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A review: Current Trends on Cystic Echinococcosis (CE) and Alveolar Echinococcosis (AE)

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Abstract

CYSTIC and alveolar echinococcosis are considered by the World Health Organization (WHO) as neglected cosmopolitan zoonosis caused by larval stages of different species of taeniid tapeworms, *Echinococcus granulosus sensu lato* and *Echinococcus multilocularis*, respectively. They are found worldwide, causing severe financial losses for farmers and cystic illness in abnormal human hosts. CE and AE are endemic diseases in Iraq and neighbouring countries. The present study aimed to provide a broad review of the status of CE and AE, summarizing the current knowledge about a brief history, the magnitude of economic losses, the host spectrum, and the life cycle. Additionally, we aimed to understand disease burden, epidemiology, transmission and risk factors, treatment, appropriate control methods in this region, and the basic requirements for establishing a surveillance system and planning prevention and control programs. None of the countries in the Middle East region has an elaborate echinococcosis control program. Multi- and inter-sectoral coordination, sustained political and administrative commitment and improved international cooperation are necessary for effective control initiatives.

Keywords: *Echinococcus granulosus*, *Echinococcus multilocularis*, Dogs, Cystic echinococcosis, Alveolar echinococcosis.

Introduction

Cystic echinococcosis (CE) and alveolar echinococcosis (AE) are severe diseases caused by a larval stage tapeworm *Echinococcus granulosus* and *E. multilocularis* from the Taeniidae family, which affects the liver and is occasionally found in other organs [1, 2]. In many countries, CE and AE are recognized as a common zoonotic illness that affects both humans and herbivorous animals [3]. Moreover, at least one of them is endemic in numerous countries, including Iraq, Jordan [4], Egypt [5], Iran, Turkey, Pakistan [6], Kyrgyzstan, Tajikistan, Uzbekistan, Afghanistan, Bulgaria, Romania, and even in developed countries; France and Germany [7].

Dogs serve as the primary definitive host for the predominant number of CE causal agents, whereas other livestock species and humans serve as the intermediate hosts [5]. The little fox tapeworm, *E. multilocularis*, is found throughout the Northern Hemisphere but is limited to it [8]. It is stated by Knapp et al. [9] that the genus is complicated, making it difficult to evaluate its taxonomy, even though phylogenetic studies have shown that the species is distinct from the *E. granulosus* complex. *E. multilocularis* is mostly spread by a wildlife cycle in which several species of rodents act as intermediate hosts and carnivores, most commonly foxes and coyotes, as definitive hosts [10]. Nevertheless, according to Manukyan et al. [11], domestic dogs and cats can also play as capable definitive hosts. Mostly due to the absence of effective treatment options, AE is a very deadly disease that has caused significant human casualties throughout Asia, especially in the autonomous territory of Tibet [12]. While not as harmful to humans, CE has a greater endemicity and causes considerable economic losses in addition to a substantial burden on public health [5, 8]. World Health Organization (WHO) [13] listed echinococcosis in the 5th place among top 20 neglected transmitted diseases (NTDs) as global aims for the prevention, control, elimination, and eradication of NTDs by 2030, which are outlined in a new WHO framework [13]. Accidental consumption of *E. granulosus sensu lato* infectious eggs, either in contact with excrement, infected dog fur, polluted

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water, or contaminated food, causes the infection [6]. It is undeniable that determining the relative significance of each of the numerous human infection pathways caused by *Echinococcus* spp. remains an obstacle. For instance, it is found that the same prevalence of CE is found in those having dogs as in those who owned dogs within semi-nomadic communities in Northwest China [14, 15].

Among livestock, sheep are the most susceptible intermediate hosts. Farmers' negligent use of anthelminthic medication, improper disposal of dead animals, farm dogs' gain access to the viscera and trimmings of a butchered sheep, and the practice of leaving flocks of sheep grazing in areas where stray dogs can easily access them are some of the factors that may increase the risk of exposure of sheep to CE [16]. CE can cause a range of signs and symptoms, with the majority occurring in the liver and/or lungs and very seldom in other organs of infected humans and animals. Clinical signs are often mild in livestock animals, and infections are typically found during routine meat inspection [6].

