The Significance (Socio-Economic Impact) and Control of Echinococcosis/Hydatidosis: A Review

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Abstract: Echinococcosis/hydatidosis is a cosmopolitan zoonosis caused by adult or larval (metacestode) stage of Cestodes belonging to the genus Echinococcus, family Taeniidae. At present, five species of the genus Echinococcus are regarded. These are E. granulosus, E. multilocularis, E. oligarthus, E. vogeli and E. shiquicus. Recently E. shiquicus had been discovered only in a specific region of the People’s Republic of China. Two major species of veterinary and public health importance are E. granulosus and E. multilocularis cause cystic echinococcosis (CE) and alveolar echinococcosis (AE) respectively. Unilocular hydatid disease (cystic hydatidosis) caused by the larval stage of E. granulosus is recognized as being one of the world’s major zoonosis. Carnivores are definite hosts for the parasite with livestock acting as intermediate hosts and human as intermediate aberrant host. It has both economic and public health significance and are associated with severe morbidity and disability. The pathogeneity of hydatidosis heavily depends on the extent and severity of the infection and the organ on which it is situated. The two most common involved organs are liver and lung. In livestock hydatidosis results in reduction of yield and quality of milk, wool, reduced birth rate, delayed performance and growth; condemnation of organs and possible indirect consequences such as ban of animal export and their products. Hydatidosis in humans is an infection which results in asymptomatic infection to fatal disease. It is well known that the main factor for the persistent of the disease is the feeding of hydatid cysts infested offals of ruminants to dogs. Breaking the life cycle is one of the main control measures. This however, largely requires awareness creation and public education.

Key words: Adama • Hydatidosis • Echinococcus species • Public health

INTRODUCTION

Echinococcosis/hydatidosis is one of the important parasitic diseases of livestock that has both financial and public health significance. It is associated with severe morbidity and disability. It is zoonosis caused by adult or larval (metacestode) stage of Cestodes belonging to the genus Echinococcus (family Taeniidae) [1]. At present, five species of the genus Echinococcus are regarded. These are E. granulosus, E. multilocularis, E. oligartthus, E. vogeli and E. shiquicus. Recently E. shiquicus had been discovered only in a specific region of the People’s Republic of China [2-4].

Two major species of veterinary and public health importance are E. granulosus and E. multilocularis that, cause cystic echinococcosis (CE) and alveolar echinococcosis (AE), respectively. Both CE and AE are serious and severe diseases, the latter especially so, with high fatality rates and poor prognosis if managed incorrectly. Unilocular hydatid disease or cystic echinococcosis (CE), caused by the larval stage of E. granulosus is recognized as being one of the world’s major zoonosis [5].

The distributions of E. granulosus is wider in developing countries especially in rural communities where there is close contacts between the dog, the definitive host and various domestic animals, which may act as intermediate hosts [6].

In Ethiopia, the status of hydatidosis in animals is not well documented and explored in the country. In some regions according to Jobre et al. [7] prevalence rate of 46.5%, 25.7% and 24.3% in cattle and 2.45%, 25.7% and
0% in sheep slaughtered in DebreZeit, South Omo and Gondar abattoirs, respectively were reported. Kebede et al. [8] found a prevalence of 34.05% and 10.6% in cattle and sheep, respectively in Bahir Dar. Ahmed et al. [9] found prevalence rate of 48.7% in cattle slaughtered in Adama Town municipal abattoir.

The pathogenicity of hydatidosis heavily depends on the extent and severity of the infection and the organ on which it is situated. The outcome of infection in livestock is hydatid cyst development in the lung, liver or other organs [10, 11].

The occasional rupture of hydatid cysts often lead to sudden death due to anaphylaxis, haemorrhage and metastasis [7, 12, 13].

The absence of proper meat inspection procedures and the presence of large stray dog population are thought to contribute significantly to the prevalence of the disease in Ethiopia. Hence, it is essential to pay a due attention to the disease and establishment of all possible control programmes are of major importance.

Therefore, the objective of this paper includes:

- Review the epidemiology of echinococcosis /hydatidosis
- Assessing control method employed to the control of echinococcosis /hydatidosis.

