.3.4 Other less successful South American programmes

Other less successful pilot or regional control programmes in South America were implemented in Neuquen, Argentina (1970), Tierra del Fuego (1976), Peru (1992) and South Brazil (1983). In Neuquen six weekly arecoline dosing and health education were implemented and canine prevalence dropped from 28% to 3% in the first 4 years (Gemmell, 1978). In Tierra del Fuego the aim was to deworm owned dogs every six months and construct dog kennels and slaughterhouses (Zanini et al., 2006). The Peruvian programme centred on the central highlands opted for an arecoline-based approach but was interrupted then halted by political insurgency. An eight month pilot programme in Rio Grande do Sul (Brazil) applied monthly dosing with PZQ and was effective at reducing copro-prevalence in dogs but was not expanded (Farias et al., 2004).

4.2 Eurasian hydatid control programmes

Human CE is endemic in less developed or resource-poor rural zones across large parts of southern and eastern Europe and in contiguous regions across to Central Asia, eastern Russia and China. At least eight formal hydatid control programmes (including Cyprus, see Section 4.1.2) have been funded in this large region, which included schemes in: mid-Wales, UK (1983—89), La Rioja, Spain (1987—2000), Sardinia, Italy (1987—97), Hutubi, Xinjiang, China (1987—94), Datangma, Sichuan, China (2000—2005), Shiqu, Sichuan, China (2006-ongoing) (see Table 1) and a pilot in the Alay Valley, Kyrgyzstan (2011—2015). The Chinese schemes are now under a National Echinococcosis Control Programme to control CE (and AE) in western Provinces and Regions (Zhang et al., 2015). All were set up to include dog dosing with PZQ as the key intervention for a potential fast track approach (i.e., Option 5). One pilot programme (Datangma, China) also included livestock vaccination with EG95 (i.e., Option 6). Primary surveillance was based on prevalence in sheep (abattoir data) and dogs (coproantigen prevalence or necropsy) for the mid-Wales and La Rioja programmes, and on dog copro-prevalence and human ultrasound prevalence for surveillance in the west China national programme.

4.2.1 Europe: Mid-Wales, La Rioja, Sardinia

In both the Powys (mid-Wales) and La Rioja (Spain) hydatid control programmes, supervised dog dosing with PZQ at a frequency of eight times per year (i.e., six weekly intervals) was carried out by government veterinarians continuously for the first 6 years. This resulted in a 90% reduction in canine copro-prevalence (Wales) or dog necropsy prevalence (Spain) and also for ovine CE a reduction of 50–75% for both regions (Palmer et al., 1996; Jimenez et al., 2002). In addition construction of burial pits for safe disposal of sheep carcasses, as well as widespread health education was included in rural communities. The Welsh programme was, however, terminated prematurely after 6 years (in 1989) for economic reasons and replaced by a health education component (i.e., Option 2) that encouraged dog owners to purchase PZQ and to dose their own dogs at least 6–8 times per year (Lloyd et al., 1998; Craig and Larrieu, 2006). However, within 7 years of withdrawal of supervised dosing, coproantigen prevalence in Welsh farm dogs had increased from 0% to 6.3% and was close to 10% by 2002 (Buishi et al., 2005b; Mastin et al., 2011).

A control programme in Sardinia was well funded with extensive health education, but poorly managed (Sardinian Experimental Institute for Zooprophylaxis) with emphasis on owner responsibility to dose dogs. The programme had poor outreach and was not fully accepted by the sheep-raising communities, so that there was no significant reduction in either dog or ovine prevalences over a 10-year-period (Conchedda et al., 2002; Craig and Larrieu, 2006). Home slaughter and poor deworming practices continued in Sardinia (Varcasia et al., 2011). In both La Rioja and Sardinia there were large stray dog populations (80,000 in Sardinia) that were considered an important reservoir of infection. Management of dog populations was difficult and a euthanasia policy was undertaken in northern Spain and an impoundment policy in northern Sardinia, the latter becoming unsustainable.

In the La Rioja, scheme interventions were overall highly successful and included euthanisation of 500–1000 stray dogs per year a proportion of which were necropsied to provide canine echinococcosis prevalence information contributing to the surveillance data, which showed a fall from 7% to 0.2% after 10 years of dog dosing (Jimenez et al., 2002).

4.2.2 China: Hutubi, Datangma, Shiqu

4.2.2.1 Hutubi (Xinjiang)

Xinjiang Uygur Autonomous Region in northwest China is the largest administrative region of the country and remains highly endemic for human

CE (National Hydatid Disease Center of China, 1993; McManus, 2014). A 3-year (1987–90)-pilot control programme was introduced in Hutubi County, mainly Han Chinese area (human CE incidence 43.8 per 100,000) with a mean of 0.86 dogs per household (Andersen et al., 1991). It emphasized supervised monthly deworming of registered dogs using a novel biscuit-baited formulation of PZQ (Chi, 1993), together with stray dog population management and health education (Andersen et al., 1991; Zhang et al., 2009b). Surveillance was based on arecoline purge prevalence in dogs, and ovine CE prevalence in cohorts of purchased sheep. Over a 3 year period canine echinococcosis prevalence was reported to have reduced from 18.5% to 0%, and ovine CE from 88.8% to 5.6%. In total >1200 unwanted dogs were culled and a distemper epidemic in 1988–89 further reduced the dog population by >25% (Zhang et al., 2009b). Community participation was also reported to be excellent even including contribution by dog owners to the cost of dog treatments (US$ 5.2 per year).

The Xinjiang pilot hydatid control scheme in Hutubi in the late 1980s helped to provide evidence that control of CE by efficient registration and dosing of dogs, using Chinese manufactured PZQ, was possible in settled poor livestock-keeping communities in China. As a result that study and others subsequently contributed to the development of a National Hydatid Control Programme launched in 2006 (Zhang et al., 2015). The challenge for the new national programme, however, would be its roll-out and implementation in hard-to-reach semi-nomadic ethnic Tibetan, Kazakh and Mongolian communities dispersed over several provinces in western China. Two such areas were Datangma and Shiqu counties in the Ganze Tibetan Autonomous Prefecture situated on the eastern Tibetan Plateau (3900–5000m altitude) in northwest Sichuan Province, a provincial region where township human CE prevalence (by ultrasound) ranged from 1% to >10% and where human AE disease (<1% to >9%) was also highly coendemic (Li et al., 2010).

4.2.2.2 Datangma (Sichuan)

A pilot intervention scheme, funded by the New Zealand Agency for International Development , was implemented in Datangma County (Ganze Tibetan Autonomous Prefecture, Sichuan Province) in four remote high altitude (>4000m) Tibetan townships (human CE prevalence 0.91–2.61%, human AE 2.59–6.35%) from 2000 to 2005. The pilot comprised twice annual dosing (April and October) of owned (n = >4200 dogs) and stray dogs (~1500) with PZQ, inclusion of a

Tibetan health education programme, and the use of the EG95 vaccine for sheep and goats with annual booster vaccination in autumn (Heath et al., 2006; Yang et al., 2009). Surveillance and monitoring was done by coproantigen testing and also necropsy of a subsample of dogs, serology for EG95 antibodies was carried out in small ruminants, also by meat inspection of purchased cohorts of sheep/goats and 4-year-old yaks. The human population was screened by ultrasound at voluntary clinics, and annual questionnaire surveys were administered to assess positive changes in knowledge and behaviour relating to transmission and hygiene (Heath et al., 2006).

After 5 years of the pilot scheme, the coproantigen prevalence in owned dogs had dropped from 50% to 17%, while necropsy of strays showed a reduction from 63% (includes both *E. granulosus* and *E. multilocularis*) to 36% prevalence. Prevalence in 4-year-old yaks and in <1−6-year-old sheep/goats after 3 years remained high at 38% for both (Yang et al., 2009). Community compliance was, however, not very good and about 25% of Tibetan households did not accept either dog dosing nor livestock vaccination. Serological testing of small ruminants indicated that around 50% had not been vaccinated; furthermore, only around 10% of people attended initial ultrasound screening clinics and even less in subsequent surveys (Heath et al., 2006). This pilot study indicated the great difficulties in applying and sustaining hydatid control measures and effective surveillance in Tibetan communities and also the complication for control in regions where dogs are involved in transmission of both *E. granulosus* and *E. multilocularis* (Lembo et al.,2013).

4.2.2.3 Shiqu (Sichuan), and the China National Programme

From 2006 the Chinese Ministry of Health launched an ambitious echinococcosis control programme at national level, which was initiated in 10 highly endemic counties in northwest Sichuan Province (including Datangma and Shiqu counties) and then extended to 170 counties in 7 provinces/regions (i.e., Sichuan, Qinghai, Gansu, Ningxia, Tibet AR, Xinjiang, Inner Mongolia) (WHO, 2011; Zhang et al., 2015). In Sichuan Province alone there were an estimated 27,000 human echinococcosis cases of which the majority were of Tibetan ethnicity, also livestock CE prevalence was 40−80% (Wang et al., 2008). The main intervention measures proposed were dog deworming using PZQ at monthly intervals and health education including encouragement of community participation. This was accompanied by free or heavily subsidized treatment of human CE and AE cases (albendazole and/or surgery), community mass ultrasound screening (with serology) and annual coproantigen surveillance in samples of owned dogs. Shiqu County (area 25,000 km^2, mean elevation 4200 m) had a population of approximately 63,000 people (97% Tibetan) with an estimated livestock population (yak, sheep, goats, horses) of 581,000, a dog population of 30,000 (including >4000 strays/community owned) and a mean of 1.34 dogs per family (Budke et al., 2005b; Wang et al., 2006a,b).

