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Control of Cystic Echinococcosis: Background and Prospects

Run title: Cystic echinococcosis. Experiences in control

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Abstract

Cystic echinococcosis (CE), caused by *Echinococcus granulosus*, is a chronic and debilitating zoonotic larval cestode infection in humans, which is principally transmitted between dogs and domestic livestock, particularly sheep. Human CE occurs in almost all pastoral communities and rangeland areas of the underdeveloped and developed world. Control programmes against CE have been implemented in several endemic countries to reduce or eliminate the disease. New Zealand and Tasmania are examples of some of the first programmes to be undertaken (in insular territories) and which were very successful in the elimination of CE. The advent and proven effectiveness of praziquantel, plus the experience of insular models, produced high expectations for rapid advances in a second generation of control programmes undertaken in continental areas (Argentina, Uruguay, and Chile). Nevertheless, only moderate gains in CE control have been made and the impact on prevalence among humans has been slight. A major impediment to the adoption of procedures that were successful in New Zealand and Tasmania has been the requirement to administer praziquantel to dogs in rural areas 8 times per year over numerous years. In addition, there have been clear technological improvements made in the diagnosis of canine echinococcosis

for surveillance, the genetic characterisation of parasite strains and in vaccination against CE infection in livestock. In order to establish new paradigms and appropriate combinations of control strategies we have carried out a review and discussion of the available control tools and control models. Control strategies must be suitable and sustainable to benefit the Echinococcosis-endemic areas primarily, which at the same time are the poorest regions of the world.

KEYWORDS: Cystic echinococcosis; control; praziquantel; EG95 vaccine, surveillance

Impacts

- Insights on surveillance and control of Cystic echinococcosis (CE) caused by *Echinococcus granulosus* have increased as a result of experiences in endemic regions of South America, Africa and Asia
- CE is a neglected zoonotic disease that causes heavy economic losses due to its impact on individual and public health associated with diagnosis, treatment, and follow-up, and on livestock through reduced productivity and viscera condemnation
- The elimination of CE in continental areas is a very difficult objective to achieve. Control, with strong decreases in transmission to human, is a realistic goal.

1 INTRODUCTION

Cystic echinococcosis (CE) or hydatidosis is a parasitic infection caused by a cestode of the family Taenidae, *Echinococcus granulosus sensu lato*. The parasite causes zoonotic disease in humans. *E. granulosus* requires two mammal hosts to complete its life cycle; the adult tapeworm is found in the small intestine of dogs and other canids, while the larval stage (commonly referred to as a hydatid cyst) is located in the viscera of ungulates, especially sheep, goats and cattle. Transmission of *E. granulosus* between domestic livestock and dogs

is predominantly a feature of pastoral communities in temperate or semi-arid rangeland areas of the world (Craig & Larrieu, 2006; Craig et al., 2017).

The transmission cycle of *E. granulosus* relies primarily on the domestic cycle where farmed livestock species act as intermediate hosts and transmission is associated with active practices of man which acts to facilitate the cycle of the disease. In contrast with the domestic cycle of *E. granulosus*, the transmission of *E. multilocularis*, *E. vogeli* and *E. oligartus* have a sylvatic cycles of transmission that involve only wild animals that are in a predator pray relationship (Otero -Abad & Torgerson, 2013).

The clinical presentation of CE is variable and depends on the size, location and number of cysts, symptoms often resemble those of a space-occupying mass. In humans, CE often remains asymptomatic until the cyst either ruptures or becomes large enough to exert pressure on the surrounding tissues (Brunetti et al., 2011).

CE is one of the zoonotic diseases with the highest prevalence in South America, where sheep farming, associated with the presence of large numbers of dogs, and the habit of slaughtering adult sheep for home consumption (with the ensuing feeding of infected viscera to dogs) generate ideal conditions for the disease cycle cycle (Craig and Larrieu, 2006; Craig et al., 2007; Carmona & Carmena, 2013; Carmena & Carmona, 2013; Otero-Abad & Torgerson, 2013; Craig et al., 2017).

From 2009 to 2014, a total of 29559 new human cases of CE were registered in Argentina, Brasil, Chile, Peru and Uruguay (Pavletic et al., 2017). The average case fatality rate (CFR) across the five countries was 2.9%. This suggests that CE led to approximately 880 deaths in the five countries with an average proportion of cases among children less than 15 years of age of 15.0%, indicative of a persistent environmental risk leading to new cases among children (Pavletic et al., 2017).