**Description of the Parasite**

**Taxonomy:** Echinococcus species and its metacestode hydatid cyst, belongs to the class Cestoda order Cyclophyllidea family Taeniidae and genus Echinococcus [14]. The genus *Echinococcus* has 5 species, which include *Echinococcus granulosus sensu lato*, *Echinococcus multilocularis*, *Echinococcus vogeli*, *Echinococcus oligarthrus* and possibly *Echinococcus shiquicus*. [2, 4, 15].

**Parasite Biology**

**Adult Parasite:** The adult *E. granulosus* inhabits in the small intestine of dog and wild canids. It is small tapeworm, measures 3 mm to 6 mm in length. It consists of head (scolex), neck and body (strobila). The scolex has 4 muscular suckers and two rows of hooks on the rostellum. The neck is short and thick; the body usually consists of three proglottids (segments). The first is immature segment the second mature segment and third terminal gravid segment. The terminal gravid segment is the largest and broadest and it contains several hundreds of eggs. This segment always bursts open before or after passage in the stool, to release hundreds of eggs (Fig. 1) [15, 16].

**Fig. 1: Adult stage of Echinococcus spp.**

**Source:** Parija, [16].

**Fig. 2: Metacestode of Echinococcus granulosus**

**Source:** Parija, [16].

**The Major Metacestodes (Larval Stages) of Echinococcus:** Hydatid disease is characterized by cyst containing numerous tiny protoscolices that most often develop in the liver and lungs and also develop in the kidneys, spleen, nervous tissue and bone and other organs. In humans, the disease is initially without any symptoms until gradually the cyst increased in size, causing local pressure effects. In animals, the disease does not produce any clinical signs and is usually only discovered during meat inspection at the slaughter house, where the affected organs (mainly liver and lung) are condemned [17]. Cysts are formed mostly in the liver and lungs. In *E. granulosus* large tubular hydatid occur, whereas in *E. multilocularis* a tubular system infiltrates the whole organ (giving rise to alveolar aspects in sections). In brood capsules of both cyst types protoscolices are formed, which may become evaginated even inside their cysts. Evaginated or not, protoscolices are fully capable of infecting final hosts when they feed on infected organs of intermediate hosts [18].
**Echinococcus granulosus (Cystic Echinococcosis):**

Unilocular hydatid disease, hydatidosis, caused by the larval stage of *E. granulosus* is recognized as being one of the world’s major zoonosis [6]. The definitive host of the parasite, *E. granulosus*, is dogs which harbor the adult parasite and excrete the parasite eggs along with their feces, while livestock and human are the intermediate hosts. Hydatid disease is characterized by cyst containing numerous tiny protoscolices that most often develop in the liver and lungs and also develop in the kidneys, spleen, nervous tissue, bone and other organs [17, 19]. The larva develops into a large cystic form or hydatid cyst, referred to as a unilocular cyst, which gives rise to unilocular hydatid disease in man. This is characterized as having only one bladder, or many completely separated bladders, each enclosed in its own well-developed envelope.

**Echinococcosis multilocularis/ Alveolar Echinococcosis:**

Alveolar Echinococcosis (AE) in humans is caused by a larval stage (metacestode) of *E. multilocularis*, which exhibits a tumor-like growth, initially in the liver, with the potential to induce serious disease. Red foxes are the principal definitive hosts of *E. multilocularis* and source of human infection, but dogs and cats can also be infected. Growing population of foxes and their increasing immigration to urban areas are new risk factors. Human alveolar echinococcosis (AE) is rare but its potential high fatality rate. It is characterized by a tumor-like proliferation which leads to infiltration of the affected organs, primarily the liver and in progressive cases to severe disease and even death. The larval cyst, referred to as an alveolar or multilocular hydatid cyst, which develops in man and animals, does not form a uniform, well-defined cyst (as in *E. granulosus*) but a multicystic structure made up of proliferating vesicles embedded in to a dense fibrous stroma, the whole resembling and often mistaken for hepatic sarcoma [16, 21].

**Eggs:** The *Echinococcus* eggs are excreted with faeces of the infected dog and are infective to man, sheep, cattle and other intermediate hosts. They are spherical in shape, brown in colour, measures 31-43 μm in diameter and consist of two layers, an outer thin wall and inner embryophore. Each egg consists of a hexacanth embryo with three pairs of hooklet (Fig. 4). The eggs are morphologically indistinguishable from those of *Taenia* species. Eggs may survive for several months in pasture, garden and on household fomites; survives in water and damp sand for 3 weeks at 30°C, 225 days at 6°C and 32 days at 10-21°C [14].

