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Problems and Perspectives Related to Cystic Echinococcosis in Pakistan: Solutions in One Health Context

AUTHORS DETAIL

Hira Muqaddas[1], Naunain Mehmood[2,3*], Fahad Ahmed[3], Madiha Fatima[1], Madiha Rasool[1], Saba Zafar[4], Amina Riaz[5] and Muhammad Nauman[2]

[1]Department of Zoology, The Women University Multan, Multan, Pakistan
[2]Department of Zoology, University of Sargodha, Sargodha, Pakistan
[3]Department of Veterinary Medicine, University of Sassari, Sassari, Italy
[4]Department of Biochemistry and Biotechnology, The Women University Multan, Multan, Pakistan
[5]Department of Pharmacy, The Women University Multan, Multan, Pakistan
*Corresponding author: naunain.mahmood@uos.edu.pk

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INTRODUCTION

Pakistan is an endemic region for cystic echinococcosis (CE) which is a disease of economic and health concern for both animals and humans. Echinococcosis, also known as hydatidosis, is one of the major neglected tropical diseases (NTDs; WHO 2019) having endemicity to regions with prominent pastoral activities (Craig et al. 2015). NTDs impact lives of over 1 billion people in low- and middle-income countries having limited surveillance capacities (Rai 2022). Currently, Pakistan bears high global burdens for seven major NTDs (Herricks et al. 2017). CE is ranked as 4th most widespread helminth disease in Pakistan (IRD 2017) with 20,500 identified human cases (Herricks et al. 2017). Being an agricultural country and hosting a large rural population, 113 million people of Pakistan are at risk, and one of the largest agrarian communities in danger of getting CE and other infections (Zhang et al. 2015).

Life Cycle of *Echinococcus granulosus*

Cystic echinococcosis is caused by larval stages of a tapeworm species, *Echinococcus granulosus*, which has cyclozoonotic pattern between different intermediate (domestic animals and humans) and definitive hosts (dogs) (Thompson et al. 2017). The dogs take up the parasite while ingesting contaminated offal containing hydatid cysts with viable protoscoleces (PSCs). Upon reaching the digestive tract of the definitive host, PSCs evaginate in upper duodenum after exposure to high stomach temperature in presence of pepsin and bile salts. Each protoscolex has the ability to develop into a mature tapeworm. Mature tapeworms release the embryonated eggs which are either passed into feces separately or through disintegration of terminal proglottid from the tapeworm body (Craig et al. 2003). Eggs are ingested by a suitable intermediate host (sheep, goat, cattle, buffalo, camel, horse) which harbors the hydatid cysts/metacestodes (larval stage) developing in main visceral organs like liver and lungs (Romig 2003). Humans also become accidental hosts after ingesting eggs of *E. granulosus* via contaminated water or food (Ito et al. 2017). Fig. 1 outlines different life cycle stages of *E. granulosus* in the intermediate and definitive hosts.

Human Cystic Echinococcosis

Humans acquire the infection by accidental exposure to eggs of the parasite. Farming and nomadic communities, having close contact with dogs are at the highest risk of infection. Human CE is usually asymptomatic and does not cause major identifiable pathologies and remains unnoticed for years until the active cyst grows large enough to exert pressure on the adjacent tissues or induce other pathological events (Eckert et al. 2001). Clinical symptomatology is highly variable, with no disease specific symptoms, largely depending on size, number and location of cyst (Moro and Schantz 2009). Usually, 38 to 60% cases are asymptomatic and accidentally diagnosed during other medical examinations (Kern 2003). Generally, patients show fever, high abdominal pain and signs of allergic reactions (Budke et al. 2013). If the liver is affected, hydatid cyst can compress the bile duct resulting in obstructive jaundice, allergic manifestations and abdominal pain (Pakala et al. 2016). Clinical manifestations associated with pulmonary cysts include chronic cough, pleuritic chest pain, dyspnoea, haemoptysis and lung abscesses (Eckert et al. 2001; Kern et al. 2017). In pulmonary CE case patient may expel remnant of hyaline membrane of ruptured cyst (Ramos et al. 2001). Symptoms and signs in atypical sites are usually pain and tumor like growth (Eckert et al. 2001).

