Impact of praziquantel baiting on intestinal helminths of foxes in southwestern Germany

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Summary

Fox baits containing 50 mg praziquantel were distributed by aircraft in a 3000 km² area of southwestern Germany from 1995 to 1999. 20 baits / km² were initially distributed at intervals of six to twelve weeks. Starting from a pre-baiting prevalence of 64 % (95 % C.I. 59 – 69), a level of 15 % (C.I. 10 – 21) was reached after 18 months. Further decreasing the frequency and discontinuing the bait distribution caused a surge to 55 % (C.I. 49 – 61) within 36 months. Other cestode species (*Taenia* spp., *Mesocostoides* spp.) showed similar responses, while the prevalence of ascarid nematodes did not decline during baiting. New infections of fox cubs with *E. multilocularis*, but not with other cestodes, drastically decreased after one year. Prevalences of fox helminths in an external control area remained stable. Our data suggest that repeated praziquantel treatment of free ranging foxes is suitable to reduce the prevalence of *E. multilocularis* in a large area.

Key words: *Echinococcus multilocularis*; alveolar echinococcosis; epidemiology; control; praziquantel; bait

Introduction

Alveolar echinococcosis (AE), caused by the fox tapeworm *Echinococcus multilocularis*, is the most severe parasitic zoonosis in Europe (Pawłowski *et al.*, 2001). Curative treatment of AE by radical surgery is possible only in an early stage of the disease, while the majority of patients is diagnosed in an advanced stage when more than one liver lobe is involved. In such cases, continuous chemotherapy with benzimidazoles (albendazole or mebendazole) is the treatment of choice. This will, in most cases, inhibit the growth of the parasitic lesion, but will not lead to cure. Thus, lifelong chemotherapy is the rule, with an estimated

cost of USD 300,000 per patient per life (Romig *et al.*, 1999a). For patients with adverse reactions to benzimidazoles there is currently no treatment option. Although the number of human AE cases in Europe is still small, this situation appears to be changing. Following a drastic increase of the size of European fox populations which had occurred during the 1990s, and a temporally correlated increase of *E. multilocularis* prevalence in foxes (Romig *et al.*, 1999b; Jenkins *et al.*, 2005), the annual incidence of human AE in Switzerland has risen from 0.10 per 100,000 population during 1993–2000 to 0.26 per 100,000 during 2001–2005 (Schweiger *et al.*, 2007). Apart from the density of infected foxes (which was estimated to have increased by the factor 10 since the 1980s – Romig *et al.*, 1999b), an increasingly close contact between wild foxes and humans due to newly established urban fox populations is likely to be responsible for this development (Deplazes *et al.*, 2004). In Europe, *E. multilocularis* is predominantly transmitted by foxes. Domestic dogs and cats are sporadically found infected, but their quantitative contribution to the transmission cycle of this parasite is minor. Although prevention of dog infection is believed to be an important means to reduce the risk for AE in humans, any control measure with the aim to interrupt or weaken the life cycle of *E. multilocularis* has to be targeted at foxes (Ito *et al.*, 2003). This could, in theory, be done either by reducing the population density of host animals (e.g. by increased hunting pressure), or by reducing the parasite population by anthelmintic treatment of foxes. Conventional hunting techniques have not prevented the drastic population increase following the elimination of rabies, and, as *E. multilocularis* was successfully transmitted even during the rabies period before 1990, there is no indication that even intensified hunting has the potential to reduce the fox

population to a level where the life cycle of *E. multilocularis* is interrupted.