An economic impact of CE arises from its impact on the health of individual people, losses in productivity of livestock, decrease in regional economies and also in public health where costs are incurred in attempting to control the disease. The human-associated economic losses include both direct and indirect costs. Direct costs include costs associated with diagnoses, treatment, and follow-up care. Indirect costs include costs associated with treatment-related travel expenses, lost wages, and decreased productivity due to CE-related morbidity and

mortality. Similarly, livestock-associated economic losses include direct costs, resulting from the condemnation of infected viscera, as well as indirect costs due to decrease productivity (Budke et al., 2006; Torgerson, 2006; Bingham et al., 2015). While there are costs associated with the parasite's impact in animals, CE should be considered primarily a health problem.

E. granulosus sensu lato is a genetic diverse group of parasites. Genetic differences were initially referred to as strains or genotypes (Bowles et al., 1992). More recently, a number of the genetic variants have been considered to have species status. While many genetic variants of *E. granulosus* have been found to cause CE in humans, parasites of the species *E. granulosus sensu stricto* (formally genotypes G1/G3) cause the great majority of human infections worldwide (88%) (Alvarez Rojas et al., 2014), with most of the remainder caused by *E. canadensis* (formally genotypes G6/7). The parasite species causing CE in South America follows a similar pattern (Cutcher et al., 2016).

It is clear from the worldwide distribution of CE in humans that the infection is transmitted principally by farmed livestock and domestic dogs. Consideration of the parasite's life cycle identifies opportunities to reduce transmission, including behavioural changes which would reduce access of dogs to the offal of slaughtered animals. The drug praziquantel became available in the 1980's as a highly effective treatment for *E. granulosus* infections in dogs, providing a readily-available and effective tool for CE control. Several CE control programmes have been effective (Craig & Larrieu, 2006; Craig et al., 2017), however many programmes that were initiated since the 1980's, were ineffective and have been abandoned (Lightowlers, 2013). More recently, the development of the EG95 vaccine for protection of livestock against infection with *E. granulosus* and its availability as a commercially produced product has presented a new tool to assist with CE control (Craig et al., 2017). The World Health Organization (WHO) has recommended implementing pilot projects in selected countries to validate the effectiveness and efficiency of current CE control tools and implementation of specific CE interventions, specifically in Latin America, to control and eliminate this public health concern by 2020. Accordingly, the Pan American Health Organization (PAHO) coordinated in 2004 the development of the Sub-Regional Project for the Surveillance and Control of CE, actuality CE Initiative for the Surveillance and Control, with Argentina, Brazil, Chile, Peru and Uruguay (Pavletic et al., 2017).

Here we consider the strategies available for control of CE, particularly in a South American context, but applicable to all countries with high levels of CE including Africa and Asia.

2 GENERAL PRINCIPLES FOR CONTROL

The aim of CE control is to manage the disease within primary health-care systems and ultimately eliminate it as a public health problem. Here we apply the following definitions:

- Control: Reduction of incidence, prevalence, morbidity or mortality to a 'locally acceptable for public health' level as a result of deliberate efforts. Continued measures are required to maintain the reduction.
- Elimination: Reduction to zero of the incidence of a disease as a 'public health problem' as a result of deliberate efforts. Continued measures are required.
- Eradication: Permanent reduction to zero of the incidence of infection caused by CE result of deliberate efforts. Intervention measures are no longer needed.

Michael Gemmell applied a four stage process for the implementation of control or eradication programme for CE (Gemmell et al., 1986; Craig & Larrieu, 2006; Craig et al., 2017) (a) preparation (organization of the programme and of the surveillance system, personnel training); (b) attack (stage that commences when the main control measure destined to destabilize the parasite is initiated); (c) consolidation (destined to identify and eliminate the remaining sources through an intense vigilance system); and (d) eradication (if transmission has ceased because the parasite is extinct, surveillance will be maintained in order to avoid its reintroduction).

Considering these steps as disaggregated, the following stages would be necessary:

1. Determine the initial level of endemicity, in the human population, disaggregated by age, and if possible in dogs and sheep with geographic maps at the smallest possible scale;
2. Define the threshold assumed for the elimination of the disease as a "public health problem" (morbidity reduction programme) or, if feasible, for the elimination of the infection (elimination programme);

3. Select control tools and monitoring tools to monitor the impact generated by the control tools. How often and at which level of coverage should be defined for the selected tools to maintain the prevalence and intensity of the infection below the levels existing before the start of the programme or to eliminate the disease; and also what are the best indicators and diagnostic tools to evaluate the progress of the control or elimination programme.
4. Define the surveillance system to be used if the transmission has been stopped.