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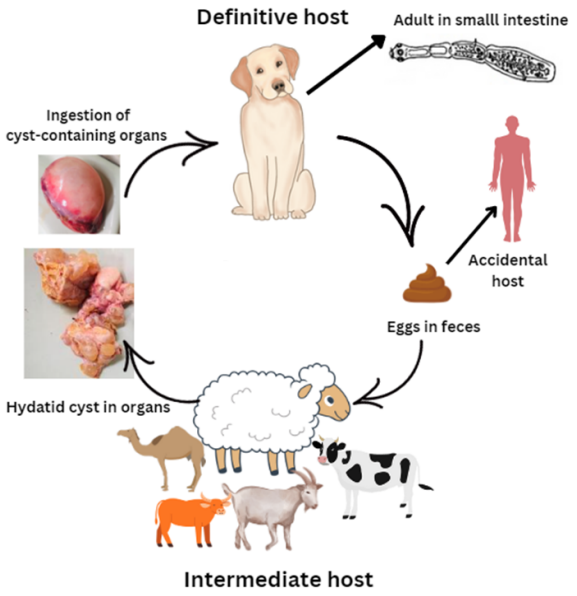

Fig. 1: Life cycle of *E. granulosus* responsible for causing cystic echinococcosis.

Cystic Echinococcosis in Livestock in Pakistan

Pakistan is the focal point for presence of *E. granulosus*, however, due to limited number of studies, the endemic situation is underestimated (Zhang et al. 2015). In Pakistan, large rural population is specially at risk due to multiple soil transmitted helminths (STHs) because of poverty, hygiene, illiteracy, poor knowledge about diseases, malnutrition, environmental degradation and security issues (WHO 2013; Blum et al. 2018). *E. granulosus* is spread all across Pakistan and in all livestock species. Apart from rural areas, urban and peri-urban localities are also at risk and there is an upward trajectory of CE in Pakistan (Haleem et al. 2018; Khan et al. 2018, 2020). Karachi and areas near Afghan border, Northern Punjab and Khyber Pakhtunkhaw (KP) are at the highest risk of contracting this disease (IRD 2017). Sindh province has also high burden of hydatidosis due to significant economic losses among livestock (Anwar 1994). Fig. 2 manifests the hydatid cysts (metacestodes) in livers and lungs of the livestock species.

CE was reported for the first time in Pakistan in 1953 by Lubinsky (1959) at Rawalpindi reporting high prevalence of 15.4%. During the subsequent years, several studies have been carried out reporting differential rates of prevalence of CE in the livestock of Pakistan (Khan et al. 2020) with highest number of studies from Punjab. Prevalence as high as 60.46% has been reported in buffaloes slaughtered at urban slaughterhouses of Punjab (Shahzad et al. 2014). A comparative picture on prevalence of CE in Pakistan among different domestic ungulates is depicted in Table 1. Lack of proper sanitation, health and education facilities also correspond to making livestock a suitable reservoir for *E. granulosus*. Moreover, economic and health conditions in the country are relatively poor compared to the developed economies of the world which further elevate the risk of hydatidosis transmission (Mehmood et al. 2020a).

Human Cystic Echinococcosis in Pakistan

The actual burden of human CE on economy is not estimated in Pakistan. The prevalence figures are inaccurate due to the lack of reporting and improper identification. Accurate estimate of incidence and prevalence of CE is always difficult because of asymptomatic nature of the disease. Additionally, access to medication and surgical interventions remains limited for most of the people in Pakistan. Rough estimate of the incidence can be given by hospital admissions/discharge data and number of cases tested at the reference laboratories (Muqaddas et al. 2019).

