International Journal for Parasitology 43 (2013) 327–337

Contents lists available at SciVerse ScienceDirect

International Journal for Parasitology

journal homepage: www.elsevier.com/locate/ijpara

Invited Review

Control of *Echinococcus multilocularis*: Strategies, feasibility and cost–benefit analyses

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ARTICLE INFO

Article history:
Received 9 October 2012
Received in revised form 29 November 2012
Accepted 30 November 2012
Available online 4 February 2013

Keywords:
Alveolar echinococcosis
Baiting campaign
Domestic dog
Emerging zoonosis
Red fox
Zoonosis

ABSTRACT

Echinococcus multilocularis, the zoonotic agent of human alveolar echinococcosis, has considerably extended its range and became more prevalent in many parts of the endemic areas. Accordingly, there is an increasing demand for measures to prevent human infections. Rising public awareness of this zoonosis and individual protective actions should be part of every prevention program. Considering the high reproduction of *E. multilocularis* in domestic dogs which live in close contact to humans, a monthly deworming scheme for domestic dogs with access to rodents is likely to be of high importance. This holds true if only low prevalences in domestic dogs are recorded, as high densities of these pets can easily outweigh low infections rates. Thus, in central Europe their estimated contribution to environmental contamination with *E. multilocularis* eggs ranges between 4% and 19%. The estimated contribution of domestic cats is insignificant (<0.3%) due to low parasite reproduction in this species. Control of the parasite by reducing its main wildlife hosts (foxes, vole species) is barely achievable on a larger scale and is generally not well accepted due to ecological considerations and animal welfare concerns. In general, the frequency of the parasite sharply decreases when anthelmintic baits are regularly distributed to foxes. However, eradication of the parasite is unlikely and long-term baiting campaigns are actually the most effective tool to significantly lower the infection pressure with parasite eggs. Regarding the long latency of 5–15 years of alveolar echinococcosis, however, 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 alveolar echinococcosis such as highly endemic areas in densely populated zones. Thus, the implementation of this approach strongly depends on factors such as public attitude, available financial resources and priority setting of political decision-makers.

1. Introduction

1.1. *Echinococcus multilocularis is an emerging parasite*

Evidence is accumulating that *E. multilocularis*, the zoonotic agent of human alveolar echinococcosis (AE), considerably extended its range and emerged in many populations of its definitive, intermediate and aberrant host species (e.g. Jenkins et al., 2005; Craig, 2006; Eckert et al., 2011; Osterman Lind et al., 2011; Siko et al., 2011; Staubach et al., 2011; Torgerson and Macpherson, 2011; Combes et al., 2012; van Dommelen et al., 2012). In many former Soviet states and in China, socio-economic and ecological changes probably favoured widespread establishment of the *E. multilocularis* cycle (Vuitton et al., 2003; Torgerson et al., 2006; Ziadinov et al., 2010). A widespread growth in red fox populations and the colonisation of urban areas by this species was another reason for this development in many regions. Thus the life cycle of the parasite is today well established in urban environments which also include large cities in Europe and Japan (Tsukada et al., 2000; Deplazes et al., 2004; Lagapa et al., 2009). A similar phenomenon was recently observed for urban coyotes (*Canis latrans*) in Edmonton and Calgary, Canada, where an *E. multilocularis* overall prevalence of 25% was determined (Catalano et al., 2012). Furthermore, globalisation processes (Davidson et al., 2012) such as increased traffic of pet dogs (Osterman Lind et al., 2011) and relocation of wildlife, e.g. red foxes (Davidson et al., 1992), beavers (Barlow et al., 2011; Ćirović et al., 2012) and voles (Henttonen et al., 2001), contribute to the spread of this zoonotic helminth.

All of these observations support the hypothesis that the infection pressure with *E. multilocularis* eggs increased in many endemic areas, including highly populated zones. Together with these epidemiological alterations, increased incidence rates of human AE have been detected. In Lithuania, zero to four annual new cases of human AE (incidence 0.0–0.1) were recorded between 1997 and 2001 but 10–16 cases (incidence 0.3–0.5) between 2002 and 2006 (Bruzinskaite et al., 2007). In Switzerland, during the first pentad of the 21st century, the incidence increased by the factor

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http://dx.doi.org/10.1016/j.ijpara.2012.11.013

2.6 compared with the 1990s (Schweiger et al., 2007). This increase started approximately 10 years after the fox populations had experienced strong growth associated with successful rabies vaccination campaigns, which is in accordance with the estimated latency of 5–15 years of the disease (Ammann and Eckert, 1996). This example provides evidence that the incidence of AE in humans responds, with a time delay, to ecological changes that affect the dynamics of the *E. multilocularis* cycle.

1.2. Human AE is still a severe and frequently incurable disease

Significant advances have been achieved in the diagnosis and the treatment of AE during recent decades (Ammann et al., 1999; Kern, 2010; Piarroux et al., 2011). In Switzerland, the life expectancy of patients in 2005 was reduced by approximately 3.6 and 2.5 years for men and women, respectively, which is far less than in the 1970s (18.2 and 21.3, respectively; Torgerson et al., 2008). Also, in France the live expectancy of patients tends to merge with that of the general French population (Piarroux et al., 2011).

However, AE is still a severe disease, curative radical surgery is not possible in 57% of cases in Switzerland (Torgerson et al., 2008) and patients have to be treated with high doses of albendazole over decades or even lifelong. A recent study estimated the global burden of disease on 666,434 disability-adjusted life years (DALYs) per annum (95% Confidence Interval (CI) 331,000–1.3 million) and an annual number of 18,235 (95% CI 11,900–28,200) new cases (Torgerson et al., 2010). Most of these people live in regions where public health care can provide only a limited treatment standard. Moreover, in very remote areas with poor medical provisions, it is likely that many infected persons never receive a diagnosis for this disease which has a fatal outcome without adequate treatment (Torgerson et al., 2010).