The elimination can be defined from the modeling of the impact of various control strategies. The breaking point of parasitic dynamics is defined by knowledge of the parasite's reproductive capacity (R_0) in the presence of acquired immunity as a distinctive regulated by density - dependent feature of *E. granulosus* where $R_0 > 1$ represents the existing endemic steady state or hyperendemic steady state and $R_0 < 1$ implies bringing the parasite to extinction (Gambhir et al., 2015). Where age-intensive prevalence surveys have been made (for example New Zealand, China and Uruguay) *E. granulosus* has been found to be endemic, never in hyperendemic state (Gemmell et al., 2001).

Gemmell & Schantz (1997) considered the various general approaches that could be taken to control CE, some of which were considered to be “horizontal” and “vertical” approaches, while different options within these were considered as representing either as representing “slow track” or “fast-track” options. These approaches have been reviewed by others (Craig & Larrieu, 2006; Moro & Schantz, 2006; Larrieu & Zanini, 2012; Craig et al., 2017). Control options involving the frequent treatment of dogs with praziquantel, without the need to drastically reduce the dog population, are considered fast track and this approach has formed the basis for several successful CE control programmes that have been undertaken in South America.

The scheme, originally applied in insular programmes such as a New Zealand (1959-1991) and Tasmania (1964-1996), carried out systematic de-worming of dogs every 45 days (with arecoline hydrobromide or praziquantel (PZQ)) with the objective of eliminating new tapeworm infections each time before they started to release eggs. PZQ (isoquinolone-pyrazine) is highly effective against cestodes, including *Echinococcus* and *Taenia* spp. at a dose of 5 mg/kg, although the drug is not ovicidal (Gemmell et al., 1986, Craig & Larrieu, 2006; Moro & Schantz, 2006; Larrieu & Zanini, 2012). As the systematic deworming begins

to cover the whole dog population of a given area, the risk of infection for humans and livestock decreases gradually and progressively, until transmission is interrupted completely. Renewal of the whole ovine population by animals born after the cessation in transmission would rise to the elimination of *E. granulosus* (Craig et al., 2017).

New Zealand and Tasmania are examples of control programmes of first generation that were very successful in the eventual elimination of CE as a public health problem, and even to the elimination of the parasite in dogs and sheep (Craig & Larrieu, 2006; Craig et al., 2017).

Following the success of the control programmes in New Zealand and Tasmania second generation programmes were initiated in continental areas of South America, in Argentina (Pilot programme of Neuquén, 1970-1985), Uruguay (phase 1 1972-1992; phase 2 1992-2009; phase 3 2009-current) and Chile (1979-1997), based on the strategy used, and experience of, the insular programmes. The schemes involved 8 deworming of dogs per year (with arecoline hydrobromide originally, and with PZQ since 1979). The exceptions were some areas in Argentina (Rio Negro with 4 treatments per year and Tierra del Fuego with 2 treatments per year since 1980), and Uruguay phase 2 and 3 (12 deworming per year) (Craig & Larrieu, 2006; Larrieu & Zanini, 2012; Irabedra et al., 2016, Craig et al., 2017). Peru has started a pilot CE control programme only in five regions that include 17 rural communities in 2015 using PZQ in dogs, 4 treatments per year.

Third generation programmes were initiated in continental areas in China. From 2006 a control programme at national level was initiated and currently covers 170 counties in northwest China (Craig et al., 2017).

However, more than 30 years after the introduction of praziquantel no endemic area has reached the eradication stage and only Chile's Region XII in the past and Uruguay have sustained the attack stage consistent with Gemmell's control plan, but these were discontinued with ensuing re-emergence of the disease (Craig & Larrieu, 2006; Larrieu & Zanini, 2012). Partial or total discontinuation of control programmes in continental areas has been a recurring issue and human cystic echinococcosis continues to be a substantial cause of morbidity and mortality in many parts of the world (Larrieu & Zanini, 2012).

Although the control programme in Argentina and Uruguay have not eliminated *E. granulosus*, they have been maintained over time, which has been their greatest virtue and

the cause of their relative success. Both of them have rendered a significantly reduction of CE prevalence in humans (Larrieu et al., 2011; Larrieu & Zanini, 2012; Irabedra et al., 2016; Craig et al., 2017), but there was an incomplete coverage of deworming, so the control effort must be sustained for a long period of time.