Risk Factors for Cystic Echinococcosis Prevalence

Frequency and intensity of CE is influenced by a number of factors operating at both the definitive host and intermediate host levels.

a- Risk factors for definitive hosts for cystic echinococcosis infection

There are around three million stray dogs in Pakistan which play a very crucial role in the continuation of life cycle of *E. granulosus* and high rate of infection among the domestic animals. Access of dogs to infected and uncooked offal, animal slaughtering locations, open butcher shops and extensive livestock farming are the major determinants favouring disease perpetuation in Pakistan (Mehmood et al. 2020a). Free roaming and stray dogs are at more risk of getting infected by *E. granulosus* eggs than to other types of dogs (Otero-Abad and Torgerson 2013). Similarly, high infection rates are reported for farm dogs living in close vicinity to the livestock (Pérez et al. 2006; Guzel et al. 2008). The dogs from rural areas have higher prevalence of *E. granulosus* (30%) than those from urban areas (18%) (Chaâbane-Banaoues et al. 2016). Younger age group and male gender of dogs are more prone to infection (Parada et al. 1995; Buishi et al. 2005). Socio-economic background of dog owners is also an infection determinant in definitive hosts as lack of knowledge on disease transmission and deficiency in deworming and anthelminthic treatment is related to high infection pressures in dogs (Buishi et al. 2005; Huang et al. 2008).

b- Risk factors for intermediate hosts for developing cystic echinococcosis infection

Epidemiology of animal echinococcosis relies primarily on the mode of transmission of the disease (Otero-Abad and Torgerson 2013). Predominantly extensive livestock

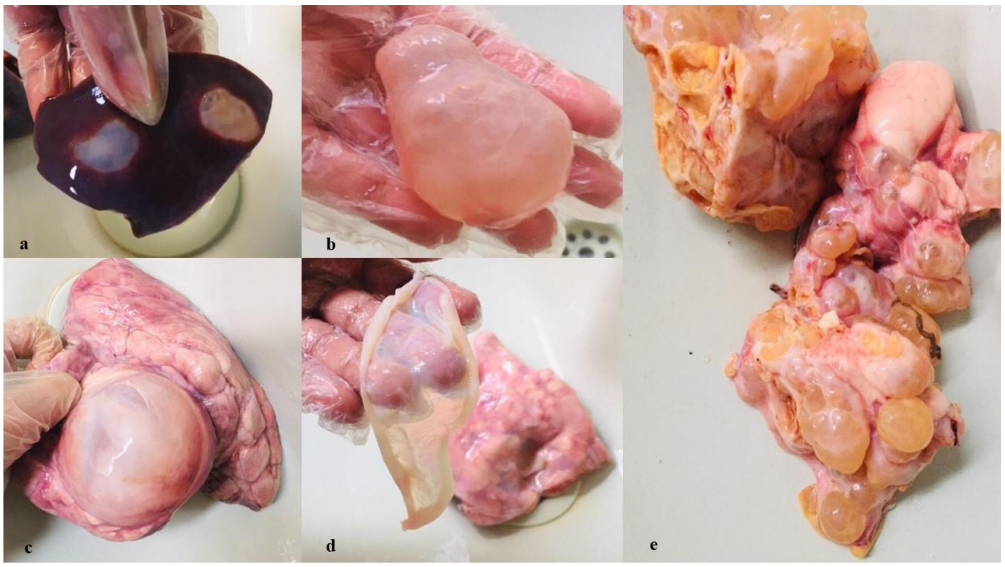

Fig. 2: Cystic echinococcosis in animals. The blocks show: a) hydatid cysts in the liver b) individual hydatid cyst c) hydatid cyst in the lungs d) germinal layer of hydatid cyst e) multiple hydatid cysts in the lungs.