1.3. Public demand for control measures

Although AE incidence rates are low in the European endemic area, the severity of the disease and the increasing population of foxes in residential areas provokes considerable anxiety in the population, which is regularly re-enforced by alarmist reporting in the media (Hegglin et al., 2008). Thus, there is an increasing public demand to control AE, especially in Europe and Japan (Ito et al., 2003; Koenig, 2007). Correspondingly, a considerable number of informative campaigns (e.g. http://www.ententeragezoonoses.com) and field studies for the control of this parasite have been performed during the last two decades (Bontadina et al., 2001; Hegglin et al., 2008; Romig, 2009).

1.4. Options for the prevention of AE

As the life cycle of *E. multilocularis* depends mainly on wild animals, including a variety of commonly found rodents and the adaptive and ubiquitous red fox, the control of AE is challenging. However, potential measures for the control and prevention of AE can be pursued at different levels (Fig. 1). On an individual level, mainly hygiene-linked measures and frequent deworming of domestic dogs are supposed to reduce the probability of exposure to infective eggs. On an environmental level, measures to reduce the contamination with infective *E. multilocularis* eggs, either by the control of the definitive and/or the intermediate host species or by directly targeting the parasite by deworming definitive hosts, have been proposed. Although it is difficult to assess the relative impact of these approaches, we intend to highlight some considerations on the strengths and weaknesses of these intervention strategies and present cost–benefit analyses of different deworming campaign scenarios.

2. Environmental contamination with *E. multilocularis* eggs

2.1. The contribution of red foxes, domestic dogs and cats

Similar to Eckert et al. (2001b), we calculated the contribution of foxes, dogs and cats to the frequency of *E. multilocularis* based on available data on definitive hosts densities and different prevalence rates in Europe. Additionally, we also included the reproductive potential of *E. multilocularis* in definitive hosts (Kapel et al., 2006) in our calculations (Table 1). It is evident that the red fox is the most important species for environmental contamination with *E. multilocularis* eggs in large parts of the endemic area as it

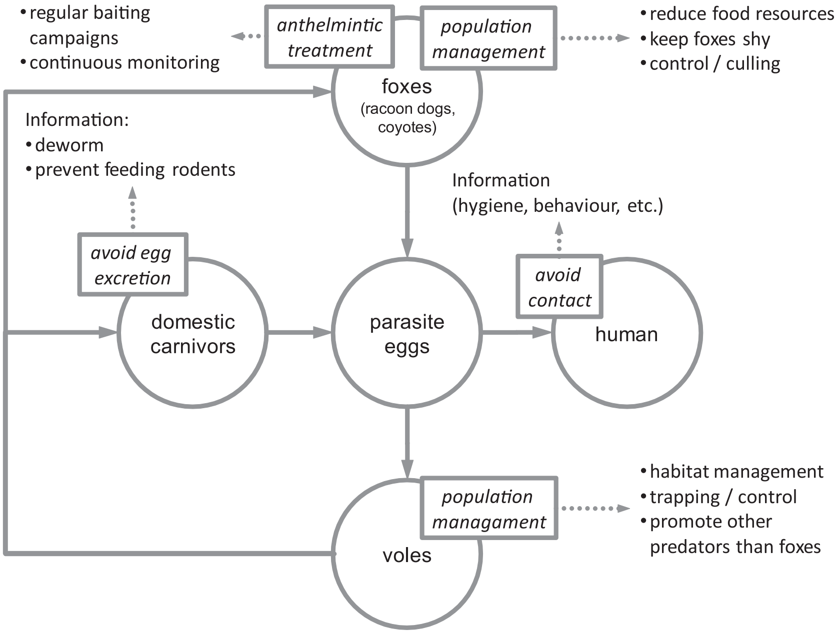

Fig. 1. Schematic representation of the different options for control and prevention of human alveolar echinococcosis. Circles represent the occurrence of *Echinococcus multilocularis* in the environment, the main intermediate and definitive hosts and in humans; rectangles show different levels for interventions which are specified by distinct actions (see Section 1.4 further explanations).

Table 1
Estimates of the contribution of red foxes and domestic carnivores to environmental contamination with *Echinococcus multilocularis* eggs for exemplary epidemiological situations in rural and urban areas in European endemic regions.

Area	Endemicity	Species	Density[a] (n/km^2)	Prevalence[b] (%)	Infected animals (n/km^2)	Biotic potential[c] (eggs/km^2)	% of environmental contamination
Rural	High	Foxes	5.00	60.00	3.00	1,039,419	95.9
		Dogs	10.53	1.50	0.16	44,227	4.1
		Cats	34.57	0.40	0.14	79	0.0
	Total					1,083,725	100.0
	Low	Foxes	0.70	20.00	0.14	48,506	84.5
		Dogs	10.53	0.30	0.03	8,845	15.4
		Cats	34.57	0.40	0.14	79	0.1
	Total					57,431	100.0
Urban	High	Foxes	32.00	60.00	19.20	6,652,282	93.2
		Dogs	115.27	1.50	1.73	483,988	6.8
		Cats	361.19	0.40	1.44	828	0.0
	Total					7,137,097	100.0
	Low	Foxes	6.00	20.00	1.20	415,768	81.0
		Dogs	115.27	0.30	0.35	96,798	18.9
		Cats	361.19	0.40	1.44	828	0.2
	Total					513,393	100.0

[a] Minimal and maximal values for fox densities were set according to the considerations of Koenig et al. (2008). Dog and cat densities were calculated based on the data provided by Mars Inc., Switzerland, considering data of typical rural cantons of Switzerland (Appenzell Innerrhoden, Nidwalden, Schwyz, Bern, Fribourg, Neuchâtel, Jura) for the rural scenarios and data from the city of Zürich for the urban scenarios.

[b] Fox prevalences were set to 60% and 20% which approximately describes the high and low bands of *E. multilocularis* prevalence rates for this species in typical endemic areas. Dog and cat prevalences were set according to the information provided by Deplazes et al. (2011). It was supposed that prevalences in dogs are higher in highly endemic areas.

