PREVENTION AND CONTROL OF HYDATIDOSIS AT LOCAL LEVEL

SOUTH AMERICAN INITIATIVE FOR THE CONTROL AND SURVEILLANCE OF CYSTIC ECHINOCOCCOSIS/HYDATIDOSIS

Pan American Health Organization

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PANAFTOSA
Pan American Foot-and-Mouth Disease Center
Veterinary Public Health

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COORDINATION:
Edmundo Larrieu[1, 10]

DEVELOPMENT AND REVIEW TECHNICAL GROUP:
Marcos Arezo[2], Eduardo Pacheco de Caldas[3], Natalia Casas[4], Leandro Del Grande[3], Víctor Del Rio[5], Cesar Gavidia[6], Andrés Giacoia[7], Eduardo Guarnera[8], Pilar Irabedra[7], Maria Isabel Jercic[9], Melody Maxwell[5], Ana Navarro[11], Carlos Pavletic[12], Julio Sayes[7], Leonardo Uchiumi[1,2], Michael Laurence Zini Lise[3], Monica Martini[5], Julio César Augusto Pompei[5], Baldomero Molina Flores[5] & Marco Antonio Natal Vigilato[5]

1. World Association Echinococcosis (WAE)
2. Ministry of Health, Rio Negro, Argentina
3. Ministry of Health, Brazil
4. National Program for the Control of Zoonotic Diseases, Ministry of Health, Argentina
5. Pan American Foot-and-Mouth Disease Center/Veterinary Public Health (PANAFTOSA/PAHO-WHO), Brazil
6. National University of San Marcos, Peru
7. National Zoonosis Commission, Uruguay
8. National InstituteAnlis/Malbran, Argentina
9. Health Institute, Chile
10. National University of Rio Negro, Argentina
11. Ministry of Health, Peru
12. Ministry of Health, Chile

LITERATURE REVIEW:
Dayse Carias Bersot[5]

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FOREWORD

HYDATIDOSIS, or cystic echinococcosis, is an important zoonotic disease in the Region, since a significant frequency is reported in many countries of the continent, with a diverse burden of presentation, affecting mainly dogs (as a definitive host), cattle, sheep and pigs (intermediate hosts), and particularly human health. At each latitude, its presentation is highly influenced not only by differences in ecosystems, but also by the way and strength in which the issue is addressed, typically overlooking interdependences beyond physical national borders.

This Guide was prepared to promote an update of the advances, challenges and perspectives of processes for the control, elimination, diagnosis and treatment of echinococcosis/hydatidosis in South American countries and is intended for managers and technicians from health and agriculture ministries, in charge of surveillance and control programs for hydatidosis. It is also aimed at all health professionals, students, teachers and educators from schools and other educational institutions.

This Guide illustrates the importance of the efforts made by the countries in relation to this zoonotic disease through the group of professionals representing the South American Initiative for the Control and Surveillance of Cystic Echinococcosis/Hydatidosis: Argentina, Brazil, Chile, Paraguay*, Peru and Uruguay, as well as the need for a joint and coordinated effort between countries, sectors and disciplines to complement each other in their respective functions.

Ottorino Cosivi
Director
Pan American Foot-and-Mouth Disease Center
Veterinary Public Health

* Joined the initiative in 2016.

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INTRODUCTION

INTRODUCTION

FOR MANY YEARS NOW, hydatidosis or cystic echinococcosis (CE) has been recognized as a significant health problem in South America, where the breeding of sheep - in particular - or other animals (goats, cows, pigs, camelids), in association with the presence of one or more dogs and the practice of feeding them with infected viscera contribute to the ideal conditions to uphold the disease cycle [1-3].

1.1. EPIDEMIOLOGY

Hydatidosis or cystic echinococcosis (CE) is a zoonotic disease caused by the parasite *Echinococcus granulosus (EG)* which, from a taxonomic perspective, is currently considered a multispecies complex referred to as *E. granulosus sensu lato (s.l.)*. The species identified in this c omplex are: *E. granulosus sensu stricto (s.s.)* (genotypes G1/G2/G3), *E. equinus* (genotype G4), *E. ortleppi* (genotype G5), *E. canadensis* (genotypes G6/G7/G8/G9/G10) and *E. felidis* ("lion strain). *E. granulosus s.s.* (particularly genotype G1) is the most widely distributed species at global level and accounts for approximately 80% of human cases of hydatidosis [4-6].

EG requires two mammalian hosts for completion of its life cycle: a definitive host (a carnivore, especially dogs) in which the adult or strobilar phase develops; and an intermediate host (ungulates, including sheep, goats and cattle, pigs, guanacos, etc.) in which the larval phase, or metacestode, or hydatid cyst, develops.

The adult tapeworm is white, 3 to 7 mm in length, and equipped with a double crown of hooks for attaching to the small intestine of dogs (or foxes) (Figure 1).

The body is segmented and consists of a number of reproductive units or proglottids (usually 4). Each mature proglottid may contain an average of 587 fertile eggs, and it is estimated that gravid proglottids are produced and passed with feces every 15 days (0.071 proglottids/tapeworm/day in average) thus contaminating soils, crops and water. A dog may harbor hundreds of EGs without showing any symptoms of the disease [7-8].

Eggs are ovoid in shape, 30 to 40 cm in diameter, and contain hexacanth embryos (oncospheres or first larval stage) surrounded by several membranes and an external keratinized highly resistant thick wall. They cannot be morphologically distinguished from the eggs of other tapeworms (*Taenia ovis*; *Taenia hydatígena*, etc.).

These eggs can survive for long periods in the environment and remain viable up to 294 days at 7º C. At temperatures of 21°C they survive for 28 days, while at 60°C - 100°C they only resist up to 10 minutes. Thus, EG eggs are more resistant to cold and humid environments than to warm and dry environments, where they become senescent and rapidly lose vitality. More recent studies have shown that in certain areas of the Argentine Patagonia eggs can remain infective after 41 months in the dry conditions present in arid climates [9].

Once in the environment, eggs can be disseminated in all directions (up to 170 meters) by wind, birds, animal footsteps, etc., and they can be dispersed in areas up to 30000 hectares by diptera and dung beetles, which act as carriers. In this way, large extensions of field, drinkable water from streams and wells, vegetables and the grounds on which dogs walk and defecate become contaminated. These eggs can also adhere to dog's hair.

Figure 1. Echinococcus granulosus attached to the small intestine mucosa of dogs (shown by the white arrow in the photograph)

When ingested (with grass or water) by susceptible intermediate hosts (sheep, goat, and cattle, pigs, guana-

cos, hares), EG eggs reach the stomach where the oncosphere is activated and passes to the small intestine. It penetrates the intestinal microvilli and passes into the lymphatic and venous systems, to lodge in various organs, mainly the liver and lungs. In these organs, the larval phase, metacestode, or hydatid cyst – which is typically unilocular and filled with fluid – develops and slowly increases in volume.

Parasites in embryonic stage (protoscolices), collectively known as "hydatid sand", develop within the cyst (Figure 2). Most hydatid cysts growth very slowly and may take many years to develop large enough to cause symptoms in the host, although in some cases they may grow fast and cause symptoms during their first years of life.

When the carrier host dies in the field or is slaughtered for consumption releasing viscera to the environment, the carnivore-omnivore or predator-prey cycle is completed; therefore, the domestic routine of slaughtering game or small animals is the main risk factor for the spread of the disease.

When a dog is fed with cyst-containing viscera, protoscolices develop into adult tapeworms and the cycle is restarted. For this reason, hydatidosis is recognized as a ciclozoonosis.

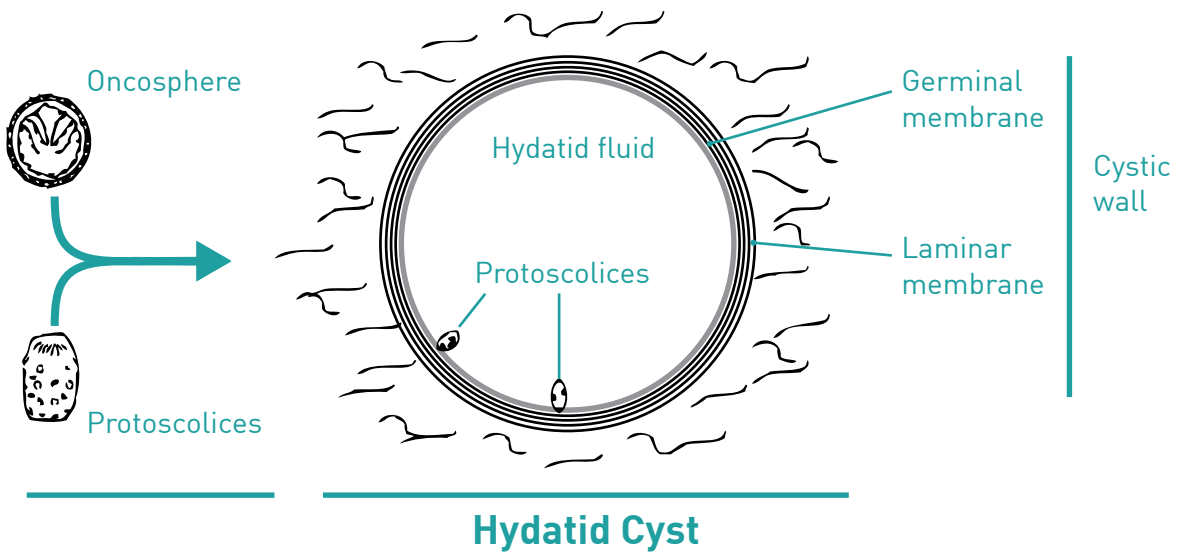


Figure 2. Structure of the hydatid cyst

The prepatent period, the time from consumption of infected viscera by dogs to the release of eggs in the feces, is short and takes approximately 7 weeks. At that point, the first mature proglottid containing infective eggs is shed into the environment in dogs' stools.