In 2002–03 human CE prevalence was 4.9% and AE 6.2% (Tiaoying et al., 2005). Infection rates in dogs by arecoline purgation for *E. granulosus* and *E. multilocularis* were 8% and 12% respectively in 2002–03 (Budke et al., 2005a), and 21% by *Echinococcus* coproantigen ELISA in 2006 (Moss et al., 2013). Although the National Hydatid Programme aimed at monthly dog dosing, this was very difficult to achieve in Shiqu County due to the dispersed Tibetan population and seasonal problems including: severe winters, the mass movement of people, dogs and livestock to summer pastures and springtime activities for traditional medicine collection of 'winter worm' (*Cordyceps sinensis*). Consequently dosing of dogs was aimed at 3–4 times per year (spring, early summer, late autumn and early spring) to be managed by local Centers for Disease Control veterinary technicians. Technicians either carried out supervised dosing or more usually placed reliance on owners to dose their dogs with drug provided free to township dispensaries. After approximately 6years canine copro-prevalence in five townships in Shiqu was reportedly below 1% (Q. Wang, personal communication). The attack phase was ongoing in 2015–16 in Shiqu County with continued evidence of a low copro-prevalence, however, seasonal logistic problems resulted in reduced dog-dosing cover. Human CE and AE age-specific ultrasound prevalence rates are under analysis to help assess any reduction in the younger age groups.

In other areas of China, for example, Hobukesar Mongolian Autonomous County in northwest Xinjiang, the National Control Programme struggled to achieve monthly dosing of owned dogs with some communities reporting only 22% of dogs dosed within six weeks of sampling. Also 41.3% of owned dogs were coproantigen positive and 42% (16/38) of necropsied unwanted dogs were infected with *E. granulosus* (van Kesteren et al., 2015).

4.3 Reasons for success and problematic outcomes in cystic echinococcosis control

Since the 1960s at least 18 hydatid control programmes, schemes or pilots have been carried out or initiated, with periods lasting from 3 to 5 years to >40 years (see Table 1). The four island programmes that were initiated between the late 1950s and early 1970s, i.e., New Zealand, Tasmania, Falkland Islands and Cyprus, were overall highly successful so that human CE has either been eliminated or is not a significant public health problem in those territories (see reviews by Gemmell, 1990; Gemmell and Roberts, 1998; Craig and Larrieu, 2006; Lightowlers, 2012); furthermore, transmission to humans had virtually ceased within 10 years of the start of vertical interventions (Gemmell et al., 2001). Common enhancing elements in these four programmes were: well structured agricultural sectors, largely literate and compliant rural populations, good veterinary outreach networks, a control authority under a Ministry of Agriculture, sustained ability to undertake supervised dog dosing with PZQ 4–8 times per year (New Zealand, Falklands) or arecoline testing at least once per year with punative quarantine (Tasmania) or euthanasia (Cyprus), efficient local abattoir inspection for surveillance in sheep, good medical data on regional incidence, and ability to transfer from an attack phase (primarily dog dosing) to a consolidation phase (i.e., abattoir surveillance and trace-back). Formal health education components were included in all programmes but appeared to have had little or no direct impact prior to the application of dog-targeted vertical interventions (Gemmell et al., 2001).

4.3.1 South American cystic echinococcosis control programmes

The above features described for the Island programmes were present and contributed to the positive outcome for three large continental-based hydatid control programmes in South America. All had adopted an 'Option 5' control approach (i.e., regular dosing of dogs with PZQ), i.e., Rio Negro (Argentina), Region XII (Chile) and Uruguay. Problems caused by a low percentage of dogs treated had slowed initial efforts in Uruguay pre-1990, which was managed by an honorary commission, but became effective when that Commission was restructured under the Ministry of Agriculture (Larrieu and Zanini, 2012). Large reductions in prevalence of ovine CE and canine echinococcosis within 5–6 years in the Region XII (Chile) programme led to a premature relaxation of dog-dosing frequency by the Ministry of Agriculture from eight times per year to four times per year then to twice per year, which resulted in a prevalence plateau in lambs at around 5%. Subsequently dosing was reintroduced to eight times per year that successfully reduced CE prevalence in lambs (Gemmell and Schantz, 1997). Transmission to humans, especially children <15 years old, significantly reduced in Rio Negro (Argentina) but has not been eliminated, in part due to logistics of dosing dogs eight times per year. A pilot to include sheep vaccination with EG95 was assessed in Rio Negro, and indicated good protection in sheep <5 years old (Larrieu et al., 2015).

4.3.2 Smaller cystic echinococcosis control schemes

In several smaller hydatid control programmes or schemes undertaken in settled rural sheep–raising communities, e.g., Sanpete County (Utah, USA), Powys County (mid-Wales, UK), La Rioja (Spain) and Hutubi County (China), there were good outcomes reported for sheep and dog infection data within 3–10 years of interventions starting (Andersen et al., 1981; Palmer et al., 1996; Jimenez et al., 2002; Carmena et al., 2008; Zhang et al., 2009b). In these four areas human CE appears not now to be an important public health problem. A key feature for success was well structured and motivated veterinary teams and compliant endemic communities that were encouraged to accept control measures by targeted information and health education. Also all these schemes included either 'Tasmania-style' dog testing field clinics with arecoline (Utah) or 'Chilean-style' regular supervised dog dosing with PZQ (mid-Wales, La Rioja, Hutubi).

4.3.3 Transfer from attack to consolidation phase

One problem for hydatid control, whether a larger or a smaller programme, is sustainability of the 'attack phase' and timing for conversion to a surveillance-based 'consolidation phase'. The costly attack phase should be under effective veterinary services with existing proven rural outreach and have reliable annual funding planned for a minimum of 5–10 years of dog-targeted measures (Gemmell and Schantz, 1997; Gemmell et al., 2001; Lembo et al., 2013). For example, funding for the attack phase in the mid-Wales programme was cut after 6 years and that effectively converted the campaign from an Option 5 'vertical' programme (i.e., frequent dosing with PZQ) to an Option 2 style 'horizontal' programme based on health promotion only. This probably led to the reemergence of echinococcosis in sheep and dogs within 5–10 years of ceasing interventions (Lloyd et al., 1998; Buishi et al., 2005b; Craig and Larrieu, 2006). A well-funded hydatid control programme in Sardinia failed, in large part, because of poor outreach and poor acceptance by sheep farmers (Conchedda et al., 2002).

Successful transformation from the attack phase to a less costly consolidation phase has required effective meat inspection and subsequent quarantine of premises/farms/ranches with infected livestock and also movement controls of livestock and dogs (Gemmell et al., 2001). This can be achieved in 10–15 years as occurred in Tasmania, Cyprus, Utah and Chile, but may take longer. Delayed transfer to a consolidation phase was the case in the New Zealand and Uruguay programmes where Honorary Commissions lacked the ability to undertake trace-back from abattoirs and were unable to enforce quarantine measures until they were restructured or replaced by the Ministry of Agriculture. Temporary or longer term reapplication of control measures, i.e., dog dosing, may be required during the consolidation phase as a result of trace-back of hydatid positive sheep at meat inspection, as occurred in Cyprus in the 1990s and in the Falkland Islands in 2000s (Lembo et al., 2013). Evidence of reemergence of hydatidosis in livestock in northern Tasmania in 2006 resulted in reactive local screening of farm dogs and high alert of authorities for potential increase in transmission (Jenkins et al., 2014). The important outcome of effective hydatid control is a significant reduction in incidence and prevalence of transmission in both livestock and dogs and in parallel fewer new human cases. However, interpretation of surveillance data needs care because a low prevalence situation, as a result of successful interventions, can lead to lower sensitivity and predictive values of surveillance measures, for example, copro-diagnostic tests in dogs and meat-inspection in lambs (Craig et al., 2015).

4.3.4 Control of cystic echinococcosis in semi-nomadic and poor pastoral communities

Hydatid control programmes have, perhaps, predictably fared less well when undertaken or attempted in underdeveloped regions characterized by transhumance pastoralism, semi-nomadism or nomadic lifestyles (Craig et al., 2007a; Lembo et al., 2013). For example, programmes undertaken in parts of East Africa, the Tibetan Plateau and in Central Asia. This may be due to many factors but include regions that are remote and harsh marginal zones, lack of roads and transport, poor general infrastructures, medically neglected illiterate populations, frequently hard-to-reach seasonally mobile populations of poor livestock keepers, lack of centralized livestock slaughter, and suspicious populations that are hard to engage (Macpherson, 1995; Zinsstag et al., 2006; Craig et al., 2007a). Planning and securing funding for control and appropriate surveillance from health or agriculture sectors are therefore difficult. Sustaining an effective attack phase (i.e., Options 3–6) that can reach >70% of owned dogs several times per year for several years is extremely challenging but has been at least partially successful in Turkana nomad communities in northwest Kenya (Machpherson and Wachira, 1997) and in Tibetan semi-nomadic communities in northwest Sichuan Province (Heath et al., 2006).

In these kinds of remote endemic areas, it could be more effective to consider grouping together several zoonotic diseases (e.g., echinococcosis, brucellosis, rabies, anthrax and/or leishmaniasis) and even include nonzoonotic human diseases (e.g., TB, vaccine-preventable diseases, sexually transmitted diseases, gastrointestinal infections, nutritional deficiencies) in a 'One Health' approach of veterinary-medical cooperation. This could provide cost benefits and economies of scale and man power, more effective outreach and appropriate setting-specific multiintervention approaches (Schwabe, 1991; WHO, 2010a,b; Marcotty et al., 2013; Rabinowitz et al., 2013).