**Life Cycle of Hydatidosis/Echinococcosis:** The life cycle of these parasites involve carnivores as definitive hosts and food animals (cattle, sheep, goats, pigs and camel) and humans as intermediate hosts. The adult cestodes inhibit the small intestine of carnivores (definitive host) and produce eggs containing infective oncospheres. Either cestode segments, proglottids containing eggs or free eggs are released from the intestinal tract of the carnivores into the environment [22]. Man and animals become infected by consuming faecal eggs containing water, or food stuffs or from handling infected dogs. The eggs hatch in the intestine and the released oncosphere penetrate the mucosa. On entering a mesenteric venule or a capillary, oncospheres are transported to and trapped largely in the liver, but may reach and develop in any of the viscera leading to the formation of cyst. The final host, dogs and other canids, acquires infection by ingestion of hydatid cyst containing fertile cyst present in the intermediate hosts. In the small intestine protoscolices envaginate, penetrate deep between villi and enter crypts of liberkhun [16]. The wide spread tradition of offering un-cooked infected offals to pet animals around home stead, poor public awareness about the diseases, the absence of proper fencing and disposal pits for slaughter houses (where dogs and other...
carnivores get an easy access) and the habit of disposing dead wild or domestic animals, unburied and left open for scavenging carnivores creates favorable condition for an environmental contamination by maintaining the life cycle of echinococcosis in stray dogs and wild carnivores [22].

**Epidemiology, Transmission and Geographic Distribution:** Dog plays a major role in the epidemiology of the disease. As it is known dog lives in close quarters with man, feeding on scrapes, on the offal of wild herbivores hunted by his master or domestic herbivores for butchering. [23]. Dogs infected with echinococcosis tape worms pass eggs in their faeces and humans become infected through faecal-oral contacts [1]. Indirect means of contact via soil, water and contaminated vegetables, or through the intermediary of flies and other arthropods, may also result in human infections. Eckert *et al.* [24] described that the disease has a worldwide distribution and is found in all continents i.e. temperate, tropical and sub tropical with the highest prevalence is found in parts of Eurasia, Africa, Australia and South America. Within the endemic zones, the prevalence of the parasite varies from sporadic to high, but only a few countries are considered as free of *Echinococcus granulosus* [24]. Morar and Felman, [25] indicated that considerable public health problems are encountered in endemic areas and most cases of the disease in the USA and Central Europe in immigrants from endemic countries. With the exception of Turkana in Kenya, the Mediterranean Basin is the largest and most focus of human and animals hydatidosis with regard to incidence in human veterinary medicine [23].

Gemmel *et al.* [26] pointed out that the parasite population, which consists of three sub-populations namely the adults in the definitive hosts, larva (metacestodes) in the intermediate host and eggs in the environment, play important role in the stability of the disease and therefore the contributions made by each segment of the parasite population need to be thoroughly understood.

The highest prevalence of hydatid disease in the world occurs in Kenya where unusual conditions prevail, in that the Turkana tribe traditionally has a very close association with dogs. Most households keep a dog which they utilize to lick clean their babies after defecation. A further factor is that human dead bodies (Which may contain hydatid cysts) are often buried in shallow graved in the bush where they may be scavenged by dogs or wild carnivores [5].

The highest human incidence rate of CE is found in areas where the greatest numbers of sheep are kept [27]. Schantz, [28] indicated that socio-economic and cultural

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**Fig. 5:** Life cycle of *Echinococcus* spp. Source: [16].
characteristics, uncontrolled slaughter of livestock and insanitary living condition and uncontrolled dogs living closely with people are among the best defined risk factors for human infection.

In Ethiopia, the status of hydatidosis both in humans and animals is not well documented and explored. In Southwestern Ethiopia (e.g. Borena and Hamer) CE is prevalent among transhumant pastoralists [29]. The incidence of hydatid disease slaughtered in various parts of the country has been reported by many individuals, which ranges from 21.1% in Addis Ababa to 75.1% in Gonder [30, 31, 32]. The variation in prevalence rate in different regions may be attributed to difference in culture, practice of back yard slaughtering coupled with provision of infected offal to dogs, social activities and other related factors [8].