Historical background and early discoveries

"Hydatids," or watery vesicles, have been found in both ritually slaughtered and food-bought animals, suggesting that they have been around for a long time [17]. The metacestode stages (filled with a translucent liquid) of *E. granulosus* are composed of variable-sized cysts. The word "hydatids" was created because of the presence of this transparent liquid. Hippocrates, Galen, Aretaeus, Wolckerus, and Bonet were among the scientists and medics who detailed the various characteristics of hydatids in their writings [7]. They were defined by some researchers as a build-up of mucus and serum between the laminar cell layers. The first person to demonstrate the metacestode character of hydatids and the ability of cysticerci to move like animals was Francesco Redi in the 17th century, who discovered that the source of hydatid cysts is from animals [7, 18]. Professor of medicine Jacob Hartman of the University of Konigsberg in Germany verified that cysticerci are animal-like structures, characterizing them as small spherical structures with a metacestode bladder [19]. Hydatids are a unique species of bladder worms that have little bodies on their inner walls, according to a description given by Simon Pallas in the Netherlands. Afterward, these tiny structures known as brood capsules were found to contain tapeworm scolices by Ephraim Goeze. After that, the term *Echinococcus* first came up in science in 1808, by Karl Rudolphi (Fig.1) [19].

Life cycle and Biology

The *Echinococcus* spp. rely on the relationship between predators and prey involving two mammals as hosts for their life cycles. Canine and feline are the final hosts for adult tapeworms, whereas hooved animals, rodents, rabbits and hares are the intermediate hosts for the metacestode (Fig.2) [20]. Humans are typically not the intermediate hosts for the metacestode of *Echinococcus species.* Although they are not directly implicated in the transmission of CE or AE, in select exceptional cases, like those documented in Kenya's Turkana region, humans may serve as intermediate hosts for *E. granulosus* [21]. The intestines of their final hosts are the place where a few hundred to thousands of 2–11mm long (3–7 segments) adult *Echinococcus sp.* worms develop (Fig.3). As each worm matures, its final part, known as the proglottid, releases eggs into the surrounding environment through the excrement of the carnivores. The eggs are subsequently consumed by humans or the intermediate hosts, whereupon they hatch in the intestine to release oncospheres that travel *via* the portal and lymphatic vessels particularly, to the liver, where they typically settle and develop into larvae (metacestodes or hydatid cysts); on occasion, they may also reach the lungs, brain, bones, or any other organ of the individual host. The fertile forms of the parasite, known as protoscolices, are produced asexually by the metacestode and released into the hydatid fluid. When consumed by the definitive host, the protoscolices evaginate their scolices with the help of bile salts and mature into adult worms that can lay eggs after adhering to the intestinal wall [7, 22]. *E. granulosus s.l.* include *E. granulosus sensu stricto, E. ortleppi*, and *E. canadensis*. Additionally, *E. multilocularis* can infect humans and cause severe illness. Furthermore, it is worth noting that *E. equinus* and *E. felidis* are classified under the broader category of *E. granulosus s.l.* On the other hand, *E. shiquicus*, a species closely related to *E. multilocularis*, has not been found to pose any danger to humans. Additional hosts may be encountered, specifically, animal hosts for *E. granulosus s.l.* and domestic hosts for *E. multilocularis* are listed [20].