A first trial with anthelmintic treatment of wild foxes was done by Schelling *et al.* (1997) in southwestern Germany. The cestodicidal drug praziquantel was administered in baits in densities of 15 – 20 baits/km² in a 566 km² study area. After six rounds of baiting during a 14-month period, the prevalence in foxes had decreased from 16 – 52 % (CI 95 %) to 2 – 7 %. An application on a larger scale, with bait distribution by aircraft, was done in northeastern Germany in a study area of 5000 km², enclosing two circumscribed endemic foci within a low endemicity region (Tackmann *et al.*, 2001). Bait distribution was done at six-week intervals for one year, followed by a second year with three-month intervals. The prevalence could be reduced from 16 – 27 % to 2 – 6 % in the endemic foci, and from 4 – 7 % to 0 – 1 % in the low endemicity area. Similar results - drastic reduction, but no elimination - were obtained in two studies on smaller areas in Japan (reviewed in Ito *et al.*, 2003). In a small-scale approach targeting urban foxes, Hegglin *et al.* (2003) distributed 50 baits per km² monthly in areas of 1 and 6 km². The proportion of coproantigen-positive fox faecal samples declined from 39 % to 5 %, and from 67 % to 2 %, respectively, in the course of 18 months. No data, however, are available on the long-term effect of praziquantel-baiting on the prevalence of *E. multilocularis* in foxes, nor on the impact of this method on other intestinal helminths of foxes. In this study, we present the impact of large-scale praziquantel baiting on the helminth fauna of foxes in an area of southwestern Germany highly endemic for *E. multilocularis*, and report on the effect during a follow-up period after discontinuation of baiting.

Material and Methods

Study area and sampling

The study was conducted from May 1995 to April 2001 in a 3,400 km² (reduced to 3,000 km² from January 1998) area of the central Swabian Jura in the federal state of Baden-Württemberg (Germany) (Fig. 1). Control area (without baiting) was a 2,440 km² area in the northern part of the state (Fig. 1). During the entire study period, foxes in the baiting area were continuously sampled from local hunters and examined for intestinal helminths. In the baiting area, sampling was - for practical reasons - restricted to 556 km², which consisted of the central part and three corridors towards the periphery of the baiting area (Fig. 2). In the control area, sampling was done by collecting foxes from the entire area, which had been sent to the governmental veterinary laboratories in Heidelberg in the context of a rabies monitoring programme. Sample size for the baiting area was a total of 4,740 foxes (mean 790 per year), which amounts to a sample density of 1.4 foxes per km² per year in the sampling area. This is well below the hunting bag of private fox hunters (2 – 3 foxes per km² in this region), and is not expected to constitute a confounding factor by decreasing the population density.

From the control area, we obtained a total of 2,657 foxes (mean 443 per year), a sampling density of 0.2 per km² per year.

Diagnosis

Fox carcasses were obtained frozen at –20 °C, transferred to a biohazard laboratory and further processed according to biohazard legislation (biosafety level L3). Foxes were allowed to thaw for 36 hours and were examined for large helminths by macroscopic inspection of the entire small intestine, and for small helminths by the intestinal smear technique (Eckert *et al.*, 2001). For *Mesocostoides* spp., *Taenia* spp., ascarid nematodes (*Toxocara* and *Toxascaris*), recording was qualitative (present or absent). Determination was not done to species level; with *Taenia*, subsamples were invariably identified as *T. crassiceps* or *T. polyacantha*. For *E. multilocularis*, recording was semi-quantitative (number of worms seen in the smears under 12x magnification).

Analysis

To obtain sufficient sample sizes in different strata, prevalence was expressed as period prevalence combining data from three- or six-month periods. Stratification was further done according to space (different areas within the sampling areas) and fox age (cubs ≤ 3 months age, juveniles ≤ 6 months age, adult > 6 months age). Confidence intervals were determined according to Cannon & Roe (1982).

Baits and bait distribution

Fox baits containing 50 mg praziquantel were used either as Droncit® bait (Bayer AG, Leverkusen), or in combination with rabies vaccine (Rabifox-Droncit® bait, IDT GmbH, Rosslau). The baits were distributed by aircraft at a density of 20 baits per km². In total, there were 18 bait distribution campaigns. Time intervals between baiting was six weeks (October 1995 to March 1997), three months (May 1997 to March 1998) and six months (May 1998 to October 1999).

