International Journal of Echinococcoses 2022;1(2):54-71
DOI: 10.5455/IJE.2021.11.07

International Journal of Echinococcoses

Journal homepage: www.echinococcoses.org

Review Article

Past and Future Methods for Controlling *Echinococcus granulosus* in South America

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ARTICLE INFO

Received: November 22, 2021
Accepted: May 21, 2022
Available online: May 21, 2022

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CITATION
Poggio TV, Jensen O, Saravia TC, Nuñez AP, Boado LA, Gómez JM, Heath D. Past and Future Methods for controlling *Echinococcus Granulosus* in South America. International Journal of Echinococcoses 2022;1(2):54-70. DOI: 10.5455/IJE.2021.11.07

The journal is the official publication of The Turkish Association of Hydatidology

ABSTRACT

The various Countries of South America (Peru, Brazil, Chile, Uruguay, Argentina) all have problems with *Echinococcus granulosus s.l* in humans. Control of the disease in dogs and grazing animals began in Uruguay in 1879, and continues in all countries from various beginnings until 2022. Our objective is to describe the new vaccine to prevent grazing animals from acquiring *E.granulosus s.l.*, and to predict the possible high degree of control using the addition of the vaccine to the normal control procedures even when programmes address many practical difficulties.
The recombinant vaccine was used under field conditions using the same protocol in sheep, goats and llamas older than 2 months and up to 6 years: Two injections, one month apart and annual booster. The baseline and the final evaluation were carried out by necropsy in control programmes included in Argentina (Chubut, 2007-2013; Río Negro 2009-2017) and in Chile (Alto Biobio, 2016-2020; Aysen 2020-2022).
Elimination of echinococcosis have been successful only in insular countries. In consequence, to validate a model supporting the One Health approach that might be reproducible successfully in different regions of South America is required. Including the socio-cultural understanding and the environmental context is mandatory to optimize the use of the vaccine under these operational conditions.
The EG95 vaccine, made in Argentina, has been tested, and continues to be tested, in Argentina and Chile, and more recently in Peru. Furthermore, the vaccine, now available, is being made in large quantities in Argentina and China, and appears to be an additional control technology that may allow elimination of *E.granulosus s.l.* from South America. The best control strategies appear to be dog treatments and regular vaccination of sheep and goats for 10 years until all old sheep have been removed. If dogs or grazing animals enter from outside the controlled environment, treatments will need to be continued. The vaccine also seems to reduce *E.granulosus s.l.* cysts reaching infectivity for dogs, and has some effect against Fasciola hepatica.

Keywords: *Echinococcus granulosus s.l.*, grazing animals, Vaccine, South America, Control

INTRODUCTION

Cystic echinococcosis (CE) is a parasitic infection caused by *Echinococcus granulosus sensu lato (E granulosus s.l.*), belonging to the family Taeniidae. The parasite causes zoonotic disease in humans predominantly from pastoral communities. The adult tapeworm is found in the small intestine of dogs and other canids, while the larval stage is located in the viscera of ungulates, especially sheep, goats and cattle. Transmission of *E. granulosus s.l.* between domestic livestock and dogs is increased by uncontrolled slaughter practices whereby dogs can access to contaminated offal (1).

Echinococcus Control Programmes in South America: the history of their control policy.

Elimination of CE as a public health problem was possible in insular countries including Iceland, New Zealand, Tasmania, Cyprus and the Falkland Islands (Malvinas) (2-6). A detailed evaluation of each control programme has been reviewed (7-15).

Since the 1970s control programmes have been developed based on new tools and approaches such as dog-targeted interventions including anthelmintic treatments; use of ultrasonography for human screening, a highly effective vaccine (EG95) to prevent CE in animal intermediate hosts; laboratory-based tests; computer-based modelling of cost-benefit for interventions; and transmission dynamics and predictive modelling for intervention combinations (2).

The impact of CE control programmes in South America during 1974–2010 was extensively reported (16). The Regional CE Initiative has been successful in promoting and developing strategies and action plans for control the disease in South America. Pavletic et al. have reported annual incidence of CE in humans, the occurrence in ovine and bovine and the prevalence in dogs in Argentina, Brazil, Chile, Peru and Uruguay in 2009–2014. Results did not show considerable progress towards control, except for in Uruguay and localized successes elsewhere (17).

We describe the history of the control policy in Argentina Uruguay, South Brazil, Chile and Peru, from its outset to the present and summarize the most important topics in Table 1.

Argentina

The legal framework of the Echinococcosis control measures and features of actions developed by the National Programme for the Control of Zoonotic Diseases (Ministry of Health), and the National Service of Health and Agro-Food quality (SENASA) were summarized in Table 1 (18,19).

Due to each province is autonomous in planning and executing its programmes, a National Framework Plan for the CE control was created based on different strategies described in Table 1 (20).

In South America, the first structured programme was developed by the Province of Neuquén between 1970 and 1985 and even today is in force (Table 1).

Decreasing CE dog prevalence (%) from 1970 to 2004 has been described in Table 1 (21).

In 2005, the validation and implementation of coproantigen ELISA test (CAg) for surveillance of CE in dogs was started (22). Since 2011, detection has been improved due to greater sensitivity of the method. During the period 2013-2018, CE dog prevalence have remained stable (11.66%), demonstrating the importance to improve control and surveillance measures (Table 1) (23).

The overall mean annual human incidences showed a significant decrease from 1995 to 1999 and remained stable from 2000 to 2004 (20,24). The Provincial Hydatid Disease Programme in 2013 implements ultrasound screening in children from endemic areas. Annual human incidences were recorded from 2013 to 2021 and ranged from 8.19 to 5.8/100.000 proving the success of the programme (Table 1). However, it is remarkable that children accounted 12,3% of cases (24).

Human infections with *E. granulosus sensu stricto (s.s.)* G1 and *Echinococcus canadensis* G6 were reported in Neuquén, whereas four genotypes were identified in livestock: G1, G3, G6, and G7. Coinfection with G1 and G7 genotypes was detected in one patient who carried hepatic cysts (25).

In the period 1975-1982, the Provincial Public Health Services extended the control programmes, based on dog deworming, to all the Patagonian Provinces (Rio Negro, Chubut, Santa Cruz and Tierra del Fuego).

The CE control programme in the Province of Tierra del Fuego was launched in 1976 and consisted of oral deworming twice a year to 100% of dogs by a veterinarian responsible.