Epidemiology, transmission and risk factors

E. granulosus s.l. is found throughout the world, including endemic regions on six continents. *E. multilocularis* is limited to the Northern Hemisphere; no reports found in endemic locations other than Tibet and the Chinese province of Sichuan [8]. Echinococcus species are probably underreported in terms of their actual range in both people and animals. Studies using animal hosts are limited by logistical issues, such as the expense of diagnosis and the challenge of acquiring and securely analyzing samples to public health. Patients with low socioeconomic status might not have the chance to seek medical attention, even if they may inadvertently be at a higher risk of parasite infection because of things like leading a pastoral lifestyle [23]. Poor rural societies that rear domestic animals, and dogs for protecting and/or shepherding animals, primarily suffer from CE [24]. The life cycle of the dog tapeworm *E. granulosus* genotypes can be

classified as domestic, including the dog as the main definitive host and various livestock animals as intermediate hosts, or as sylvatic, including wild canids and ungulates as intermediate hosts [25]. The transmission of the cystic hydatid disease is accelerated by certain human activities such as feeding dogs the offal of home slaughtered livestock's especially sheep [26] (Fig.4). For the reason that stray dogs have access to livestock offal and carcasses in rural areas, it is believed that a high number of stray dogs contribute to the transmission of *E. granulosus* infection in humans and animals. It is customary to butcher animals at home, consuming the animals without a permit to inspect them. As a result, stray dogs that are infected with the parasite gain access to livestock yards and contribute to the general environmental contamination caused by the parasite's eggs. Furthermore, because they possess pet dogs primarily to protect their property from wild animals and wanderers, these dogs are free to roam, which contributes to the ongoing spread of echinococcal infections [27].

Since sheep serve as the parasite's intermediate host and because working dogs are permitted to consume the offal of infected sheep, the prevalence of CE in humans is highest in rural areas and among those who raise sheep. The internal organs of livestock can harbor ingested eggs that develop into metacestodes [4]. The hydatid cysts usually only become visible during normal meat inspection since they grow slowly and show few clinical symptoms in livestock animals. The liver and/or lung are the most prevalent locations for cysts in most animals with hydatidosis [4, 11]. Thus, the sheep strain cestode (G1 genotype) raises the possibility of the human infection [28]. In addition, eggs can be indirectly transferred to humans and carnivores, particularly through drinking contaminated water or soil [10].

Significance and impact on human and animal health

CE and AE can cause a range of signs and symptoms, with the majority occurring in the liver and/or lungs and very seldom in other organs of infected humans and animals [5, 29]. Clinical symptoms in livestock animals are often mild, and infections are typically found while inspecting meat regularly [30]. *E. granulosus* and *E. multilocularis* (Fig.3) employ humans and monkeys as aberrant hosts, and illnesses can escalate from asymptomatic to serious clinical conditions that can ultimately be fatal [7]. Because sheep serve as the parasite's intermediate host and dogs are permitted to consume the offal of infected sheep, the prevalence of CE in humans is highest in pastoral areas and among those who raise sheep and cattle. Since many infected patients have no symptoms, CE is frequently regarded as a chronic illness in humans, leading to an underestimation of the overall infection rate [31]. The yearly incidence of CE varies from 1 to 200 per 100,000 in endemic areas, while the incidence of AE varies from 0.03 to 1.2 per 100,000 annually [19]. Although the CE mortality rate is lower (2% to 4%), it could rise significantly if care management is inadequate [32].

Based on the latest global burden estimates, there is an average of 666,434 disability adjusted life years (DALYs) for AE and 285,500 DALYs for human CE. However, if underreporting is accounted for, the total number of DALYs for human CE is estimated to be 1 million [20]. The severity of the disease (greater mortality and fewer treatment options) accounts for the much higher DALY for AE (despite the lower number of cases), especially in areas with less developed medical systems [6].

The group of mysterious species known as *E. granulosus s.l.* differs significantly in terms of host specificity, pathogenicity, ecological distribution, dynamics of transmission, and potential for zoonotic disease [33]. At least ten genotypes (G1–G10) of CE have been identified through sequencing of the mitochondrial cytochrome-c oxidase (*COX*) and NADH-dehydrogenase genes [7]. Throughout the world, the *E. granulosus s.l.* species complex is a serious veterinary and medical problem that causes CE in the target species. According to the results of the genome-wide analysis, the species complex comprises *E. granulosus s.s.* (G1 sheep genotype, G2 Tasmania sheep genotype, and G3 buffalo genotype), *E. equinus* (G4 horse genotype), *E. ortleppi* (G5 cattle genotype), and *E. canadensis* (G6 camel genotype, G8 cervid genotype, G9 human genotypes and G10 Fennoscandian cervid genotype) [7, 33].