The Uruguay control programme and the control programme of the island of Tierra del Fuego in Argentina are the firsts in many years (Uruguay is also the first in continental areas) to be close to reaching the control and elimination of CE (Larrieu & Zanini, 2012; Irabedra et al., 2016; Craig et al., 2017), Uruguay with 12 deworming/years and Tierra del Fuego in Argentina with only 2 deworming/years associated with the development of rural infrastructure (such as slaughterhouse with viscera disposition areas and restraining dogs when they were not working).

The use of PZQ in dogs has been associated with some operative problems such as its unpleasant taste and smell for dogs (a problem that can be mitigated by smearing the tablets with pate de foie, for example), difficulties for the personnel in dosing dogs and ensuring they ingest the complete dose, inadequate estimation of dog's weight and probably incorrect dosage (underdosage), reticence of the dog owners to administer a large number of pills at each time deworming is required, and dogs that are not at home at the time of control staff visit rural properties.

Those problems become significant when the recommendation is to treat dogs at predetermined intervals, for example every 6 weeks (8 times annually) and throughout a prolonged period of years (10 to 15) (Gemmell et al., 2001). This strategy, therefore, has not been sustainable either economically politically or logistically in most endemic regions which, as a rule are often amongst the poorest regions in CE endemic countries.

The following considerations concern options for approaches that could be implemented for control of CE in South America, in the future which may expand the areas where transmission has been reduced to levels below those at which the disease would be considered a significant public health risk (Table 1).

2.1 Control through de-worming dogs

A substantial reduction in transmission of CE can be achieved using dog dosing with PZQ at doses of 5 mg/Kg at intervals that are greater than the worm's prepatent period (Cabrera et al., 2002; Craig et al., 2017). Choosing dog dosing intervals that are less frequent than the worm's prepatent period (6 weeks) is more sustainable. In order to use such an approach, it is required first to identify human populations at risk, and farms and villages with persistent levels of transmission; second, to determine the speed of reinfection in dogs, so that the frequency of de-worming can be adjusted to local epidemiological characteristics (Cabrera et al., 2002; Craig et al., 2017).

An alternative to individual treatment of dogs (personnel required) may be baiting. Several studies of *Echinococcus multilocularis* (EM) control programmes, have shown that the parasite infection rate sharply decreases when antihelmintic baits were regularly distributed to foxes (Hegglin & Deplazes, 2013; Yang et al., 2015). In the Emin County of Xinjiang, China, a programme of CE has been implemented involving monthly treatment of dogs with PZQ together with the establishment of bait stations to reach stray dogs where PZQ is provided mixed with food CE control programs might develop similar strategies by using PZQ baits in selected communities (e.g. endemic areas), increasing the coverage and treatment frequency at a low operational cost (Yu et al., 2017).

2.2 Control through dog population reduction

The reduction of the population of unwanted dogs is another recommended strategy to control this zoonosis, although its effect on the prevalence of infection in dogs is not clear. Owned and unowned dogs have been shown to be a major source of *Echinococcus* spp. infection in developing countries (Kachani & Heath, 2014). Unowned dogs are the most challenging category in dog population management for the control of zoonotic diseases, including CE. Unowned dogs are those that do not have an owner, including dogs whose owner cannot readily be identified. Control of unowned dogs can be done in various ways if funds are available. Fertility control is likely to be the most effective procedure and the ethically

approved in developing countries (Kachani & Heath, 2014). Nevertheless, dog fertility control might not be culturally accepted in some rural communities, particularly for male castration.

2.3 Control by health education

Health education for prevention of CE appears generally not to lead to significant reduction in transmission but provides an important avenue to enable endemic rural communities to accept and participate in a fast-track vertical CE control programme. The support of education programmes that promote adopting healthy practices such as not feeding raw offal to dogs is important for control program (Varcassia et al., 2011; Xiao et al., 2012).

2.4 Control through vaccination of animal intermediate hosts.

Vaccination of intermediate hosts of *E. granulosus* with the EG95 recombinant vaccine are used to reduce the level of parasite transmission and decrease the incidence of human infections. Torgerson and colleagues have used mathematical models to predict the impact of various options for control of CE. It was considered that a programme involving vaccination of intermediate hosts (sheep) together with 6-monthly treatment of dogs with praziquantel would decrease the time needed to achieve control of disease transmission (Torgerson, 2006; Torgerson & Heath, 2003).