In humans, infection occurs after accidental ingestion of parasite eggs. Infection is acquired in childhood mainly due to geophagy and careless contact of children with dogs (they allow face and hand licking, etc.) [1-3].

The main risk factors found to be significantly associated with Hydatidosis in children in case-control studies were spending the first years of life exposed to a large number of dogs (OR = 2.11; CI = 1.2 to 3.5) and having a parent who slaughters sheep (OR = 1.14; CI = 1.04 to 1.24). Having a relative with the disease poses a high but not significant risk (OR = 3.11, CI = 0.92 to 10.47), while, in this study, the availability of drinking water at home appears as a protective factor, although not statistically significant (OR = 0.28, CI = 0.08-1.01). Several studies in different regions confirm these are key risk factors, including the lack of access to drinking water, which facilitates the ingestion of EG eggs in contaminated water [10-15].

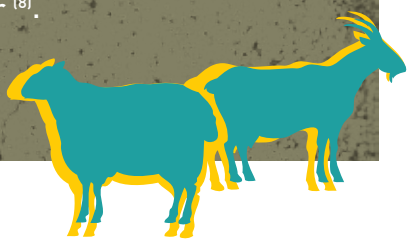
As in cattle, the shell of tapeworm eggs is dissolved in human small intestine, releasing embryos which penetrate the intestinal mucosa and pass into the bloodstream to reach different organs, most commonly the liver (67-89%) followed by the lungs (10-15%) (Figure 3). They may also reach other organs such as the kidneys, brain, heart, bones, muscle, etc., although these locations do not exceed 10% of detected cases [16].

The ratio found between liver and lung localizations is 5/1 and up to 9/1, as determined in several endemic areas from South America when cysts were detected in asymptomatic populations using ultrasound and radiographic techniques simultaneously. These coefficients show the importance of the hepatic filter as a key factor for the localization of the cyst, being the lungs the next most important site when cysts escape this filter. Cysts may also be found simultaneously in multiple organs [16].

The incubation period in man is generally several years, and it may last more than 40 years.

Disease symptoms are associated with cyst expansion and pressure on adjacent structures, infection, rupture and spillage of cyst contents into neighboring body cavities. The rupture of cysts, either spontaneous or secondary to trauma or surgery, can result in the formation of multiple cysts (multiple secondary hydatidosis), secondary bacterial infections, anaphylactic reactions, etc.

Hydatidosis (CE) is associated with livestock – especially sheep and goats – production areas with poor sanitary infrastructure (lack of slaughter rooms, drinking water networks, pits for viscera disposal, etc.), poor knowledge of the disease and a large dog population, with or without an identifiable owner [8].



Liver cysts cause nonspecific signs and symptoms which most frequently include: abdominal pain, fever, nausea, vomiting, hepatomegaly and jaundice. When located in the lung, where dissemination of cyst contents may occur due to cough attacks (throwing up), the most common signs and symptoms are fever, pain, chronic cough, expectoration, dyspnea, hemoptysis, pneumothorax or asthma.

In humans, cysts may persist and never develop symptoms throughout life (asymptomatic carrier). This is usually observed in liver cysts (17), so the ratio between liver/lung symptomatic cysts in surgery departments may be 2/1 or even a larger number of pulmonary cysts may be encountered. These findings support the relevance of active surveillance techniques using ultrasound to improve overall sensitivity of hydatidosis surveillance.

In South America, the most important natural epidemiological cycle is the primary domestic one (dog-sheep) as it involves dogs, particularly those used to herd sheep.

Hydatidosis produces economic losses. Human-associated losses include direct and indirect costs. Direct costs are associated with diagnosis, treatment and follow up of cases. Indirect costs arise from travel expenses from rural zones to hospitals, loss of wages, and reduced productivity due to morbidity and mortality. Likewise, economic losses associated with livestock production include direct costs due to condemnation of infected viscera, and indirect costs due to decreased productivity of infected animals [18-20].

Total annual losses due to medical care and animal production loss in the region have been estimated to be between US$ 120 and 141 million [18].

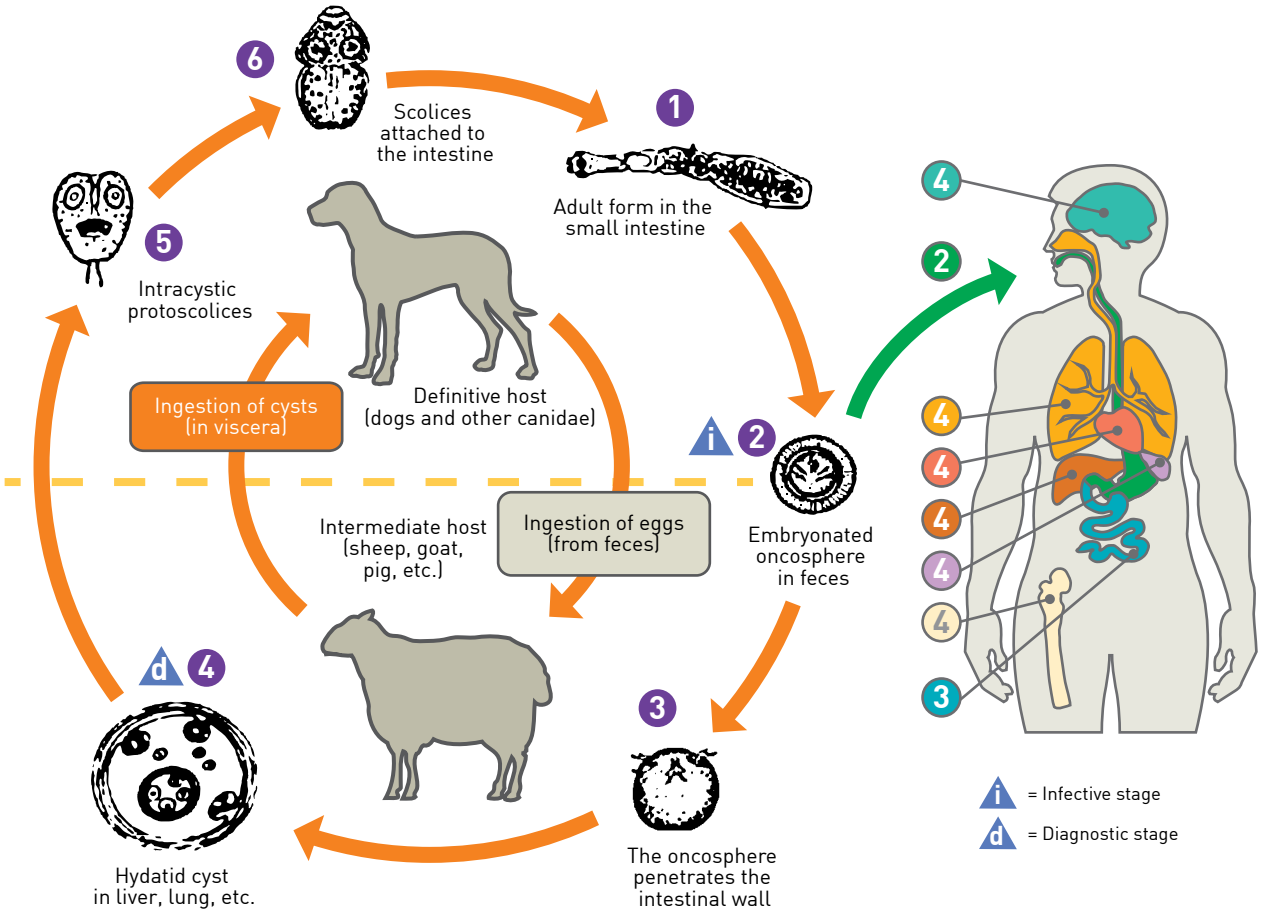


Figure 3. Transmission cycle diagram (adapted from C.D.C. Atlanta, USA) – https://www.cdc.gov/parasites/echinococcosis/biology.html)

1: Forma adulta en intestino delgado del perro;
2: Oncósfera embrionada en materia fecal;
3: Oncósfera penetra en pared intestinal del hospedador intermediario;
4: Principales localizaciones del metacestode: hígado y pulmón;
5: Protoescólices intraquísticos;
6: Escólices enganchados en pared intestinal.