The economic impact of CE on livestock can be split into two categories: indirect costs (such as decreased growth, fertility, and milk production of infected animals) and direct costs (primarily the financial loss brought on by the offal's condemnation). If hydatid cysts are found during normal meat inspection at the abattoir, the infested offal (primarily livers and lungs) will be condemned. The dog-sheep transmission cycle depends critically on fertile cysts (with viable protoscolices) in livestock offal [4].

In Iraq, the data availability of economic loss due to CE among livestock is limited; however, several studies have been conducted and estimated the economic burden. An investigation between (2011–2018) in Duhok province of Northern Iraq determined the economic cost around ($1.20 million). This results from various organ condemnations, particularly the liver [33]. An additional study reported an annual $72000 loss due to carcass and organ condemnation in Basrah abattoirs related to CE of livestock [4]. These did not include indirect loss, which comprises decreased weight and milk production and low quality of hide and wool.

CE is thought to cause an annual loss in cattle productivity of at least US $141.6 million and potentially as much as $2.2 billion worldwide [35]. In Iran, it is stated by Borhani et al. [6], more than $236.7 million is assumed to be the average yearly cost of CE in Iran (including indirect costs). With direct expenditures of $23.7 million and indirect costs of $114.4 million, the estimated annual cost of CE in cattle is $138.1 million. Furthermore, in 2020, Turkey's overall estimated financial loss due to CE was $565,448. The projected economic losses were $466.891 for indirect and $98.558 for direct losses [35].

Diagnosis of CE and AE

Accurate diagnosis and early detection of infected cases are essential. Parasite detection, immunological assays, molecular biology methods, and imaging diagnostics are currently used diagnostic approaches; each has unique uses, benefits, and drawbacks [36]. Hydatid cysts are frequently identified in animals during post-mortem (PM) examinations [8] and in humans through laboratory testing and radiological imaging because they lack clear clinical signs and symptoms [37]. The diagnostic sensitivity and specificity of tests employed in surveillance and monitoring programs should be well defined [38]. Immunodiagnostic laboratory methods, particularly the Enzyme Linked Immunosorbent Assay (ELISA) and the Indirect Hem-agglutination Test (IHAT), are frequently used to confirm the diagnosis of CE in suspected cases [15, 36]. With its high sensitivity and specificity, ELISA is a quick, simple, and affordable test to conduct. The main obstacle is not possible to distinguish between CE and AE using either approach [15]. Abdominal ultrasonography (US) exams are used to diagnose CE in humans at both the individual and population levels [8]. When parasite cysts are found in the lungs' periphery, this method can also image them. Computed tomography (CT), magnetic resonance imaging (MRI) [36, 37], microscopic detection of protoscolices in aspirated cyst fluid, and traditional X-ray for pulmonary cyst diagnosis are other imaging modalities [37]. Molecular biological methods, which have a high sensitivity and specificity, are crucial for diagnosing echinococcosis. Early detection, quantitative measurement, and species identification through gene sequencing are made possible by PCR and real-time PCR [8, 15, 38]. Through the use of new technologies such as isothermal nucleic acid amplification (e.g., LAMP, RAA, RPA) and early detection and environmental monitoring of *Echinococcus* eggs, the diagnostic capacities have been substantially improved [38]. Together with biomedical breakthroughs, these developments have greatly increased the efficacy and reliability of CE and AE diagnostics.