The construction of closed slaughterhouses and kennels to decrease reinfection among the dogs was the main priority (16). The insular programme has been maintained over time and it is to be close to reaching the control and elimination of CE.

The Rio Negro CE Programme has operated continuously since 1980. The "One Health" strategy including methods and activities for control of CE and their results has been described in detail by Mujica et al, 2021 (26).

In 1980 the pilot plan for CE control was launched in the Department of Cushamen, endemic area from Chubut

Province. Human serology (DD5) and registration of positive cases were included. The spreading to the entire province started in 1984 (24,27).

CE control and surveillance measures and its impact have been detailed in Table 1.

Results of the inclusion of the EG95 vaccine for sheep in control programmes from Rio Negro and Chubut will be exposed in the next section.

Uruguay

The implementation of government policies related to the study and prophylaxis of CE started in 1939 (Table 1).

In 1965 Uruguay (28) introduced the dog patent, allowing departmental governments to collect the tax to fight against zoonoses and vector-borne diseases.

The first structured programme was developed by the Department of Flores in 1973 (29). It was based on dosification with arecoline hydrobromide provided for the owners to treat dogs every six weeks. Regrettably, the prevalence in livestock was not decreased because the owner may have not given anthelmintic to their dogs properly (30).

In 1991 a new national control programme was started and all dogs are treated with praziquantel monthly. The programme schedules for control included planning and diagnosis phase (phase 1: 1972-1992); attack phase (phase 2: 1992-2009) and consolidation phase (phase 3: 2009-to present) (31).

Since 2005, the National Commission for Zoonoses (NCZ) obliges by Law No. 17,930, all dog owners to register them and comply with their obligation to pay the tax. The money raised is used to combat zoonoses such as CE, rabies, Chagas disease and Leishmaniasis, providing the canine population with the infrastructure to carry out deworming (32). The NCZ has so far conducted preventive and control programmes profiling CE.

The current control programme, implemented since 2006, has employed strategies described in Table 1. Based in the published results, the programme has been successful, suggesting that Uruguay is on the right track to control CE (Table 1) (33).

Chile

An unique national CE control programme including dog treatment was launched in 1982 by the Servicio Agrícola Ganadero, (SAG, official phytosanitary institution of Chile) in Regions XI and XII (Aysen and Magallanes respectively). The CE incidence rates in humans dropped leading E. granulosus s.l. to a probable state of elimination (Table 1) Unfortunately, this vertical programme was dismantled in 1998 (16,35).

One of the most relevant and successful local control programmes was developed in Magallanes region between 1979–2004. The main strategy of the control programme was the use of praziquantel together with register of dogs. Other measures that have contributed to sustain the programme and its impact have been described in table 1 (36).

During the period 2008–2015 the O'Higgins region launched a programme based on educational activities in eight municipalities (36).

At the moment there is no official national programme for the CE control and statistical data are based on CE cases discharged only from hospitals indicating an important level of underreporting of the disease in Chile (17).

Since 2015 four different control programmes have been initiated in Coquimbo, Biobio, Araucania and Aysen. Results of the inclusion of the EG95 vaccine for sheep in control programmes from Biobio and Aysen will be exposed in the next section.

Peru

In Peru, within the framework of the Agrarian Reform, the creation of agricultural societies of social interest (SAIS) was implemented from 1975 to 1984. SAIS Túpac Amaru and Pachacutec (Department of Junín) considered carry out periodic dosages to dogs and health education. The programme demonstrated the feasibility for control reducing the infection rate in dogs and the human seroprevalence. The latter indicator tripled during 1994-1995, the increased human seroprevalence is explained by the high percentages of infected sheep (89%) and dogs (33%), the two most important hosts to maintain the biological cycle of the parasite (38) (Table 1).

The programme did not achieve continuity and human CE remains as a not notifiable disease (39).

In 2015 Peru has started a pilot CE control programme only in five regions that include 17 rural communities (31). In 2019, the Permanent Multisectoral Commission for the prevention and control of Zoonotic Diseases was created with the aim of evaluating the strategies implemented in the pilot CE control programme: canine deworming with praziquantel alone, sheep vaccination alone or combined with dosification, and sheep deworming with oxfendazole plus dog deworming. Health education and control of slaughterhouse and home slaughter, besides of active surveillance through coproELISA in dog feces and sheep serology were included. The cost/benefit analysis and the required time to achieve control is being evaluated and it could provide information on the effectiveness and feasibility of each strategy (40).

Brazil

In Brazil, an attempt to implement a control programme was carried out in the city of Santana do Livramento in Rio Grande do Sul in the 1990s, based on treatment of dogs (41). Despite causing a decrease in the number of infected dogs, the project failed to raise awareness in the rural population, in relation to the prophylaxis of the disease, not being able to establish a permanent survey. It was finished in 1999 by the Health Secretary.

Human CE is a notifiable disease in only one state of Brazil (Rio Grande do Sul) (Table1).

It is noteworthy that, the National Reference Laboratory in Hydatidosis of Brazil (LRNH-IOC/Fiocruz) receives samples countrywide for serological diagnosis using an "in-house" IgG anti-Echinococcus sp immunoblotting (42).

EG95 Vaccine Development as a new control tool

New Zealand & Australia's development of a vaccine against hydatid disease (1960 – 1993) has now been used in China for the past 4 years in grazing animals. Two injections, one month apart, provide protection to animals for up to a year. A third injection, 6-12 months after the second, provides protection for up to 5 years (43).

Chonqing Auleon Biologicals Co. Ltd has produced 40-45 million vaccine doses each year (2016 – 2019) for the Chinese Ministry of Agriculture (US$ 0.28/dose).

Since 2010, praziquantel has been used in the endemic and hyperendemic areas of China. Transmission by dogs has been reduced, from 8% in 2010 (95% CI: 6.0–10.2) to 1.7% in 2018 (95% CI: 0.5–3.6) and a high heterogeneity between region and province subgroups has been found, thus the public health situation remains serious (44).

From 2016 – 2019, Central Government launched comprehensive compulsory vaccination of sheep and goats in the hyper-endemic areas of Western China (45). The praziquantel programme continues as before. After 4 years, slaughter examination of sheep and goats evidenced a reduction in prevalence from 5 to 1% and from 44 to 20%, the findings of cysts in liver and lung respectively (46).