Table 1: Disease prevalence among the livestock (intermediate hosts) from different geographical areas of Pakistan

Province	City	Prevalence (%) in domestic ungulates				Reference
		Sheep	Cattle	Buffalo	Goat	
Punjab	Rawalpindi	4.6	15.4	-	2.1	Lubinsky 1959
	Faisalabad	-	35	-	-	Anwar 1994
	Rawalpindi	-	38.90	33.06	-	Khan et al. 1990
	Lahore	-	6.43	-	-	Khan et al. 2010
	Chakwal	8.55	8.42	6.90	2.99	Khan et al. 2018
	Lahore	11.36	-	-	7.77	Iqbal et al. 2012
	Lahore	8.3	9.6	12.3	7.5	Khan and Haseeb 1984
	Lahore	-	27	35	-	Sheikh and Hussain 1968
	Lahore, Jhang, Okara	20	45.45	60.46	20	Shahzad et al. 2014
	Lahore, Gujranwala, Gujrat, Faisalabad, Sheikhupura, Pakpattan	7.52	5.18	7.19	5.48	Latif et al. 2010
	Sargodha	3.24	2.44	-	2.44	Mustafa et al. 2015
	Lahore, Rawalpindi, Multan, Sargodha	8.99	9.13	9.49	3.58	Mehmood et al. 2020a
Khyber Pakhtunkhaw	Peshawar, Swabi, Bannu, Charsadda, Mardan, Swat, Laki Marwat, Nowshera, Karak, Kohat	15.38	15.79	15.88	3.25	Haleem et al. 2018
Balochistan	Peshawar	21.73	11.39	19.07	3.57	Mehmood et al. 2020a
	Quetta	31.1	-	-	21.1	Ahmed et al. 2006
	Quetta	25.00	-	-	7.93	Mehmood et al. 2020a
Sindh	Larkana	-	-	24.4	-	Mirani et al. 2002
	Larkana	10.6	-	-	10.02	Surhio et al. 2011
	Hyderabad	-	-	13.46	-	Ehsan et al. 2017
	Larkana	16.66	6.05	24.40	3.27	Mehmood et al. 2020a

production systems, traditional animal husbandry practices, nomadism and uncontrolled animal movements favor the occurrence and endemicity of the disease (Dakkak 2010). Principal factors promoting disease among domestic animals are the extent of contamination in environment by parasitic eggs and age of the intermediate host (Otero-Abad and Torgerson 2013). More cyst abundance is observed in older farm animals (Tashani et al. 2002; Umur and Kaaden, 2003; Erbeto et al. 2010). Sheep and goats of 3 years or older are at 1.6 times more risk to CE infection than the younger animals (Marshet et al. 2011). Certain other factors complementing disease dispersal are gender (Daryani et al. 2007; Ibrahim 2010) and type of livestock species (Cardona and Carmena 2013). Females are at high risk of disease contraction due to slaughtering at old age which increases the exposure to parasitic infection (Pour et al. 2012; Otero-Abad and Torgerson 2013). Animal echinococcosis is more frequently seen in small ruminants which show higher infection rates compared to large animals. Sheep are more vulnerable to *E. granulosus* infection than goats and cattle (Erbeto et al. 2010; Marshet et al. 2011), however it is important to note that buffaloes and sheep are the key hosts in CE epidemiology in Pakistan (Mehmood et al. 2020b). Additionally, cattle could also be considered to have prominent role in disease spread as South Asian clime offers a suitable environment for development of *E. granulosus* besides harboring a large

Fig. 3: Risk factors for perpetuation of cystic echinococcosis in Pakistan.