There is little published information about the impact of the EG95 vaccine when used under field conditions and the potential problems that could arise when the vaccine has to be applied on a large scale in livestock flocks (Larrieu & Zanini, 2012). In this context, the Ministry of Health in Rio Negro (Argentina) performed a field trial using the EG95 vaccine in lambs as an additional tool to the existing CE control programme in the area (dog PZQ treatment). In this pilot field trial lambs received two initial immunizations with EG95 vaccine, manufactured by the University of Melbourne, (the first dose was applied to animals at 30 days of age and the second dose at 60 days of age, before weaning) and animals also received a booster immunization at approximately 1-1.5 years of age. Lambs born on those farms in subsequent years would undergo the same vaccination scheme until the end of the trial (Larrieu et al., 2013).

That vaccination programme in Rio Negro, Argentina began in December 2009 and an evaluation of the impact was undertaken using serological methods in 2012 (Larrieu et al., 2013) and using necropsy of old sheep in 2015 (lambs vaccinated in 2009) (Larrieu et al., 2015). In the vaccinated group, 4 sheep showed 6 hydatid cysts, all of which were small (1 x 1.3 cm to 0.2 x 0.2 cm in diameter); 2 cysts were found in the liver (only one was fertile), and 4 in the lung (average 0.3 cysts per animal). In the unvaccinated control group, 47 hydatid cysts were detected in 13 animals (1.4 cysts per animal, some cysts were larger than 5 cm in diameter). Statistically significant difference was demonstrated in the number of cysts between control group and vaccinated animals ($p=0.02$). Regarding to the farms, 94.7% had at least one positive animal by necropsy in 2009, whereas only 23.5% of them were positive in 2015 (Larrieu et al., 2015). Using coproELISA for diagnosis of infection in dogs, the differences were statistically significant (p value= 0.04) between baseline (2009) and impact (2017) studies in the proportion of positive samples, and, in relation to the farms, the differences were not significant among producers with farms with active transmission (by the presence of an infected dog) (p value= 0.1) (Larrieu et al., 2018).

Sheep were vaccinated at a coverage close to 85% for each dose. Full vaccination was considered to involve two immunizations in lambs and one additional vaccination when the animals were approximately 1 year of age. This being the case, three immunizations at a compliance rate of 80%-85% for each vaccination represents an effective vaccination compliance of 57.3% (Larrieu et al., 2018).

This highlights the importance of the sheep receiving the full 3-dose vaccination regime over their first year of life. The effectiveness of the vaccination programme was adversely affected by our inability to deliver all 3 doses to approximately 40% of the sheep due to the inherent difficulties of working in remote communities with poor animal handling facilities and deficient methods of communication between the control staff and the residents (public radio).

New data confirm that the specific IgG responses to EG95 vaccination after the third or fourth vaccination, induce an increased level of antibody greater than two immunizations and that this response is maintained longitudinally over time for at least 5 years. It would be sufficient time to avoid infection of the sheep and/or development of fertile cysts during the period of its life span in the region (Poggio et al., 2016; Larrieu et al., 2017).

Despite the difficulties that were experienced in implementing vaccination, a significant reduction in prevalence of CE and in the number of cysts in the vaccinated animals was achieved. The trial has demonstrated that the EG95 vaccine is a valuable tool to assist by reducing *E. granulosus* transmission to sheep. However, the EG95 effect on the reduction of infection in dogs and humans needs to be demonstrated in future years.

Vaccination of livestock, however, requires more infrastructures and must be completed in a short period of time to minimize the costs. Although sheep vaccination needs fewer interventions compared with dog treatments per year (2 vaccinations versus 8 dog treatments) it also involves a higher number of animals compared with dog dosing.

Although the EG95 vaccine has demonstrated a high efficacy, there has been few studies that have evaluated the effectiveness of the vaccine under field conditions (Larrieu et al., 2015; 2018). Additional studies of vaccination are required; for example, it is necessary to look for different vaccination schemes (only lamb vaccination, whole sheep population vaccination); also, animal species involved in the vaccination programme (bovine, goats, pigs, camelids) considering costs of the vaccine and the costs of its placement in the field.

The EG95 vaccine has been registered for use in China, where there is, for example, a pilot programme in Datangma in the Ganze Tibetan Autonomous Prefecture they used EG95 in combination with PZQ (Craig et al., 2017). The EG95 vaccine is also registered by Argentinian company Tecnovax with a cost of US\$ 0.50 per dose. In this moment, is being used in pilot programme in Chile since 2016 (in Alto Bio Bio and in Aysen) and, from 2018 in the Rio Negro programme in Argentina. In Peru, likewise, a pilot program has been initiated in Junín, Huancavelica, and Pasco, with vaccine provided by the University of Melbourne alone or in combination with praziquantel from 2015. The evaluation of an overall program strategy has to be considered according to the required time to achieve control and the cost/benefit analysis in association with other control strategies such as praziquantel dosing.