5. TARGETS AND TOOLS FOR CONTROL OF *ECHINOCOCCUS MULTILOCULARIS*

The life cycle (and therewith the zoonotic risk) of *E. granulosus* depends mainly on domestic animals, which are under direct control of the animal keepers. As for *E. granulosus*, domestic dogs can be an important or even the main source for human infections and should always be regarded as an important target for control measures against *E. multilocularis*. However, in contrast to *E. granulosus*, its life cycle is mainly maintained by wild intermediate and final hosts, which are much more difficult to manage than owned dogs and livestock. Even where domestic dogs are considered to be the main source for human infections, the cycle frequently is closely related to wild canids that contaminate rodent or other small mammal habitats with infective eggs. Therefore over large areas the main targets for the control of *E. multilocularis* life cycle are wild canids, mainly the adaptive and ubiquitous red fox (*Vulpes vulpes*) and abundant susceptible rodent species (mainly members of the family Cricetidae), which are frequently predated by final hosts.

Control and prevention measures for human AE can be taken at different levels (Hegglin and Deplazes, 2013). Hygiene-linked measures and frequent deworming of domestic dogs are important tools to reduce exposure to infective parasite eggs and can be pursued on an individual level. On an environmental level, measures to reduce the contamination with infective *E. multilocularis* eggs aim at the direct control of the parasite by deworming definitive hosts or at the control of the wildlife host populations. Population control measures for the fox definitive host, mainly hunting, trapping and culling methods have been proposed in the past. However, also ecological changes (e.g., changes in agricultural methods or in the predator community) and their effect on host populations should be considered when interventions in the host populations are discussed (Hegglin and Deplazes, 2013). Japan and France have proven the feasibility to lower the infection pressure with *E. multilocularis* eggs by deworming red foxes on the basis of regular baiting campaigns.

5.1 Targetting fox populations for control of *Echinococcus multilocularis*

5.1.1 Culling fox populations

The substantial increase in prevalence rates and the spread of *E. multilocularis* to new regions observed in many European countries have been attributed to increasing population densities of red foxes after the eradication of rabies as a major mortality factor for this species (e.g., Schweiger et al., 2007). Therefore there is good reason to consider culling foxes as an effective measure to control *E. multilocularis*. Indeed hunting activities strongly affect wildlife populations. However, the effects of hunting and culling on wildlife can be very complex, and there is a broad debate on how such interventions are shaping red fox populations and if they really can contribute to lower the infection risk for human AE.

Heydon and Reynolds (2000) gave evidence that intensive culling under strict conditions can reduce fox population densities even in extended areas. Nevertheless, it is generally accepted that in most settings the regulation of fox populations is difficult to achieve on a larger scale (Baker et al., 2000). Hunting foxes is not as attractive as it was in the past, especially as fox fur prices are very low and therefore fox carcasses are usually disposed without making any use of the dead animals. Accordingly the population losses of regular hunting activities are easily buffered by a fox population, as the red fox has a high reproduction rate and any possible regulating effects of culling are hampered by compensatory mortality because the natural mortality in fox population is generally high. Furthermore, it is difficult to maintain a strong hunting pressure on a larger scale as fox hunting is time-consuming and requires substantial man power. Therefore, foxes can rapidly recruit and compensate for losses within a population or swiftly recolonize vacant territories (Newsome et al., 2014). There may also be ethical objections to fox hunting.

A strong compensatory density feedback was found to be acting through immigration, allowing red fox populations to resist high culling rates (Lieury et al., 2015). Furthermore, hunting can have strong impacts on the population dynamics (Minnie et al., 2016) and has to be considered in regard to disease transmission (Woodroffe, 2007). For instance, culling can increase the proportion of subadult foxes, which disperse over large distances (Harris, 1977; Harris and Trewhella, 1988). This could result in a higher spatial dynamic of parasite transmission and also boost the parasite biomass as subadult foxes can harbour higher worm burdens (Hofer et al., 2000; Morishima et al., 1999; Fischer et al., 2005). This assumption is supported by a recent French study. In a periurban area around Nancy, the proportion of immature foxes and also the prevalence of *E. multilocularis* (after an initial slight decrease) increased to significantly higher levels in areas with a high hunting pressure than compared to control areas (Comte et al., 2014).

The difficulty to control red fox populations is supported by observations from Australia where the introduced nonnative red fox population is treated as a pest species and thus much less protected by animal-welfare regulations in contrast to many other countries. However, although poisoning programmes are an accepted management method, control objectives are only partly achieved (Gentle et al., 2007). Hegglin et al. (2015) discussed possible behavioural effects of fox hunting that could be relevant for transmission of *E. multilocularis*. Hunting activity by humans can be regarded as a type of predation that not only has the direct effect of mortality but also results in behavioural responses of prey species to lower the 'predation' risk. In particular, this risk increases vigilance and decreases boldness. Shy wildlife is more restricted in its activity periods and its spatial behaviour and therefore has limited access to essential resources, which in turn could limit the population growth especially in and near urban settings (Kotler et al., 1994; Tambling et al., 2015). This hypothesis is supported by the fact that foxes — which are known nocturnal species — can quickly shift their activity pattern and become active during the daytime in reserves with no hunting activities (Servin et al., 1991). Cromsigt et al. (2013) discussed how such behavioural effects of hunting could be used for the management of wildlife by directly targeting the hunting strategies or the behavioural response of hunted species ('hunting for fear').

5.1.2 Praziquantel baits for fox populations

Baiting foxes has already been a very successful technique to control a zoonotic agent. In the 1960s the fight against the spread of rabies in Europe started with strong efforts to control the fox population densities by extensive culling. However, control and finally eradication of rabies was only possible when oral vaccine baiting campaigns were initiated in the 1970s. In the late 1980s the first field trials were performed to assess the suitability of this successful technique also for the control of *E. multilocularis* by the delivery of deworming baits for foxes.

It was clear, however, from the beginning that the *E. multilocularis* cycle is much more resistant to such an intervention than rabies. Whereas rabies vaccinated foxes have lifelong protection from rabies virus infections, dewormed foxes (using PZQ baits) can be reinfected at any time after treatment as soon as they predate on infected intermediate hosts. A further challenge is longevity of the parasite eggs and the larval stages which are not affected by the anthelmintic treatment of foxes. The metacestode stages in the intermediate host and infective eggs in the environment can survive from several months to more than one year (Veit et al., 1995). This means that individual foxes have to be dewormed at regular intervals. The prepatency period for *E. multilocularis* is roughly 30 days. Therefore it is necessary to deworm individual foxes at monthly intervals if an intervention aims at completely disrupting the life cycle. Regarding these challenges the control of *E. multilocularis* by baiting red foxes is much costlier than control against rabies and it is unlikely to eradicate the parasite over large areas (Hegglin and Deplazes, 2013). However, different studies from Germany, Switzerland, Japan, Slovak Republic and France have proven the feasibility to lower infection pressure with *E.multilocularis* eggs by deworming red foxes based on regular baiting campaigns (see Table 5).

5.1.3 Fox population ecology

Fox densities can strongly be affected by infectious diseases like mange or rabies. In Great Britain and Sweden, sarcoptic mange was responsible for strong population declines of up to 95% (Baker et al., 2000; Soulsbury et al., 2007) and there is strong evidence that red fox populations were also heavily affected over larger parts of Europe by rabies during the epizootic periods in the 1960s (Chautan et al., 2000; Hegglin et al., 2015).

In many countries red fox densities have increased strongly after the elimination of rabies and reached densities that never have been recorded before. Also in regions where rabies never has been detected increases of fox populations have been recorded, e.g., Donaña National Park and the United Kingdom (Chautan et al., 2000). This long-term increase of many fox populations is considered to be related to the opportunistic feeding

Table 5 Experimental setting of different studies for the control of *Echinococcus multilocularis* by distributing Praziquantel baits for foxes

Positive samples after treatment (%)		Low (<7%)						Medium (8–18%)					Failure	
Study[a]		**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**J**	**E**
Treatment area (km^2)	Large (432–4568)	X	X					X						
	Medium (33–213)			X	X	X			X	X			X	
	Small (1–6)						X				X	X		X
Bait density (baits/km^2)	High (40–50)				X	X	X					X	X	
	Low (15–20)	X	X	X				X	X	X	X			X
Bait frequency (campaign/year)	Monthly (12)				X		X				X			X
	Not monthly (<10)	X	X	X		X		X	X	X		X	X	

The studies are grouped depending on the outcome of the experimental baiting measured by the investigation of fox intestines or copro-tests (low: significant decrease of parasite abundance end final portion of positive samples <7%; medium: significant decrease of parasite abundance end final portion of positive samples between 8 and 18%; failure: no significant effect on parasite abundance detected: (A) Schelling et al., 1997; (B) Tackmann et al., 2001; (C) Tsukada et al., 2002; (D) Koenig et al., 2008; (E) Comte et al., 2013; (F) Hegglin et al., 2003; (G) Romig et al., 2007; (H) Takahashi et al., 2013; (I) Inoue et al., 2007; (J) Antolova et al., 2006; (K) Hegglin and Deplazes, 2008.