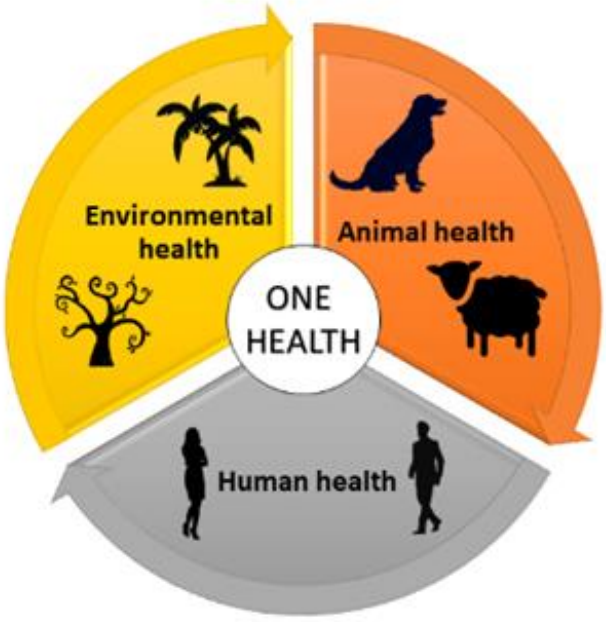

Fig. 4: One Health concept unifying human, animal and environmental health

population of buffaloes and cattle (Mehmood et al. 2022). Livestock infection is also modulated by meteorological conditions like humidity and environmental temperature, however, seasonal differences in prevalence (Mehmood et al. 2020a) are of negligible importance due to chronic nature of the disease (Otero-Abad and Torgerson 2013). Fig. 3 highlights the possible risk factors responsible for spread of cystic echinococcosis in Pakistan.

Risk Factors for Human Cystic Echinococcosis

A sound understanding of the risk factors associated with human CE is essential for reducing the disease incidence (Possenti et al. 2016). Chances of disease increase in pastoral and nomadic communities which live in close association with dogs having low socioeconomic status. Human hydatidosis is a public health problem of rural communities. A study from Sindh and Punjab concluded that people associated with farming and aging between 21-30 years were at more risk of contracting the disease (Muqaddas et al. 2020). Transhumant movement of people, along with their livestock can aid in the transfer of CE in both animals and humans (Eckert et al. 2001). Limited access to health care facilities and using contaminated water sources due to low socio-economic status results in high incidence of CE (Barnes et al. 2017). All these putative factors could play their role in transmission modalities of hydatidosis particularly in rural areas with limited resources. Due to lack of resources and poor infrastructure of slaughterhouses, eradication of zoonotic echinococcosis is extremely difficult to achieve (Maudlin et al. 2009).

Problems Linked to Diagnosis of Human Cystic Echinococcosis

Preoperative diagnosis of human CE is reliant on imaging techniques including ultrasound imaging (US), computed tomography (CT), magnetic resonance imaging (MRI) and radiography and serological methods including enzyme linked immunosorbent assay (ELISA), latex agglutination, direct heamagglutination and immune electrophoresis (Hernández-González et al. 2018) whereas, histopathological diagnosis confirms hydatidosis at the postoperative stage. IgG ELISA (anti-*Echinococcus* serum antibodies) is a readily available technique but often fails to diagnose CE as it does not have desired specificity and sensitivity (Craig et al. 2007). IgG antibodies detection may sometime give false-negative results as reported for 20% cases of hepatic cysts and 40% of the pulmonary cysts (Eckert et al. 2001). Calcified cyst or cysts from brain or eye usually give low or no antibody titre. Similarly, false positive results have been documented from individuals having other helminthic diseases (Eckert et al. 2001) due to cross reaction (Brunetti et al. 2010). Though imaging techniques are commonly the primary approach for CE diagnosis, but often lead to misdiagnosis or misjudgement, when hydatid cyst is localized at atypical sites or presents confusing lesion features (Shang et al. 2019). Due to misdiagnosis, relapse or metastasis of echinococcosis after the surgery is also documented (Kern et al. 2017).

Problems Linked to Treatment of Human Cystic Echinococcosis

Human CE is complicated to treat as in some cases cyst remains asymptomatic for over 10 years (Frider et al. 1999). WHO advocates stage based therapeutic approach based on cyst characteristics and available medical facilities. The method of treatment includes four approaches i-e