[c] Values for the biotic potential were set according to the data provided by Kapel et al. (2006).

is the most widespread wild canid and frequently occurs in high densities (up to 20 adult foxes/km^2 in urban and suburban areas; density estimates compiled in: Koenig and Romig, 2010). Additionally, prevalence rates frequently exceed 50% (Vuitton et al., 2003). Nevertheless, the relative contribution of domestic dogs to the environmental contamination should not be ignored, even in highly endemic regions of central Europe, where prevalence rates in average dog populations are generally low (approximately 0.3–0.4%, Deplazes et al., 2011). It was calculated that approximately 10% of dogs become infected once in their life-time assuming, a uniform infection risk even if prevalences are at such a low level (Deplazes et al., 2004). Furthermore, in highly endemic rural areas prevalence rates in dogs can increase to >1.5% (Deplazes et al., 2011), and in periurban and urban areas dog densities are usually much higher than fox densities. Therefore, even if prevalence rates in dogs are generally 10–100 times lower than in foxes, the dog population can still substantially contribute to the environmental egg contamination in the immediate vicinity of humans when faeces are not removed by the dog owners. As shown in Table 1 for typical rural and urban environments of central Europe, the contribution of the dog population to environmental contamination with *E. multilocularis* eggs is estimated to range between 4–15% and 7–19%, respectively.

Especially in the former Soviet states and China dogs are considered to be of major importance for the transmission of AE (Vuitton et al., 2003; Craig, 2006; Ziadinov et al., 2008). In these countries high *E. multilocularis* prevalences and high population densities have been reported for domestic and stray dogs whereas it is unlikely that foxes occur in the same density as in many urbanized areas of Europe.

On the contrary domestic cats, which occasionally also harbour intestinal stages of *E. multilocularis*, are apparently of minor significance (Eckert et al., 2011). Egg counts during patency revealed that the mean egg production per animal was not significantly different in red foxes, raccoon dogs and domestic dogs despite large differences in worm burdens. In contrast, cats excreted only low numbers of eggs and those eggs were not infective for mice (Kapel et al., 2006). Accordingly, domestic cats can contribute only marginally to environmental contamination with *E. multilocularis* eggs despite their higher population densities (Table 1). Therefore, measures targeting the control of *E. multilocularis* in foxes and domestic dogs should have a clear priority.

3. Deworming foxes

3.1. The challenge to deworm foxes

Probably inspired by the successful rabies control with oral vaccine baits for foxes, pioneer work was initiated by Professor Werner Frank at Hohenheim University, Stuttgart, Germany to investigate the feasibility of *E. multilocularis* deworming of foxes with baits containing praziquantel, in the late 1980s. For several reasons, it can be predicted that the *E. multilocularis* cycle is much more resistant to such an intervention than rabies. Thus, vaccinated foxes have lifelong protection from rabies virus infections whereas dewormed foxes can be re-infected a few days after treatment as soon as they predate on infected intermediate hosts. Furthermore, metacestode stages in the intermediate host and infective eggs in the environment are not affected by the treatment and can survive from several months to more than 1 year (Veit et al., 1995). All of these factors contribute to the complexity of *E. multilocularis* control.

3.2. Impact of deworming foxes on environmental contamination with *E. multilocularis* eggs

Overall, several studies have clearly shown that the distribution of praziquantel-containing baits can considerably lower environmental contamination with *E. multilocularis* eggs. The first field experiment in southwestern Germany demonstrated the feasibility of this approach in the late 1980s (Schelling et al., 1997) by revealing a decrease in *E. multilocularis* prevalence in foxes from 32% (95% CI; 16–52%) to 4% (2–7%) after six baiting campaigns within 14 months. In the meantime, several studies from Germany, Switzerland, France, Japan and the Slovak Republic confirmed the feasibility of this control strategy. Table 2 summarizes methodologies of the different studies and their outcomes. Promising results have been obtained with very different and locally-adapted settings in regard to the size of the treated area (range 1–5,000 km^2), bait

Table 2

Field studies on the effectiveness of the control of *Echinococcus multilocularis* by the distribution of praziquantel-containing baits for foxes: methods and key results. Study areas were situated in Germany (DE1–DE3), Japan (JP1–JP3), Switzerland (CH1–CH2), Slovak Republic (SK) and France (FR).

Study area		DE1[a]	DE2[b]	DE3a[c]	DE3b[c]	DE4[d]	JP1[e]	JP2[f]	JP3[g]	CH1a[h]	CH1b[h]	CH2[i]	SKa[j]	SKb[j]	FRa[k]	FRb[k]
Baiting methods																
Bait area (km^2)		566	3000	432	4568[l]	213	90	135	110[m]	6[n]	6	3[n]	2	2	33	33
Bait period (months)		14	48	26	26	16	13	51	43	19	19	26	9	9	32	32
Bait density (bait/km^2)		15–20	20	20	20	∼50	2	15	n.a.[m]	50	50	50	20	20	40	40
Bait frequency (campaigns/year)		5	2–9	4–9	4–9	12	12	∼3[o]	2–7	12	12	4	12	12	5	5
Bait distribution		air_h	air_h	airc.	airc.	air_h	dens	car	car	hand	hand	hand	hand	hand	car_h	car_h
Monitoring methods																
Definitive hosts		IST	IST	IST	IST	IST	eggs[p]	necr.	SCT	ELISA	ELISA	ELISA	ELISA	ELISA	ELISA	ELISA
Intermediate host prevalence		no	no	no	no	no	no	n.i.	no	yes	yes	no	no	no	no	no
Control area (km^2)		0	2440	n.a.	n.a.	228	n.a.	n.i.	n.a.	6	6	3	1	1	160	160
Follow up			yes									yes			no	no
Selected results for definitive hosts																
pre-treatment	% Positive	32	64	16–26[q]	4–6[q]	35	27[p]	67	58	39	67	30	±38[r]	±50[r]	13.3	10.9[r]
	95% CI	16–52	59–69			22–50	20–35[p]	n.i.	47–69	26–52	46–84	23–39	n.i.	n.i.		
Treatment result	% Positive	4	15	2–6[q]	0–1[q]	1	6[p]	16	11	6	2	18	±8[r]	±50[r]	2.21	7.1[r]
	95% CI	2–7	10–21			0–4	2–14[p]	n.i.	4–24	3–9	0–7	13–23	n.i.	n.i.		
	After (months)	14	18	19–30	19–30	4–16	13	51	38–41	16–19	16–19	24–26	9	9	9–32	9–32
Resilience to pre-control level after (months)		36									24–26[s]	None[t]				
Results for intermediate hosts																
Prevalence reduction (from/to)											7/2	22/9				