[a]Analyses of parasite abundance by intestinal scrapping technique (A, B, D, G), sedimentation technique (I), necropsy (H), taenid eggs (C), copro-antigen ELISA (E, F, J, K).

behaviour of foxes as they can profit from increased agricultural productivity and a throwaway mentality in prosperous economies. In urbanized areas food resources for foxes are readily available. It has been shown that four average households in Zurich provide enough food (e.g., food waste, compost, garden fruits) to feed an adult fox (Contesse et al., 2004). Correspondingly, an Israeli study showed how red fox densities decreased after an experimental reduction of anthropogenic food resources (Bino et al., 2010). Thus the variation in the available food resources for foxes has to be considered as an important determinant to explain fox densities and therewith the transmission dynamic of *E. multilocularis*.

In many countries populations of large carnivores have decreased dramatically and became extinct over large areas during the 19th and 20th Centuries. It is likely that the red fox as a medium-sized predator profited also from this development as competition and intraguild predation is a strong driver of population dynamics in predator communities. It is known that larger canid species generally do not tolerate smaller canid species in their range. For example, it has been shown in North America that wolves reduce coyote densities and coyotes in turn lower densities of grey, swift and red fox populations, by competition, agonistic behaviour and/or by direct predation (Berger and Conner, 2008; Fedriani et al., 2000). A similar pattern has also been shown in Australia where dingo abundance negatively correlates with fox abundance (Colman et al., 2014). In many regions of Europe, formerly extinct large predators like wolves and lynx are making comebacks as a consequence of strong protection and ongoing conservation programmes. This development possibly can affect the dynamic of red fox populations (Helldin et al., 2006; Ritchie and Johnson, 2009) and therewith also the dynamic of *E. multilocularis* transmission in those regions.

5.2 Targetting dogs for control of *Echinococcus multilocularis*

Dogs are an excellent host for *E. multilocularis* as evidenced from natural infections (Rausch et al., 1990; Craig et al., 1992; Budke et al., 2005c; Deplazes et al., 2011) and from experimental infections (e.g., Kapel et al., 2006). Dog ownership or contact in endemic areas appears to increase the risk of acquiring human AE (Kern et al., 2004; Wang et al., 2014). Therefore deworming dogs to reduce biomass of worms and environmental contamination is an important aspect of control especially to reduce the risk of human AE disease (Hegglin and Deplazes, 2013). Dogs have an important role in transmission of *E. multilocularis* in parts of Eurasia with epidemiological studies recording postmortem or arecoline purge prevalences of 10–19% in western China (Craig et al., 1992; Budke et al., 2005c), 18% in Kyrgyzstan (Ziadinov et al., 2008) and 5% in south Kazahkstan (Torgerson, 2013). The potential role of dogs in zoonotic risk for human AE in Europe is also gaining increased acknowledgement (Hegglin and Deplazes, 2013).

There are several studies, mainly in China and Central Asia that have demonstrated high prevalences of *Echinococcus multilocularis* in dogs (Budke et al., 2005a; Ziadinov et al., 2008). Furthermore, in regions with high prevalences of *E. multilocularis* in dogs there is frequently a high incidence of human AE (Craig et al., 2000; Tiaoying et al., 2005; Torgerson, 2013; Usubalieva et al., 2013; Wang et al., 2014, 2006a,b; Yang et al., 2006). It has been hypothesized that the close contact between dogs and humans may be an important factor resulting in the high incidence of human AE in such regions. Where dogs are infected, then routine treatment with PZQ is essential to prevent transmission to humans. As many of these areas are coendemic for *E. granulosus*, a dog treatment programme to control CE will contribute to ameliorating transmission of AE to humans. However, the life expectancy of *E. multilocularis* in dogs is only about 90 days (Kapel et al., 2006) – somewhat shorter than the estimated life expectancy of *E. granulosus* of approximately 10–12 months (Torgerson and Heath, 2003).

This has a very important implications in populations of dogs with a similar prevalence of *E. granulosus* and *E. multilocularis* (for example, in Kyrgyzstan or the Tibetan plateau see Budke et al., 2005a; Ziadinov et al., 2008). There may be a much higher infection pressure and infection frequency of *E. multilocularis* to dogs compared to *E. granulosus*. So whilst treating dogs four times a year might be sufficient to reduce the transmission of *E. granulosus* it might have much less effect on *E. multilocularis* because of the probable more rapid reinfection rate. Therefore an increased frequency of treatment might be required. It also appears likely that in these communities *E. multilocularis* has developed an anthropogenic cycle between dogs and small rodents. This would help facilitate the control of AE as dosing of dogs would then reduce infections in rodents with a subsequent negative feedback to dogs and long-term reduction in infection pressure (Moss et al., 2013). In contrast if it were purely a spill over from a fox–rodent cycle, the infection rates in rodents would remain unaffected by treatment of dogs as they would be continuously be infected from foxes. In such a scenario the routine treatment of dogs would be seen as a permanent measure to prevent human infection (Rausch et al., 1990).

Where dogs are an important definitive host of *E. multilocularis,* then many of the schemes to control dog populations described for the control of *E. granulosus* would be applicable to prevent AE transmission. High prevalences in dogs are often found in communities, such as the Tibetan plateau or rural Kyrgyzstan, where there is widespread poverty. A consequence of this is that dogs may not receive enough food from their owners so are forced to scavenge or hunt small mammals such as rodents. Ziadinov et al. (2008), for example, found that free-roaming dogs in central Kyrgyzstan were more likely to be infected with *E. multilocularis*.

5.2.1 *Praziquantel dosing of dogs for* Echinococcus multilocularis

Experimental infections in dogs can be terminated using PZQ at 5 mg/kg (Eckert et al., 2001). The prepatent period of *E. multilocularis* in experimentally infected dogs was around 30 days (Kapel et al., 2006) and therefore a monthly (4 weekly) dosing frequency (rather than six weekly as recommended for *E. granulosus*) would be justified from a theoretical transmission viewpoint. In areas where human AE and human CE are coendemic (e.g., Kyrgyzstan, northwest Sichuan), then regular dosing of owned dogs with PZQ at a frequency of 4–8 times per year, as routinely carried out for control of *E. granulosus* (see Section 2.2.2), will also have an impact on *E. multilocularis* and reduce the risk human AE as well as CE. However, because of the shorter prepatent period for *E. multilocularis* in dogs (i.e., 30 days vs. 42 days for *E. granulosus* s.l) the potential for reinfection of dogs with *E. multilocularis* (if they predate/scavenge small mammals) would be greater than for *E. granulosus*.

A reinfection study that followed a cohort of 276 owned dogs in Tibetan communities of Shiqu County (Sichuan) after a single treatment with PZQ indicated a baseline copro-PCR prevalence for *E. multilocularis* of 11.2% and a reinfection prevalence of 2.9% after only 2 months posttreatment (Moss et al., 2013). In such regions monthly dog dosing with PZQ would be the gold-standard to reduce or eliminate viable canine infections with *E. multilocularis*, but seasonal factors and semi-nomadic movements make that extremely difficult to achieve. Very few *Echinococcus* control programmes could effectively undertake monthly dog dosing for sustained periods (>3 years) even if they have good resources. Nevertheless, this has been recommended for western China because both CE and AE are coendemic in many regions (Craig, 2004; Li et al., 2010; Huang et al., 2008; WHO, 2011), but this is very unlikely to be achievable in all areas (van Kesteren et al., 2015).

An intensive dog-dosing scheme using PZQ (5 mg/kg) at monthly intervals for 10 years was introduced into an Inuit community on St Lawrence Island (Alaska) through the 1980s to reduce the village-level transmission of *E. multilocularis* and eliminate human AE as a public health problem (Rausch et al., 1990). The impact of dog-dosing intervention was measured by monitoring prevalence of AE infection in commensal vole populations of *Microtus oeconomus*, which decreased from 29% to 1–5% after 10 years, despite the continued transmission between voles and arctic foxes outside the village (Rausch et al., 1990).

5.2.2 Dog population management and control of alveolar echinococcosis

The same considerations and criteria apply here as described in Section 2.2.3. In some AE endemic regions in Asia, stray dog, unowned dogs and/or community-owned free-roaming dogs, as well as free-roaming owned dogs, can potentially contribute to the zoonotic risk and even transmission of *E. multilocularis* (Budke et al., 2005a; Vaniscotte et al., 2011; Moss et al., 2013; van Kesteren et al., 2013). In Tibetan communities in Ganze Prefecture

(Sichuan, China) presence of a Buddhist temple in or near a village often increased stray dog or community-dog populations because monks usually feed dogs. Culling dog numbers or impounding animals in such communities is either not accepted or not sustainable (Wang et al., 2014). The use of PZQ baits to dose stray dogs may be a useful approach, if affordable.

5.3 Small mammal populations and control of *Echinococcus multilocularis*

Rodents and other ground-foraging small mammals are an important component of the food web and can provide ecosystem services such as soil aeration and fertilization (Jacob et al., 2014; Martin, 2003). However, some rodent species can cause substantial economic losses due to their high reproductive rate and the high densities they can reach. For example, in Europe two fossorial rodent species, the common vole (*Microtus arvalis*) which, together with *Arvicola scherman*, is considered as the most important intermediate host for *E. multilocularis* over a large part of Europe can begin reproducing at only two weeks of age (three week gestation period) with an average five to six pups per litter and 4.5 litters per breeding season thereby reaching population densities of more than 2000 individuals per ha (Jacob et al., 2014). Due to regular population outbreaks they can cause substantial economic damage to grasslands, e.g., in Poland, common voles accounted for a financial loss of about 3.5% of farmers' income (Truszkowski, 1982).