Results from the use in sheep of the EG95 oil-based inclusion body vaccine (approximately 50% pure) commercially manufactured by Tecnovax S.A., Buenos Aires, Argentina (Providean Hidatil EG95®) demonstrated 84.2% and 94.7% of reduction in fertile cysts with 3 and 4 vaccinations on day 0-30-465 and 1440 respectively after experimental challenge (47).

In 2017 Tecnovax S.A. launched a new lyophilized formulation called Providean Hidatec EG95® which is bioequivalent to the Australian vaccine. The company has produced 30-50,000 doses each year (2017– 2020) for the SAG included in the Echinococcus control programmes from Rio Negro in Argentina and from Alto Biobio, and also, the Aysen region in Chile.

Lyophilization process is an expensive technology thus increase the cost of the vaccine and low demand due to the few ongoing programmes in South America, makes the cost go up. Currently, 40-50 million doses are made each year in China for these reasons the price get close to one fifth of that reached by the Argentine vaccine.

An EG95 vaccine plus 10 Clostridial antigens for use in sheep is now in progress and the registration by Tecnovax company is expected in 2022.

CONTROL PROGRAMMES IN SOUTH AMERICA INCLUDING VACCINATION

We described each participating country and their regions to provide a complete report to estimate the degree of control from each programme reducing the CE infection.

Patagonia region, shared by Argentina and Chile, is inhabited by Mapuche, Tehuelche and Pehuenche native communities, whose religious-political leader is the "Lonco" (cacique). Native communities live in a common property land without subdivisions. The region has no road infrastructure and the extreme cold climatic conditions during autumn and winter limits the accessibility to the farms in remote communities with poor animals handling facilities and poor communication technologies.

Veterinary and technician teams involved in control programmes reported an adequate knowledge of non-verbal language. Furthermore, a relative knowledge of the culture and of the customs and rites of the inhabitants were useful to cement the bases of trust in the community (48).

There, CE is endemic in sheep and goats and therefore all strategies for control and surveillance must consider not only the technical and epidemiological study, but also the social-cultural context, not usually addressed in conventional animal health criteria.

In Argentina, mediation between healthcare team and indigenous was found through Mapuche or Tehuelche health worker residing in the place, who communicate to the community by public radio the schedule and the precise tasks that veterinarians and technicians will carry out in the area.

In Chile, mediation between healthcare team and Pehuenche communities was reached by means of the training of indigenous technicians as a way of inducing trust between farmers and healthcare team involved in vaccination activities. The training was carried out through a living-learning experience.

Argentina Chubut Province, El Chalia Colony (2007-2013)

From 1984 to 2015 the colony called El Chalia, was inhabited by 20 families of Tehuelche indigenous origin. Description of the detailed programme is shown in Table 2.

From 1984 to 2007 the control programmme (49), located in the South West of the Province of Chubut (including El Chalia) had planned deworming of dogs 8 times a year with 2 tablets 50mg/each one of praziquantel and health education. However, an average of four visits could be completed annually by the same health agent (also belonging to a Tehuelche family) submitted praziquantel dog dosing "to the owners", who gave the pill to their dogs in each farm.

From 2007 to 2013 treatment of dogs was carried out each season (4 times/ year), only on request of farmers and health education activities were covered.

Vaccination schedule was done as follows: Lambs and goats received 2 doses of EG95 vaccine 1 month apart produced by the University of Melbourne and AgResearch containing 50μg EG95 plus 1 mg Quil A/dose (43) (2007-2011) and the bioequivalent by Tecnovax S.A (47) (2012-2013) injected subcutaneously into the rib-cage area of the animal, and an annual booster for all mature animals during each of the 7 years of the control programme.

In December, the first dose of the vaccine was administered to lambs and goats from one to two months of age, and the second dose was received in February. Vaccination was carried out by the Ministry of Health staff and technicians from SENASA.

During seven years of the programme, 32,000 doses were applied. However, 60-70% of livestock received vaccination out of 70% of farms (14/20); later, 95% of dwellings had joined to the programme (19/20).

The inconvenience to gather the livestock made harder the vaccination procedure having no facilities. In every season, for different reasons, some farmers could not gather the livestock. At other times, lambs and goats that received primo-vaccination were often sold at the time of second dose. Sometimes, bad climatic conditions did not contribute to support the two doses schedule. When the animals are gathered, not all the animals in an establishment could be collected at shearing in December. At the February vaccination, which coincided with the mandatory bath, we had the maximum number of animals and better facilities to work with.

As a consequence of a poor reproductive management system, lambing occurred at any time of year. Because of the extreme climatic conditions, not all offsprings were born alive.

In the first two seasons' lambs and goats were vaccinated. From the third-year pregnant livestock were added to the programme promoting adequate colostral immunity to breeds.

Each family, dwelling or farm was equivalent to one Epidemiological Unit (UE) including livestock and many dogs sharing the same habitat with children, and having its assigned place to herd their sheep or goats and the tradition of home slaughter.

The vaccination programme was not mandatory, but it could be carried out with the willing of owners. The farmers accepted the vaccine (because in every family there was someone carrying CE), as well as other aspects of the control programme (dog deworming and education activities) that have continued to be implemented.

In 2013 the programme has ended because it was planned for seven years.

Evidence for E.granulosus s.l. worms was monitored before and after vaccination programme by arecoline test in 100% of dogs and by necropsy in old livestock. Serology and ultrasound screening in humans have also performed.

In 1984, the prevalence of E.granulosus s.l. infection in dogs was found to be 55% by arecoline test, and 73% of the households had parasitized dogs.

In 2007, arecoline test demonstrated that the prevalence of CE had reached 25% in dogs and 72% of the houses had dogs infected with the *E granulosus s.l.* tapeworm (Table 2). Furthermore, arecoline tests carried out every three years (from 1984 to 2007) never detected a dog prevalence lower than 25%. In other words, previous 23 years of regular treatment of dogs does not appear to be highly effective. However, in three surrounding rural towns, Aldea Beleiro, Ricardo Rojas and Lago Blanco, which had similar characteristics, the prevalence of E.granulosus s.l. infection in dogs was found to be 44% , 25% and 15% respectively, in 1984. After 23 years of Control Programme including health education and deworming, the canine prevalence decreased to minimum values ranging from 0 to 3 % in these three locations. It is noteworthy, that these areas were visited by the same health agent than El Chalia. In other words, the control programme worked in rural areas where most people live in small villages (towns), but not in El Chalia when praziquantel is given to the owners.