n.a., not available; airc., by aircraft; air_h, by aircraft and by hand; hand, manual distribution by foot; dens, manual distribution at fox dens; car, manual distribution with cars; car_h, with cars and by hand; IST, intestinal scraping technique; necr., necropsy; SCT, sedimentation and counting technique; n.i., not indicated.

[a] Schelling et al. (1997).

[b] Romig et al. (2007).

[c] Tackmann et al. (2001).

[d] Koenig et al. (2008).

[e] Tsukada et al. (2002).

[f] Takahashi et al. (2002) (in Japanese) discussed in Takahashi et al. (2005).

[g] Inoue et al. (2007).

[h] Hegglin et al. (2003).

[i] Hegglin and Deplazes (2008).

[j] Antolova et al. (2006).

[k] S. Comte and B. Combes, personal communication.

[l] initial baiting area was reduced to 768 km2 during the baiting period.

[m] bait distribution was restricted to streets (20 baits/km).

[n] several baiting plots, each with an area of 1 km^2.

[o] 17 baiting campaigns in 51 months.

[p] All faeces were additionally investigated with a coproantigen ELISA. The proportion of coproantigen-positive samples decreased from 60% (95% Confidence interval (CI) 52–67) to 30% (95% CI 20–42).

[q] Minimal and maximal values during the year before treatment and during the last year of baiting (for CI see reference).

[r] Values read from figures,

[s] See Hegglin and Deplazes (2008).

[t] No resilience after 36 months, see Hegglin and Deplazes (2008).

density and baiting frequency. Most studies demonstrated, at the end of the baiting period, a four to 35 times lower frequency of the parasite than before or at the beginning of the baiting campaigns (Table 2). Furthermore, one study showed that the parasite prevalence also decreased in the intermediate host, *Arvicola scherman* (formerly *Arvicola terrestris*), in the second baiting year (Table 2), substantiating the lower environmental contamination with *E. multilocularis* eggs and demonstrating the lower re-infection pressure for the definitive hosts (Hegglin et al., 2003). In contrast, some studies also demonstrated that baiting regimes may not or only marginally control the parasite, with low baiting frequencies, a high supply of susceptible intermediate hosts and a high density of other species competing for the bait being the most likely factors for these failures (Hegglin et al., 2003; Antolova et al., 2006; S. Comte and B. Combes, personal communication).

3.3. Economic benefit of long-term deworming of foxes

Considering the high burden of AE (Torgerson et al., 2010), the evaluation of costly measures for the control of this zoonosis is justified. This viewpoint is also supported by a recent Swedish study which showed that pet owners are willing to pay between € 54 and 99 to comply with the existing Swedish rules to prevent the introduction of *E. multilocularis* to the country (Höjgård et al., 2012). Considering the long latency of human AE (Ammann and Eckert, 1996), new clinical cases, which refer to infections that occurred before the deworming campaigns started, can be expected to appear up to 15 years after the initiation of a control program. Therefore, even if long-term baiting campaigns could completely stop parasite transmission in a defined area, such an intervention would become cost effective only in the long term. We calculated the accumulated economic costs and benefits over several decades and under different epidemiological settings. These cost–benefit analyses revealed that in a medium sized conurbation of western Europe such an intervention would have a positive economic return after 35 years (Model 3 in Table 1 and Fig. 2A).

Expenses would come to an end only if eradication was accomplished. Such an intervention would need a large-scale intervention including areas with low human population densities. Correspondingly the per capita costs would be higher, up to € 22 per inhabitant during the first 10 years of the intervention before any savings in medical costs could be made (Model 4 in Table 1 and Fig. 2B). In addition there remains a considerable risk that eradication could not be achieved. Different studies have shown that the parasite population can recover within 24–36 months after the end of a baiting campaign (Table 2) to the pre-control level (Romig et al., 2007; Hegglin and Deplazes, 2008). It has been shown that micro foci of some 10 m^2 with high prevalence rates in intermediate hosts can exist (Giraudoux et al., 2002), and a modelling study gave evidence that such spatial aggregations of the parasite can be crucial for the persistence of *E. multilocularis* (Hansen et al., 2004). Furthermore, modelling and field studies have demonstrated that the parasite can also persist when the overall prevalence in intermediate host species is very low (Takumi and Van der Giessen, 2005; Schaerer, O., 1987, Die Metacestoden der Kleinsäuger (Insectivora und Rodentia) und ihre Wirtsarten, Verbreitung und Häufigkeit im Kanton Thurgau (Schweiz), Inaugural Thesis, University of Zurich, Switzerland). In addition, the life span of different intermediate hosts has to be considered. For instance, although muskrats (*Ondatra zibethicus*) are not a frequent prey of foxes (e.g. Sidorovich et al., 2006), they could play an important role in the persistence of the parasite, as they are highly susceptible to infections, frequently develop fertile metacestodes and at the same time can survive for several years (Proulx and Gilbert, 1983: 6.0% > 2 years, 1.7% > 3 years; up to 10 years in captivity (http://animaldiversity.ummz.umich.edu)). The same could be true for the Coypu (*Myocastor coypus*) and the beaver (*Castor castor*), which both can have fertile metacestodes (Janovsky et al., 2002; Hartel et al., 2004) and have even longer life spans than the muskrat.