Despite the strong interest of the agriculture sector to prevent rodent induced damage, there are no simple measures to control such pest species sustainably in the long-term. Although rodenticides can effectively reduce rodent populations over large areas (Tobin and Fall, 2004), due to the high reproduction rates many rodent species are resilient to such interventions (Jacob et al., 2014). Furthermore, such interventions can heavily affect the environment by secondary poisoning of predators such as mustelids, canids and raptors (e.g., Giraudoux et al., 2006b) and may also poison domestic dogs (Giraudoux et al., 2013a). Furthermore, it has to be considered that foxes may have certain prey preferences. For example, *Microtus arvalis* is a very attractive prey to red foxes in Europe (Macdonald, 1977). Therefore certain vole species can be predated frequently (and therewith be important for the parasite transmission), even when they occur at low densities (Hegglin et al., 2007). Correspondingly, only minor increases in the abundance of *Arvicola scherman* and *M. arvalis* host species were linked with a strong increase in the infection levels in foxes (Raoul et al., 2010, 2015).This means only when intermediate host populations, of such preferred prey species, can be reduced to a very low level can a substantial decrease of prevalence rates in foxes be expected.

In southern Switzerland, where seven arvicolid species occur, it has been shown how the distribution of *E. multilocularis* is closely linked to the distribution of *M. arvalis* but not to the other six arvicolid species that occur in the region (Guerra et al., 2014). A Japanese study demonstrated how changing vole densities affected the prevalence rates in red foxes (Saitoh and Takahashi, 1998). Thereby, it has to be considered that agricultural practices and landscape management are important determinants for rodent communities and thus can shape the transmission dynamics of *E. multilocularis* (Giraudoux et al., 2002; Viel et al., 1999). Thus changes in land management practices could have considerable influence on the incidence rates of AE in humans by influencing rodent communities (Giraudoux et al., 2006a; Viel et al., 1999; Wang et al., 2006b). For example, it has been shown in the Massif Central, France, that the risk for outbreaks of *A. scherman* populations is high in regions where the proportion of permanent grassland exceeds 90% and low in regions where this proportion is <80% (Fichet-Calvet et al., 2000). It is, therefore, worth considering how agricultural practices and landscape management sustain high densities of known or potential intermediate hosts (Giraudoux et al., 1997). Altering the habitat and reducing its potential for maintaining populations of relevant small mammal intermediate host species near human settlements could play an important role in the framework of integrated control programmes (Hegglin and Deplazes, 2013; Giraudoux et al., 2013b).

5.4 Modelling the transmission of *Echinococcus multilocularis*

There have been a number of mathematical models developed to describe the transmission of *E. multilocularis*. These include relatively simple extensions of the models developed by Roberts for *E. granulosus* (Roberts, 1994). This model has been used to consider the infection pressure to dogs in China (Budke et al., 2005b) and to describe the force of infection to foxes in Switzerland (Lewis et al., 2014). In this case the models have a simple 'black box' approach that only examines the infection pressure to the definitive host and some aspect of parasite–host ecology. It does not incorporate any analysis of the population dynamics of rodents.

Despite this relative simplicity, the models can estimate the likely frequency of infection and any seasonal variations in such force of infection. Thus it should be possible to use the results of such a model to target fox baiting in the most cost-effective manner (Lewis et al., 2014). Thus baits could be distributed more frequently in seasons when the force of infection is at its highest and less frequently at other times of year. This would likely be both more effective and more cost-effective than simply distributing baits at a fixed frequency. Other models have demonstrated that once treatment has successfully reduced fox prevalence, treatment of the definitive host needs to continue as otherwise the parasite is likely to reemerge from a remaining persistence of the larval stage in intermediate hosts (Takumi and Van der Giessen, 2005). This has been confirmed by field observations in Germany and Switzerland where there was a rapid rebound in fox prevalence following cessation of baiting campaigns (Hegglin and Deplazes, 2008; Romig et al., 2007).

More complex models have also incorporated seasonal dynamics of rodent populations which also helps to clarify the dynamics of seasonal transmission (Ishikawa et al., 2003). These models also can be used to estimate the basic reproductive number or R_0 and possibly what type of interventions could drive R_0 below 1, which is required to control or eliminate the parasite. However, the force on infection rather than R_0 could be a more useful parameter to estimate from the point of view of control (Lewis et al., 2014).

Another important application of a transmission model has been to estimate the risk of introducing the parasite into a previously nonendemic area by dogs. The United Kingdom, Ireland, Finland and Malta currently have derogations from EU law that allows them to obligate the praziquantel treatment of dogs before the dog is allowed into the country. Torgerson and Craig (2009) used this model to estimate the probability of a dog becoming infected whilst resident or visiting an endemic country such as Germany. Based on the number of dogs entering the United Kingdom and this probability of infection it was possible to conclude that it was virtually inevitable that *E. multilocularis* would be introduced into the United Kingdom if the obligation to treat with PZQ immediately prior to importation was abandoned.

More complex spatial models have modelled the distribution of *E. multilocularis* and could be used to predict the likely future expansion of endemic areas (Staubach et al., 2011; Takumi et al., 2008). Spatial models have also been used to describe and predict the endemic areas of *E. multilocularis* and possible risk of human disease. These have been developed in Germany (Berke, 2001; Berke et al., 2002; Staubach et al., 2011), Belgium (Vervaeke et al., 2006), France (Pleydell et al., 2004) the Netherlands (Takumi et al., 2012) and China (Danson et al., 2003; Graham et al., 2005, 2004; Giraudoux et al., 2013a).

5.5 Health education and prevention of human alveolar echinococcosis

Educational efforts to prevent AE will depend on the major transmission routes to humans. Where dogs are the main source of human infection, then similar efforts to that of CE with an emphasis on dogs is warranted. Here the importance of prevention of dogs scavenging rodents, regular anthelmintic treatment of dogs and routine hygienic precautions taken when there is contact with dogs. As with the case of *E. granulosus*, food is also a possible vehicle of transmission (Torgerson et al., 2015) and the same recommendations for ensuring kitchen gardens are secure from dog (or fox) faeces and the safe preparation of fresh produce can be made. In Europe, it has been shown that the infection risk is clearly linked to a rural life style with working in agriculture or growing own vegetables as important risk factors (Kreidl et al., 1998; Kern et al., 2004; Piarroux et al., 2013). It was further suggested that wild berries, contaminated with fox faeces might also be responsible for transmission to humans. However, there is no epidemiological evidence that this is a major transmission pathway (Kreidl et al., 1998; Kern et al., 2004; Piarroux et al., 2013). Nevertheless, in a recent Polish study, *E. multilocularis* DNA has been reported from 23% of environmental samples including fruits and vegetables collected from forests, but also from plantations and kitchen gardens in Poland (Lass et al., 2015). However, considering the generally low prevalence rates found in wild rodents such a high degree of environmental contamination seems rather unlikely. But generally in Europe such recommendations will depend on the knowledge with regard to *E. multilocularis*, which seem to vary across the European endemic region. For example, fewer people had heard of *E. multilocularis* in the Czech Republic (14%) and France (18%) compared to Germany (63%) and Switzerland (70%) (Hegglin et al., 2008).

6. SURVEILLANCE FOR *ECHINOCOCCUS MULTILOCULARIS*

6.1 Surveillance of alveolar echinococcosis in humans

In Europe where human AE is a rare disease, hospital records and specific registers are important for epidemiological and surveillance data and are reasonably reliable when based on histo-pathological and/or molecular DNA confirmation (Kern et al., 2003; Vuitton et al., 2003, 2015; Said-Ali et al., 2013). In underdeveloped resource-poor endemic regions, for example, in Central Asia and western China, hospital records may be of some value (e.g., Raimkylov et al., 2015), but often do not clearly differentiate AE and CE cases, may misdiagnose AE disease, and pathological details may not be recorded effectively. Furthermore, hospital records are usually more reliable for human CE and may not even closely reflect the burden of human AE disease in the community. This is because human AE usually has a longer asymptomatic period and is also more likely to cause nonspecific symptoms. For example, hospital records examined in south Ningxia Hui Autonomous Region (northwest China) confirmed that 96% of hospital cases were due to CE; however, community mass screening by ultrasound showed that 56% of hepatic cases detected in the surrounding rural communities were actually due to AE and only 44% detected were confirmed as CE (Yang et al., 2006).

6.1.1 Active mass screening for human alveolar echinococcosis

Serological diagnosis for human AE is relatively sensitive and specific for antibody detection in advanced cases using either native antigens or recombinants (Sako et al., 2010) and has been applied as a primary mass screening tool for AE in parts of Europe, northwest China, northern Japan and Alaska, where seropositives were then clinically followed up (Gottstein et al., 1985; Craig et al., 1992; Bresson-Hadni et al., 1994; Ito et al., 2003a). Test sensitivity should be maximized to increase the likelihood of case detection because of the high fatality rate of untreated AE cases (Bartholomot et al., 2002). A seropositive test on its own does not confirm an AE diagnosis and requires an image-based follow-up investigation, e.g., by ultrasound, CT scan, and/or MRI (Brunetti et al., 2010).

Mass screening of humans in resource-poor AE endemic zones in China has been undertaken successfully using portable ultrasound scanners (Craig et al., 1992; Macpherson et al., 2003; Tiaoying et al., 2005; Yang et al., 2006). Furthermore, ultrasound data have been used to provide baseline data and to inform the progress of CE/AE control programmes in China (Li et al., 2010; WHO, 2011). One problem encountered for AE diagnosis during community ultrasound screening in highly endemic (especially under-developed) areas, is the occurrence of small hepatic lesions (0.5–2 cm) of unknown aetiology that could be early AE disease, abortive AE lesions, or due to other causes (e.g., haemangiomas, TB, ascariasis). Serological confirmation may be useful for these query cases (Bartholomot et al., 2002; Yang et al., 2007).