1.2. DISTRIBUTION IN THE AMERICAS

During the period January 2009-December 2014, 29,556 CE cases were reported to the official authorities in the five countries included in the Sub-Regional Initiative for the Control of CE (Argentina, Brazil, Chile, Peru and Uruguay), with incidence rates

ranging from 0.012 to 13 per 100,000 population among countries. However, underreporting of cases is very often in neglected diseases, including Hydatidosis, so the number of cases is certainly higher [21].

The actual number of cases in certain endemic areas may be as high as 2,500 per 100000 population, considering asymptomatic carriers of hydatid cyst, or even exceed 10,000 per 100000 population in some areas with a predominant indigenous population[16].

The mean lethality rate, estimated in 2.9% during the 2009-2014 period for the five countries of the Initiative, suggests that there were more than 800 deaths due to Hydatidosis.

The proportion of Hydatidosis cases reported in children under 15 years old (suggesting persistent environmental risk leading to new cases) was 15% in the same period. The percentage of cases in children ≤15 years old by country was 15.8% in Argentina, 18.5% in Brazil, 15.1% in Chile, 17.04% in Peru, and 6.45% in Uruguay [21].

National data do not to show the heterogeneous distribution of Hydatidosis within each country, where the disease is found to be more prevalent in some regions, particularly those in which the production of small ruminants is predominant. Besides, cases of hydatidosis have been reported in other South American countries, such as Bolivia, although prevalence data are not available since this country is not included in the Initiative.

Argentina shows three high-incidence areas: the Patagonia region, in the south of the country (where the provinces of Neuquén and Chubut show the highest national rates), the Northwest region (including the provinces of Catamarca, Santiago del Estero and Salta), and the province of Entre Ríos in the East. In Chile, the highest incidence is observed in the south and far south of the country, the former including Bio Bio, La Araucanía, Los Ríos, Los Lagos, while Aysén and Magallanes, in the far south, show the highest rates. In Peru, the highest incidence is seen in the highlands in the south and center of the country (Arequipa, Cusco, Huancavelica, Junín, Pasco and Puno). In Uruguay, the highest incidence of Hydatidosis is found in the northwest and central regions. In Brazil, Hydatidosis is mainly found in the states of Acre and Rio Grande do Sul (Figure 4).

Figure 4. Cumulative incidence of hydatidosis in Argentina, Brazil, Chile, Peru, and Uruguay, by administrative unit (province or region)

Fuente: 21. Brasil incluye casos de equinococosis neo-tropicales.

2

LEVELS OF HYDATIDOSIS PREVENTION

PREVENTION

PREVENTION IS DEFINED as *"Measures not only to prevent the occurrence of disease, such as risk factor reduction, but also to arrest its progress and reduce its consequences once established"*. Preventive activities may be classified into three levels: Primary, Secondary and Tertiary prevention, involving different techniques and objectives since they consider the health-disease as a continuum according to the health status of the individual, group or community to which they are oriented [22].

2.1. PRIMARY PREVENTION

Primary prevention avoids the occurrence of disease through measures of health education and specific protection (immunization, elimination and control of risks). It prevents disease or injury in healthy people.

Secondary prevention is aimed at detecting the disease before the manifestation of signs and symptoms, for some kind of intervention to reduce associated morbidity and mortality.

Tertiary prevention involves measures aimed at treatment and rehabilitation from a disease in order to stop its progression and prevent worsening and the resulting occurrence or worsening of complications in an attempt to improve patients' quality of life.

2.2. HEALTH EDUCATION

2.2.1. ACTIVITIES AT LOCAL LEVEL

Primary prevention is the most effective and efficient way to control Hydatidosis. To that end, the development of health education and promotion activities in the community, oriented toward disease control, is essential. **The aim is to bring about changes in habits and health behavior of humans, especially in children.**

Another important objective is to encourage the population, especially adults, to cooperate with the local control program [23].

The activities recommended to meet these two objectives should focus on providing people with the following information:

a. Knowledge about the parasite cycle:
    1. Explain this cycle using audiovisual media.
    2. Highlight the fact that the **DOG** is the only agent that can transmit and spread Hydatidosis.

b. Actions to prevent infection in dogs:
    1. Systematic deworming, checking with the control program staff, veterinarian or Healthcare Center, the mode and frequency of deworming, according to local epidemiology and conditions.
    2. Dogs should not be fed with viscera (particularly liver and lungs).
    3. Animals for consumption should be slaughtered in premises not allowing the access of dogs and allowing disposal of viscera in a safe manner (slaughterhouse and septic tank).

c. Actions to avoid infection of human population (particularly, children):
    1. Always wash hands with water and soap before eating.
    2. Avoid being licked by dogs.
    3. Wash vegetables and fruits thoroughly before eating.
    4. Consume mains drinking water only. If not available, water should be boiled for 5 minutes.

d. Actions to avoid contamination in the household area (peridomicile):
    1. In the field, working dogs should be maintained in their kennels while not working.
    2. Avoid the access of dogs to the well from which water to drink and wash vegetables is extracted. Keep the well water safe.
    3. Prevent the access of dogs to the family vegetable garden or orchard.

e. Additional information necessary for the community:
    1. The Health Care Facility can provide information on how to find out if a person is a carrier of a hydatid cyst.
    2. Disease treatment will depend on the location of cysts and overt symptoms. The appropriate therapy for each case will be determined by the Healthcare Facility. Besides traditional surgical treatments, effective therapies with antiparasitic drugs are currently available, which can be used before the cyst becomes too large.
        - Any area (cattle ranches, posts, farmhouses, summer pastures) where dogs and cattle (especially sheep and goats) cohabit, and/or where sheep or other adult animals are slaughtered, should be considered a risk area.
        - Hydatidosis is not transmitted from person to person. It is only transmitted by the dog, through the EG eggs passed in the stool.
        - Dogs should not be fed with animal viscera and should be periodically dewormed in order to prevent the disease.

2.2.2. INFORMATION AND EDUCATION STRATEGIES

1. Training of teachers in rural schools, particularly to act as knowledge multipliers and promoters for the adoption of healthy habits in children.

2. Active participation of students (poster contests, murals on public places, etc.).

3. Use of community radios to disseminate educational messages (avoid feeding your dog with viscera) and to achieve people's participation in the program ('deworm your dog today'), as used, for example, in the province of Rio Negro, Argentina, to remind deworming date.

4. Creation of self-help groups, with the presence of surgically treated patients or mothers of surgically treated children: the experience in Uruguay.

5. Design of novel educational materials (puppets, short-films, posters), trying to present examples, drawings and photographs representative of dogs, sheep or people of the intended community.

6. Inter-institutional coordination so that school teachers, staff of Healthcare Facilities and control program workers can bring their efforts and capabilities together. Important participation experiences of educators (Uruguay) and anthropologists are available to understand the social perception of the disease (for example, Coyhaique, Chile).

Figure 5. Sample educational material

7. In all circumstances, it is important to keep records of ALL the activities performed, describing the activity and stating the objective, message, platform used (e.g., radio, theaters, etc.); frequency and location; target audience or populations (e.g., children, teachers); number of people reached by the activity, etc. Likewise, it is important to generate impact indicators of these activities in the target population. These may be simple tests with questions about Hydatidosis prior to and following the activity, etc.

8. Links to educational material on Hydatidosis by country of origin:
   a. Argentina: http://www.msal.gob.ar/zoonosis/
   b. Uruguay: http://www.zoonosis.gub.uy/webzoonosis/index.php/91-zoonosis
   c. Chile: http://www.aysensinhidatidosis.cl/
   d. Brazil: https://www.youtube.com/watch?v=VpM2OugOduk

2.3. INTERRUPTING THE TRANSMISSION CYCLE

The following strategies are essential to disrupt the transmission cycle:

- Continued deworming of all dogs;
- Vaccination of sheep;
- Creation of infrastructure for slaughtering (slaughter room and fenced pit) in urban areas and livestock farms;
- Management of canine populations.

2.3.1. DOG DEWORMING

Praziquantel is the drug of choice for systematic dog deworming, used at 5 mg/kg in a single dose [24]. Given its bitter taste, masking the tablets within a piece of meat or pate is recommended. In some countries, the drug is delivered to the community by program personnel or in Healthcare Facilities, where control programs are in place.

When administered every 30-45 days to 100% of the dogs, it prevents the spreading of mature proglottids which can cause sheep reinfection. If treatment is maintained until total renovation of sheep population present at the beginning of the deworming program, transmission to humans could be completely stopped. This strategy requires significant field infrastructure and a prolonged period of time (10 or more years, depending on average lifetime of sheep in the area and the survival of EG eggs in the environment).