After the fourth year of vaccination, no cysts were found in 100 animals slaughtered for human consumption, or were small non-fertile cysts (<10mm) (Table 2).

Surveillance using arecoline test carried out 2 years after the end of the vaccination programme (2015) demonstrated that 2 dogs from 83 dosed (2.4%) were found with *E granulosus s.l.* The dogs belonged to 2 dwellings, decreasing to 11% the proportion of homes with parasitized dogs. Workers from these dwellings also worked on other farms away from this project.

Even so 18 dogs belonging to 7 dwellings presented tapeworm infection caused by *Taenia hydatigena*. This finding was an indicator of ingestion of untreated viscera and non-dog dosing with praziquantel.

In 2007 and 2011, human cases notified in this area were 4.6/100.000 and 0.6/100.000.

From 2014 to 2021, no human cases of CE have been reported in El Chalia colony (data obtained from the National Health Surveillance System) (Table 2). No place in Chubut province, the prevalence returned to its initial level.

In El Chalia area, the Provincial Government continues the development of the CE programme through dog treatment with PZQ (4 times a year), until it decides to use the vaccine on a wide area for a long time.

Argentina, Rio Negro Province (2009-2017)

Rio Negro has introduced the vaccine as an additional control tool to treat dogs in some areas of the province since December 2009. Features of this vaccination programme and its control area have been described in Table 2 (50).

For the duration of the trial, other CE control activities (praziquantel treatment of dogs every 3 months) continued throughout the regions comprising the vaccination areas and control areas.

Evaluation of vaccine effectiveness and its impact under operational conditions was undertaken using necropsy of sheep and serological methods.

The decreasing prevalence of E. granulosus s.l. infection in adult grazing animals and the reduced percentage of UE with at least one sheep positive to necropsy have been described from 2009 to 2015 after 6 years of control programme including vaccination (Table 2).

In addition, CE prevalence in 6-year-old sheep after necropsy and percentage of farms having infected sheep comparing the same period have been shown in Table 2.

It is noteworthy that the cysts found in older sheep after vaccination were quite small (Table 2) (50).

In 2011, the specific EG95 antibody response could be detected for at least a year after two immunizations in lambs and long lasting following the annual booster (Table 2) (51).

In 2009 4.3% of the dogs were positive for E. granulosus s.l. infection using the arecoline test, 9.6% of dog feces gave positive result by copro-ELISA demonstrating the higher sensitivity of the immunotest. Besides, 20.3% of the farms had at least one infected dog.

In 2017, 4.5% of dogs were found positive for E. granulosus s.l. by arecoline purgation, 3.7% of feces were positive using copro-ELISA and 8.9% of farms have a positive dog (Table 2) (52).

Ultrasonography screening showed no symptomatic cases in the period. Only one asymptomatic case of E. granulosus s.l. infection having a lung cyst was diagnosed among 84 school children (1.1%; ranging 6-14 years old) (52).

Chile, Alto Biobio Region (2016-2020)

In the 8th Region of Alto Biobío-Chile (53), the vaccination of 8137 sheep from 454 small farmers mainly Pehuenches was carried out by SAG. The control programme started in November 2016 with the first administration (V1) (Tecnovax S.A.) to all sheep flocks (2-3 and 5-9 months of age). An attempt was made to administer a second vaccine 1 month after the first, but given the difficult land work, a 12-month delay in the second vaccinations (V2) were recorded (November 2017). Annual boosters were applied in November 2018 (V3), and V4 in December 2019. Over November 2016 and December 2019, 90% of animals received the full dose vaccination schedule. The programme included local Pehuenche workers as vaccinators who were trained by SAG`s veterinarians.

A non-vaccinated control group was not available for comparison with the vaccinated one.

A baseline was established in 2016 and the presence of cysts in viscera (liver and lungs) was analyzed on a sample of 224 sheep (62.5% of them were 2–4-year-old).

In 2020 SAG decided that necropsies should be carried out to show how Echinococcus cyst can perhaps be reduced after 3 or 4 years, even though most dogs will still be shedding Echinococcus eggs for all that time. In 2020, necropsy was done in 200 animals that were vaccinated being lambs in their first year of life.

After vaccination with 3-4 doses, 200 livers of vaccinated sheep were analyzed and it was observed that only a few numbers of liver presented damage, injury, inflammation, scarring and thickening of the bile ducts consistent with the infestation by *Fasciola hepatica*, compared with those necropsied in 2016 (data not shown).

Features of vaccination schedule and necropsy results (Table 2) showed that similar frequency of cysts was obtained by sheep during the 4 years of vaccination (55%) to those seen before the trial began (46.8%). However, the vaccinated sheep had small cysts after 4 years (and very few of the cysts had protoscoleces) (53).

International Journal of Echinococcoses 2022;1(2):54-71
DOI: 10.5455/IJE.2021.11.07

Table 1: Echinococcus Control Programmes in Argentina, Uruguay, Chile, Peru and Brazil: the history of their control policy and impact of actions taken to date

Please add the following sentences: * canine CE through arecoline purgation. ** CE through CoproElisa. *** Dogs examined were obtained from scattered rural areas, small towns with risk characteristics and suburban areas of critical socio-economic context. © Prevalence of E. granulosus s.s. using polymerase chain reaction in environmental dog faecal samples (37).