6.2 Surveillance of *Echinococcus multilocularis* in foxes

In recent years, new highly sensitive and specific diagnostic strategies have been developed and knowledge about the spatial distribution is increasing year by year. However, the distribution of the parasite's range is dynamic (Davidson et al., 2012), and there is a need for defining minimal requirements and harmonised approaches for assessing the epidemiological situation and generate comparable results over different countries (Conraths and Deplazes, 2015).

6.2.1 Necropsy

The collection and dissection of foxes is still the most widely used approach to monitor occurrence and the only method allowing estimation of the abundance of *E. multilocularis*. Although applied laboratory techniques (see below) have a high specificity and a sufficient sensitivity for most purposes, they are very laborious and depend on access to fresh fox carcasses and safety requirements (Conraths and Deplazes, 2015). The investigations rely in most cases on hunted foxes during the regular hunting season, or which were found as road kills. This sampling has to be critically assessed as hunting activities are seasonally restricted (mainly winter) and shot foxes do not reflect a random sample (Tryjanowski et al., 2009). Furthermore, hunting interventions affect the fox population dynamic, age structure and the spatial behaviour of the fox population under study which in turn could affect the transmission dynamics of the parasite (Conraths and Deplazes, 2015; Hegglin et al., 2015).

The SCT in several modifications and the less laborious but also less sensitive intestinal scraping technique are the two standard techniques to isolate and identify *E. multilocularis* from the intestines of final hosts (Conraths and Deplazes, 2015). These methods rely on the morphological identifications of *E. multilocularis* and are herewith highly specific (unless in areas where coinfection with *Echinococcus granulosus* are likely). They allow the determination of the development stages (premature, mature and gravid) and to perform quantitative analysis of the parasite burden. The SCT is intended to determine the total biomass of the parasite and has an estimated sensitivity of 83% as determined by a recent comparative study with a highly specific copro-PCR (Wahlstrom et al., 2016).

6.2.2 Serology for Echinococcus multilocularis *in foxes*

Crude parasite antigens or affinity-purified Em2 antigen in ELISA have not been considered as suitable for serological screening mainly due to the persistence of antibodies after elimination of the cestodes and the poor correlation between the presence of specific antibodies in the serum and worms in the intestine (Conraths and Deplazes, 2015; Craig et al., 2003).

6.2.3 *Copro-tests for* Echinococcus multilocularis

The detection of *E. multilocularis* infection in final host populations by coprological tests has several advantages. The sampling does not rely on dead animals and therefore does not affect the population under study. Furthermore, the sampling of faeces has also no seasonal restriction as it is the case for hunting that has to follow the regulations of the local game law and respect closed periods. In addition some coprological methods are rather efficient, e.g., coproantigen ELISA, and are therefore very suitable for monitoring studies over large areas (Sakai et al., 1998; Deplazes et al., 1999). On the other hand, studies based on fox scat samples collected in the field are confronted with several challenges. These include difficulty to assess to which extent different vegetation types and weather conditions affect the detection rate for faeces. Furthermore, the identification of carnivore faeces based on morphological features can sometimes be difficult when no molecular techniques are used to confirm proper identification. Most importantly the sampling of faeces in the field is not suited for determining prevalence rates, as it is difficult to exclude that several samples from one individual have been collected unless genetic analyses, allow the determination of individuals.

Classical routine diagnostic methods to concentrate proglottids and worm eggs from faeces for microscopical detection lack sensitivity and specificity. The morphological differentiation between *E. multilocularis* and other taeniid eggs is not possible. However, an efficient technique to concentrate taeniid eggs with a combination of sequential sieving and flotation in zinc chloride solution (F/Si-method) (Mathis et al., 1996) followed by PCR analyses is a widely used method to identify patent *E. multilocularis* infections. In an experimental study with foxes, the sensitivities for this method were 100% for high patent (30−70 dpi) and 80% for low patent infections (71−90 dpi) (Al Sabi' et al., 2007).

Another approach is direct copro-DNA isolation and amplification; several PCR approaches have been validated and used in epidemiological studies (Conraths and Deplazes, 2015). The most sensitive (81% and 96% for foxes with less and more than 100 worms, respectively) and the costliest method was recently developed for extended studies in a low endemic *E. multilocularis* area in Sweden (Isaksson et al., 2015). This semi-automated magnetic capture probe-based DNA extraction and real-time PCR method (MC-PCR) proved to be similar in sensitivity and specificity as the SCT (Wahlstrohm et al., 2016).

Sandwich ELISA has been proven to be a very efficient way to detect *E. multilocularis* coproantigens in field samples of fox faeces (several tests have been validated and are summarized in Conraths and Deplazes (2015). With this approach 500–800 field samples can be analyzed by one trained person per five working days, which is roughly 5 to 10 times less time-consuming than most PCR techniques (Conraths and Deplazes, 2015). Another advantage is that prepatent infections can also be detected. Depending on the test, sensitivities of 80–87% (compared to SCT) and specificities of 70–95% have been recorded. A recent study based on a latent class analysis revealed a sensitivity of only 55% in dogs (Hartnack et al., 2013). Considering the limited specificity this technique can be used to monitor low endemic areas only when ELISA positive samples can be confirmed with PCR analyses.

6.3 Surveillance of *Echinococcus multilocularis* in dogs

The tools and approaches available for detection and surveillance of *E. multilocularis* in dogs are essentially the same as described for infection in foxes (Section 6.2), i.e., necropsy, coproantigen ELISA and coproPCR, but also includes arecoline purgation as described for detection of *E. granulosus* in dogs (see Section 3.2).

The small average size of *E. multilocularis* tapeworms (2–3 mm), however, presents potential difficulties for necropsy and purge examination, especially in the field, and when worm burdens are low. At necropsy and examination of the dog small intestine (preferably after deep freezing at −80°C for 5 days) the sedimentation and counting technique is a gold-standard for sensitivity and specificity (close to 100%), reported to detect single worm burdens in foxes (Hofer et al., 2000). In AE/CE coendemic areas, it is important to identify samples of adult worms recovered from dogs by morphological or PCR methods (Budke et al., 2005c; Craig et al., 2015). When arecoline purgation is used on dogs then washed purges need to be carefully examined (preferably after boiling or formalin fixation or after bagging and freezing at −80°C) on a black background with a magnifying glass or low power microscopy. *E. multilocularis* infections, including mixed infections with *E. granulosus* s.l, have been detected after arecoline testing, in owned dogs in Tibetan (Budke et al., 2005c) and

Kyrgyz (Ziadinov et al., 2008) pastoral communities that were coendemic for human AE and CE.

Coproantigen detection is a useful primary screening test for *Echinococcus* spp. in dogs (and cats), but is not able to reliably differentiate *E. multilocularis* and *E. granulosus* s.l infections (Mathis and Deplazes, 2006; Allan and Craig, 2006; Huang et al., 2013). Secondary screening using a copro-PCR to amplify species-specific DNA is currently the only laboratory test method to confirm *E. multilocularis* infection in dogs (or foxes) (Dinkel et al., 2011; Boufana et al., 2013; Wahlströhm et al., 2016). This makes mass screening of dogs more difficult, expensive and time-consuming, but can provide useful surveillance data for intervention programmes and epidemiological studies, especially in coendemic areas (Ziadinov et al., 2008; Moss et al., 2013). DNA tests also have the potential to confirm whether dogs and foxes in a transmission zone are infected with the same haplotype of *E. multilocularis*, for example, as described in south Kyrgyzstan (Afonso et al., 2015).

6.4 Surveillance in small mammals

Studies on the distribution and abundance of *E. multilocularis* are generally based on investigations on final hosts as prevalence rates combined with host density estimates can be used to directly assess the environmental contamination with infective *E. multilocularis* eggs. Furthermore, final hosts roam over much larger areas than small rodents and better reflect the parasite population dynamics on a larger scale. However, it is crucial to determine which species act as intermediate hosts to understand the transmission pathways in a given region. With this approach different transmission studies have been described in China (Giraudoux et al., 2013b).

It, therefore, has to be considered that *E. multilocularis* infections in rodents frequently are very heterogeneously distributed over space and time (Liccioli et al., 2014; Burlet et al., 2011). This makes it difficult to get representative samples to assess comparable prevalence rates across different wild rodent species and over larger areas. Thereby, it is important to note that the predation of final hosts on different intermediate host species is a very selective process. Red foxes show preferences for certain prey species and *Microtus* species appear to be more attractive than other arvicolid species, and arvicolid species in general are more attractive than murid species (Macdonald, 1977; Green, 2002). Furthermore, the predation rates on different species can depend to a large extent on the density of a specific rodent and of alternative prey species (Raoul et al., 2015). Therefore, it is important to assess not only the prevalence rates of different rodents species but also to which extent these species are predated by the final hosts (Hegglin et al., 2007).

Investigations on small mammals rely on the dissection of trapped animals and the careful examination of the liver for suspicious lesions. Fertile infections can be identified by microscopical analyses of the suspected metacestode tissue for protoscoleces. Whenever possibly the number of protoscoleces should be estimated to get data on the parasite fertility in different intermediate host species. Visually unidentifiable lesions should be investigated by a PCR specific for *E. multilocularis*. As the age structure of rodent populations usually vary over seasons and years and the prevalence rates increase with age, it is recommended to use age indicators for the dissected rodents (eye lens weight Burlet et al., 2011).