However, the frequency or periodicity of drug administration to dogs should be locally adjusted according to the assessment of reinfection rate and, particularly, local operating capacity to distribute antiparasitic drugs in rural households. In all circumstances, when dog deworming is systematically performed over time, the risk of humans getting the disease is reduced.

When administered at the recommended dose, praziquantel is 100% effective in treating EG, but it does not kill the eggs. Therefore, it is important to remove dog stools from the environment, especially when animals are dewormed for the first time. It is also important to remember that praziquantel has no lethal dose nor causes side effects in dogs; consequently, full dose should be used according to the dog's weight.

When control programs are in place, dog deworming activities are generally performed by Public Health personnel (healthcare workers or other properly trained personnel) or livestock workers (veterinarians or paratechnicians). Sometimes, especially in urban areas, the activity can be delegated to municipalities. Besides, when drugs are given to dogs by program personnel the strategy is more efficient than when tablets are given to the owners for later deworming of their dogs.

Some operative issues have emerged with praziquantel use, such as unpleasant taste and odor for dogs, hampering full dose administration by healthcare workers and other personnel (for this reason, it is usually given with meat or pate); difficulties to properly estimate dogs' weight, thus resulting in the use of wrong doses (almost always less than the required dose); some reluctance of dogs' owners to administer many pills with each deworming; and the recurrent need to give the pills to the owners instead of administering them directly to the dog – which is strongly recommended – because the dog is not present at the time of the visit.

Figure 6. Dog deworming by health workers

There are currently programs implemented in South America using this drug which have achieved significant reductions in the prevalence of the disease in humans, e.g. in Uruguay and in the provinces of Rio Negro and Tierra del Fuego in Argentina [25-27].

2.3.2. VACCINATION OF SHEEP

Vaccination of potential intermediate EG hosts with the **EG95 recombinant vaccine developed by the Melbourne University** may be a useful strategy to reduce the level of transmission as well as the incidence of infection in humans [28].

In a pilot program initiated in 2009 in the province of Rio Negro, Argentina, **lambs received two initial doses of EG95** (the first one given to animals at 30 days of age and the second at 60 days of age before weaning) **with a booster dose approximately at 1-1.5 years of age**. Lambs born in the following years received the same immunization schedule.

So, in this experience, EG95 vaccine could significantly prevent infection in animals, although it failed to eliminate it despite the strong staffing infrastructure supporting these activities [29].

Figure 7. Vaccination of sheep by program professionals

Before the introduction of the vaccine, 56.3% of 6-year old animals were positive at necropsy. Five years after initiating vaccine use, prevalence was reduced to 21.1%. The number of cysts per animal decreased from 1.4 to 0.3. All cysts were small (‹1 cm). The number of farmers with infected animals was reduced from 94.7% to 23.5% [29].

The efficacy of vaccination may be hindered by factors not related to the vaccine itself. Vaccination in sheep requires a great deal of infrastructure and should be completed within a short timeframe. Although vaccination requires less intervention compared to dog treatment (2 vaccine doses versus 8 treatment courses every 45 days in dogs), it involves a higher number of animals to work with and higher costs (treatment and logistics).

A vaccination-only program will take many years to show some results and will not ensure elimination of transmission. A combination of dog deworming and vaccination may prove to be an adequate strategy. Apart from Rio Negro (Argentina), there are current experiences combining treatments in dogs and sheep in the highlands of Peru.

2.3.3. DEVELOPMENT OF HEALTH INFRASTRUCTURE

Every establishment in which animals are slaughtered for family consumption, especially large livestock farms, should have a slaughter room available which prevents dogs' access of and a pit with a lid or other system for the destruction or sterilization of viscera. Kennels may be built to keep the dogs while not working. This strategy was successfully developed in the program in Tierra del Fuego, Argentina.

Developments in slaughtering urban infrastructure are also particularly important to avoid dog contact with viscera from slaughtered animals.

Figure 8. Infrastructure in cattle establishments in Tierra del Fuego. Slaughter room with pit and kennels

2.3.4. MANAGEMENT OF CANINE POPULATIONS IN ENDEMIC AREAS

In rural and some periurban areas as well as in small towns, dogs with no documented owner, feral dogs and stray dogs may be a source of *Echinococcus spp*.[30]. Unowned dogs are those having no or unknown owner, while feral dogs are those living in rural areas as part of the fauna.

Management of these canine populations may include several strategies based on operational, financial, social and cultural assessments, and those considered most cost-effective by the countries to meet the required control objective.

For example, programs in Tierra del Fuego and Rio Negro included specific laws to identify the responsibilities of dog owners in livestock farms and to establish the mandatory health infrastructure for these premises, such as kennels. In other programs, as in the case of Uruguay, dog sterilization campaigns are carried out in areas of hydatidosis transmission and the owners of dogs contribute with an annual payment intended to fund control program activities. Other countries, such as Chile and Brazil, do not consider that the evidence of direct impact of dog sterilization campaigns is enough for their implementation in official control plans. Some programs are currently trying out dog identification with microchips in order to foster higher levels of responsibility among dog owners in relation to the risks posed by dogs in the community.

The following links provide access to information and international recommendations about management of canine populations.

- **FAO:** http://www.fao.org/3/a-i4081e.pdf
- **International Companion Animal Management Coalition:** http://www.icam-coalition.org/downloads/Guia_Para_El_Manejo_Humanitario_de_Poblaciones_Caninas_Spanish.pdf
- **OIE:** http://www.oie.int/doc/ged/D9926.PDF
- **WHO:** http://apps.who.int/iris/bitstream/10665/70253/1/WHO_HTM_NTD_NZD_2010.1_eng.pdf
  http://apps.who.int/iris/bitstream/10665/85346/1/9789240690943_eng.pdf

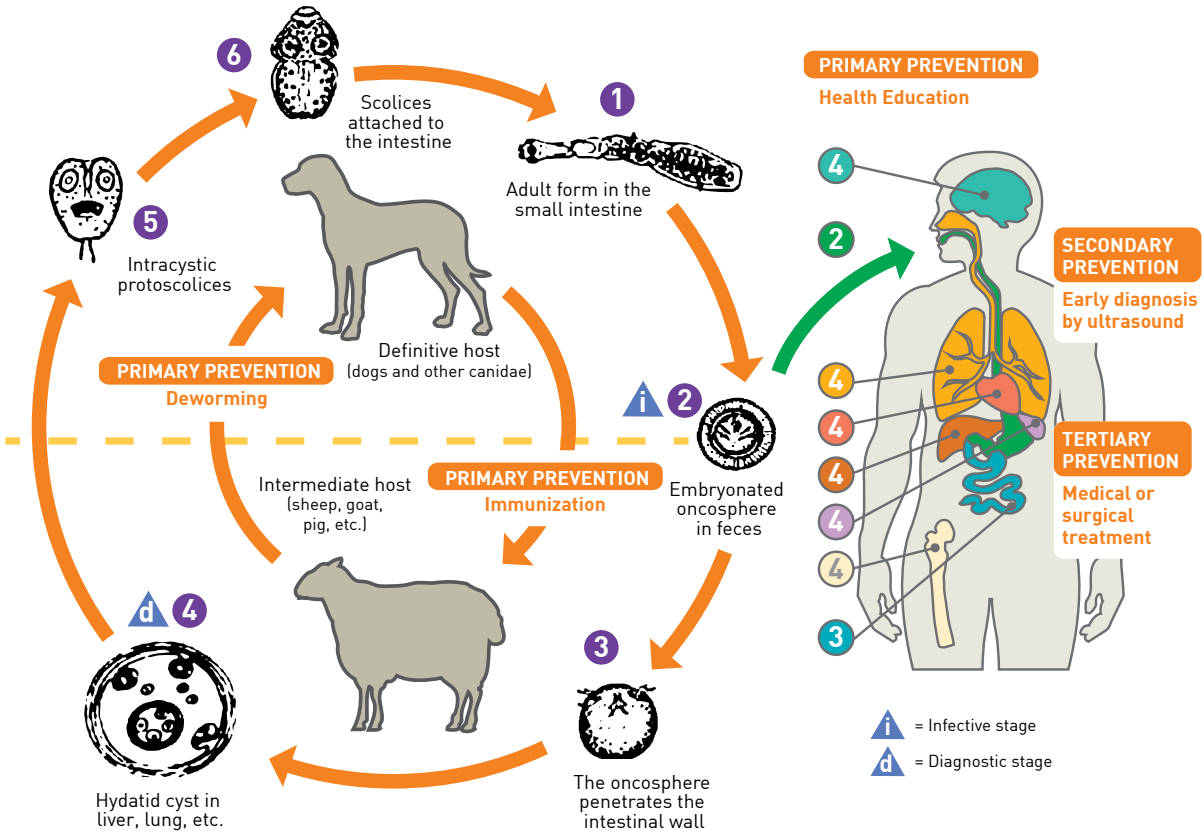


Figure 9. Diagram of levels of hydatidosis prevention (adapted from C.D.C. Atlanta, USA) – https://www.cdc.gov/parasites/echinococcosis/biology.html)

2.3.5. EPIDEMIOLOGICAL SURVEILLANCE: BASELINE AND IMPACT STUDIES

A relevant aspect when control activities are to be developed is a previous identification of the level of infection in dogs, in the environment, in sheep and humans, especially in children under 15 years old. Ongoing surveillance activities will allow comparison with baseline data by monitoring the impact of control actions on CE occurrence.

