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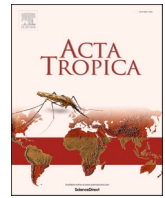
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Epidemiological update of cystic echinococcosis in livestock and assessment of practices related to its control in the Mediterranean area

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ABSTRACT

Cystic echinococcosis (CE), caused by the tapeworm *Echinococcus granulosus*, is a zoonotic parasitic disease that still represents a serious threat to human and animal health worldwide. The Mediterranean basin is recognized as one of the major hotspots of CE due to several factors, including the presence of diverse intermediate host species as well as socio-economic and cultural conditions of local communities. This study aims to take a closer look at epidemiological data on CE in the Mediterranean area and assess the knowledge attitudes and practices of shepherds towards this disease in four countries (Algeria, Greece, Italy and Tunisia), highly endemic for CE, with the final goal of identifying highly endemic risk areas and practices in use which might potentially allow the persistence of *E. granulosus* infection in these areas. To update the epidemiological scenario of CE in Mediterranean areas, a comprehensive review of peer-reviewed literature on CE prevalence data published during the 2017–2023 period was carried out and, through a geographical information system (GIS), a map displaying the current CE distribution in the Mediterranean area was generated. In addition, a questionnaire survey was conducted through in-depth interviews of the farmers to collect information on their management system as well as knowledge attitudes and practices towards CE. From the farmer-participatory survey some risky practices emerged including the non-regular deworming of dogs or the use of ineffective drugs or dosing, as well as the provision of uncooked animal viscera to dogs. Finally, lower levels of knowledge and awareness of the disease was observed among farmers from North Africa compared with those of European countries. In conclusion, the results obtained highlight that CE is still a very serious problem in Mediterranean areas and increased efforts are needed to promote awareness among farmers and to turn research results into policy in order to reduce the spread of this disease, according to the One Health perspective.

1. Introduction

Cystic echinococcosis (CE) is a zoonotic parasitic disease caused by the larval stage (metacestode) of the small tapeworm *Echinococcus granulosus sensu lato* (s.l.). Cystic echinococcosis is one of the 20

neglected tropical diseases (NTDs) identified by the World Health Organization (WHO) and for which effective control measures are needed (Casulli et al., 2023). In endemic regions, CE has significant health and socio-economic consequences for affected populations (Budke et al. 2006). At global level, estimates indicate 1–3 million cases of human CE,

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with a burden of 1–3.6 million disability-adjusted life years (DALYs) and over \$2 billion in expenses every year, due to human treatment and livestock production losses (Torgerson et al. 2015; Tamarozzi et al. 2019; WHO, 2021). Some studies have shown that CE can result in a 10 % decrease in the productivity of infected animals, lowering quality of meat, production of fibre and milk, and number of surviving offspring (Merino et al. 2017).

The Mediterranean basin is recognized as one of the major hotspots of CE (Borhani et al. 2020) and, in these areas, the genotype *E. granulosus sensu stricto* (s.s.) is highly represented (Casulli et al. 2022). Although its real burden is underestimated, CE is especially endemic in areas where livestock breeding is practiced, such as European Mediterranean countries with an average annual incidence rate of human CE ranging from 0.10 to 7.74 per 10⁵ inhabitants (Tamarozzi et al. 2020; Casulli et al. 2023). On the other hand, in north African countries annual incidence rates range from 5 to 10 cases per 10⁵ inhabitants (Deplazes et al. 2017). In ruminants, particularly sheep, CE prevalence in Mediterranean European countries, up to 10 years ago, reached 75 % in southern Italy (Deplazes et al. 2017; Bosco et al. 2021; Cringoli et al. 2021) and 30.4–53.8 % in Greece (Christodouloupoulos et al. 2008; Chaligiannis et al. 2015). Similarly, in North Africa, CE prevalence in sheep ranged from 17.5 % to 78.0 % in Algeria (Hamrat et al. 2011; Ouchene et al. 2014; Laattamna et al. 2019) and from 12.5 to 53.0 % in Tunisia (Lahmar et al. 1999, 2007, 2013).

The persistence of CE transmission in these regions is largely dependent on several factors, including mainly the presence of diverse intermediate host species (sheep, goats, camels, cattle, buffaloes and wild boars), as well as socio-economic and cultural conditions of local communities. Common practices associated with increased prevalence and risk of exposure to CE for domestic animals are (i) home slaughtering practice, (ii) access of dogs to infected offal, (iii) inadequate facilities for slaughter and destruction of infected viscera, (iv) neglected de-worming of dogs (Varcasia et al. 2011). Among these, the practice of feeding dogs infected offal is by far one of the most significant factors for the persistence of this disease. Other factors also play a role, including the lack of regular deworming of dogs and the lack of knowledge pertaining to infectious and parasitic diseases such as CE (Acosta-Jamett et al. 2014). Thus, human behaviour remains a key determining factor in the continued transmission of this disease maintained by a domestic lifecycle (Porcu et al. 2022).