3.4. Necessity for optimising baiting strategies

Considering the long period (several decades) until anthelmintic baiting campaigns become beneficial, it becomes obvious that fox baiting campaigns should only be implemented if long-lasting and intense baiting programs can be guaranteed. At the same time, long-term and large-scale implementations of such control measures should carefully consider and monitor possible side effects. It cannot be excluded that delivery of praziquantel baits, which are also consumed by non-target species such as hedgehogs, different rodents species and invertebrates (Hegglin et al., 2004), could have unexpected effects on ecosystems, e.g. by affecting the parasite community in different wildlife species (Hudson et al., 2006). Furthermore, the risk of parasite resistance should be assessed and carefully monitored. However, due to the high efficacy (>99%) of praziquantel against intestinal *Echinococcus* stages, the low reproductive potential of the single worm (Kapel et al., 2006)

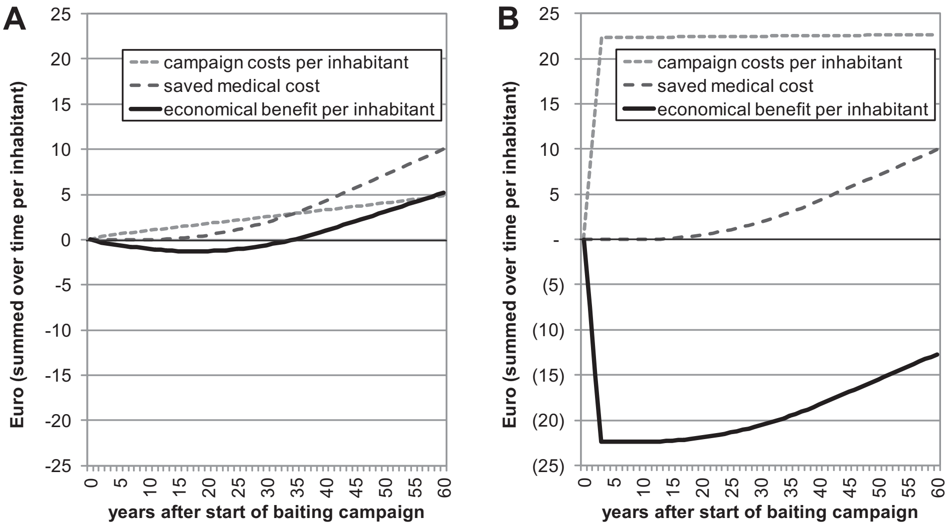

Fig. 2. Visualisation of cumulative costs and benefits per inhabitant for two different control scenarios for *Echinococcus multilocularis* by deworming foxes over 60 years (*x*-axis). (A) Scenario for a medium sized city in Europe (see Table 3, Model 1 for parameter settings). (B) Scenario for a large-scale control program with successful removal of the parasite after 5 years (see Table 3, Model 4 for parameter settings).

and the multi-host cycle, the establishment of a resistant strain seems unlikely.

Regarding the high costs of deworming programs, a careful evaluation of measures to make deworming programs more cost effective is also required. However, at least during an initial phase, the intervals between consecutive baiting campaigns should not be longer than the period of prepatency in foxes (approximately 1 month; Kapel et al., 2006). Later, once the frequency of the parasite is low, a reduction in the baiting frequency seems possible. Thus, in a large-scale baiting study in Germany (Romig et al., 2007), a baiting interval of 3 months was effective in keeping the prevalence low. This finding is supported by a modelling study which predicted that baiting every 2 months can be effective (Hansen et al., 2003). Nevertheless, with baiting over small areas, only monthly baiting was effective to keep the infection pressure at a low level as demonstrated by a baiting study in the urban periphery of Zurich, Switzerland (Hegglin and Deplazes, 2008).

To lower the costs, baiting interventions should be strategically chosen for the time of major parasite transmission. Thus, studies in France (Delattre et al., 1988) and Switzerland (Burlet et al., 2011) demonstrated that voles are mainly infected during the winter season. These results indicate that deworming is especially important just before and during winter. However, such optimised baiting strategies need to be critically evaluated in future field trials.

A crucial parameter for the success and the cost effectiveness of any baiting campaign is the efficiency of the bait uptake by foxes. In a Japanese baiting study with a relative low bait density (20 baits/km along streets), tetracycline was added to the praziquantel baits as a biomarker, revealing that at least 39% of the investigated foxes had consumed such baits in the year when they were hunted (Inoue et al., 2007). However, the authors supposed that the true uptake rate was higher as tetracycline cannot always be detected in the marked animals. Thus, several other studies give evidence that baits containing praziquantel are generally well accepted. A German study revealed that >75% of the distributed praziquantel baits disappeared within 3 days after bait delivery and approximately 90% after 7 days (Janko and Koenig, 2011). A camera trap study in an urban environment demonstrated that approximately half of the removed baits were taken by foxes (48%; 95% CI, 38–59), although the same study revealed that the presence of camera traps lowered the uptake rate by foxes compared with competing species such as hedgehogs, dogs and rodents (Hegglin et al., 2004). Interestingly cats, which were the predominant species that triggered the camera traps, never consumed the delivered praziquantel baits. However, species other than foxes that compete for the baits could hamper parasite control by this approach. In the Slovak Republic, for instance, there was evidence that a high density of wild boars in one study area was the likely reason for the failure to control *E. multilocularis* (Antolova et al., 2006). Therefore the development of species-specific baiting systems remains an important issue.