chemotherapy, percutaneous methods, surgery and wait and watch strategy (Brunetti et al. 2010). Despite the importance of surgery, medicosurgical approach is gaining wide spread acceptance (Craig et al. 2007). Chemotherapy involves treatment with benzimidazole carbamtes (mebendazole and most commonly used albendazole) which kills the whole metacestode stage whereas praziquantel has a substantial effect on protoscoleces (Kern 2003). Both anthelmintic drugs have broad spectrum action and show symptom alleviation. Chemotherapeutic treatment often reduces the internal pressure by softening the cysts which can be later removed/excised easily during surgery (Pawlowski et al. 2001). Patients receiving albendazole and praziquantel prior to surgery have reported nonviable protoscoleces in comparison to the patients receiving only albendazole. Albendazole interacts with eukaryotic β-tubulin (cytoskeleton protein) by inhibiting its polymerization to microtubules. Cyst glycogen reserves start to drain (as a secondary effect), bringing degenerative changes in mitochondria and endoplasmic reticulum of germinal layer of hydatid cyst which leads to cellular autolysis (Scholar and Pratt 2000). Commonly used surgical interventions are partial or total cystectomy and organ resection such as lobectomy depending upon the nature of cyst. There are 2-25% chances of relapse in postoperative cases (Eckert et al. 2001). Puncture-Aspiration-Injection-Re-aspiration (PAIR) technique is commonly used to aspire hydatid fluid (HF) form the cyst of CE patients (Smego et al. 2003). Clinical outcome can be improved by combination of chemotherapy and medical treatment (Kern et al. 2017).

Cystic Echinococcosis Associated Economic Losses and Socioeconomic Burden

According to an estimate, globally 1 million or more individuals are suffering from CE and livestock sector is facing annual loss of 2 billion US $ due to *E. granulosus* infection (Torgerson and Macpherson 2011). Hydatidosis has become serious economic burden for resource-poor low-income countries like Pakistan. Public health spending (US $ 36.2 per capita) in Pakistan is even below the WHO low-income countries bench mark of 86 US $ (PES 2017-2018). Clinical diagnoses, surgical operation, long-term chemotherapy by albendazole along with chronic impairment of patients' quality of life are the main factors for the socioeconomic cost of the disease. CE is not only a significant burden for family of infected individual, but also for the community as a whole (Torgerson 2003).

Health surveys are important to assess the mental and physical health state of CE infected person in comparison with a control population. Surgically treated patients for CE report significant decrease in their quality of life (Torgerson and Dowling 2001), along with considerably higher unemployment rate (Torgerson 2003). CE burden on human population is estimated by calculating monetary losses and disability adjusted life years (DALYs). Direct monetary losses due to CE include costs of diagnostic tests, surgery and postsurgical care and treatment (Mastrandrea et al. 2012; Kern et al. 2017) whereas indirect costs are related to lost wages as a result of reduced competence to work during and after hospitalization (Harandi et al. 2012). Human CE is responsible for 19, 300 deaths worldwide and around 8,71,000 disability adjusted life years per annum where one DALY can be thought of as one lost year of healthy life (WHO 2019).

Due to asymptomatic nature of CE (Brandt et al. 2003) its economic impact is substantially underestimated (Budke et al. 2006). However, in Pakistan the estimation of actual losses is difficult because of lack of identification and under-reporting in both humans and livestock. Incidence rates are difficult to determine because of large number of asymptomatic cases which go unnoticed providing only rough estimates based on information from testing laboratories and hospital admissions data (Muqaddas et al. 2019). Lost wages, treatment costs and production losses in livestock (condemnation of viscera and significant decrease in fecundity, milk production, hide value and carcass weight) are a few major economic losses associated with cystic echinococcosis (Torgerson 2003).

Prevention and Control Strategies for Cystic Echinococcosis

Control of CE requires targeted control at three levels including human, livestock and dogs. Without appropriate surveillance, impact of prevention and control programs becomes difficult to measure. The control approaches are given below:

i) Control of hydatid cysts needs regular dosing/deworming of dogs with praziquantel (PZQ), which will reduce *Echinococcus* worm burden in the definitive hosts (Lembo et al. 2013). PZQ is a highly effective anthelmintic drug to date, with limited toxicity (Macpherson and Craig 2000). The prepatent period of *E. granulosus* is approximately six weeks, therefore, dosing dogs at frequent intervals is the most effective and quickest control measure for reducing both dog-livestock transmission and dog-human transmission, decreasing egg production and infection pressure (Torgerson and Budke 2003). Managing dog populations to reduce their numbers could help to reduce transmission, especially in conjunction with other measures such as dosing dogs and stricter livestock slaughter practices.