In every case, especially to assess infection in dogs and livestock, surveys should rely on statistically significant and properly randomized designs, taking into account expected prevalence and significance level in order to determine the sample size.

ZONING CHARACTERIZATION BASED UPON THE PRESENCE OF INFECTION IN DIFFERENT HOSTS

An approach to characterization of transmission levels involves using mathematical models based on an estimation of the reproductive capacity of the parasite and acquired immunity (31). In these models, EG is never found in hyperendemic state.

Alternatively, new models are under development to characterize endemicity levels in any given area (32) in a convenient and simple way.

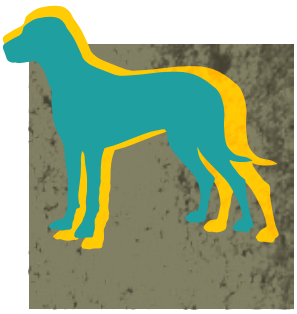
As reference, in regions historically recognized as highly endemic and where hydatidosis was, or still is, a serious health problem, such as the Patagonia region in the south of Argentina (Neuquén 1970, Rio Negro and Tierra del Fuego 1980), the central highlands in Peru (1980) and the Regions XI (1982) and XII (1979) in Chile, the prevalence of CE infection was ›50% in sheep at necropsy and ›25% in dogs by using the arecoline test (25,26).

Considering the experience with programs that achieved complete elimination of infection, as those from New Zealand and Tasmania (25), an approach to the disease elimination criterion would be to certify the absence of cases in children under 15 years old, either symptomatic or detected by ultrasound surveys, co-existing with an infection prevalence detected at necropsy or by serological tests below 0.9% in sheep and below 0.01% in dogs.

This indicator is selected in the PAN AMERICAN HEALTH ORGANIZATION (PAHO) PLAN OF ACTION 2016/2022 (see Annex 1).

2.3.5.1. IN DOGS

A taenifuge, arecoline hydrobromide was used in the past in dogs, which allowed the identification of infected animals on the spot thus providing an estimate of disease prevalence.



However, indirect techniques are currently used which allow identification of infection in dog stools, collected from the surroundings of the house. This technique is called **co-proELISA**, and may be confirmed later by **coproPCR** or **Westernblot**, or diagnosis can be established directly using coproPCR, an alternative of choice, but at higher costs [33-35].

Using coproELISA, every livestock establishment or rural household, referred to as Epidemiological Unit (EU), is classified as transmission present or transmission absent upon identification of a single positive sample in the lab.

Results are expressed as the number of EU with at least 1 positive sample/total of EUs in which samples were collected * 100.

If it is possible to obtain samples specifying to which dog they correspond (for example, collecting it directly from the dog or keeping dogs tied separately), it is also possible to express results as the number of positive dogs/total of samples studied * 100.

The collection of samples requires the following equipment:

a. Transport unit for parasitological specimens;
b. Clean 100-ml plastic bottles (with wide mouth and screw cap);
c. Labels;
d. Permanent marker;
e. Disposable tablespoon (number enough for the entire working day);
f. Container for spoons;
g. 10% chlorine solution for decontamination of reusable material;
h. Cooler or specimen transportation unit;
i. Bags for biological waste (red-colored) and domestic waste (black-colored) disposal;
j. Personal protection equipment (see biosafety).

Sampling procedure: Sampling unit refers to a portion of canine stools collected in the soil of an EU.

Samples collected may be either recently passed, liquid, solid, or semi-solid stools. If fresh feces are not available, solid samples passed on the days prior to collection day should be collected. If fresh feces are selected, take the equivalent to two full tablespoons of feces and put them in a 100-ml plastic bottle with screw cap, without preservatives.

In the case of dry feces, the whole stool should be collected. If the sample is too large it should be fractionated taking parts from different sites of the whole sample. Ensure the bottle containing the sample is tightly closed and labeled with the sequential sample number, owner name and address. Once collected, samples should be stored in a transport unit or cooler with refrigeration units.

Avoid sample contamination with excessive earth, grass or other soil contaminants. Whitish feces should not be collected as they might contain high levels of calcium, which affects the PCR (Polimerase Chain Reaction) technique performance.

The identification of each labeled sample in its respective bottle should be consistent with the information provided in the collection data form, which should include the following information for each sample: sequential number or assigned code, name of the owner or the person living in the household, address (street, number, area, town, municipality as available in rural areas), geographic coordinates using GPS, sampling date and last date of deworming. If available, history of feeding with viscera and access to street and/or field should also be recorded. This data collection record should be sent to the lab together with the samples for subsequent entry in a database.

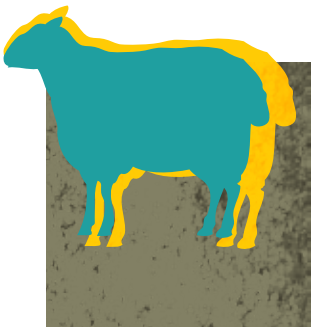
Only samples collected in an adequate amount, with minimal levels of environmental contamination, and properly identified, stored and transported until reception at the lab, will be considered suitable to be processed for molecular diagnosis (PCR).

All samples from the same location should be put within the same bag with a label identifying the EU in which they were collected. Samples from each EU should be kept refrigerated in their respective bags at 2-8ºC from the time of collection to shipping, and shipped using a triple packaging system due to the potential contaminant content of the samples if infected with EG. If samples are not sent immediately with refrigerating units, they should be kept frozen at least at -20°C.

For the final shipment of the samples to the lab, and in order to meet biosafety standards for sample transportation, the use of a box which can be placed inside a larger one with plenty of absorbent paper in between should be considered, following the triple packaging system. The corresponding form, together with the shipping document and sample information sheet should be attached to the secondary packaging.

The outer packaging should have the upper side clearly identified together with the indication not to drop it.

2.3.5.2. IN SHEEP



Post mortem identification of the presence of hydatid cysts is the diagnostic method traditionally used in sheep. It is important to know the age of the animals for epidemiological interpretation of data (those from young animals are more important because they indicate current transmission. Young animals can be identified by the number of temporary teeth still left). Moreover, if allowed by animal production system and traceability, it is worth identifying the source EU of infected lambs.

Limitations include difficult detection of cysts in young animals (which are of primary interest for surveillance in a control program) and diagnostic errors in adult animals (suppurative and calcified cysts). Another important limitation is that many endemic areas lack slaughterhouses in which these studies can be performed, or areas in which many sheep are slaughtered at home with no records; therefore, representative information cannot be obtained [36].

Results are expressed as the number of positive sheep / total sheep studied * 100. In this case, it is advisable to disaggregate lamb data (indicating recent infections) from those of the remaining sheep (indicating parasitic biomass).

Alternatively, available serological techniques **(Elisa)** with an acceptable level of sensitivity and specificity can be used, being especially useful in recently infected animals (humoral response in lambs is detected within 10 days from infection). When applied to lambs, it may be useful to evaluate the presence or absence of transmission: a positive diagnosis in at least one lamb implies infected dogs in the EU and, therefore, a contaminated environment. What is important in sheep is not the confirmation of the individual diagnosis, but the identification of current transmission, at least while the program is not in a virtual elimination phase. In sheep vaccination programs it is also possible to measure the humoral response to identify the attained level of protection [37, 38].

Results are expressed as the number of EU with at least 1 positive lamb / total EUs in which samples were collected * 100.

The presence of parasitized or serologically positive lambs indicates current and/or present transmission, while the absence of parasitized or serologically positive adult animals indicates past transmission. This information is useful during elimination phases as it suggests the presence of a parasitic mass potentially infectious for dogs.

2.3.5.3. IN HUMANS

In humans, the information can be obtained from official systems of:

a. case reporting;

b. hospital discharge or outcomes;

c. population-based surveys using ultrasound (method of choice) or;

d. serological tests.

The advantages of the survey system are standardization and lack of conditioning from administrative issues usually associated with reporting. In any case, the most important information for the program is that related to children 0-10 or 0-15 years old as it is associated with the presence of transmission [39] and should be captured through ultrasound or, eventually, serological surveys.

In this case, results are expressed as the number of positive children at screening / total children studied * 100. This indicator is included in the **PAHO PLAN OF ACTION 2016/2022** (see Annex 1).

The presence of cases in children 0-10 years old suggests transmission in the recent past. The absence of cases in children is an indication that transmission to humans has ceased or been reduced.

Thus, in control settings, the local surveillance system should allow the identification of Epidemiological Units with present transmission (by coproElisa or PCR in dog stools and necropsy or serologic testing in lambs) or recent transmission (occurrence of new cases in children under 15 years old, either symptomatic or detected in surveys) in which measures to stop the transmission cycle should be intensified.