When the situation is very unclear, it is advisable to make exploratory studies where rodent trapping is based on assumptions about the predation on intermediate hosts, where predation is expected and final hosts defecate. Such defined places are supposed to be hot spots and can be starting points to understand the role of different rodent species in a given area.

In some circumstances the trapping of rodents can also be used to document changes in environmental egg contamination. For example, in Zurich a control study investigated the prevalence rates in *A. scherman* in baited and unbaited areas. In this study a lower prevalence in baited studies documented the lower contamination and the lower reinfection level in baited areas. Furthermore, only the abundance of *A. scherman* could be used as an indicator of higher human AE infection pressure (Viel et al., 1999).

7. CRITICAL APPRAISAL OF ALVEOLAR ECHINOCOCCOSIS CONTROL PROGRAMMES

7.1 Island programmes for alveolar echinococcosis control

7.1.1 Reuben Island (Japan)

An early example of the successful control of *E. multilocularis* has been reported from Rebun Island in Japan (Ito et al., 2003a). In 1937 a first case of human AE was diagnosed on this small island, which comprises an area of not more than 83 km^2. In the following decades human AE became highly prevalent and until 1964 a total of 111 patients had been diagnosed for this previously unknown disease on the island. This sudden occurrence of human AE was linked with the introduction of 12 pairs of red foxes, which were imported between 1924 and 1926 for the control of voles and the production of fur (Takahashi et al., 2005). It is reported that poachers were successful in completely eradicating foxes on this island after 1935. In the early 1950s, more than 2000 foxes and 3000 dogs were killed (Eckert et al., 2001) and in the framework of a control programme dogs and cats were captured and autopsied until 1970 (Minagawa, 1999). These efforts proved to be very successful. After 1964 the number of newly diagnosed AE patients dropped sharply and since 1994 no new records of human AE have been registered giving evidence that it was possible to eradicate the parasite completely from the Island (Ito et al., 2003a).

7.1.2 Hokkaido (Japan)

In 1965 another AE endemic area was detected in the Nemuro district, in the eastern part of Hokkaido main island (Takahashi et al., 2005). A total of 148 human AE cases have been recorded between 1965 and 1997 whereby the prevalence rates in foxes strongly increased between 1985 and 1999 (Ito et al., 2003a). The life cycle depends to a large extent on red foxes and their predation on *Clethrionomys* species mainly *Clethrionomys rufocanus* (Takahashi et al., 2005) which lives in the undergrowth of forests and bushland.

Different baiting studies in Hokkaido have demonstrated lower environmental contamination with *E. multilocularis* eggs following the delivery of anthelmintic baits for foxes. PZQ baits have been placed over an area of 90 km^2 near fox dens in monthly intervals during a 13 month period (Tsukada et al., 2002). Taeniid egg detection in fox faeces decreased from 27% to 6% and the prevalence in *C. rufocanus* born after the onset of the baiting campaigns was significantly lower in the baited areas than compared to the nonbaited areas (1.7 vs. 13.5%). A second control study has been conducted in the Nemuro peninsula over an area of 135 km^2 where commercially available PZQ baits were distributed along roads (bait density: 15 baits/km^2) and additionally around fox dens. The prevalence in foxes decreased from 49% to 16% with 27 baiting campaigns during 63 months, whereas it remained stable in a control area of 27 km^2 (Takahashi et al., 2013). Also the distribution of PZQ baits in a highly epizootic suburban area of Otaru proved to be successful in lowering the prevalence in foxes during a period of 43 months with 14 treatments (20 baits/km^2) from 58% to 11% (Inoue et al., 2007).

7.1.3 St. Lawrence Island (Alaska)

A successful control programme was implemented on St. Lawrence Island in Alaska in the late 1970s, where domestic dogs preying on tundra voles (*M. oeconomus*) in villages were frequently infected with *E. multilocularis*. In this area the life cycle depends on the predation by the arctic fox (*Vulpes alopex*) on these voles (Rausch et al., 1990). Before the treatment started the prevalence rates in *M. oeconomus* ranged from 22 to 35% (mean 29%). After 2 years of a monthly delivery of PZQ to owned dogs, the prevalence rates in *M. oeconomus* dropped to a relatively stable value of 5%, thus not only demonstrating that the treatment was effective in establishing a lower reinfection pressure on the dog population but also that the rodents around the villages got infected mainly by parasite eggs excreted by domestic dogs and not arctic foxes (Rausch et al., 1990).

7.2 Continental programmes for alveolar echinococcosis control

7.2.1 Germany

In the late 1980s the first field experiment was initiated to investigate the feasibility for control of *E. multilocularis* by the delivery of anthelmintic baits to foxes in south-western Germany (Schelling et al., 1997). This study over a baiting are of 566 km^2 revealed a decrease of *E. multilocularis* prevalence in foxes from 32% (95% CI; 16–52%) to 4% (2–7%) after six baiting campaigns within 14 months. A follow-up study confirmed the success of the bait delivery. In baited areas the baseline prevalence of 64% (59–69%) decreased to 15% (95% CI; 10–21%) whereas the prevalence rates in foxes in the control area remained stable (Romig et al., 2007). After reducing the baiting intervals to 6 months, the prevalence increased during 15–21 months to 31–41% (95% CI) and finally to 49–61% in 13–18 months after the last bait distribution (Romig et al., 2007).

A field study using PZQ baits in north-eastern Germany was also successful to lower prevalence rates from 16–27% to 2–6% in an endemic foci and from 4 – 7% to 0–1% in an area of low endemicity by baiting at six-week intervals for one year, followed by a second year with three-month intervals (Tackmann et al., 2001). Also a fourth control study in the south-east of Germany was successful and reduced the fox prevalence rate from 35% (95% CI; 22–50%) to a very low prevalence of 1% (0–4%) (Koenig et al., 2008). The authors of this study conclude that the strong decrease was linked to a high baiting frequency (monthly), high bait density (50/km^2) and the good coverage of the baiting area with the inclusion of densely populated areas.

7.2.2 Switzerland

In Switzerland several consecutive anthelmintic baiting studies have been performed in the city of Zurich. Whereas the baiting studies in Germany aimed to control the parasite in extended areas over areas of 213 km^2 (Schelling et al., 1997) up to 4568 km^2 (Tackmann et al., 2001), the areas in Switzerland comprised only a set of small experimental plots (areas of 1−6 km^2), which were situated in the urban periphery of the city of Zurich (Hegglin and Deplazes, 2008; Hegglin et al., 2003). In this transition zone between rural and urban areas a high population density of foxes was sustained by the rich anthropogenic food resources and at the same time foxes had access to suitable intermediate host species, like *A. scherman* and *M. arvalis* and therefore were frequently infected with *E. multilocularis* (Hegglin et al., 2007; Stieger et al., 2002). Therefore these highly populated urban areas are considered to be especially relevant for the potential transmission of human AE (Deplazes et al., 2004). Surprisingly the delivery of baits on a monthly basis was very effective even on plots of only 1 km^2 (decrease of coproantigen positive fox faeces from 39% to 6%) and was even shown to be successful at lowering the reinfection pressure to rodent intermediate hosts in which the AE prevalence significantly dropped from 7.3% to 2.1% (Hegglin et al., 2003).

Furthermore it has been shown in Zurich that over an area of only 6 km^2 which was baited during a 3.5-year-period at monthly intervals, the contamination was still very low for 3 years after all bait delivery ended (Hegglin and Deplazes, 2008). The feasibility of successful baiting was attributed to the fact that resident foxes in the urban area of Zurich have very small home ranges, i.e., mean home range sizes: females 29 ha, males 31 ha (Gloor, 2002) and therefore the spatial dynamic is far less pronounced than in areas where foxes have larger home ranges and spatial organization is more disturbed by stronger hunting activities (Hegglin et al., 2015).

7.2.3 France

So far experimental fox baiting campaigns to control *E. multilocularis* in France have also concentrated on urban areas. During 32 months, 14 baiting campaigns were performed in the two medium-sized cities of Annemasse and Pontarlier (Comte et al., 2013). The treated areas comprised in each city an area of 33 km^2 and 40 baits had been distributed per km^2 and baiting campaigns. The study achieved contrasting results between the two cities. Whereas the contamination with *E. multilocularis* positive fox faeces decreased significantly from 13.3% to 2.2% in Annemasse, no significant change was detected in Pontarlier (i.e., 9.1%) where the contamination of the treated area followed the temporal trend observed in the control area. It was supposed that the greater resilience of the parasite's life cycle in this city was related to a strong pressure of recontamination from outside the treated area. These contrasting results give evidence that the intensity of the control efforts have to be adjusted to regional needs.

7.2.4 Eastern Europe

During a field study in the Slovak Republic two areas of 2 km^2 each were treated during 9 months with a monthly delivery of 20 PZQ baits per km^2 (Antolova et al., 2006). Similar to the French studies, two contrasting results were achieved in the two baiting areas. Whereas in one area the portion of *E. multilocularis* positive fox faeces dropped significantly from roughly 38% to 8% (Antolova et al., 2006). However, no significant change was observed in two control areas and in the second baiting area where it remained stable on a level between roughly 40–60%. The failure in the second baiting area was attributed to the high density of wild boar in this area, which most likely consumed a substantial amount of the distributed baits (Antolova et al., 2006).