Human hydatidosis in Ethiopia is very well known that hydatid disease is becoming a problem of human concern throughout the world. But in Ethiopia information and compile data is lacking in most hospitals and health centers due to the absence of well equipped diagnostic facilities, asymptomatic and chronic nature of the disease. However, based on community base survey for CE, during 1987 in Southwest Ethiopia 1970 people were screened with ultrasound and 31 CE cases were detected with prevalence of 1.6%. In addition, 3224 persons were screened with ultrasound survey in Southern Ethiopia and 16 (0.5%) were positive for CE in 1996 [24].

Pathogenesis: Depending on the mode of development CE is of two types, primary CE and secondary CE. Primary CE occurs after per oral infection with *E. granulosus* egg which gives rise to hydatid cyst in different parts of the body while secondary CE occurs by rupture of primary hydatid cyst due to trauma. In this condition the protoscolices are carried by the blood to different body parts and develop into secondary hydatid cyst [16]. Calcification can occur in pericyst, mother cyst and daughter cyst. Calcification of endocyst indicates the cyst is non viable. However, calcification of pericyst is found in one third of cysts and occurs in all stages of cyst development [33].

During natural course of infection some cysts may grow to certain size and continue to remain so without producing any pathological change for many years. Other cysts may rupture spontaneously or collapse and disappear completely [16]. Pressure effect by cyst may develop in sensitive areas. Hydatids may cause blocking effect and mechanical compression leading to collapse of infected bones, blindness, rupture of cyst induce sudden anaphylactic shock [24].

Clinical Manifestations: Dogs and other definitive hosts may have thousands *Echinococcus* tapeworms in their intestine without developing signs of infection. Rarely there may be diarrhea [33].

Sheep and other intermediate hosts with hydatid cysts are indistinguishable from uninfected animals (no obvious signs). However, the results of some studies have shown that infection can reduce meat, milk and wool production. Sometimes depending on localization of cyst the following signs can be seen bronchopneumonia, hepatic disorder leading to ascites and jaundice, heart failure, slow growing, weakness and lameness [21].

In humans the clinical manifestation depends on the site of organ involvement, organ involved and size of the cyst, stage of cyst development and viability of cyst contents. The majorities of cysts produce no symptoms and are detected as incidental finding on routine imaging or at autopsy (surgery). Symptoms are related to expanding mass, pressure on adjacent structure, infection and rupture of cyst contents in to surrounding body cavity [33]. Accidental rupture of cysts can be followed by massive involvement of cyst fluid and dissemination of protoscolices, resulting occasionally in anaphylactic reaction and or multiple secondary CE [34].

The incubation period is highly variable, the cyst may produce clinical symptoms even 5 years to 20 years after infection when it attains sufficient size to cause disturbances by mechanical pressure on surrounding tissue. The cysts situated in vital organs interfere with the function of the affected organ [16]. Hydatid cyst of the liver causes hepatomegaly with or without palpable abdominal mass, the condition is associated with abdominal pain, nausea and vomiting, portal hypertension and biliary peritonitis [16]. Intact hydatid cysts in the lung often cause no symptom. However, a large cyst may cause pressure symptoms and lead to cough and haemoptysis. Complication arise when cyst rupture either in to bronchial tree or pleura and may cause allergic reaction including an aphylaxis, pleural effusion, emphysema [33].

Importance of the Disease

Veterinary Health and Financial Losses: The importance of echinococcosis is mainly due to its impact on the animal production and economic losses due to disability and death and losses from costs of applying control. The reduced yield and quality of meat, milk and wool, reduced birth rate, delayed performance and growth condemnation of organs, especially of liver and lung. Costs for destruction of infected and dead animals, ban on export of animals and their products and cost of control.
Losses in sheep with echinococcosis have been reported to approximate 7%-10% of milk yield, 5%-20% of meat or total carcass weight and 10%-40% of wool production. Researchers estimated that birth weight of lambs from infected sheep may be 20%-30% less than that of lambs from healthy sheep. The financial impact in domestic food animals due to condemnation of offals in local abattoir in Chile between 1983-1988 (liver and kidney) alone were valued USD 6,364,563 [35]. With respect to a reduction in the production of milk studies in Sardinia may amount to a loss of 20,075 billion litres per annum [26].