3.5. Baiting interventions: focus on densely populated, highly endemic areas

Living in the countryside is mostly linked to a rural life style including close contact with soil and vegetation which can be considered a risk factor for AE. Furthermore, it was suggested that once the parasite is established, the individual infection risk could be elevated in countries where outdoor activities such as hiking, camping and berry- and mushroom picking are long standing traditions (e.g. Sweden) (Wahlström et al., 2012). However, by colonizing urban areas, foxes have become resident in a very productive habitat which offers much more food resources than rural areas (Gloor et al., 2001; Contesse et al., 2004). A high food supply is an important factor for the development of exceptionally high population densities of more than 10 adult foxes per km^2 (Gloor, S., 2002, The rise of urban foxes (*Vulpes vulpes*) in Switzerland and ecological and parasitological aspects of a population in the recently colonised city of Zurich, Zoological Museum, PhD Thesis, University of Zurich, Switzerland). Furthermore, urban peripheries can provide suitable habitats for the most important intermediate hosts, e.g. *A. scherman* and *Microtus arvalis* (Hegglin et al., 2007). Accordingly, several studies and also the calculation presented in this article (Table 1) show that highest environmental contaminations with *E. multilocularis* eggs can be observed in urbanised areas where exceptionally high fox densities intersect with suitable habitats for voles (Deplazes et al., 2004; Hegglin et al., 2007; Janko et al., 2011; Robardet et al., 2011). Data from Switzerland revealed that the majority of patients (56%) diagnosed from 1984 to 2010 were living in urban areas (P. Deplazes, unpublished data), indicating that foxes living in or close to human settlements are of special importance for the transmission of human AE. This was also highlighted by a study from Germany (Koenig and

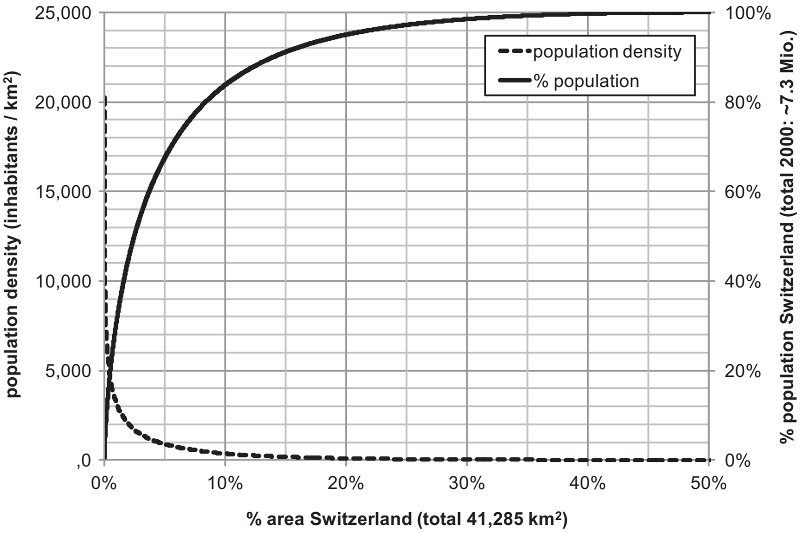

Fig. 3. Population density and percentage of the Swiss population in relation to the surface of Switzerland (calculated on the basis of a 1 km^2 grid of the Swiss population census of the year 2000). Approximately 50% and 25% of the surface of Switzerland is situated more than 1,000 and 2,000 m above sea level, respectively, and therefore has a low population density. Mio., million inhabitants.

Table 3

Accumulated financial costs and benefits of anthelmintic treatment of foxes for different scenarios. The following parameters were set as constant in the presented models: (i) incidence of human alveolar echinococcosis = 0.26, incubation period = 10 years; (ii) mean life time with disease = 30.75 years, total costs per patient = € 108,762 (Torgerson et al., 2008), (iii) cost per bait = € 0.75; (iv) bait density = 50 per km^2; (v) work cost = € 20 per h; (vi) search time per fox dropping = 15 min; (vii) number of required fox dropping for control = 400 per year; (viii) laboratory costs per fox dropping = €10. Bold characters indicate the values which changed in comparison with the previous model.

Parameter	Model 1	Model 2	Model 3	Model 4	Unit
Area[a]	100	100	**1,000**	**10,000**	km^2
n inhabitants	400,000	400,000	400,000	**1,000,000**	Persons
Human population density	4,000	4,000	**400**	**100**	Person/km^2
Infection prevention rate[b]	100	**75**	75	**100**	%
Bait intervals phase 1[c]	12	12	12	12	Times/year
Portion of treated area[d]	50	50	**80**	80	% of areas
Work hours per km^2	3.00	3.00	3.00	**2.00**	h/km^2
Duration phase 1[e]	3.00	3.00	3.00	**5.00**	Year
Bait intervals phase 2	5.00	5.00	5.00	–	Times/year
Costs/benefits					
Accumulated after 20 years					
Saved AE cases	10.40	7.80	7.80	26.00	Persons
Total saved medical cost	202,315	151,736	151,736	505,788	€
Invested campaign costs	709,875	709,875	9,558,000	22,440,000	€
Net benefit	−507,560	−558,139	−9,406,264	−21,934,212	€
Accumulated costs per inhabitant	1.27	1.40	23.52	21.93	€
Accumulated after 40 years					
Saved AE cases	31.20	23.40	23.40	78.00	Persons
Total saved medical cost	1,710,481	1,282,861	1,282,861	4,276,204	€
Invested campaign costs	1,317,375	1,317,375	17,478,000	22,560,000	€
Net benefit	393,106	−34,514	−16,195,139	−18,283,796	€
Accumulated costs per inhabitant	−0.98	0.09	40.49	18.28	€

[a] Surface of area for control intervention.

[b] Proportion of prevented human infections due to the deworming campaigns.

[c] Frequency of baiting campaigns during a first period of the intervention.

[d] Proportion of control area on which baits are delivered (no baits are delivered on areas without vole habitats).

[e] Duration of initial phase with intense baiting.