Mathematical modelling as well as control programmes implemented in the last years in some countries have shown that the most effective intervention to reduce the spread of this zoonosis is a combination of several actions including: regular dog deworming treatment, surveillance in livestock, vaccination of sheep and public health education campaigns (Sotiraki et al. 2003; Torgerson, 2006; Larrieu et al. 2019; Amarir et al. 2021; Cringoli et al. 2021).

In order to design an effective control programme for CE in a given geographical area and to reduce its spread in animals and humans, a thorough analysis of its epidemiology is needed. In particular, a sound understanding of the epidemiology of infection in animals is a key factor in limiting the transmission to humans (Otero-Abad and Torgerson, 2013). Furthermore, it is of fundamental importance to evaluate the local population's level of knowledge about the disease, their awareness of preventive measures, and the existence of risk practices which may favor *E. granulosus* infections (Abdulhameed et al. 2018).

In light of the above, the aim of the present study is to carefully analyse epidemiological data on CE and assess the knowledge attitudes and practices of shepherds towards this disease in four countries of the Mediterranean basin (Algeria, Greece, Italy and Tunisia), highly endemic for CE, to better understand the perspectives of different stakeholders and identify factors correlated with the persistence of *E. granulosus* infections. The final goal is to identify highly endemic risk areas and practices in use that potentially allow the spread of CE in order to implement effective control programmes.

This work provides baseline data on farming practices in the context

of the project named ECHINO-SAFE-MED “New sustainable tools and innovative actions to control cystic ECHINOCoccosis in sheep farms in the MEDiterranean area: improvement of diagnosis and SAFETY in response to climatic changes (supported by PRIMA - Partnership for research and innovation in the Mediterranean area) (Nocerino et al. 2024) which aims to develop and validate innovative and sustainable strategies to control CE in sheep in these four countries of the Mediterranean area.

2. Materials and methods

2.1. Updating epidemiological data

To update the epidemiological scenario of CE in Mediterranean areas, a comprehensive review of peer-reviewed literature was undertaken at continental, regional, national, provincial, departmental (or any jurisdiction) administrative levels regarding CE in ruminant intermediate hosts (sheep, goats, cattle and buffaloes). The focus of this study is on ruminants as these are by far the main livestock found at pasture in the Mediterranean region and therefore the ones exposed to infection. Systematic research was conducted combining structured searches of: (i) electronic bibliographic databases; (ii) “grey literature”, including unpublished studies and (iii) direct contact with researchers and health managers. Data was gathered on the prevalence and geographical distribution of CE in Mediterranean countries from research works and prevalence data published during the 2017–2023 period. This time-frame was chosen based on the last update reported for the same areas by Deplazes et al. (2017). A combination of search words was used, including “cystic echinococcosis”, “hydatidosis”, “*Echinococcus granulosus*” and the name of each intermediate host and of each country. Subsequently, the database previously created by Deplazes et al. (2017) was updated with the data obtained for each animal host (e.g. geographical distribution, number of screened animals, number and percentage of infected animals, etc.) and a geographical information system (GIS), using Arc-GIS 10.3 software (ESRI, Redland, CA, United States), was developed to produce CE distribution maps. Furthermore, in two European countries, namely Greece and Italy, where control programmes against CE had been implemented for several years (Sotiraki et al. 2003; Cringoli et al. 2021), the effect of the control activities was investigated. To this end, highly endemic areas were selected in Greece and Italy and CE prevalence figures reported in sheep during the last 20 years were mapped to show changes in prevalence levels over time.

2.2. Study area

The study was conducted in sheep farms located in different pilot areas of four Mediterranean countries, highly endemic for CE, including Algeria (high plateaus areas of Bordj Bou-Arredj and Guelma provinces in east-central and eastern parts of Algeria, respectively), Greece (Central Macedonia and Thessaly), Italy (Campania region), and Tunisia (North-West – Siliana governorate). These pilot areas were chosen based on both the endemicity of CE in livestock and the presence of a significant number of grazing sheep. The location of sheep farms included in the present study, selected based on their history of animals testing positive for CE during slaughtering, was geo-referenced using the GIS (ArcGIS version 10.3 ESRI, Redlands, CA, USA).