Likewise, the evaluation of an overall programme strategy has to be considered according to the required time required to achieve control and the cost/benefit analysis in association with other control strategies such as praziquantel dosing.

2.5 Control by removal of older sheep

It is well established that in endemic areas of echinococcosis, the prevalence, abundance, cyst size and fertility of hydatid cysts in sheep and goats increase with the age. 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 (Craig et al., 2017). Based on this, the elimination of these animals could mean a strong risk reduction, but there is no history of applying this strategy in any control programme.

In South America it would not be an applicable strategy. Mainly for the costs of paying animal farmers who are producing wool or meat.

2.6 Vaccination of definitive hosts

A vaccine that limits *E. granulosus* egg production in dogs would provide a valuable option for control of CE. Although there have been some studies that have published encouraging preliminary results (Zhang et al., 2006; Petavy et al., 2008) these results have not been confirmed. Follow-up investigations in one case suggested that the effects may have been caused by the adjuvant that had been used (Zhang et al., 2018). The potential for effective vaccination of definitive hosts against *E. granulosus* is uncertain at this time.

2.7 Control through chemotherapy in sheep

Combination albendazole/PZQ have been found to be effective against *E. granulosus* infections in sheep in experimental situations and warrant consideration as an additional control measure which merits further study. Further investigations on different schedules of monotherapy or combined chemotherapy are needed (Gavidia et al., 2010).

It has been demonstrated that oxfendazole (OXF) 60 mg/Kg of body weight weekly for four weeks, the combination of albendazole (ALB) 30 mg/Kg + PZQ 40 mg/Kg BW weekly for 6 weeks, and OXF 30 mg/Kg + PZQ 40 mg/Kg biweekly for 3 administrations (6 weeks) are successful schemes to significantly reduce the protoscolex viability in naturally infected sheep. The percentage of either “noninfective” or “low-medium infective” sheep was 90%, 93.8%

and 88.9% for OXF, ABZ/PZQ and OXF/PZQ group as compared to 50% “noninfective” or “low-medium infective” for placebo. These chemotherapy strategies can be added to other control measures in animals and merits further study for the treatment of animal CE (Gavidia et al., 2010).

A pilot programme being undertaken in Peru in Pasco and Puno is evaluating the use of OXF in sheep alone or in combination with praziquantel in dogs or EG95 vaccination in sheep, which could provide more information on the effectiveness and feasibility of this strategy.

3 CE SURVEILLANCE

Accurate determination of infection rates with *E. granulosus* in humans and in animals is crucial. The importance of CE in humans plays an important role in establishing early treatment and it is used to evaluate the effectiveness of CE control programmes (Table 2).

3.1 Characterization of disease status

The design and launching of an epidemiological surveillance system for cystic echinococcosis requires building a baseline of specific prevalence information for each of the hosts included in the parasite life cycle, in such a way that future progress of the programme can be observed and quantified. Local epidemiological aspects and conditioning and predisposing factors that allow and facilitate the existence of the transmission cycle should be included.

The first aspect to consider is the characterization of the endemic area. The levels of transmission and identification whether an area is endemic or hyperendemic corresponds to a mathematical model based on the reproductive capacity of the parasite and concepts of acquired immunity (Torgerson, 2006). In practical terms we can adopt a new classification scheme that could be easily applied as an orientation in the control programmes, this classification arises from the analysis of the prevalence reported by different programmes over time (Table 3).

3.2 Surveillance in the intermediate host

In the animal intermediate hosts of CE (sheep and goats specially) the method used traditionally for diagnosis in livestock is post-mortem identification of the presence of hydatid cysts; it is important to consider the age of the animals for epidemiological interpretation of data. One of the disadvantages of this method is the limitation in detecting growing cysts in young animals, which are the ones of greatest interest for surveillance in a control programme. Identification of cysts in young animals is very hard and needs experience and careful examination of the organs.

Diagnostic errors can also occur in purulent, degenerated and calcified cysts in old animals. These problems can be overcome by incorporating histopathology or PCR confirmation of the diagnosis.