Country	Regions	Actions	Impact of actions (Prevalence-Incidence)		
Argentina	Nationwide	1941. A National Law established that CE must be confronted by the State through a control programme (18) 1948. The Ministry of Agriculture began control of E. granulosus s.l. by treating dogs against the parasite, and health education in Buenos Aires, Corrientes, Rio Negro and Chubut provinces (19). 1960. Mandatory notification through the National Surveillance System for Health (SNVS) and the National Surveillance System from Laboratories (SIVILA) National Programme for the Control of Zoonotic Diseases (Ministry of Health) provides dog and human anti-parasitic drugs. It carries out canine surveillance and ultrasound screening of schoolchildren in control areas based on risk criteria. It supplies training in ultrasonographic assessments to CE national field staff. SIGICA system from SENASA gathers the data loaded by the slaughterhouses (seizures, the animal identification and traceability, and georeferenced farms) 2015- to present. Due to each province is autonomous in planning and executing its programmes, a National Framework Plan for the CE control was created based on different strategies: - Periodic deworming of definitive hosts - Vaccination of intermediate hosts - Control of slaughter and notification through SIGICA - Control of the orchard - Responsible dog ownership - Health education of the exposed population - Surveillance in canines (coproELISA analysis, PCR assay) - Considering the role of regional wildlife in the disease cycle			
	Neuquen Province (1970- to present)	1970-1977. Dog deworming with Arecoline hydrobromide (4 mg/kg) every six weeks 1978- to present. Praziquantel 5mg/kg twice/year (non-endemic area) and every 45 days in high-risk zone 1978-1986. X-Ray and serologic cadastral 1984-to present. Ultrasound screening in children from endemic areas. 1970-2004 Surveillance of canine CE through arecoline purgation * (Sensitivity 73.3%; Specificity 89.9%) 2005- to present. CoproElisa ** (Sensitivity 93.6%; Specificity 88.5%). Surveillance of livestock through postmortem inspection at official slaughterhouses (SENASA) Health education		Human (100.000)	Dog (%)
			1970	54.6	28.2*
			1985	-	1.0*
			1995	43.9	1.4*
			2000	15.9	0.5*
			2004	15.5	0.85*
			2005	-	10.7**
			2007	-	8.7**
			2009	-	12.5**
			2011	-	5.6**
			2013	8.19	2013-18 1.66 (22)
			2016	6.36	
			2017	9.72	
			2018	6.96	
			2019	7.32	
			2020	5.12	
			2021	5.80(23)	

DOI: 10.5455/IJE.2021.11.07

Argentina	Rio Negro Province (1980-to present)	1980- to present Control of tapeworm in dog populations and farms with Praziquantel 5mg/kg 4 times/ year was carried out by sanitary agent. Health education 1980–2003 the arecoline test* was performed in dogs for surveillance purposes CoproElisa** and confirmation of positive dogs by Western blot analysis and PCR assay 2003-to present) 1980-1997 Search for asymptomatic carriers through serology (DD5) 1984 First use of ultrasonography (US) 1997 Cadastral as method of choice for chidren diagnosis 2009- to present Vaccination of sheep in endemic areas (Mapuche community) Surveillance of livestock offal at official slaughterhouses (SENASA)	Dog / Sheep (%) / (16,25) (%) 1980 / 41.5 * / 61.0 1981 / 6.1* / - 1982 / 4.5* / - 1998 / 2.9* / 18.0 2003-05 / 4.8 *- 17** / - 2009-10 / 18.2 ** / - 2017-18 / 8.2 ** / - Children 0–16 years of age (25) (%) / DD5 / ELISA / US 1980 / 2.05 / - / - 1984 / 0.41 / 1.70 / - 1986 / - / - / 5.6 1993 / - / 1.0 / - 1999 / - / - / 1.2 2005 / - / - / 0.3 2018 / - / - / 0.2
	Chubut Province (1975-to present)	1980. Started a pilot plan for CE control in the Department of Cushamen (endemic area) based on human serology by DD5 (programme justification) 1984 CE Control Progamme including active searching by DD5 serology and registration of positive cases throughout the entire province. 1987-2000, relaunched from 2005 -to present) Search for asymptomatic carriers through ELISA serology and cadastral ultrasonography and pharmacologic treatment. 1980 Control of tapeworm in dog populations and farms with Praziquantel 5mg/kg 4 times/year in endemic region and twice in non-endemic areas carried out by sanitary agent 2007-2013 Vaccination of sheep and goat in endemic areas Surveillance of livestock offal at official slaughterhouses (SENASA)	/ Dog (%) / Sheep (%) / Human (100.000) 1984 / 70 / 25-60 / 84 2008 / 3-6 / 0-10 / 15 2010 / - / - / 12.75
	Tierra del Fuego (1982-to present	CE Control Programme focused on canine deworming twice/year in rural area (with coverage of 97%), elimination of viscera in farms, identification of dog owners, epidemiological surveillance in hosts, information to the community and a legal framework of reference.	/ Children / Dog (%) / Sheep (16) 1980 / - / 41.1 / 52.0 1996 / 0.0 / 2.5 / 1.5 2001 / 0.2 / 2.5 / 2.5 2008-10 / 0.0 / - / 0.3 2013 / 0.0 / 0.9 / 2.0 2016-17 / 0.0 / 6.0 / 0.85

Uruguay	Nationwide (1972-to present)	1939. The creation of the Center for the Study and Prophylaxis of Hydatidosis, was legitimized. The mandatory reporting of human and animal echinococcosis cases, the ban on feeding dogs with offals, surveillance of slaughterhouses, the limitation of the number of dogs, and health education in rural areas were stablished. 1965. Introduction of dog patent and tax collection (28) 1970– 1992. First CE control programme was based on dosing dogs with arecoline hydrobromide every six weeks (30) 1991 A National control programme was started and all dogs were treated with praziquantel monthly. 2005 to the present. The NCZ has obliged the dog registration and payment of the tax to owners and the money has been conducted to CE preventive and control programmes employing the following strategies (32) (33): 2007 A voluntary and free surgical castration for owned dogs was introduced. 2008 Treatment of dogs with praziquantel 5 mg/kg/bw (monthly) or broad-spectrum anthelmintics (pyrantel pamoate + PZQ + febantel) administered once a year to all registered dogs and three times per year in areas with other parasitic zoonoses, such as toxocariasis and ancylostomiasis - Health education conducted by the Working Days on Health (WDH) programme, at Public Health Centres (as one of the most important tools for the control and prevention of CE): Verbal, visual and graphic methods were employed Surveillance measures: - CoproElisa for canine diagnosis -. - Dog population control: spaying of dogs of both sexes - Human Diagnosis by ultrasonography - Surveillance in livestock by the Ministry of Livestock, Agriculture and Fisheries - A strengthened community participation.	Dog Human Sheep Cattle (33) (%) (%) (rate per 1000) 2004 6.4 - 7.85 11 2006 - 1-2 - - 2008 10.2 6.5 - - 2009 4.4 3.8 5.5 7.2 2013 1.6 2.8 3.2 5.3
Chile	Nationwide	1951. Mandatory notification system (34) E granulosus s.l. is the second most important cause of condemnation of viscera in livestock (after Fasciola hepatica). The most affected regions are Los Lagos, Araucania, Los Rios, Aysen and Magallanes (35) 1982-1998 A national CE control programme deal with by SAG including -Deworming of dogs with praziquantel every 45 days for 15 years in Magallanes and Aysen regions (16)	Magallanes Aysen (16) Human (100.000) 1982 38 80.7 1998 6 44.8 2001-2005 9.2 38 2008-2017 7.8 40.1 2019 - 38.4
	Intermittent local control plans	1979–2004 Magallanes region: a programme including PZQ treatment in dogs with register of dogs, surveillance (dogs and sheep infection), sanitary control,building of diagnostic laboratories and training in diagnostic techniques, and creation of new laws and regulations (36) 2008–2015 A CE programme based on educational activities was launched in eight municipalities from O'Higgins region In total, 8,909 students from primary and secondary schools have received instructions in prevention of CE by the team of the Epidemiology Department (36). Since 2015 Control programmes have been initiated in Coquimbo, Biobio, Araucania and Aysen, including health education, canine deparasitation, spaying of dog and the pilot sheep vaccination in some of these.	Magallanes Region Dog Sheep (%) 1979 70 60 2004 0.5 0.73 2015 - 2.9 2021 18© (37)