2.3. Study design

A cross sectional study was conducted from May 2021 to December 2021 by using a questionnaire-based interview of 219 sheep farmers in the four pilot areas.

To ensure internal validity and reliability of the survey, the method of backtranslation was implemented. The survey was developed in English and then translation-actions were performed by the participating countries, in Arabic, Greek and Italian. The survey with farmers was

delivered by face-to-face conversation in the languages spoken locally. First, the aim of the study was explained to them and then, if they were willing, the farmers were asked questions orally and their answers were noted on the questionnaire (Fig. 1).

The structured questionnaire comprised two sections. Section 1 included general questions related to key farm characteristics and the management system (e.g., farm size, number and breed of sheep, presence of other animals, typology of farming). Section 2 was designed to include possible factors associated with the transmission of CE, including ownership and number of dogs, dog keeping practices, the use of anthelmintic drugs against cestodes of dogs and the frequency of this anthelmintic treatment. In addition, the practice of home slaughter and the disposal of slaughter offal were also investigated. Finally, farmers were also asked about their knowledge and awareness of CE and transmission sources. The data collected from the questionnaire surveys were entered into a repository database for further analysis.

Moreover, the sheep farmers were provided with key information regarding the lifecycle of *E. granulosus* and the main recommendations to prevent CE transmission in animals and humans. Specifically, dissemination materials (translated into five languages including Arabic, English, French, Greek and Italian) including brochures and posters on the disease with cartoon pictures suitable for both children and adults were distributed to farmers (Fig. 2).

3. Results

3.1. Epidemiological updates

The literature search identified a total of 495 potentially relevant

papers. Of these, studies dealing with human CE infections or addressing the genetic diversity of the parasite were excluded. Only cross-sectional/longitudinal studies based on the *post-mortem* inspection of carcasses and reporting the prevalence of CE infection in cattle, sheep and goats were included. Data were extracted from a total of 20 eligible papers (see Supplementary Material). The data obtained showed a prominent presence of CE in the Mediterranean region with high prevalence rates. The spatial distribution of the prevalence values is shown in Fig. 3.

The results of the literature review were also used to produce the following two sets of maps (Fig. 4) showing the temporal trend of CE prevalence in sheep, in southern Italy (i.e., Campania region) and in central-northern areas of Greece, where control programmes against CE had been implemented for several years.

3.2. Questionnaire survey

The sheep farms included in the present study were located in 74 different municipalities within the four pilot areas and the distribution of the questionnaire for each country was as follows: Algeria (no. = 13), Greece (no. = 89), Italy (no. = 90) and Tunisia (no. = 27).

The point locations of the sheep farms included in the study are reported in Fig. 5.

3.3. Farm profile

The characteristics of sheep farms for each country are summarized in Table 1. The majority of interviewees had other animals on their farms (88.6 %), and out of these 69.4 % had goats, 12.3 % cattle and 3.2 % donkeys. Most sheep farms showed a semi-intensive management



Fig. 1. Face-to-face interviews with farmers conducted in the local language of the different pilot areas.