Public Health Importance and Financial Losses: Cystic echinococcosis (CE) in humans is an infection, which is caused by larval stage, the metacestode of Echinococcus species and may result in asymptomatic infection to severe disease, which may be fatal. The metacestode all five recognized Echinococcus species can infect humans and cause varies forms of the disease. Among these forms CE caused by Echinococcus granulosus and alveolar echinococcus (AE) caused by Echinococcus multilocularis are of special importance [34].

Echinococcus granulosus following primary infection may inhibit many anatomic sites. The two most common organs involved are liver (65%) and lung (25%) other less common sites affected by cysts include the muscle (5%), spleen (1%), bone (3%), kidneys (2%), heart (1%) and CNS (1%). The majorities of patients have single organ involvement (18.7%) and harbor solitary cyst (72%) [33].

The presence of hydatid cyst in liver, lung and other organ can lead to varied clinical manifestations such as:

- In the liver: Tumor, hepatomegaly, cholestasis, jaundice, secondary biliary cirrhosis, biliary colic like symptoms, liver abscess, calcified lesions in the liver, portal hypertension and thrombosis.
- In the lung: Lung tumour, chest pain, chronic cough, dyspnoea, haemoptysis, pneumothorax, pleuritis and lung abscess.
- In the heart: Pain, tumour, cardiac insufficiency and embolism.
- In the bone and muscles: Pain, bone out growth, bone fragility, muscle cyst.
- In the brain and spine: Head each, tumour with neurological symptoms and back pain.
- In the eyes: Pain, ptosis and visual disturbances [36].

Cyst rupture in the liver to the biliary tree leads asthma like symptoms, coughing, dyspnoea and haemoptysis, fever [36]. The socio-economic consequences of echinococcosis in human is mainly due to:

- Cost for diagnosis of the infection. Medical and surgical fees and costs of hospitalization nursing and drugs. Loss of working days or “production”. Cost of travel to seek treatment for both patient and family members. Mortality (potential years of life lost). Suffering and social consequences of disability. Abandonment of farming or agricultural activities by affected or at – risk persons. Costs of control programs [26].

Diagnosis: In dogs diagnosis can be made based on detection of eggs and proglottids in the faeces. Definitive diagnosis to the species is difficult because eggs of all Echinococcus and Taenia species are morphologically indistinguishable and characteristic small segments of Echinococcus species may be absent from faeces or can be easily over looked. Purgation with arecoline hydrobromide and necropsy of small intestine has been extensively used for diagnosis in dogs. Immunodiagnosis/coproantigen test based on faecal antigen detection, antibody sandwich ELISA can be used with 70% and 98% sensitivity and specificity, respectively [4].

Diagnosis of CE in livestock is mainly based on necropsy findings. Clinical symptoms may frequently be overlooked. Ultrasound examination for cystic structure may be used for diagnosis in small animals. In Kenya, ultrasound examination of lung and liver was used for detecting hydatid cyst in sheep and goats, sensitivity and specificity were 54% and 97% respectively. Immunological tests can be tried with various sensitivity and specificity [36].

Diagnosis of CE in humans can be done by microscopic examination of aspirated hydatid fluid specimen to demonstrate brood capsule and protoscolices (hooks), but aspiration is not recommended because of danger of spillage viable protoscolices. Occasionally protoscolices may be demonstrated in urine, bile, stool or sputum by acid fast staining after rupture of cyst in liver, lung or kidney [16].

Serological tests detect specific serum antibodies or circulating antigens by various methods. Currently indirect hemagglutination antibody (IHA) and double diffusion immunoelectrophoresis tests are frequently used with variable sensitivity and specificity [37]. ELISA employing hydatid fluid antigen for detection of
echinococcus antibody (IgG) in serum is most widely used. This test has sensitivity of 80-100% and specificity of 88-96% in hepatic cyst. However, sensitivity of this test is around 50-60% in pulmonary cyst and 25-26% in cysts involving other organs [33].

Casoni skin test is an immediate hypersensitivity skin test performed in injecting 0.2 ml of sterile hydatid fluid intradermally in one arm. Sterile normal saline (0.2 ml) is injected on other arm as control. Development of large wheal greater than 5 cm in diameter indicates positive reaction but with limited diagnostic value due to low sensitivity and specificity (55-75%) [16].