Romig, 2010) in which the relative risk of contact with faeces of infected foxes in urban and rural areas was estimated. Considering the high densities of foxes and people in urbanised areas (e.g. in Switzerland as much as 80% of the population lives in an area covering only 8.4% of the country, Fig. 3), it was concluded that the likelihood of contact between people and fox faeces containing *Echinococcus* eggs can be much higher in these zones. Therefore cost-effectiveness of deworming campaigns is considered to be highest in endemic areas with high human population densities (Fig. 2A and Model 1 in Table 3). Thus it needs to be considered that the spatial dynamic of foxes is limited in urban areas and baiting campaigns are therefore also effective in considerably lowering environmental contamination with *E. multilocularis* eggs if they are restricted to very small patches, covering only 1 km^2 (Hegglin et al., 2003; Table 1). Interestingly, the effect of bait delivery was restricted to an area of 500 m around the bait area and no lowered egg contamination could be detected at further distances. This finding provides further evidence for the low spatial dynamic of the *E. multilocularis* life cycle in urban settings with high fox population densities (Hegglin et al., 2003).

However, it is not yet known to what extent people become infected by buying and consuming food products which are contaminated with *E. multilocularis* eggs. If further studies should show that certain egg-contaminated food, such as certain vegetables, contribute to the transmission of human AE, local baiting campaigns restricted to such agricultural areas could also be considered.

4. Regulation of host species

4.1. Regulation of fox population density – a difficult task

Rabies most likely strongly influenced the population dynamic of red foxes during the past, and the successful rabies vaccination campaigns are regarded as an important factor in the widespread increase in fox population densities throughout Europe during recent decades (Chautan et al., 2000). Incidence rates of human AE seem to follow these changes in wildlife host densities (e.g. Schweiger et al., 2007), albeit with a time delay. This finding is supported by a French study, where unintentional poisoning of foxes during a vole control program significantly reduced the fox density (Raoul et al., 2003). The infection level of the local fox population (as determined using copro-antigen ELISA for field samples of fox faeces) already dropped during the first year following the decline in the fox population, although during this period the density of the intermediate host, *A. scherman*, was still at a high level. Accordingly, fox population management as a possible control option has to be considered. On a small scale, this approach proved successful on the Japanese Rebun Island (80 km^2). In the early 1950s, >2,000 foxes and 3,000 dogs were killed, and the AE incidence dropped sharply during the following decades (Eckert et al., 2001a).

However, on a larger scale, the control of fox populations is difficult and depends on different parameters (e.g. Heydon and Reynolds, 2000). Even in Australia, where foxes are treated as alien pest species and poisoning programs are an accepted management method, the control objectives are only partly achieved (Gentle et al., 2007). In accordance with the principles of animal welfare, the permitted culling methods for native wildlife are much more restricted in Europe and their application is controversially discussed (Reynolds, 2004; Littin and Mellor, 2005; Koenig, 2007). Therefore, a sustained and significant large-scale reduction of fox numbers by hunting can hardly be achieved (e.g. Baker et al., 2002). Furthermore, intense culling has fundamental effects on the population dynamics in the affected species which must be considered in regard to the dynamics of disease transmission (Woodroffe, 2007). For instance, culling could increase the proportion of sub-adult foxes which could increase the spatial dynamic of parasite transmission because sub-adults disperse over large distances (Harris, 1977; Harris and Trewhella, 1988) and/or boost the parasite biomass as sub-adult foxes can harbour higher worm burdens (Morishima et al., 1999; Hofer et al., 2000).

However, it is reasonable to take measures that help to limit close contact between foxes and humans. In this regard, the shyness of foxes could be a relevant factor which possibly is affected by hunting practices and by the human attitudes towards this wildlife species. Therefore, information on keeping foxes shy, i.e., wary of humans, and not feeding them should be also an integral part in any information campaign on AE (Hegglin et al., 2008).

4.2. Control of intermediate host species – a sensitive ecological task

Agricultural practices and landscape management can strongly affect rodent communities and thus the occurrence and frequency of *E. multilocularis* and most likely the incidence of human AE (Viel et al., 1999; Giraudoux et al., 2002). However, the reduction of intermediate rodent hosts is very difficult and controversial from the ecological, as well as from the animal welfare, point of view. Although rodenticides can effectively reduce rodent populations over large areas (Tobin and Fall, 2004), such interventions had severe impacts on the environment by secondary poisoning of predators such as mustelids, canids and raptors (e.g. Giraudoux et al., 2006b). In addition, the density of suitable intermediate hosts does not necessarily directly affect the prevalence of *E. multilocularis* in definitive hosts. Since foxes have a selective predatory behaviour (e.g. foxes show a preference for *Microtus* spp., Macdonald, 1977) some intermediate hosts are predated frequently, even when they occur in low densities, thus buffering the effect of a lowered supply of infected voles.

In a French study, higher numbers of *A. scherman* were associated with higher predation rates on this species by foxes with a type III-like (sigmoidal) dietary response, whereas no response was detected to the abundances of *M. arvalis*. However, minor increases in the densities of both intermediate host species were linked with a strong increase in the infection levels in foxes to a maximal level (Raoul et al., 2010). These results imply that densities of intermediate hosts have to be diminished to a very low level before such a measure becomes effective to decrease prevalence rates in foxes.

However, it has been shown that changes in vole densities can affect the prevalence in red foxes (Saitoh and Takahashi, 1998) and that changes in land management practices can have considerable influence on the incidence rates in humans by influencing the rodent communities and thereby the supply of suitable intermediate hosts (Viel et al., 1999; Giraudoux et al., 2006a; Wang et al., 2006). It is therefore worth considering how agricultural practice and landscape management, especially close to densely populated areas, can promote or prevent the development of high densities of relevant intermediate hosts. It is likely that appropriate management of rodent habitats (Tobin and Fall, 2004; Artois et al., 2011), combined with other control measures such as traditional trapping and/or the promotion of vole-consuming raptors or owl species (Sundell, 2006), could contribute within an integrated approach to lower the infection risk of AE.