2.4. SECONDARY PREVENTION

2.4.1. TIMELY DIAGNOSIS

2.4.1.1. CASE CLASSIFICATION

There are several ways to classify cases according to each country.

For example, in Argentina, **Suspected case** is:

i. any symptomatic individual with a cystic mass located in different organs and systems, most frequently the liver and the lungs, and associated with epidemiological aspects of the disease (place of origin, contact with dogs, family history of hydatidosis) or;

ii. An individual positive at ultrasound or serologic screening, and associated with epidemiological aspects of the disease (place of origin, contact with dogs, family history of hydatidosis).

Confirmed case is considered as a suspected case with positive imaging tests (X ray, ultrasound, and/or computed tomography) and/or serological tests (ELISA/Western-blot). In Uruguay, these are considered **Probable cases**.

Likewise, in Argentina, **parasitological confirmation** requires direct visualization of protoscolices or parasitic hooks by microscopy, remnants of membranes and histo-pathological examination of surgically removed sample, which constitute a **Confirmed case** in Uruguay.

The use of the term Confirmed case in Argentina without visualization of the parasite is due to the fact that, currently, a large number of cases do not undergo surgery and, therefore, confirmation is not possible, a situation which in Uruguay is resolved using the term Probable case.

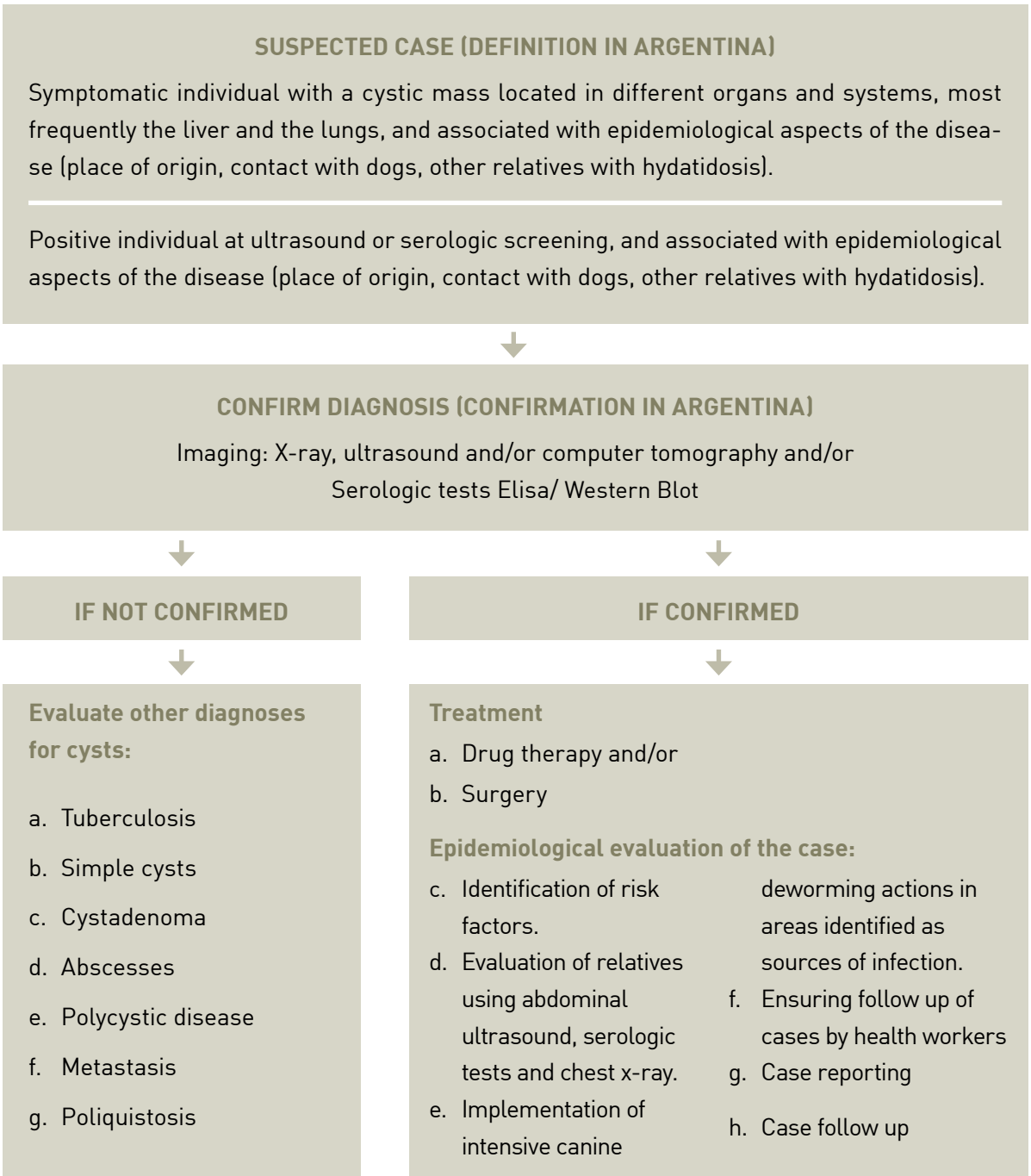


Figure 10. Flow diagram of the management of suspected cases of cystic echinococcosis/hydatidosis in humans.

2.4.2. DIAGNOSIS OF HYDATIDOSIS

At present, the use of imaging diagnosis methods (ultrasound, x-rays, computed tomography) allows identification of the affected organ in suspected cases [39].

2.4.2.1. ULTRASOUND IN HYDATIDOSIS

Several pathognomonic features have been defined by ultrasound imaging of hydatid cysts:

a. Cystic image with a single vesicle: laminar membrane is clearly identified as a well-defined, hyperechoic linear image (differential diagnosis from simple serous cysts).
b. Detached membrane image: clear and pathognomonic image of type II liver hydatid cysts (Gharbi's classification). Images like this are not frequently found during natural evolution, they are most often observed during the follow up of patients receiving albendazole as their only treatment.
c. Cystic image with multiple daughter vesicles inside: this is the typical image with a wheel-spoke or honeycomb pattern (differential diagnosis from liver cystadenoma or liver polycystic disease).
d. "Snowflake" sign caused by hydatid sand when the patient is mobilized abruptly through 180º.

Ultrasound diagnosis should include Gharbi's or World Health Organization (WHO) classification [39] (cyst type) as detailed below:

- TYPE I (CE1)*: Hyaline cyst full of liquid, with laminar membrane clearly visible, with or without snowflake sign.
- TYPE II (CE3)*: Hyaline cyst with "detached" or "folded" laminar membrane.
- TIPO III (CE2)*: Multivesicular: multiple cystic images within a cyst (wheel-spoke or honeycomb pattern).
- TYPE IV (CE4)*: Heterogeneous appearance (mainly solid contents).
- TYPE V (CE5)*: Calcified cyst (partial areas or the full image).

As regards serological tests, ELISA/Westernblot are the methods of choice using total hydatid fluid or purified antigens.

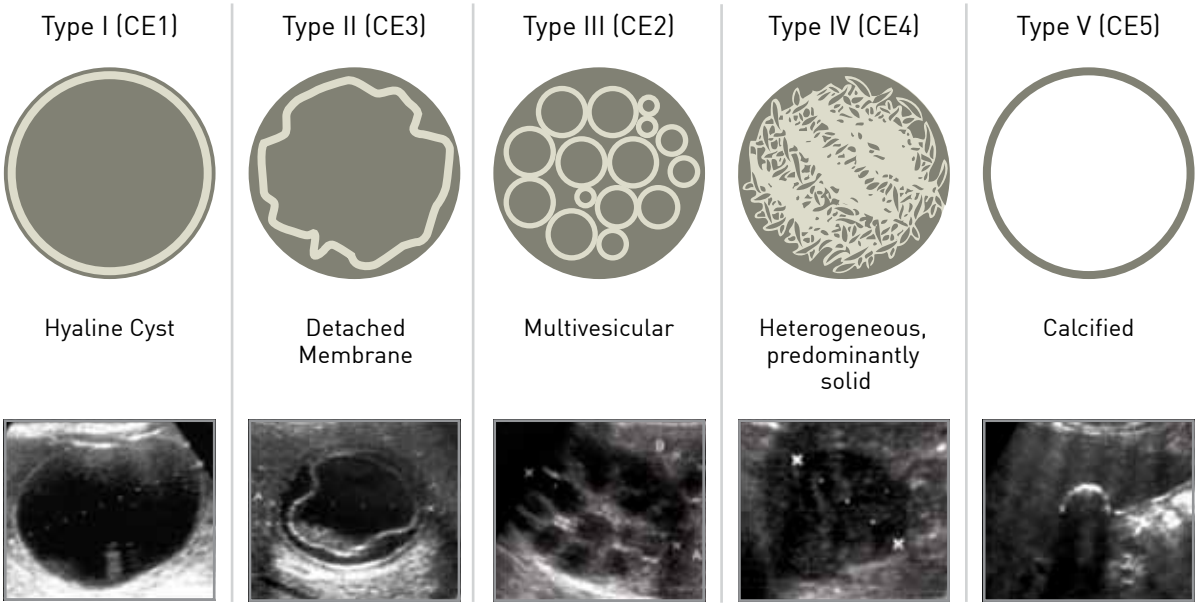


Figure 11. Types of liver hydatid cysts. Gharbi's classification (and WHO equivalents)

The main limitation of immunodiagnostic tests is the lack of diagnostic usefulness in cases of cyst carriers with undetectable antibody levels in serum. This is common in small or calcified hydatid cysts and most frequent in lung cysts, explaining the high seronegativity in patients with positive imaging findings. Likewise, there may be seropositive patients in which hydatid cysts cannot be found [40].