Peru	Junin Five regions- 17 rural communities	Human CE is not a notifiable disease (39) 1975-1984 SAIS Túpac Amaru and Pachacutec The Pilot programme for CE control considered periodic dosages to dogs and health education (38) 2015-2019 Pilot CE control programme: canine deworming with praziquantel alone, sheep vaccination alone or combined with dosification, and sheep deworming with oxfendazole plus dog deworming. Health education and control of slaughterhouse and home slaughter, besides of active surveillance through coproELISA in dog feces and sheep serology were included.effectiveness and feasibility of each strategy are still being evaluated (31, 40)	SAIS Tupac Amaru (Junín) Dog / Human (%) / Sheep 1974: 11.6 / 0.1[1] / - 1984: 2.6 / - / - 1989: - / 1.9[2] / - 1994-1995: 33 / 6.4 / 89 1 Isoelectric focusing (IEF) 2 DD5-Immunoblot
Brazil	Local	Human CE is not a notifiable disease in only one state of Brazil (Rio Grande do Sul) (17) 1990-1999 Santana do Livramento - Rio Grande do Sul, based on treatment of dogs (41). Brazil remains without a national coordinated effort, though there are incipient initiatives towards enhanced data collection and coordination (17) (e.g. 2010 – 2021 Serological diagnosis by immunoblotting countrywide (LRNH-IOC/Fiocruz National Reference Laboratory in Hydatidosis of Brazil) (42)	Annual human cases reported[a] / Sheep (%) / Bovine (17) (%) 2009: 11 / 8.76 / 0.37 2010: 12 / 12.04 / 0.45 2011: 30 / 11.15 / 0.44 2012: 15 / 8.65 / 0.35 2013: 12 / 3.12 / 0.29 2014: 11 / 4.64 / 0.27 [a] At the National Surveillance System

Table 2: Description of Control Programmes for CE including vaccination in Argentina and Chile

Country Province Region	Duration of the Programme	Area	Population and species	Control tool	Initial Prevalence of E.granulosus s.l. infection	Final Prevalence of E.granulosus s.l. infection
Argentina Chubut El Chalia Colony (49)	2007-2013	Southwest of the Senguer Department 30.000 hectares	20 farms, 90 people (between 1 and 10 per farm), 100 dogs, 1500 goats, 10000 sheep Health staff : 2 teams (3 people each one onboard two vans) Vaccination of Complete rodeo took 5 days Registration of all inhabitants, and their dogs and livestock	Dog treatment "upon request" (4times/year) EG95 Vaccination of sheep & goats (University of Melbourne & AgResearch (2007-2011) and Tecnovax (2012-2013): Two injections, one month apart and annual booster with 60-70 % average for fully sheep vaccinated along the area Health education	2007 Dog Prevalence 25% *E. granulosus s.l.* (Arecoline test). 72% of farms with at least 1 infected dog Human Incidence: 4.6/100.000	2015 Dog Prevalence 2% *E. granulosus s.l.* (Arecoline test). These dogs also worked on farms outside the test area. 11% of housing had at least 1 parasitized dog 35% of dwellings presented infection by *Taenia hydatigena* Sheep prevalence: 0% No cysts were found in 100 sheep slaughtered for human consumption (or its were smaller than 10mm). Human Incidence: 0.6/100.000 (Ultrasonography) No new human cases were detected from 2014 to 2021 The programme is in force and include health education and dog deworming

Argentina Rio Negro (Anecon Grande, Rio Chico Abajo, Nahuel Pan, Manuel Choique, Blancura Centro, Lipetren) (50,51,52)	2009-2017	1054 km^2	Vaccinated Group: 79 farms, 8443 sheep. Control Group: 71 farms, 2255 sheep and 2096 lambs which received no vaccinations. 309 dogs belonging to both areas. Goats were not included in the vaccination trial Health staff : 3 teams (4 people each one onboard three vans) Vaccination of the complete rodeo took 3 days	Dog Treatment: Praziquantel 5mg/kg 4 times/ year in control and vaccination areas. EG95 Vaccination of sheep (no goats were vaccinated) (University of Melbourne & AgResearch (2009-2017) Two injections, one month apart and annual booster with 57.3% average for fully sheep vaccinated along the area	2009 Dog Prevalence 4.3% (arecoline test) Dog Prevalence 9.6% (CoproELISA) 20.3% of farms with at least 1 infected dog Sheep Prevelence 56.3% 94.7% of had at least 1 sheep positive 56.3% of 6-year-old sheep showed CE and 84.2% of the farms had at least 1 infected sheep (necropsy).	2011 EG95 antibody response: Testing in lambs, and 1 to 6 years old vaccinated sheep and non-vaccinated control. Specific antiodies could be detected for at least a year after two immunizations in lambs and long lasting following the annual booster 2015 Sheep prevalence 21.1% 23.5% of farmers have least 1 sheep positive. 21.6% of sheep older than 6 years were positive. 20.2% of the farms showed to be infected (necropsy) Vaccinated group: 4 sheep showed 2 cysts in liver (only one was fertile) and 6 cysts in lung (1 × 1.3–0.2 × 0.2 cm in diameter) Average: 0.3 cysts/sheep. Control group: 13 sheep showed 47 cysts (some >5 cm in diameter) Average: 1.4 cysts/sheep (p = 0.02). 2017 Dog Prevalence 4.5% E. granulosus s.l. (Arecoline test). Dog Prevalence 3.7% (CoproELISA). 8.9% of farms have at least 1 positive dog. Human Incidence: 1 case (1,1% ranging 6-14 y.o) (Ultrasonography) No symptomatic cases in the eriod. The programme is in force and Tecnovax vaccine has been included since 2018.