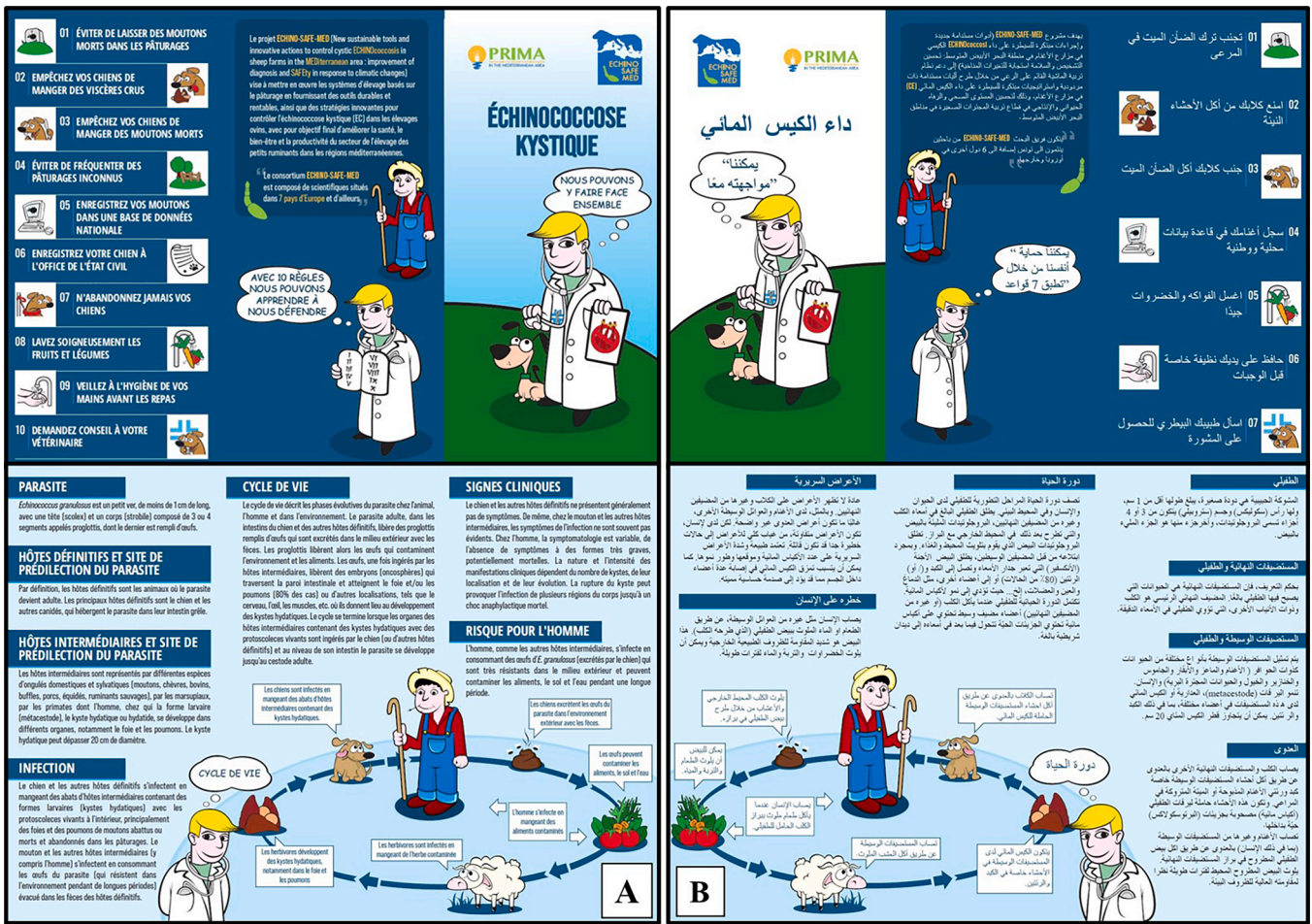


Fig. 2. Example of brochures translated into two languages: French (A) and Arabic (B).

(51.1 %), followed by an extensive management (45.2 %) and only 4.1 % of farms had an intensive farming system.

3.4. Practices towards CE prevention

Based on the interviews, 97.7 % (214/219) of farmers stated to have shepherd dogs on their farm, with an average of 5.0 dogs per farm. Specifically, 50.9 % of the farms had between 1 and 4 dogs, 40.1 % had between 5 and 8 dogs, but 6.5 % had between 9 and 12 dogs. Out of a total of 219 farmers, 12.6 % reported the absence of stray dogs around their farms, whereas 41.5 % stated that they did not know, and 34.1 % of respondents mentioned the presence of stray dogs in their area.

More than half of farmers (54.8 %) stated that they did not apply any anthelmintic treatment to dogs whereas only 43.8 % (96/219) of farmers treated the dogs regularly. Of these, 12.5 % (12/96) used anthelmintics that have no effect against dog's cestodes (e.g. Afoxolaner + Milbemycin oxime and Epsiprantel + Pyrantel). The most widely used treatment against dog cestodes was a combination of milbemycin oxime and praziquantel (77.1 %; 74/96), especially in Greece and Italy, with a frequency of one (8.1 %), two (67.6 %), three (23.0 %) and four (1.3 %) times per year.

In addition, only 21.0 % (46/219) of participants, mostly from Algeria and Tunisia, reported slaughtering livestock at home and 53.0 % (116/219) said that they give uncooked animal viscera to their dogs. The table below reports the descriptive results of practices towards CE prevention and control adopted by each country (Table 2).

3.5. Knowledge and awareness of cystic echinococcosis

Almost half of the interviewed livestock farmers (44.5 %) in Mediterranean areas revealed that they did not know that CE can cause harm to human health and were not aware of how humans can be infected. In addition, 51.6 % of farmers were not aware that livestock animals could also get infected and act as carrier for the parasite causing CE. Finally, low awareness of the behaviours that increase the risk of CE infection emerged (36.9 %). These low levels of knowledge and awareness have appeared more markedly among farmers from North Africa compared with those of European countries (Fig. 6).