7.2.5 Western China

The highest global burden of human AE disease occurs in west China where prevalences ranged from <1% to >10% in upland agricultural or high-altitude pastoral communities (Craig, 2006; Li et al., 2010; Torgerson et al., 2010). The highest numbers of AE cases occur in Tibetan pastoral communities above 3500m altitude in Sichuan, Qinghai and Tibet Autonomous Region (Giraudoux et al., 2013a), but significant numbers also in lower altitude (<2500m) Han and Hui farming communities in south Gansu and south Ningxia (Craig et al., 1992; Yang et al., 2007). The China National Echinococcosis Control Programme consequently is required to consider control of not only CE but also AE in these areas many of which are coendemic. Dogs are known to be infected in all these zones and thus regular anthelmintic dosing would be expected to reduce the prevalence of both *E. granulosus* and *E. multilocularis* (Wang et al., 2014). In Shiqu County in northwest Sichuan Province a natural reinfection study in owned dogs after a single PZQ dose, showed that at baseline using copro-PCR

11.2% of dogs had *E. multilocularis* DNA positive faeces and after two months posttreatment 2.9% were copro-PCR positive, i.e., reinfected; in comparison *E. granulosus* prevalence was 3.6% at baseline and 0.5% after 2 months (Moss et al., 2013).

The transmission ecology of *E. multilocularis* in western China and Central Asia is complex with three species of fox host including the red fox, Tibetan fox (*Vulpes ferrilata*) and corsac fox (*Vulpes corsac*) and a large number of small mammal families and species potentially able to transmit *E. multilocularis*. Understanding small mammal host ecology and how landscape can affect their population distribution and densities have important practical applications. Spatially explicit models were constructed to investigate the epidemiology of human AE in south Gansu and Ningxia (Danson et al., 2003, 2004), and these were later refined to enable predictive approaches to identify communities at particular risk of AE at local and regional landscape levels (Giraudoux et al., 2013a).

7.3 Reasons for success and problematic outcomes in alveolar echinococcosis control

Control measures for *E. multilocularis* have concentrated mainly on targetting the adult parasite by deworming or culling of fox hosts. Different characteristics of *E. multilocularis* make the control of this parasite very challenging. The parasite has very endurable eggs that can survive in the environment for long periods, and it can survive also in a wide range of small mammal intermediate hosts without being affected by deworming and/or culling measures (Veit et al., 1995; Federer et al., 2015). Regardless of these difficulties, different studies have proven the feasibility to control this parasite and thus to significantly lower the infection pressure for human AE (Hegglin and Deplazes, 2013). However, the outcomes between the different studies differ strongly. Whereas some baiting experiments had only minor or no effect on the parasite abundance in some study plots (Antolova et al., 2006; Comte et al., 2013), other baiting trails were successful to lower the prevalence in foxes and the environmental contamination with *E. multilocularis* eggs to a very low level (Schelling et al., 1997; Hegglin et al., 2003; Koenig et al., 2008). In the case of Rebun Island it was even possible to remove the parasite by eradicating the local fox population (Ito et al., 2003a). However, this example refers to an atypical situation. Foxes are a non native species and their removal was not only accepted but also feasible due to the limited size of this isolated island where no foxes could immigrate from surrounding areas.

The different PZQ baiting studies differed considerably in respect to the size of the baiting area, the bait density and baiting frequency. Interestingly it was possible to reduce the abundance of the parasite strongly in most studies even on very small scale baiting areas (≤ 6 m^2), with low baiting density (≤ 20 baits/km2) and with baiting periods lower than the prepatency period of *E. multilocularis* (Table 5). However, the different studies give evidence that better results can be achieved when bait density is high and urbanized areas with high fox densities are included in the baiting areas (Koenig et al., 2008; Hegglin et al., 2003), when baits are distributed over long periods and in monthly intervals (Koenig et al., 2008; Hegglin and Deplazes, 2008). Failures to control the parasite were attributed to the presence of species that compete for the baits (e.g., wild boars, Antolova et al., 2006) and by the immigration of infected foxes into baiting areas of limited size (Comte et al., 2013). It is noteworthy that even in a small scaled baiting urban area of only 6 km^2 a persistent low contamination has been detected, even 3 years after the discontinuation of an intensive baiting programme. It was supposed that this small scale effect could be a result of the special urban situation with a high fox density and a low hunting pressure on the fox population, which could explain a low spatial dynamic within the fox population (Hegglin and Deplazes, 2008).

Regardless of these successful studies, it is questionable to what extent such control programmes can be implemented on a long term and over larger areas. The resilience of the parasite makes it very unlikely that a sustained elimination of the parasite is feasible. It has been shown that from a purely economic point of view such measures can only be cost-effective if they are pursued for several decades and concentrate on restricted areas, which are most relevant for the transmission of *E.multilocularis*, such as highly endemic areas in densely populated zones (Hegglin and Deplazes, 2013).

7.4 Integrated control

As outlined the transmission dynamics of *E. multilocularis* is affected by many different factors that can vary from region to region (e.g., rodent communities, agricultural practices, fox and dog densities, sanitary conditions, bait competitors), and it is unlikely to control the parasite by relying only on deworming programmes. Also the control of wildlife host populations is very challenging, linked with animal-welfare problems and at some point also questionable from an ecological point of view (Hegglin et al., 2015). Therefore it is suggested that all control programmes should be based on a detailed knowledge of the regional peculiarities and integrate different measures in a holistic approach (Hegglin and Deplazes, 2013). An important component is to improve the awareness and give specific advice how the personal risks can be lowered (Ito et al., 2003a; Hegglin et al., 2008). Thereby it has to be considered that the risk varies strongly within the population with much higher risks for certain groups such as people working in agriculture or owning dogs (Kern et al., 2004; Piarroux et al., 2013; Wang et al., 2006a). Such groups have to be clearly defined and specifically addressed in any information campaign.

An important baseline for the implementation of an integrated control strategy is a detailed knowledge about the occurrence and ecology of the intermediate and final hosts (Deplazes et al., 2004; Liccioli et al., 2015; Raoul et al., 2015). Knowing the importance of different intermediate and final host species for parasite transmission in a given region and an understanding how their population dynamics are affected by wildlife management measures and agricultural practices are fundamental to develop regionally adapted control and prevention measures (Giraudoux et al., 1997, 2002).

In areas where AE and CE are coendemic various control measures that target owned and stray dog populations can act to lower the risk of both diseases.

8. CONCLUSIONS AND FUTURE PROSPECTS FOR CONTROL OF ECHINOCOCCOSIS

The global burden of human CE remains significant in the early part of the 21st century. In addition, although human AE is a globally rare disease there remain significant hotspots of transmission in Eurasia. The WHO has added echinococcosis to a list of 17 neglected tropical diseases, and it is prominent in the list of 12 NZDs (WHO, 2010a,b). Control and prevention of NZDs is difficult especially when treatment of humans has no ability to interrupt transmission as is the case for echinococcosis; furthermore dog, fox and livestock hosts are generally asymptomatic, and the effects of CE on livestock health is chronic and of perceived low priority (Craig et al., 2007a). The main reservoir animal hosts that sustain AE transmission are wildlife and thus hard to target practically and ethically (Hegglin et al., 2015).

Despite this, a number of intervention programmes since the 1960s have shown that the transmission of *E. granulosus* can be controlled effectively and human CE eliminated or significantly reduced as a public health problem in both island (Gemmell et al., 2001) and continental settings (Larrieu and Zanini, 2012). Successful CE control required government support with a veterinary sector as the key to delivery, long-term commitment and ability to deliver dog dosing with PZQ at a frequency of at least four times per year. Hydatid control programmes directed to resource-poor pastoral communities and semi-nomadic regions have fared less well (Lembo et al., 2013). In future, especially with global warming, such marginal regions will likely be the main zones of endemicity (Atkinson et al., 2013).

Control of transmission of *E. multilocularis* has been shown to be costly and difficult to sustain but readily achievable through targeting red fox populations using PZQ baits as indicated in several European and Japanese endemic areas including both rural and urban settings (Hegglin and Deplazes, 2013). Therefore the multifaceted human—wildlife interactions that affect the population dynamics of intermediate and final host communities should always be included in the assessment of any intervention and prevention strategy (Hegglin et al., 2015). Furthermore a landscape ecology approach to identify key host species and to understand behaviour and monitor small mammal population changes have provided robust spatial models that can help in the prediction of where human communities are at higher risk of AE disease whether in Europe or Eurasia (Giraudoux et al., 2013b). In addition the growing evidence for the role of dogs in zoonotic risk of AE disease especially in China and Central Asia can be used favourably by dosing dogs in AE endemic as well as CE/AE coendemic areas.

The development of a livestock vaccine (EG95) to prevent CE infection (Lightowlers, 2006) and of copro-tests for screening and specific identification of infected definitive hosts (Allan and Craig, 2006) have been the most important developments to aid control programmes since the discovery of PZQ in the 1970s. Integrated use of the EG95 vaccine and PZQ dosing still requires full assessment (Torgerson and Heath, 2003; Lightowlers, 2012). Future effective vaccines for echinococcosis in definitive hosts would be a major game changer for control of CE and AE (Zhang et al., 2014).

Human CE and AE cases should have access to optimal treatment, especially in resource-poor settings, for control initiatives to be viable and accepted in endemic communities. The potential to combine treatment and control measures for echinococcosis in an integrated way with other zoonotic diseases and other human and animal health issues (i.e., 'One Health' approaches) should optimize delivery and cost benefits (Zinsstag et al., 2006; Rabinowitz et al., 2013). Such intervention approaches that include echinococcosis still remain to be undertaken.

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