Chile Biobio (Alto Biobio Communities: Butalelbún, Trapa-Trapa, Malla-Malla, Cauñicu and Pitril, Guallalí, El Barco, Ralco-Lepoy, El Avellano, Los Guindos and Quepuca-Ralco)	2016-2020	2.125 km² (10% grassland)	8137 sheep 454 farms Average animals: 18 Sheep/ flock 1 Dog/farm	No deworming of dogs EG95 Vaccination of only sheep >2-3 month of age (Tecnovax S.A) V1 with Providean HidatilEG95® (Oiled adjuvanted vaccine) V2 (delayed by 12 month), and annual bosters (V3andV4) with Providean Hidatec EG95® (Lyophilized)	2016 Frequency (95% CI) of infection in 223necropsied sheep (2-4 y.o sheep) 46.8% (38.4–55.2) Frequency of Fertile Cysts 28.1% Size: All > 5 mm	2020 Frequency (95% CI) of infection in 200 necropsied sheep (Lambs vaccinated during 1st year of life receiving 3-4 doses) 55% (48.0–62.0) Frequency of Fertile Cysts 8 % Size: 64.74% < 5 mm
Chile Aysen (Capitan Prat Province : Chile Chico, Mallín Grande, Puerto Guadal and Puerto Bertrand towns)	2020-2022	29796 km²	16,000 sheep in 206 herds	Canine deworming (4 times a year, in the mouth of the dog.) EG95 Vaccination includes pregnant sheep (one dose) and lambs (two doses, one month apart) and annual booster V1: September 2020 V2: December/ january 2020 V3: June 2021	2020 - Baseline survey -Registration and ID of vaccinated sheep and dogs associated with herds -Slaughter control using containers for offals. -EG95 serology 0-30-60 days post vaccination -Necropsy and cyst count in vaccinated sheep (baseline) Dog prevalence CoproAg - 2018 (IC90%) 19% (15%-22%)	2022 -Endline survey -Slaughterhouse control results. -EG95 serology after annual booster -Necropsy and cyst count in vaccinated sheep (endline) Dog prevalence CoproAg - 2022 (Data are not yet available)

DOI: 10.5455/IJE.2021.11.07

Aysen Chile Control Programme (2020-2022)

The CE control programme in Aysen (54) promotes the repopulation of the regional sheep mass through the improvement of the productivity of the farms.

The programme proposes the creation of a high herd immunity against CE in Capitan Prat Province including small towns as Chile Chico, Mallín Grande, Puerto Guadal and Puerto Bertrand. In addition, the baseline survey about health education, registration and identification of vaccinated sheep and dogs associated with herds, canine deworming (4 times a year, in the mouth of the dog.), and slaughter control using containers for offals.

EG95 Vaccination includes pregnant sheep (one dose) and lambs (two doses, one month apart) comprising 90% of the reference population (16,000 sheep in 206 herds).

Between September 2020 and October 2021, 5.807 doses were applied in lambs according to dental chronometry and 17.662 doses in adult sheep that included also clostridial vaccination and its corresponding internal and external deworming.

The baseline survey showed a good knowledge of sheep-dog transmission, low level of knowledge of the dog-sheep contagion, confusion of hydatid disease with distomatosis due to liver fluke, and the use of viscera in feeding of dogs for economic reasons.

The ongoing programme includes EG95 antibody level detection and the lasting following 2 vaccinations, cyst count in vaccinated animals and, parasitological diagnosis in dogs (Table 2). Data will be published by SAG elsewhere.

DISCUSSION

Echinococcus remains a problem in South America

The most important CE programme topics in South America such as dosification using Praziquantel and health education (no feeding viscera to dogs) have proven to be successful.

However, holding a programme including dog dosification 12 times a year is an arduous, if not almost impossible, task in endemic areas with difficult environments and communities with entrenched customs (e.g. Chubut, Rio Negro Province or Alto Biobio, Chile).

At this time, 2022, although better anthelmintics have been discovered for treating dogs, *E granulosus s.l.* is still common in all these countries.

The schedules of dog-dosification have as main limitation the difficulty to achieve the effective coverage desired (higher to 80% of the existing dogs), in each round of deworming, due to the economic, geographical and climatic difficulties or to existing socio-cultural conditions in the areas under treatment.

Uruguay, with a monthly dog deworming process has moved to the Consolidation Phase, but it will take many years to achieve elimination. Interesting, the control programme that is currently implemented considered health education to be one of the most important tools for the control and prevention of CE.

According to Iriarte J (55), it is difficult to understand why two instructions, in theory, as simple as avoiding giving raw viscera to dogs and periodical dosification of dogs, are so difficult to implement in practice.

Socio-cultural patterns from Mapuche, Tehuelche and Pehuenche communities generally are not included in control programme criteria, demonstrating difficulties in the approach to these populations.

Mapuche and Tehuelche communities do not relate CE as a disease, but as a common suffering of parents, children, grandparents that responds to a cultural logic (56). Suarez Rojas describes (57) “CE is not just a disease; it is a social experience”. In the Biobio (Chile) vaccination programme, Pehuenche community vaccinators acquired skill in the handling of the biological product, as a plus to their integrated knowledge about the cultural logic and the set of practices and symbolic aspects. Mapuche and Tehuelche sanitary agents in Chubut and Rio Negro Provinces respectively, living in the site, served as the link between Health Care team and the community.

This approach including the social-cultural context offers an effective and comprehensive response from the communities avoiding the damage of behavior patterns.

Assessment of the EG95 vaccine efficacy in different conditions in the setting of control programmes.

A. Impact of vaccination of intermediate hosts without treatment of dogs in control programmes

The new technology of a vaccine to prevent sheep, goats and llamas from being infected with E. granulosus s.l. could add the extra control required (43, 47). EG95 vaccine testing has shown that a high degree of protection against sheep, especially if given 2 doses about a month apart, and a third after 12 months (43). However, if eggs are eaten before the second dose of vaccine, some cysts will grow slowly (c.f. Alto Biobio). The vaccine is most useful when added to an Echinococcus normal control programme.

Because Biobio programme only included sheep vaccination and, no deworming treatment of the entire dog population were implemented in the commune prior to or during the vaccination trial, likely almost all areas could have had large numbers of E. granulosus s.l. eggs that young lambs might ingest, even at 2 months of age (53).