Imaging to detect hydatid cyst, plain radiography (x-ray) has role in lung and bone cysts [33, 36]. Ultrasonography-abdominal cysts, particularly in the liver and cysts in soft tissue are well visualized by ultrasound [33, 37]. In epidemiological studies ultrasound used to study prevalence of CE in population [16].

**Treatment:** In the definitive host the choice of drug is praziquantel and purging with arecoline hydro bromide is possible [38].

In the intermediate domestic animals promising results were obtained with anthelmintics benzimidazole group (albendazole and mebendazole). At present no routine treatment of domestic animals against CE since application of benzimidazole in effective dosage would be too expensive. Trials with benzimidazole in sheep and pig have only been carried out using mebendazole administered daily at 50 mg/kg for up to 3 months. Praziquantel has also been tested for hydatid cyst in animals but results were discouraging [36].

In humans surgery is the treatment of choice in large hepatic cysts with multiple daughter cysts, subcapsular or pedunculated liver cyst, infected liver cysts, cysts communicating with bile ducts and cysts in lungs, brain, kidney, bone and other organ [33].

Chemotherapy with albendazole given orally at a dose rate of 10 mg/kg body weight daily in two divided doses for minimum of 3 months and mebendazole given orally at a dose rate of 400-600 mg thrice daily for 21 days to 30 days are effective against CE, have scolicidal activity [16].

Praziquantel administered at dose of 40 mg/kg once a week concomitantly with benzimidazole has shown to increase scolicidal activity of imidazoles [33].

Chemotherapy is effective in smaller cysts (less than 4 cm in diameter), cysts with thin wall and in younger patients. It is indicated in patients who are at high risk of surgery, in patients with multiple peritoneal cysts after spillage during surgery and as concomitant therapy with percutaneous drainage [33, 36].

PAIR (Puncture, Aspiration and Installation of scolicidal agent and Reaspiration) is the treatment of choice in patients with hepatic hydatid cyst who either refuse surgery or have significant co-morbid disease. The procedure is minimally invasive, cost effective; reduce hospital stay and less morbidity and mortality than surgery [33].

**Control Measures:** Control of hydatidosis is less effective without the support of dog owners and this support can only be contained if the people have clear understanding of the life cycle of the hydatid disease.

The following are important measures for the control preventing access by dogs to uncooked organs of livestock and dead human body, removal of unwanted dogs (or stray dogs), regular treatment of dogs with praziquante, persecution of illegal slaughtering, movement control of dogs and food animal, changing animal husbandry practices to limit the number of old animals, vaccinating sheep and goats (Eg 95 vaccine), education and surveillance, avoidance of intimate contact with dogs, monitoring control changes in age/ incidence of new human infections and the statistics of the parasite in slaughtered live stock [39, 40].

Public education program educate hotel owners and other citizens to have their animals slaughtered in slaughter house. Educate and convey message to people (farms, children) that infected dogs present danger to human population and livestock and prevention of infections in dogs.

Slaughter houses facilities should have properly trained meat inspector, dog proof fencing and have adequate, deep and wide disposal pits.

Meat inspections and effective disposal of offal at abattoir and prevention of clandestine leakage of offals, banning dogs form abattoir and closure if necessary, prevention of feeding raw offal to dogs including inspection of offal disposal facilities on farm or other premises where live stock are killed, control of dogs including registration and elimination of unwanted (stray) dogs and quarantine of premises with infected livestock.

**CONCLUSION**

The wide spread tradition of offering uncooked infected offals to pet animals around homestead, poor
public awareness about the diseases, the absence of proper fencing and disposal pits for slaughter houses (where dogs and other carnivores get an easy access) and the habit of disposing dead wild or domestic animals, unburied and left open for scavenging carnivores creates favorable condition for environmental contamination by maintaining the life cycle of *Echinococcus granulosus* in stray dogs and wild carnivores. Echinococcosis is zoonosis whose successful control and resulting reduction of socio-economic impact demand continuous resources and activities in long term, specially because it is often necessary to influence habits, customs, traditions, cultures and living working environment which cannot be changed in short time.

In order to formulate and implement feasible control program and reduce the economic and public health impact caused by the disease strong continual commitment and the collaboration of several professional categories such as veterinarians, physicians, public health personals, teachers, polices, wildlife attendants, waste disposal personals, dog owners and community leaders and public administrators is recommended.

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

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