Another important limitation of post-mortem diagnosis is the absence of abattoirs in many endemic areas. People from poor, rural and isolated communities do not bring their animals to slaughterhouses (if any), which are far away from their towns. It is costly for them and sometimes they are scared of getting their animals confiscated by Veterinarian officials (inspectors). Therefore, it is not possible to obtain representative information (or any information) of sheep, goat or cattle infection rates or disease burden by abattoir records.

The availability of specific serological test would greatly improve surveillance in livestock. However unfortunately many published studies on serological diagnosis of CE in livestock are compromised by use of inappropriate controls and/or necropsy methods that are inadequate for the detection of small cysts (Craig et al., 2015). These techniques can give cross-reactions in animals infected with other taeniid cestodes (including *T. hydatigena* or *Taenia ovis*) and, therefore, have poor diagnostic value at the individual level.

However, despite its limitation, it could be used to measure the trend of the programme with a simple and economic indicator, applied on lambs, especially when there is no slaughterhouse from which to obtain representative information.

Surveillance with serological tools (Western blot) (Moro et al., 1997) in sheep are used in the control programme of Peru.

3.3 Surveillance in dogs

Diagnosis of *E. granulosus* infections in dogs can currently be carried out on faecal samples using immunologic methods such as Enzyme Immunoassay - coproantigens (coproELISA). This can be used as a screening method, but these techniques can give cross reactions with other *Taenia* infections (including *T. hydatigena* or *T. ovis*) too (Craig et al., 2015).

PCR is recommended as a confirmatory diagnosis (Cabrera et al., 2000; Abbasi et al., 2003; Stefanic et al., 2004; Craig et al., 2015). However, the use of coproELISA assays is limited due to the lack of appropriate standardization and the low repeatability of the test (Jercic et al., 2019). However, its systematic use in a program would allow the identification of trends in relation to changes in animals infected with either *E. granulosus* or other taeniid cestodes.

In recent years, several coproELISAs have been standardized for use in existing control programs in endemic areas of the world (Guarnera et al., 2000; Pierangeli et al., 2010; Morel et al., 2013; Jara et al., 2019) and they have been included in the surveillance systems of the countries, such as Peru, Argentina, Uruguay, China and Kyrgyzstan (Larrieu & Zanini, 2012; Irabedra et al., 2016; van Kesteren et al., 2017; Centro Panamericano Fiebre Aftosa, 2018).

3.4 Surveillance in humans

While echinococcosis is primarily a human health problem, it is necessary to establish vigilance systems of the infection in man, especially in children (between 0/10 years old) or schoolchildren (between 6-14 years old), which can be efficiently carried out by using ultrasound (US) screenings (Frider et al., 2000; Perez et al., 2006; Larrieu et al., 2011). Early detection of CE children might facilitate the beginning of albendazole treatment (Frider & Larrieu, 2010; Brunetti et al., 2011; Larrieu et al., 2018).

US detection in children is indicative of transmission in the recent past. On the other hand, detection by the US in the adult asymptomatic population may represent infections that occurred many years ago, so they are not indicated in the surveillance of control programs. The absence of detection of cases in children indicates that the transmission probably is not present, and it may not be necessary to maintain control activities.

3.5 Surveillance in a farm

In the past, surveillance of control programmes was performed by determining the prevalence of infection in dogs, sheep and children, expressed as percentage of positive, by species. However, it may be more efficient to determine farms or livestock with present-absent transmission, and then adjust the areas where control measures should be concentrated.

Thus, the indicator of progress will be the percentage of farms or houses with present transmission.

Surveillance of echinococcosis in domestic dogs with coproELISA allows for a practical evaluation of a control programme, with the benefit that dogs can be sampled and tested non-invasively through analysis of faecal samples collected from the ground (Guarnera et al., 2000; Perez et al., 2006; van Kesteren et al., 2017) or obtained directly from the anus of the dog. A positive sample of dog determines that probably a farm has current transmission or at least indicate feeding the dog with viscera and deficient deworming with PZQ which identifies a problem in the control program. Serology in lambs with ELISA or WB could fulfil a similar function.

CoproELISA can be used provided it is understood it has cross-reactions and can only give a guide to what might be infection levels in dogs.

Too little work has been done in most places that coproELISA has been used, and with most in-house coproELISAs about a) the prevalence of *Taenia* infections that are not *T. hydatigena* and about cross reactions with these species in the test. If the primary control method is PZQ in dogs, all dog taenia should be reduced so coproELISA is a guide to the reduction if taeniid cestodes in dogs. But if other measures are used (for example only

EG95 vaccination) this will have no effect on another dog-transmitted taeniid infections other than *E. granulosus*

4 CONCLUSION

Since the introduction of current (and past) CE control campaigns, there have been clearly technological improvements made in the diagnosis of canine and the genetic characterisation of strains and vaccination against *E. granulosus* in animals (Barnes et al., 2012; Craig et al., 2017). It has been noted that the incorporation of these new measures could increase the efficiency of CE control programmes (Barnes et al., 2012; Wen et al., 2019).