Results

Echinococcus multilocularis

Bait distribution in six-week intervals lead to a reduction of the observed prevalence from initially 59 – 69 % (CI 95 %) to less than 20 % within 12 months of baiting (Fig. 3). This level stabilized with no further tendency for decrease, leading to a prevalence of 13 – 24 % (CI 95 %) during the baiting months 15 – 21. After increasing the intervals between baiting to three months, no prevalence change was observed: during the period 8 – 14 months after the introduction of the three-month schedule, the prevalence was still 10 – 21 % (CI 5 %) (Figs. 3, 4, 5). However, the consecutive change of baiting intervals to six months coincided with a prevalence increase to 31 – 41 % (CI 95 %) during months 15 – 21 after the introduction of that schedule. During months 13 – 18 after the last bait distribution,

the prevalence had increased to 49 – 61 % (CI 95 %) (Figs. 3, 6). The changes of prevalence were closely similar in

Fig. 1. Map of Baden-Württemberg (federal state in the Southwest of Germany), showing the baiting area (B) and control area (C)

Fig 2. Map of the baiting area (as reduced by January 1998), showing central and peripheral sampling areas (light and dark shading)

the central and peripheral parts of the study area (Figs. 4, 5, 6). During the entire study period, no significant preva-

lence change was observed in the control area, which was stratified for two adjacent sub-areas with different pre-

Fig. 3. Temporal development of prevalence estimates of *E. multilocularis* in foxes in all sampling areas of the baiting area (three-month period prevalences with 95 % confidence intervals)

Fig. 4. Prevalence distribution of *E. multilocularis* before the start of praziquantel baiting (May to October 1995) in four parts of the sampling area (in brackets: 95 % confidence intervals)

valence levels (Fig. 7).

During the summer months (April to September) foxes were stratified for age. During all periods of the study, juvenile foxes were more frequently infected and had larger numbers of worms, whereas the proportion of different infection intensities remained similar (Fig. 8). It was also apparent that prevalence reduction was more pronounced in adult foxes than in juveniles during the baiting period. Of special interest is the prevalence in fox cubs in the period from April to June with their limited mobility and limited access to baits: prevalence reduction in this age group

showed a one-year delay in comparison with adults (Fig. 9).

Fig. 5. Prevalence distribution of *E. multilocularis* 8 – 14 months after the three-monthly baiting schedule was started (February to July 1998) in four parts of the sampling area (in brackets: 95 % confidence intervals)

Fig. 6. Prevalence distribution of *E. multilocularis* 13 – 18 months after discontinuation of baiting (November 2000 to April 2001) in four parts of the sampling area (in brackets: 95 % confidence intervals)

Other cestodes

In comparison with *E. multilocularis*, the reduction of *Taenia* spp. prevalence during praziquantel baiting was less pronounced, and the recovery to (and above) the pre-baiting level was achieved far earlier than with *E. multilocularis*. When looking at the age stratification, the reduction of prevalence is almost entirely due to the effect on adult foxes, while the prevalence in fox cubs remained al-

most unchanged (Figs. 10, 11). The overall response of *Mesocostoides* spp. rather follows that of *E. multilocularis*,

Fig. 7. Temporal development of prevalence estimates of *E. multilocularis* in foxes in the control area (six-month period prevalences with 95 % confidence intervals). Black dots, black line: counties Rhein-Neckar, Mannheim and Heidelberg. White dots, dotted line: county Neckar-Odenwald

Fig. 8. Age-stratified prevalence of *E. multilocularis* in adult and juvenile foxes (April to September). Worm burden is classified in two categories (high ≥100 worms, low <100 worms). Worm numbers are those counted on the slides of the mucosal smears (ITS method), not the total number of worms present in the intestine. Six-month period prevalences with 95 % confidence intervals

Fig. 9. Age-stratified prevalence of *E. multilocularis* in adult foxes and fox cubs (April to June). Worm burden is classified in two categories (high ≥100 worms, low <100 worms). Worm numbers are those counted on the slides of the mucosal smears (ITS method), not the total number of worms present in the intestine. Three-month period prevalences with 95 % confidence intervals

Fig. 10. Temporal development of prevalence estimates of *Taenia* spp. in foxes in all sampling areas of the baiting area (six-month period prevalences with 95 % confidence intervals). Dotted line: prevalence of *E. multilocularis*

Fig. 13. Age-stratified prevalence of *Mesocostoides* spp. in adult foxes and fox cubs (April to June). Three-month period prevalences with 95 % confidence intervals