2.4.3. EARLY DIAGNOSIS OF HYDATIDOSIS

Early detection of hydatid cyst carriers allows for more treatment options to be used in detected cases, while avoiding the complications in symptomatic cases with a late diagnosis.

Figure 12. Asymptomatic hydatid cyst detected by ultrasound survey

Abdominal ultrasound is increasingly accessible, with low operational cost and, most importantly, 100% sensitivity and 95% specificity [41]. It should be considered the method of choice for the diagnosis of abdominal hydatidosis, mainly liver hydatidosis, to perform large-scale surveys in risk populations. Surveys may be performed by spe-

cially trained clinicians, who will select the cases to be classified as suspected, while specialists will be in charge of diagnostic confirmation of suspected cases [42, 43].

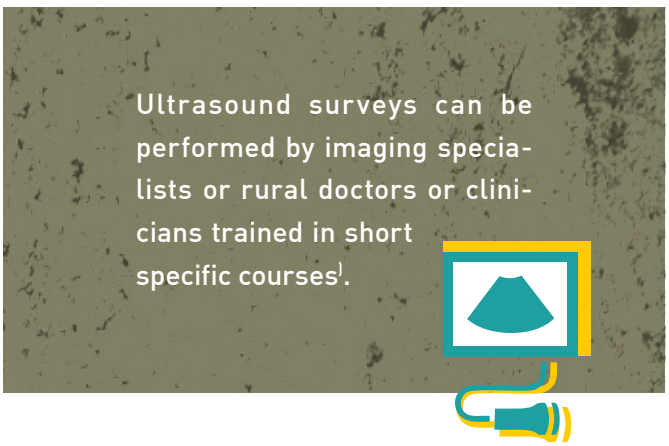
2.4.4. CONDUCTING POPULATION-BASED SURVEYS

One of the most important strategies to be developed at local level is **conducting population-based surveys to identify asymptomatic carriers**, whether or not measures to stop the transmission cycle have been put in place in the area.

The objective is the early diagnosis of cases, ensuring timely treatment. **In this way, morbidity and mortality due to hydatidosis, healthcare costs and the need of prolonged absence of patients when referred to tertiary care facilities far away from their homes are markedly improved.**

Surveys can be performed in all age groups, although they are more frequently required and efficient **in children and risk groups**.

If performed in the general population, special attention should be paid to the therapies to be used since, in the adult population, many cases will correspond to non viable or dead cysts (types IV or V) not requiring any treatment at first.



The implementation of early diagnosis activities requires:

a. Ensuring the informed consent for the survey in the case of minors, or the approval of an ethics committee when required by the country;
b. Ensuring the confirmation of cases;
c. Ensuring treatment and longitudinal follow-up of detected cases, being this indicator one of those selected in the **PAHO PLAN OF ACTION 2016/2022** (Annex 1).

Figure 13. Ultrasound screening in a rural school conducted by a general practitioner

Abdominal ultrasound is increasingly accessible, with low operational cost and, most importantly, 100% sensitivity and 95% specificity, and should be considered the method of choice for the diagnosis of abdominal hydatidosis, mainly liver hydatidosis, to perform large-scale surveys in risk populations. In this case, lung localizations will be overlooked, which could be identified by X-ray surveys, although the proportion of lung cases is lower and symptoms appear earlier. Alternatively, serological surveys may be performed and, in this case, ELISA is the method of choice. A negative examination means that no hydatid cysts are observed at that time.

2.4.5. MONITORING OF PATIENTS AND THEIR CONTACTS

When hydatidosis cases are confirmed in children under 15 years old, the family should be visited and the following actions should be performed:

1. Report the case.
2. Fill in a form to identify risk factors, including place of current residence and of the first five years of life, number of dogs at the time, source of drinking water, access to dog deworming, habit of slaughtering sheep and goats, history of hydatidosis in cohabitants.
3. Evaluate the entire family with abdominal ultrasound, chest x-ray and serological testing.
4. Implement diagnostic and deworming actions in every dog from areas identified as probable source of infection.
5. If the case has been diagnosed with an ultrasound or serological study, ensure diagnosis confirmation and further treatment.
6. Ensure regular supervision by health worker in order to follow up of new detected cases and dog deworming.

2.5. TERTIARY PREVENTION

2.5.1. TREATMENT

The treating physicians should take into account every patient individually, having in mind that guides are just general instructions. So, doctors should be able to identify and evaluate particular situations such as: age, previous illnesses, specific contraindications, occupation, place of residence, treatment and follow up possibilities, etc., that may require treatment adjustments [39, 44, 45].

Two scenarios should be considered:

a. asymptomatic patients, and

b. symptomatic patients with complicated or uncomplicated cysts.

Symptoms referred by the patient should be properly evaluated in order to determine if they are actually caused by the hydatid cyst or secondary to an associated illness.

In addition to ultrasound, a chest (front) x-ray should be performed in every patient before deciding the action to be followed.

For every confirmed **symptomatic** case, either uncomplicated or complicated (presenting with abscess, rupture into the abdominal cavity, opening in the biliary tract, abdominal-thoracic migration, or palpable tumor), **surgical treatment** (conventional or laparoscopic according to the case and the experience of the surgical team) is recommended.

Where possible, preoperative therapy will albendazole 10-15 mg/kg./day, e.g. for 7-10 days, and post-operative therapy for 60 days will be implemented, adjusted according to medical judgment.

This is not agreed by consensus, but preoperative Abz should be administered for no less than 30 days.

In patients with ruptured liver or spleen cysts in which the content is poured into the abdominal cavity, antiparasitic therapy with albendazole (at the abovementioned dose) for no less than six months after surgery is recommended.

In **asymptomatic** carriers, once the case is confirmed, treatment should be decided according to cyst localization, type, and size.

Therapeutic options in these cases include:

a. follow up only;
b. albendazole therapy; and
c. conventional surgery.

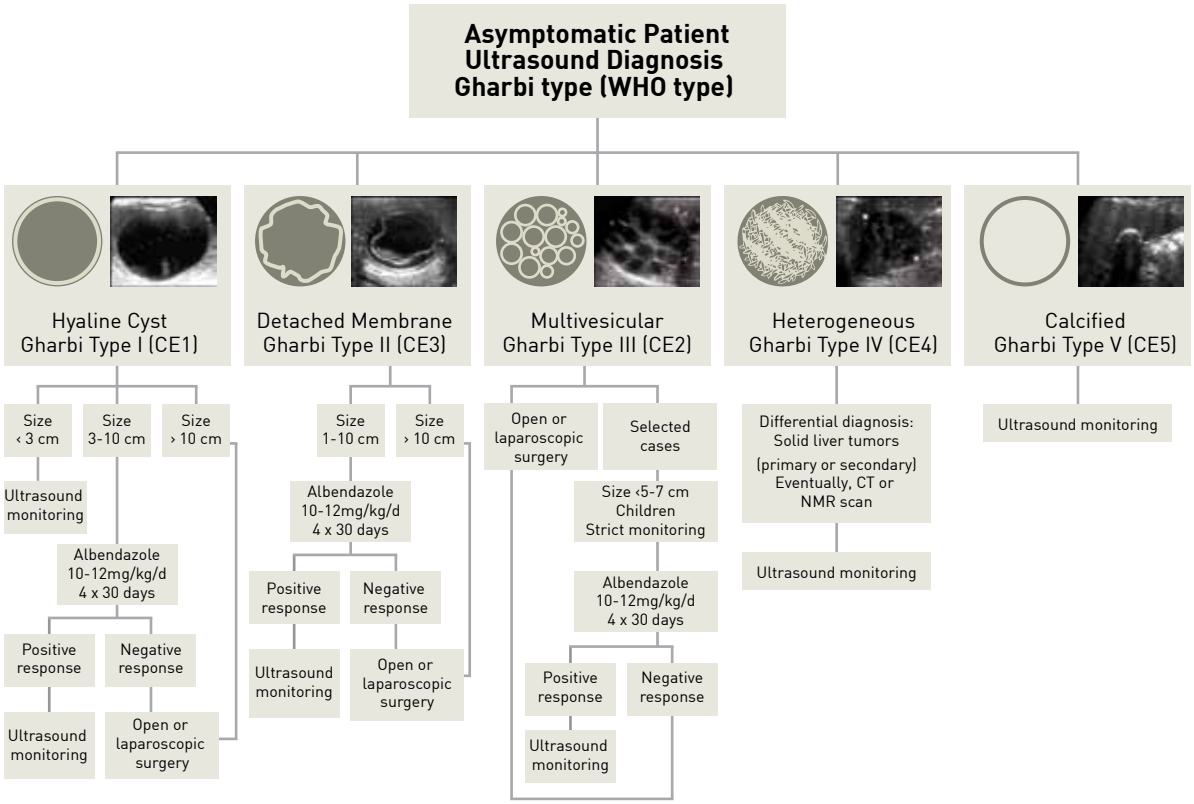


Figure 14. Tentative treatment schedule according to cyst type and size

Albendazole is prescribed at 10-15 mg/Kg of bodyweight/day, once daily after a high-fat breakfast or meal, in four 30-day cycles together with antacids (ranitidine 300 mg/day or omeprazole 20 mg/day) throughout therapy.