ii) Vaccine (EG95) against ovine echinococcosis has been recommended to control infection in livestock (Lightowlers et al. 1999). This vaccine is not uniformly effective for *E. granulosus* intraspecific variants or genotypes. Additionally, there is no vaccine available for the definitive host (Craig et al. 2017).

iii) Vaccination in conjunction with other measures such as the inspection of animals at the slaughterhouse, improving hygiene practices and husbandry, regulated slaughtering at

abattoirs and proper dumping of offal are useful in the control of hydatid cyst (Craig et al. 2017).

iv) Health education of the general public and rural communities by increasing their awareness about the disease, efforts to change social practices including fencing of vegetable gardens to prevent access by dogs, avoiding use of raw vegetables without washing, improved sanitary conditions in slaughterhouses and preventing access of dogs to raw viscera would help to control the disease (Craig et al. 2007).

v) Modelling for CE

Quantitative and qualitative forms of mathematical models provide a straightforward means to estimating the infection pressure to animals and humans (Torgerson and Heath 2003).

vi) Surveillance studies describing the rates of infection and molecular investigations determining etiological agents at particular geographical areas are of primary importance while implementing a control program. Data sources from epidemiological surveillance reporting livestock infections and hospital admission data are of central importance to initiate a control program (Craig et al. 2017).

vii) An **integrated approach** combining vaccination of intermediate hosts and anthelmintic treatment of dogs is by far the most effective intervention to control CE (Craig et al. 2007).

One Health Action and Implementation Measures

One Health is a unifying concept which aims at achieving sustainable balance between animals, humans and the environment (ecosystems), signifying integration of these elements and that the human health is dependent upon ecosystem health (Fig. 4).

A complete control initiative taken under the umbrella of One Health requires reduced disease transmission and infection risks and complementing the regional chemotherapeutic campaigns for disease prevention and subsequent control. Unfortunately, no measures have been taken on any scale for disease prevention from the relevant authorities in Pakistan. Despite endemicity and considerable hospital records and animal infections, nothing has been done so far on any interventional front described by WHO to tackle NTDs including i) preventive chemotherapy ii) innovative and intensified disease management iii) water, sanitation and hygiene (WASH) and iv) veterinary public health services. One important aspect to be specifically focused is to break the transmission cycle of CE by identification of main reservoir species, climatic factors, areas with higher prevalence, routes to human infection and sociocultural practices involved in disease dissemination. Once these factors are taken into account, targeted control programs based upon approaches given above can be designed to mitigate the risk of disease in endemic foci. Ideally, search for new drugs and vaccine targets must also be carried out since current anthelmintic drugs are losing their efficacy due to development of resistance among the parasites. Additionally, trainings and workshops must be conducted for the healthcare professionals/workers to enhance their skills for disease management (NTDs are barely given consideration during routine medical examination in Pakistan). Improving basic sanitation, provision of clean water, management of slaughtered animals' waste, regulated animal slaughtering at fixed areas, regular deworming of dogs and health education of agrarian communities regarding disease and dog-contact can substantially reduce disease burdens and may result in sustainable elimination of CE (Mehmood et al. 2020a).

Conclusion

Cystic echinococcosis is endemic to Pakistan and no effective surveillance programs have been implemented to monitor yearly disease prevalence in animals and humans. Due to the infectious nature of disease and adaptability to domestic herbivores, CE control would require years of consistent efforts and commitments for complete elimination. Understanding the disease distribution, economic impacts, and risk factors is critical while developing a control program. Identification of research gaps and definition of priorities within the contextual framework of health preparedness in Pakistan would be a suitable approach for these poverty-associated diseases. Following the WHO roadmap guidelines for elimination of NTDs and optimizing strategies for long term eradication programs must be prioritized by the health authorities. In the absence of sustainable efforts, it is highly probable that CE will remain in steady equilibrium in host animals maintaining its life cycle between dogs and domestic herbivores and remain a nuisance for human population.

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