Treatment of CE and AE

Since the majority of cysts or cystic lesions in humans arise in the liver, lungs, or other organs. Surgical operation is still the primary treatment for hepatic cystic echinococcosis, but medical-surgical methods are now becoming more popular. Percutaneous drainage is another such method. Praziquantel, mebendazole and albendazole have cure rates of about 30%. Additionally, 10–20% of patients will show significant reductions in cyst size and symptom relief [24]. AE has an asymptomatic latency period of approximately 5–10 years and it leads to the development of a liver tumor-like lesion, which then spreads and invades other organs such as the lungs, brain, bone, and others. The mortality rate among individuals who are not treated or receive insufficient treatment is substantial [11, 39]. Managing AE poses significant challenges and incurs substantial expenses [24]. It is recommended to diagnose the condition early and do radical/curative surgeries, such as liver resections, that can completely remove the metacestode tissue from the liver. This should be followed by a long-term use of albendazole for preventing reinfection.

Control of echinococcosis

To make blameless decisions on control procedures, the social structure of the community needs to be considered. The government should create guidelines with a suitable funding structure that would be communicated through cadres at country, district, township and village levels, and would be enforced by veterinarians and the police department. Sometimes this organization is not accepted by a minority of people, and an arrangement with greater sympathy, suggested by local ethnic leaders, is more expected to be effective. It is stated by Craig et al. [3] Krabbe in the 1860s formulated measurements to control the risk of hydatid disease, which are applicable today and include: prevent dogs from having access to offal; deworm dogs; examine meat and dispose of offal properly; avoid home slaughter; and provide health education regarding sanitation and canine interaction.

Cystic hydatid disease control can be classified into four stages: the planning stage (1–5 years), attack stage (1–5 years), consolidation stage (8–10 years after start), and maintenance elimination (20 >30 years after start). At the first phase, cost-benefit analysis, burden of human disease, funding sources and expectation for 5–10 years, identify control authority, integrated measures, select intervention region and communities, applied research needs, participatory planning, outreach ability, transport, quality of baseline data (humans, livestock and dogs). Furthermore, surveillance options, registration of households and dogs, stray dog issues, select staff required, training, health education aspects, medical support, treatment and follow-up of CE cases. Inter-sector cooperation may perhaps take a look through a

pilot program [3]. A sociological survey and starting age/incidence baseline for the parasite in canids, particularly dogs, in addition to cysts in ungulates (sheep) and humans, are involved in the planning phase [6]. Identifying the human genotype of the tapeworm and which animals (genera) are involved in the transmission of the infection is acknowledged as a vital first step. Government leaders and dog owners should be involved in participatory planning in addition to financial support systems, which should be accepted by all members [3].

Secondly, the attach phase includes many techniques and methods that were accepted in the first phase. These may include; education about echinococcosis, risks and control, dog registration, elimination of stray and unwanted dogs, using of praziquantel for treatment of dogs; dog investigation approach (arecoline and/or copro-antigen testing), and preventing dogs from getting offal of animal species that have a significant role in disease transmission; vaccination (EG95) of livestock particularly sheep and goat; building of slaughterhouses in areas where they needed [3]. Annually surveillance must be done after this phase. An Ultrasound survey of all children over 12 years old should be done yearly. Finally, all data and statistics for *E. granulosus* infections should be collected. Dogs and domestic animals' infection prevalence should have decreased within 5–7 years, but human CE within 10 years. The time required for this phase is 10–15 years [40].

Thirdly, the consolidation phase, which is a very long-term or may be permanent. The key factor to succeed is surveillance, and the goal of control measures is to target areas with a high risk of the disease [41]. At this phase, home slaughtering practice could be prosecuted and dog-owners should be provided with praziquantel at a low cost for deworming. In addition, meat inspection at the abattoir should be activated and identification of infected carcasses. During this phase, the number of staff who work in the field should be reduced [40]. Detection of *E. granulosus* copro-antigen in fecal samples of dogs, antibody positive of primary school pupils, prevalence of the disease in children aged 7–16 years old [42], arecoline purging of dogs, sheep CE survey at abattoir (meat inspection) should be performed [5]. Immunization of both livestock and dogs showed effects in controlling hydatid cysts. Subsequently vaccinated dogs showed no more adult worms [3]. Regarding humans, using relatively less expensive techniques and painless methods such as ultrasonography, which is acceptable by the majority of people and immune-diagnosis, which are essential for a large-scale screening of residents in endemic areas [26, 43] . Additionally, space-occupying cysts can be detected using magnetic resonance imaging (MRI) [44].