Fig. 11. Age-stratified prevalence of *Taenia* spp. in adult foxes and fox cubs (April to June). Three-month period prevalences with 95 % confidence intervals

Fig. 14. Temporal development of prevalence estimates of ascarid nematodes (*Toxocara* and *Toxascaris*) in foxes in all sampling areas of the baiting area (six-month period prevalences with 95 % confidence intervals). Dotted line: prevalence of *E. multilocularis*

Fig. 12. Temporal development of prevalence estimates of *Mesocostoides* spp. in foxes in all sampling areas of the baiting area (six-month period prevalences with 95 % confidence intervals). Dotted line: prevalence of *E. multilocularis*

Fig. 15. Age-stratified prevalence of ascarid nematodes (*Toxocara* and *Toxascaris*) in adult foxes and fox cubs (April to June). Three-month period prevalences with 95 % confidence intervals

but the age-stratified results differs totally. Before the influence of praziquantel baiting, most *Mesocostoides* infections were found in adults (in contrast to *Echinococcus* and *Taenia*). Again, the infection rate of adults was drastically reduced during the baiting period, while it hardly changed in fox cubs (Figs. 12, 13).

Ascarids

The prevalence of ascarids increased during the period of baiting, coinciding with decreased infection rates of cestodes. This effect was due to a larger proportion of infected adult foxes, while the prevalence in cubs remained unchanged (Figs. 14, 15).

Discussion

E. multilocularis

We could show that the prevalence of *E. multilocularis* substantially decreased after repeated air distribution of praziquantel baits in a high endemicity area. After seven baiting campaigns in the course of twelve months the prevalence was reduced by approximately 75 %, but did not decrease further. However, only six months after this level was reached, the six-weekly baiting intervals had to be increased to three months due to financial constraints. Whether or not a further decrease could have been achieved by continuing with shorter baiting intervals remains speculative. It is, however, suggestive to look at infection rates of fox cubs of less than three months of age. In this age group, the radius of movement is still small, and access to baits is unlikely. Thus, the prevalence in cubs may serve as an index for the presence of infected rodent intermediate hosts. In the first year of baiting this was still high (Fig. 9), and the general prevalence decrease was apparently caused by the increased mortality of the worm population in adult foxes due to anthelmintic treatment. In the second year, infection of fox cubs was drastically decreased (suggesting a similarly drastic decrease of re-infection of adult foxes), which is likely to be caused by a lower number of infected rodents. Reduced prevalence in rodents, in turn, should have been caused by two factors: fewer eggs were shed by foxes due to praziquantel baiting, while eggs persisting in the environment from the pre-baiting period would have gradually decayed. This is in agreement with the observation that *E. multilocularis* eggs survive for less than one year in the environment under favourable conditions (Veit *et al.*, 1995). This reduced re-infection rate of foxes may be the reason, why the general prevalence level remained low despite the reduced baiting frequency. A further decrease of baiting frequency to once in six months was accompanied by a prevalence increase in all age groups. This increase, initially slow, accelerated one year after the last distribution of baits, and the prevalence resurged to that of the pre-baiting period a further six months later.

The prevalence decrease observed in the initial two years of this study is in accordance with previously published data (Schelling *et al.*, 1997, Tackmann *et al.*, 2001, Ito *et al.*, 2003, Hegglin *et al.*, 2003), which were, with