5. Significance of deworming dogs and cats

Highest prevalences of human AE are detected in rural communities in parts of China and in different countries of central Asia where people live in close contact with domestic dogs that both have unrestricted access to infected intermediate hosts and are not regularly dewormed (Ito et al., 2003). In such areas high prevalence rates can be found in village dogs. Correspondingly, studies from Alaska and China revealed that high prevalence or incidence rates of AE in humans were associated with high parasite prevalences in domestic dogs (Schantz et al., 1995; Vuitton et al., 2003). Furthermore, contact with dogs was identified as a risk factor for human AE in Chinese regions (Craig et al., 2000; Tiaoying et al., 2005; Yang et al., 2006) and in Europe (Kern et al., 2004). A case–control study from Alaska revealed that contact with contaminated dog faeces in the environment was a more important risk factor than the direct contact with dogs through feeding, watering and harnessing in this region (Stehr-Green et al., 1988).

Although the mechanism for how humans contract the infection is not fully understood, the significance of dogs in the transmission of this zoonosis might be more pronounced in Europe than is generally assumed (Deplazes et al., 2011). Among the individual-based prevention measures, deworming of privately owned dogs has been considered to be of particular importance. In a well-documented study in a village on St. Lawrence Island, Alaska, the monthly deworming of dogs was effective in reducing the infection rate in local vole populations from 29% to 5%, which provides evidence that environmental contamination with *E. multilocularis* eggs was substantially reduced by this measure (Rausch et al., 1990). The association of dog ownership with AE (Kern et al., 2004; Yang et al., 2006) and the high biotic potential of *E. multilocularis* in dogs, which has been shown experimentally to be similar to that of foxes (Kapel et al., 2006), strongly indicates that a monthly deworming scheme for dogs with potential access to wild rodents considerably contributes to lower human infections. Therefore, individually designed and risk-based anthelmintic treatment of dogs should be promoted to minimise the risk of dog transmitted helminthic zoonoses. Uniform guidelines for veterinarians and leaflets for dog owners addressing the control and treatment of parasites in pet animals have been published and are actively distributed by the expert groups Companion Animal Parasite Council (CAPC) in the USA (www.capcvet.org) and European Scientific Counsel Companion Animal Parasites (ESCCAP) in Europe (www.esccap.org). However, implementing control strategies to regularly deworm free-roaming village and farm dogs as well as stray dogs is challenging (Yang et al., 2009), and new strategies including the use of heat-tolerant praziquantel baits have to be considered.

Praziquantel treatment of cats with free access to rodents has been proposed by several authors to reduce *E. multilocularis* egg excretion but as outlined above, cats might play only a minor role in AE transmission. Nevertheless, frequent anthelminthic treatment of cats is of importance in the reduction of the *Toxocara cati* egg contamination of the environment.

6. The human dimension

6.1. Human behaviour – a crucial risk factor

Case–control studies provide evidence that infection risk is significantly affected by individual behaviour and life style. In a German study, Kern et al. (2004) showed that factors such as “dog ownership”, “was a farmer” and “used to chew grass” applied significantly more to people diagnosed for AE (odds ratios, ORs: 4.2 (95% CI 1.7–9.9), 4.7 (95% CI 1.8–12.1) and 4.4 (95% CI 1.7–11.2), respectively). In Austria (Kreidl et al., 1998), several individual risk-associated factors such as “cat ownership”, “working with grass” and “hunting in forest” were identified (ORs: 6.6 (95% CI 1.8–24.5), 3.4 (95% CI 1.0–11.9) and 8.1 (95% CI 1.5–43.1)) and “rearing of cattle and pigs” and the “use of well water” were significant risk factors in Hokkaido, Japan (Yamamoto et al., 2001). However, the investigated factors are not necessarily the proximate causes for the observed association. Nevertheless, the above mentioned high ORs for several life style related factors provide evidence that appropriate recommendations for behavioural changes could contribute to a lower individual infection risk (Eckert et al., 2011).

6.2. Information as an integral part of a prevention strategy

Following an international survey in four countries (France, Germany, Switzerland and Czech Republic), significant differences in the perception and the knowledge of AE were documented in different highly endemic regions. For example, in Switzerland where comparably high incidence rates were recorded (Schweiger et al., 2007), only 12.1% of the persons who knew of *E. multilocularis* considered it as a high risk. In France, this percentage was considerably higher at 42.5% (Hegglin et al., 2008), although the overall disease incidence is much lower (Kern et al., 2003; Torgerson et al., 2010). Furthermore, in the Czech Republic and Switzerland, measures such as deworming dogs were not recognized as prevention options to reduce the infection risk for dog holders (Hegglin et al., 2008), and in countries where *E. multilocularis* was only recently detected, knowledge on how to minimise the risk of exposure is not yet established (Wahlström et al., 2012). We therefore hypothesise that proactive information programs, which enable the public to achieve a realistic risk perception and provide clear information on how people may minimize their infection risk could, in the long term, substantially contribute to reducing incidence rates of AE.

7. Concluding remarks

Besides public health considerations, future decisions for the implementation of control programs against AE will be influenced by political and economic reasoning and by the public risk perception (Koenig, 2007) which differs greatly between regions (Hegglin et al., 2008). As novelty is a factor that increases risk perception (Brun, 1992), public concerns are probably more pronounced in areas where the parasite only recently emerged whereas people in old highly endemic regions are accustomed to the presence of this zoonotic agent. Baiting programmes have to be implemented in a coordinated manner over large areas and they always depend on political decisions, which in turn depend on factors such as public attitudes, available financial resources and priority setting of political decision-makers. These factors and the epidemiological settings (e.g. population break down of fox populations due to other diseases such as rabies, mange or distemper) can change in the short term, which makes long-term planning and the mutual assessment of different prevention and control measures difficult. Therefore, the prevention of human AE should rely not only on one strategy, but follow an integrated and locally-adapted approach integrating measures such as public information, improved veterinary practice regarding domestic carnivores and direct interventions in the life cycle of the parasite (e.g. vole habitat management, anthelmintic treatment).

Acknowledgements

The authors thank Alexander Mathis, Andrew Thompson and Helen Wahlström for valuable comments on the manuscript and acknowledge the support of our research activities by the Swiss Federal Veterinary Office (Nr. 1.07.04).

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