Finally, the maintenance phase is implemented once control activities cease, after elimination was near or declared, and when caution was maintained by identifying small lesions in meat and hospital records for children, tracing back when necessary, and imposing movement restrictions (passport or license) on dogs, particularly on islands [3].

Conclusion

International cooperation is significant in the improvement and development of diagnostic techniques, treatment, prevention and control of cystic hydatidosis. Sharing ideas, resources and collaboration facilitates control and elimination program. CE and AE are endemic in numerous countries and the development of new diagnostic techniques may help in controlling the disease in many regions. It is important for those countries that are suffering from cystic hydatidosis to allocate a great annual budget to control zoonotic diseases, particularly neglected diseases including hydatidosis. Understanding biology and the transmission of diseases through further investigations funded by local government or other organizations, such as WHO, plays a role in controlling the disease. Such programs and investigations need millions of US Dollars and need several years to eradicate echinococcosis. There are many ways to reduce the period to control and decrease the fund, for example, assembling with village residents to parasitologists, veterinarians, physicians and giving information about the risks of the disease. Moreover, publishing information and brochures about the problems of home practice slaughtering, feeding offal to dogs and close contact with stray dogs. Free vaccine (EG95) should be provided for both dogs and domestic animals. These approaches can increase the effectiveness of control programs and protect the community from getting the infection.

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Declaration of Conflict of Interest

The authors declare that there is no conflict of interest.

Fig. 1. Karl Rudolphi (1771-1832) Swedish born naturalist known as "father of helminthology" [19].