exception of the first study, obtained under different epidemiological conditions (low endemicity level, small-scale, or urban area). In all studies, a drastic prevalence reduction was observed. Complete interruption of the life cycle of the parasite could not yet be demonstrated, although hitherto published studies are characterized by rather short baiting periods of up to two years and do not include follow-up data. In the present study, the transmission of *E. multilocularis* persisted throughout the baiting period. Immigration of infected foxes from outside the study area appears to play a marginal role – if any –, as the prevalences during the course of the study were closely similar in central and peripheral parts of the baiting area. In addition, fox cubs of ≤ 3 months were found infected, although at a much reduced rate, throughout the baiting period. Various factors might have contributed to the persistence of the life cycle. (1) The period of high baiting frequency may have been terminated too early, as a reduced re-infection rate only became apparent in the second year. (2) The number of baits may not have been adequate. The bait density of 20 per km² was chosen from previous experience with praziquantel baits (Schelling *et al.*, 1997) and from rabies campaigns. However, the population density of foxes in the study region – as in other areas of Europe – had increased drastically during the 1990s (Romig *et al.*, 1999b). (3) Bait distribution by air is restricted to open areas without human settlement, as bait must not be distributed closer than 300 m from buildings. Foxes, however, increasingly utilize towns and villages ('urban foxes') (Gloor *et al.*, 2001). Although such foxes are less frequently infected with *E. multilocularis* than those in rural habitats, their population density is often higher, which may amount to an equal, or even larger, number of infected foxes per area (Deplazes *et al.*, 2004). In the present study, a large proportion of these foxes had home ranges restricted to areas without bait distribution (Thoma *et al.*, 2004), which may have contributed to the persistence of autochthonous transmission. There is a number of additional variables, which could be used to optimize the distribution schedule. Specific targets could be juvenile foxes, which showed a higher prevalence and – more importantly – had higher infection intensities than adults during the summer months. Increased baiting frequency during this period may enhance the efficiency of the method. The impact of these variables cannot be evaluated by large-scale field trials. Instead, mathematical models will in future be important tools to optimize baiting schedules (Hansen *et al.*, 2003).

Other helminths

The development of total prevalence of the praziquantel-sensitive cestodes *Taenia* spp. and *Mesocostoides* spp. rather resembled that of *E. multilocularis*. However, when looking at the age stratification during the cub rearing months, differences became apparent. With *Taenia*, the prevalence decrease seemed largely due to the anthelmintic effect on the adult worms. Looking at the re-infection rate (inferred from the prevalence in fox cubs – Fig. 11), only a

slight decrease is notable in the second year (with broadly overlapping confidence intervals). Apparently, the life cycle of *Taenia* is less sensitive to an increased worm mortality, and the extent of anthelmintic treatment in this study may not have substantially reduced the number of infections in rodents. This can serve as an explanation of the rapid resurgence of *Taenia* prevalence to the pre-baiting level, which occurred two years earlier than with *Echinococcus*. This observation is in agreement with Gemmell & Lawson (1986), who demonstrated a higher resilience of *T. ovis* and *T. hydatigena* in comparison with *E. granulosus* against control measures in dogs. With *Mesocestoides*, prevalence decrease and subsequent increase follow more closely those of *E. multilocularis*, although a prevalence rise at the end of the study to almost double the pre-baiting figure remains unexplained. The seasonal dynamics of *Mesocestoides* – whose transmission cycle is still enigmatic (Loos-Frank, 1991) – appear different from *Taenia*. Even without the influence of praziquantel, fox cubs show much lower infection rates than adults. This is in stark contrast to *Echinococcus* and *Taenia* and could be explained by a generally lower density of infected intermediate hosts, and/or by seasonal transmission peaks in months other than April to June. As with *Taenia*, the baiting impacted largely on the prevalence in adult foxes, while no significant change was observed in fox cubs throughout the study period. As expected, ascarid nematodes, which are not sensitive to praziquantel, showed no prevalence decrease during the baiting period. Rather, ascarid prevalence increased in those periods with the lowest prevalence of cestodes (years two and three). Whether or not this is the result of reduced interspecific competition among large intestinal helminths is not known. However, the prevalence increase in years 2 and 3 was not due to increased incidence, as the prevalence in fox cubs remained unchanged. Rather, a larger proportion of foxes appears to have kept the ascarid worms into adulthood than in the period before baiting.

Conclusion

Our data show, that praziquantel baiting has a drastic effect on *E. multilocularis* and other cestodes of foxes, but that even local elimination of the parasite transmission is not achieved under the described regimen. *E. multilocularis*, however, is the only helminth of foxes where – with time delay of one year – a reduced re-infection could be demonstrated. This instability of the life cycle to increased mortality of adult worms provides a perspective for a more substantial reduction, or elimination, of the parasite transmission using modified baiting schedules.

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