Treatment should be supervised and assisted by healthcare personnel, such as nurses or health workers. If this is not possible because the patient lives in a rural area far from the healthcare facility, the number of home visits should be increased in order to ensure treatment compliance.

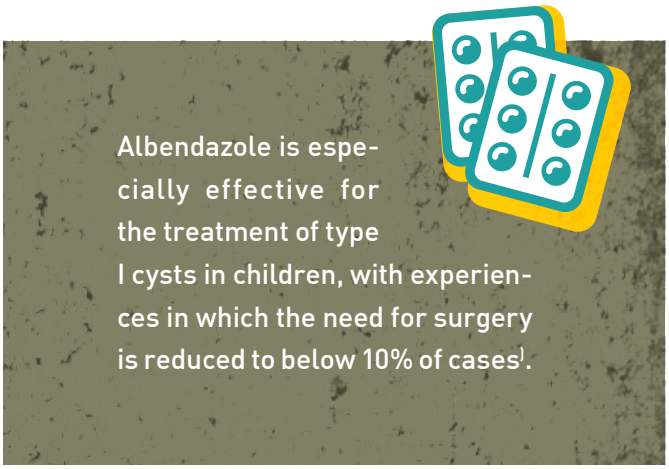
Cycles are continued without interruption, unless intolerance and/or lab abnormalities develop. In these cases, treatment is discontinued for 15 days and laboratory tests are repeated. If results are normalized, treatment is restarted.

CONTROLS IN THE PATIENT TREATED WITH ALBENDAZOLE FOR HYDATIDOSIS:

Prior to treatment:	Every 30 days before starting each cycle	Two months after treatment was started	At the end of therapy	Six and twelve months after finishing therapy
Laboratory*	Laboratory	Abdominal ultrasound	Abdominal ultrasound	Abdominal ultrasound
Chest X-ray	Medical control**	Medical control **	Medical control **	Medical control **

* Laboratory: complete blood count, creatinine, liver enzymes.
** Medical Control: check for intolerance, undesirable effects and/or occurrence of symptoms.

Albendazole is well tolerated in most patients. The most frequent adverse effect is an elevation of liver transaminases. As this drug is teratogenic and embryogenic in animals, its use should be avoided in pregnant women. It is also contraindicated in breastfeeding, epilepsy and chronic liver disease.



Surgical treatment will be indicated in asymptomatic patients with cysts:

a. who become symptomatic.
b. patients with asymptomatic cysts that grow significantly.
c. when frequent controls or albendazole therapy cannot be ensured by the healthcare system (which is usually the case with patients living in remote rural areas), especially if cysts are ›5-10 cm in diameter.

3

BIOSAFETY

BIO SAFETY

BIOSAFETY and personal protection measures are especially required in activities implying the handling of dogs and stools during surveillance activities.

Samples of feces should always be considered as potentially infected with EG eggs, so barrier personal protection measures should be taken and activities should comply with good laboratory practices to avoid infection and environment contamination. The use of personal protection equipment such as hat, glasses, gloves, masks, boots and gown is mandatory throughout the sampling process.

Special attention should be paid to personal hygiene practices, such as proper hand washing after work. Personnel should undergo ultrasound and/or serologic testing for hydatidosis diagnosis at least once annually [46].

In the lab, stool samples for coproantigen diagnosis are sterilized by freezing them at –80º C for 48 hr, or at –70º C for 4 days [46].

Contamination with EG eggs in stool samples may be eliminated by boiling for 5 min, using steam sterilization (autoclave) or ultra-freezing at -80°C for 2 days.

EG protoscolices and cyst germ cells inactivation may be achieved with heat, freezing and using some chemical agents, such as ethanol (40% or higher concentration) or formalin (4%). EG protoscolices as well as germ cells are usually eliminated by ultra-freezing (-20°C or lower) [46].

4

SOUTH AMERICAN INITIATIVE


IN
TIA
TIME

IN THE XIX INTERNATIONAL CONGRESS of the International Association of Hydatidology held in San Carlos de Bariloche, Río Negro, Argentina, in 1999, the Director of the Pan American Health Organization (PAHO) convened a working group which reviewed and analyzed experiences about perspectives and possibilities of control and eradication of hydatidosis.

Consequently, during the Inter-American Meeting at the Ministerial level on Health and Agriculture (RIMSA XII) held in Sao Paulo, Brazil, in May 2001, recommendations were given for the countries to continue strengthening the veterinary public health approach. Within this framework, PAHO convened the First Meeting of Directors of Hydatidosis Programs which was held in the Pan American Foot-and-Mouth Disease Center (PANAFTOSA), Río de Janeiro, Brazil, in October 2001 in which a document called "Plan of Action and Core Regional Strategies for the Elimination of Human Hydatidosis in South America" was elaborated.

Currently, the initiative gathers officials and scholars from Argentina, Brazil, Chile, Paraguay, Peru and Uruguay, under the umbrella of PANAFTOSA/PAHO-WHO Secretariat and with the technical cooperation of the International Association of Hydatidology. The main objective of the Initiative is the prevention, control and potential elimination of CE through advances in communication, health education, epidemiological surveillance coordination and control programs in the entire region [21, 47].

The inclusion of CE in the Plan of Action for the control of neglected infectious diseases for the period **2016/2022** recently approved in the 55th Meeting of the Directing Council of the Pan American Health Organization (Annex 1) implies support and guidance for the actions of the Initiative.

The initiative for the control of hydatidosis in South America offers an accessible and open online course with experts conferences about all the topics included in this Guideline, also including reference books.

- International Course on Echinococcosis/Hydatidosis (curso_hidatidosis@salud.rionegro.gov.ar)
- International Association of Hydatidology. Counseling and consultations aihwae2015@gmail.com

ANNEX 1

PAHO PLAN OF ACTION 2016-2022 FOR THE CONTROL OF NEGLECTED INFECTIOUS DISEASES

PLAN OF ACTION (2016-2022)

12. The general objectives and priorities of the Plan of Action, which can be reached through the strategic lines of action (see below), are to:

    a. Interrupt transmission of and eliminate eight neglected infectious diseases for which there are cost-effective tools: blinding trachoma, Chagas disease, dog-mediated human rabies, leprosy (as a public health problem), human taeniasis/cysticercosis, lymphatic filariasis, onchocerciasis (river blindness), and schistosomiasis.

    b. Prevent, control and reduce the burden of disease from five neglected infectious diseases for which there are integrated and innovative management tools: cystic echinococcosis (hydatidosis), fascioliasis, human plague, leishmaniasis (cutaneous and visceral) and soil-transmitted helminthiasis.

    c. Assess the regional epidemiological situation with respect to other neglected infectious diseases affecting groups living in vulnerable conditions, such as brucellosis, Buruli ulcer, ectoparasitic infections (e.g., lice, scabies, tungiasis), selected fungal infections, myiasis, strongyloidiasis, poisoning.

Objective	Indicator	Baseline (2016)	Target (2022)
6.1 Develop and implement actions to monitor and sustain the achievement of control and elimination of neglected infectious diseases in countries that have reached specific elimination goals	**6.1.1** Number of countries with endemic neglected infectious diseases that have achieved the goals of elimination of one or more of them and have put in place measures to prevent disease resurgence or reintroduction of Chagas disease, onchocerciasis, lymphatic filariasis, blinding trachoma, dog-mediated human rabies, or cystic echinococcosis (hydatidosis)	Chagas disease 9	Chagas disease 16
		Onchocerciasis 3	Onchocerciasis 6
		Lymphatic filariasis 3	Lymphatic filariasis 6
		Blinding trachoma 0	Blinding trachoma 4
		Dog-mediated human rabies 28	Dog-mediated human rabies 35
		Cystic echinococcosis (hydatidosis) 0	Cystic echinococcosis (hydatidosis) 3

5

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