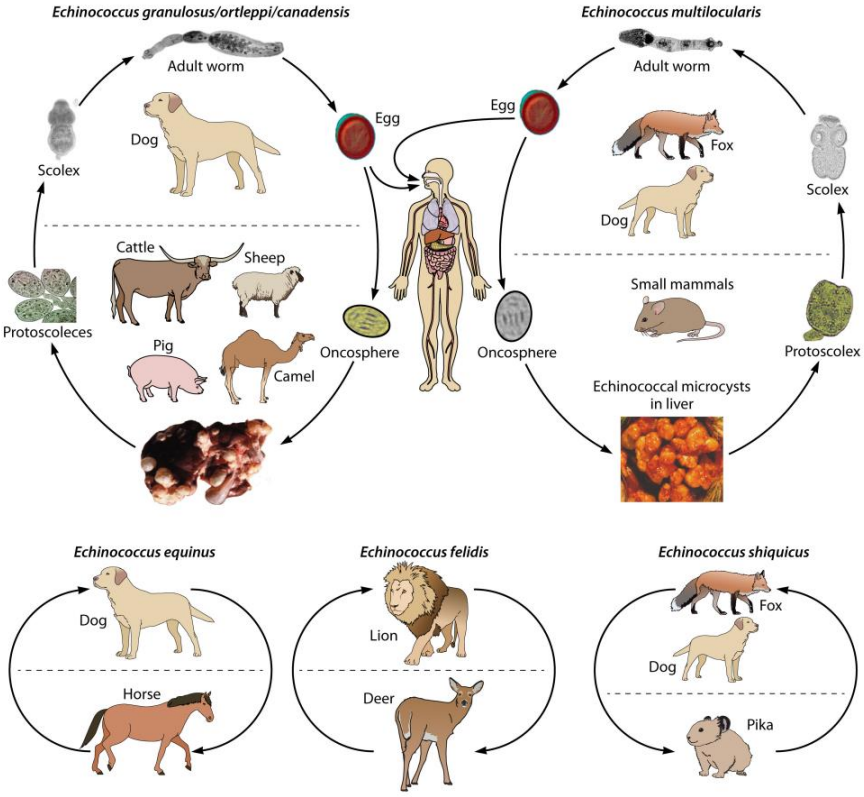

Fig.2. Shows life cycle of *Echinococcus* species which displays the species that infect humans and non-infecting human species. All *Echinococcus* species have indirect life cycles, with predator and prey species serving as the definitive and intermediate hosts, respectively. The definitive host's small intestine is home to the adult worm, which excretes eggs into the surrounding environment along with excrement. The intermediate host consumes the eggs, which grow into a metacestode. After protoscoleces mature, metacestodes are deemed viable, and the cycle is finished when a definitive host consumes the infected organs of the intermediate host [7, 19].

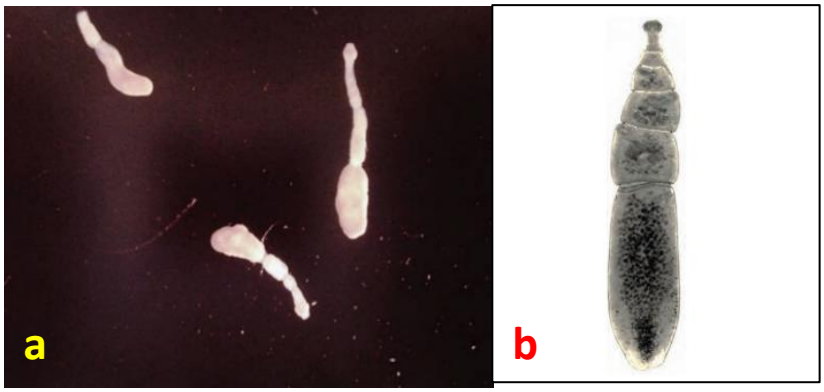

Fig.3. *E. granulosus* (a) and *E. multilocularis* (b) [21].

Fig.4. Shows dogs wait to get offals of the slaughtered animals[23].

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مراجعة: الاتجاهات الحالية حول الإكينوكوكوز الكيسي (CE) والإكينوكوكوز الألوي (AE)

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الملخص

تعتبر الإكينوكوكوز الكيسي والإكينوكوكوز الألوي من قبل منظمة الصحة العالمية زونوز غير مهملة تنتشر في جميع أنحاء العالم وتسببها مراحل اليرقات لعدة أنواع من الديدان الشريطية التينية، إكينوكوكوس غرانولوسوس وسينسو لاتو وإكينوكوكوس ملتي لوكولاريس. توجد هذه الأمراض في جميع أنحاء العالم، مما يسبب خسائر مالية كبيرة للمزارعين وأمراض كيسية لدى البشر غير الطبيعيين. تعتبر CE و AE أمراضاً متوطنة في العراق والدول المجاورة. تهدف هذه الدراسة إلى تقديم مراجعة شاملة حول حالة CE وAE، ملخصة المعرفة الحالية حول التاريخ المختصر، وحجم الخسائر الاقتصادية، وطيف المضيفين، ودورة الحياة. بالإضافة إلى ذلك، نهدف إلى فهم عبء المرض، وعلم الأوبئة، وطرق الانتقال، وعوامل الخطر، والعلاج، وطرق السيطرة المناسبة في هذه المنطقة، فضلاً عن المتطلبات الأساسية لإنشاء نظام مراقبة وتخطيط برامج الوقاية والسيطرة. لا تمتلك أي من دول المنطقة برنامجاً متقدماً لمكافحة الإكينوكوكوز. هناك حاجة إلى تنسيق متعدد وقطاعات مشتركة، والالتزام السياسي والإداري المستدام، وتحسين التعاون الدولي من أجل مبادرات السيطرة الفعالة.

الكلمات الدالة: إكينوكوكوس غرانولوسوس، إكينوكوكوس ملتي لوكولاريس، الكلاب، الإكينوكوكوز الكيسي، الإكينوكوكوز الألوي.