After the experiences of insular control programs in New Zealand and Tasmania and the continental programmes of Argentina, Uruguay and Chile, there have been a few reports in the scientific literature to show significant results or advances in new control programmes in the last 5/10 years (for example in the Alay Valley, Kyrgyzstan or in Emin County, Xinjiang, China (van Kesteren et al., 2017; Yang et al., 2015). Renewed efforts are needed for reduce the health burden of CE in many parts of the world. In this respect it is heartening that an initiative for the elimination of echinococcosis in South America is being lead by WHO/PAHO in the area (Irabedra & Salvatella, 2010; Pavletic et al., 2017; Centro Panamericano Fiebre Aftosa, 2018).

For surveillance, CoproELISA in dogs offers logistical advantages because samples can be obtained with a single staff, considering also that echinococcosis often affects rural and relatively remote communities (Craig et al., 2015; van Kesteren et al., 2017). The technique does suffer from problems with specificity, but it is simple and economical and hence accessible to countries with few resources and limited technology in their laboratories, but they need to have a surveillance system for their programme.

On the other hand, the diagnosis and treatment of CE in humans have experienced big changes such as the use of ultrasound and other imaging diagnosis techniques, and the albendazole or PAIR use. These advances have allowed not only an early and quick diagnosis of CE but also the initiation of ALB or PAIR treatment instead of operating many cases that might not be necessary (Frider & Larrieu, 2010; Brunetti et al., 2011; Larrieu et al., 2011; 2018). Active

surveillance seeking for human CE cases is an obligation in every prevention and control programme.

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CONFLICT OF INTEREST

The authors report no conflict of interests.

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Table 1. Highlight for CE control

ACTION	RESULTS
Dog deworming	A deworming frequency of 2 or more per year with PZQ will produce a decrease in the number of cases in people
Sheep vaccination	Vaccination of sheep with EG95 vaccine will produce a decrease in the number of cysts in sheep and in the number of CE infected sheep
Dog population reduction or health education	Control through dog population reduction and/or health education are complementary tools, but without attack strategy, they cannot control the disease.
Mathematical model	Evidence from the programs indicates that with praziquantel we can expect to take the <i>E. granulosus</i> $R_0 < 1$, and eventually to its elimination. More evidence is needed to see if EG95 can do the same.
Elimination	The elimination of CE in continental areas is a very difficult objective to achieve. Control, with strong decreases in transmission to human, is a realistic goal.

Table 2. Proposal of scheme of classification of levels of endemicity in CE according to prevalence in different hosts

Level of endemicity	Human incidence (x 100000 *)	7/14 years old prevalence (% **)	Sheep prevalence (% ***)	Dog prevalence (%****)
Highly endemic	> 35	> 1,5	> 49	> 25
Endemic	4 to 34	0,6 to 1,4	5 to 49	5 to 24

Low endemicity	1 to 3,9	0,1 to 0,5	1 to 4,9	0,6 to 4,9
Controlled	< 1	< 0,1	< 1	< 0,5
Eliminated	0 (< 20 years old)	0	< 0,09	0

*New cases in all age group, **prevalence by ultrasound screening in schoolchildren
 prevalence in slaughterhouse in all age group, *coproELISA screening,
 coproPCR screening in the last step

Table 3. Highlight for CE surveillance

ACTION	RESULTS
Surveillance in farms	CoproELISA in dog and ELISA in lambs can give cross-reactions with other tapeworms. In any case, the presence of infected animals with other cestodes within a surveillance system indicates, the presence of dogs fed with raw viscera and / or insufficient deworming with PZQ. If the number of faecal samples or blood samples of the farm is representative of each one, the classification of a farm as positive will be adequate and useful for the surveillance in a control program, to determine farms where control measures should be increased, least until it is entered into the elimination phase that requires adjusting the specificity of the techniques used (for example PCR or lamb necropsy)
Surveillance in children	US screening in schoolchildren is sensitive and specific to assess transmission in the recent past and to measure the evolution of prevalence with the control measures implemented. The active search of cases through the US, in addition, allows to give timely treatments to the detected cases, reducing the complications of the disease, mortality and the costs of hospitalization.



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