Thus, with no dog-dosing, sheep receiving the first vaccination and the second one long after birth and continuing 2 or 3 years, and if no controls of non-vaccinated group of sheep is included, it could be point out that the vaccine will not work correctly for Echinococcus control without other procedures, such as deworming. Vaccination for only 2 or 3 years are not long enough, especially without dog dosing because we do not know whether lambs had seen eggs later, while the vaccine was working.

After 4 years of programme, if vaccinated animals and some control animals were necropsied, perhaps the cysts from the vaccine group were not infective, compared to the controls (50). In this case, probably the vaccine would reduce markedly the number of cysts with protoscoleces, even though when sheep had been infected before vaccination (53).

Considering the 2 -3 and 4 year- naturally infected group, normally cysts should be 20 mm and with protoscoleces as was describes in New Zealand work without EG95 vaccine (58). In New Zealand trial, the size and the mean of the number of cysts were compiled in 40 sheep infected of which, 2 sheep were necropsied every 3 months for the 5 years.

Trials done in Chubut - Argentina including vaccinated sheep (43, 47, 59), necropsied 23 months after experimental challenge demonstrated that 50% of cysts in liver, and 15% of cysts in lung had smaller than 10-20 mm and were not infective. On the other hand, control non vaccinated sheep necropsied 9 and 14 months after challenge showed size of cysts higher than 20-30 mm carrying protoscoleces.

In addition, field evaluation of EG95 vaccine in sheep with no dog treatment carried out in Morocco (60) have shown that vaccinated animals had an average burden of viable cysts of 0.28, while in control animals the average burden was 9.10 ($p<0.001$), representing a reduction in the average burden of 97%. This means that vaccinated animals present far less viable cysts being an effective control option when 2 doses about a month apart, and a third after 12 months is performed.

Thus, if a CE control programme should be implemented, we recommend:

1. Two supervised annual deworming in the dog's mouth should be included in addition to vaccination.
2. Vaccination of young lambs and goats with V1 during shearing and V2 before winter (during obligatory bathing, eye peeling, broodstock release) including all adult females that could be pregnant during winter. It is very important to induce colostral immunity because lambs would be protected (43), until the first dose could be applied, by the antibodies that the mother passed to them through the milk. Lambs and goats start grazing after their third week of life. This possibility would be available from the second year of the vaccination programme.
3. Annual booster vaccination. It is noteworthy that, 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 avoid infection of the sheep and/or development of fertile cysts during the period of its life span in the region (47, 51).

B. Prevalence of infected dogs with *E granulosus s.l.* even though vaccination of livestock was carried out in the programme

In programmes including intermediate host vaccination has been shown that infection in dogs decreased substantially (Table 2). However, in Rio Negro, after 8 years of vaccination and deworming programme, the infection in dogs was still detected with the arecoline and CoproELISA tests, indicating that dogs could have had access to viscera from non-vaccinated livestock and/or the ability of the dogs to feed outside of the vaccination area (although dogs have received 4 annual deworming). It should be noted that, Rio Negro trial had difficulty in that (a) Dogs were infected when tested, even though dogs were treated with praziquantel every 3 months, and (b) Dogs and sheep belonged to both areas – Vaccinated and Controls (50).

In El Chalia colony, surveillance using arecoline test carried out 2 years after the end of the vaccination programme demonstrated that *E granulosus s.l.* was found in dogs that also worked on other farms away from the project.

On de other hand, Rio Negro and Chubut programmes showed a significant compliance of sheep vaccination rate (57.3% and 60-70% respectively) receiving the full threedose schedule over their first year of life even under unfavorable conditions (although no goats were vaccinated in Rio Negro programme). It has been demonstrated that the effectiveness of the vaccination programme is seriously affected by the inability to deliver all three doses to approximately 40% of the livestock (31).

C. Additional findings associated to vaccination of intermediate hosts

With regard to Biobio trial, few findings consistent with the infestation by *Fasciola hepatica* were detected in vaccinated sheep that received 3-4 doses compared with those belong to the baseline. The EG95 is a fusion protein with glutathione S-transferase (GST) and GST constitute approximately 4% of the total soluble protein content of Fasciola hepatica. They have been extensively studied as candidates for sheep vaccines from 1990 (61, 62, 63).

These results suggest that an immunogenicity and challenge test with metacercariae in target species (sheep) should be carried out in order to confirm the possibility to extend the EG95 vaccine register for use in the prevention of fasciolosis.

The duration of the vaccination programme

Since the vaccine does not affect established echinococcal cysts in animals, the vaccination schedule must be maintained until the replacement of all the grazing animals from the farm.

This livestock replacement is different according to specie, the productive system, sales season, climatic conditions and access to pastures which differs by year.

Along the Patagonian plateau, sheep often do not live beyond seven years of age. The productive systems make use of dental chronometry. Especially in El Chalia, hard grasses that concentrate silica correlate wearing with durability of the denture. At four years of age, sheep complete their 8 teeth ("full mouth") which then gradually suffer wear until they reach "half a tooth" indicating the end of their useful life (64).

CONCLUDING REMARKS

"One Health Programmes" attempting to eliminate CE using both old and new technology -knowing that even with the use of the vaccine, probably 10 years will be required.

Once the vaccination programme is over, health education and deworming should be continued.

A vaccination programme is not recommended where the disease prevalence is low and there are no children carrying CE.

The CE could quickly (or slowly) return to the existing previous time if:

1. The health education and dog dosification has no continuity or it is done for a short time

2. The programme do not manage to clean the environment of *E granulosus s.l.* eggs, to prevent the lambs born becoming infested or to develop the habit of not feeding the dogs with untreated viscera

The vaccine, now available, is being made in large quantities in Argentina and China, and appears to be the extra control technology to perhaps eliminate E.granulosus from South America.

The best procedure seems to be some dog treatments and regular vaccine to sheep and goats for 10 years including a comprehensive approach avoiding the damage of the community social matrix. If dogs or grazing animals enter from outside the controlled environment, treatments will need to be continued.

Acknowledgments: We thank all the workers from CE Control Programmes: Edmundo Larrieu, Guillermo Mujica, José Luis Labanchi, Patricia Blanco, Romina García, Claudia Grizmado and Guido Merino Rubilar.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: Proyectos Unidades Ejecutoras PUE 22920180100014CO ICT - MILSTEIN.

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