4. Discussion

Cystic echinococcosis remains one of the most important helminthic zoonoses of the Mediterranean areas. Since the potential impact of climatic effects on Echinococcus transmission over the longer term remains uncertain (Paternoster et al. 2021), improving CE control programmes is of paramount importance. Understanding the level of knowledge about the disease, awareness of preventive measures and risky practices that prevent the disease within a community have played a crucial role in planning control activities in a given geographical area. In addition, investigating the farm characteristics and management system in each endemic area could help to adapt control strategies accordingly.

This study used face-to-face questionnaires administered to 219 livestock farmers, in the four pilot areas of the ECHINO-SAFE-MED project, to collect baseline information on sheep farms and their management systems and practices towards CE. However, the major

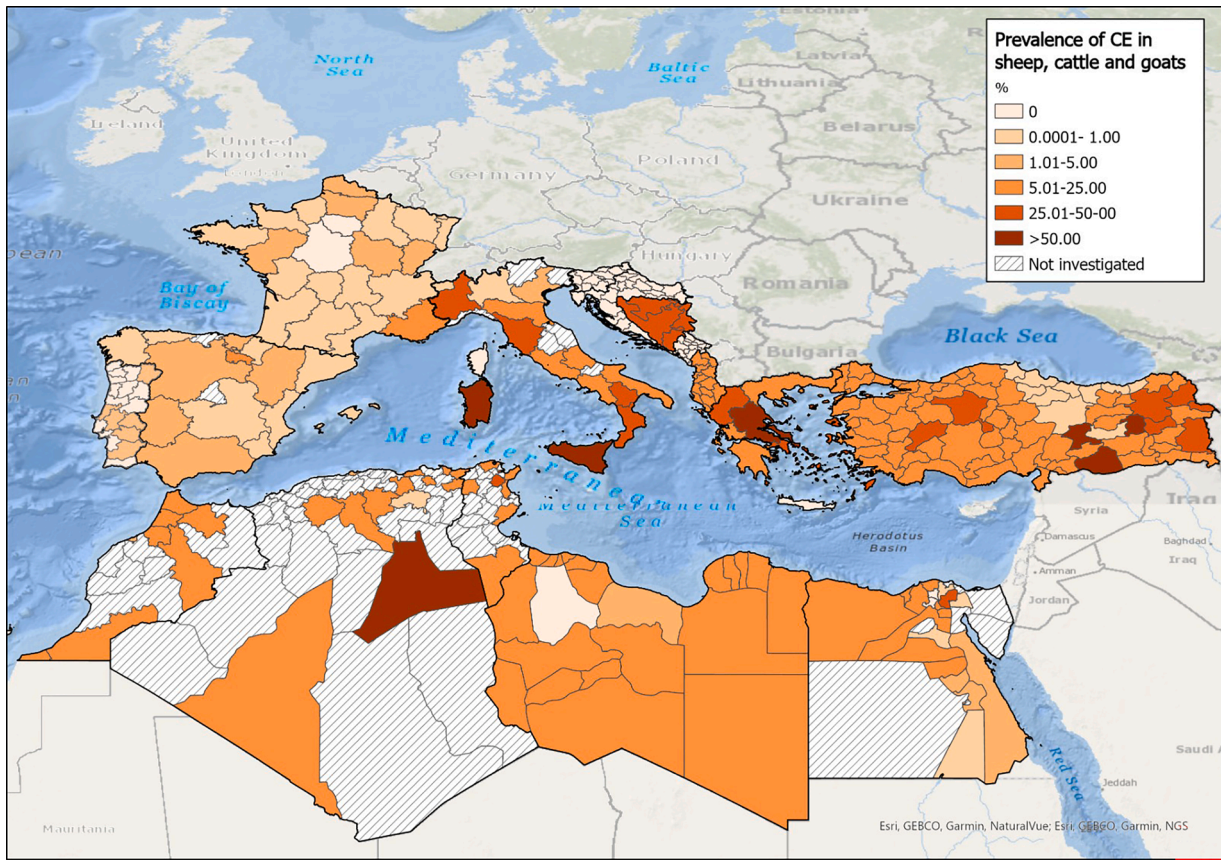


Fig. 3. Updated spatial distribution of CE prevalence from published and unpublished data in domestic intermediate hosts (sheep, cattle and goats).

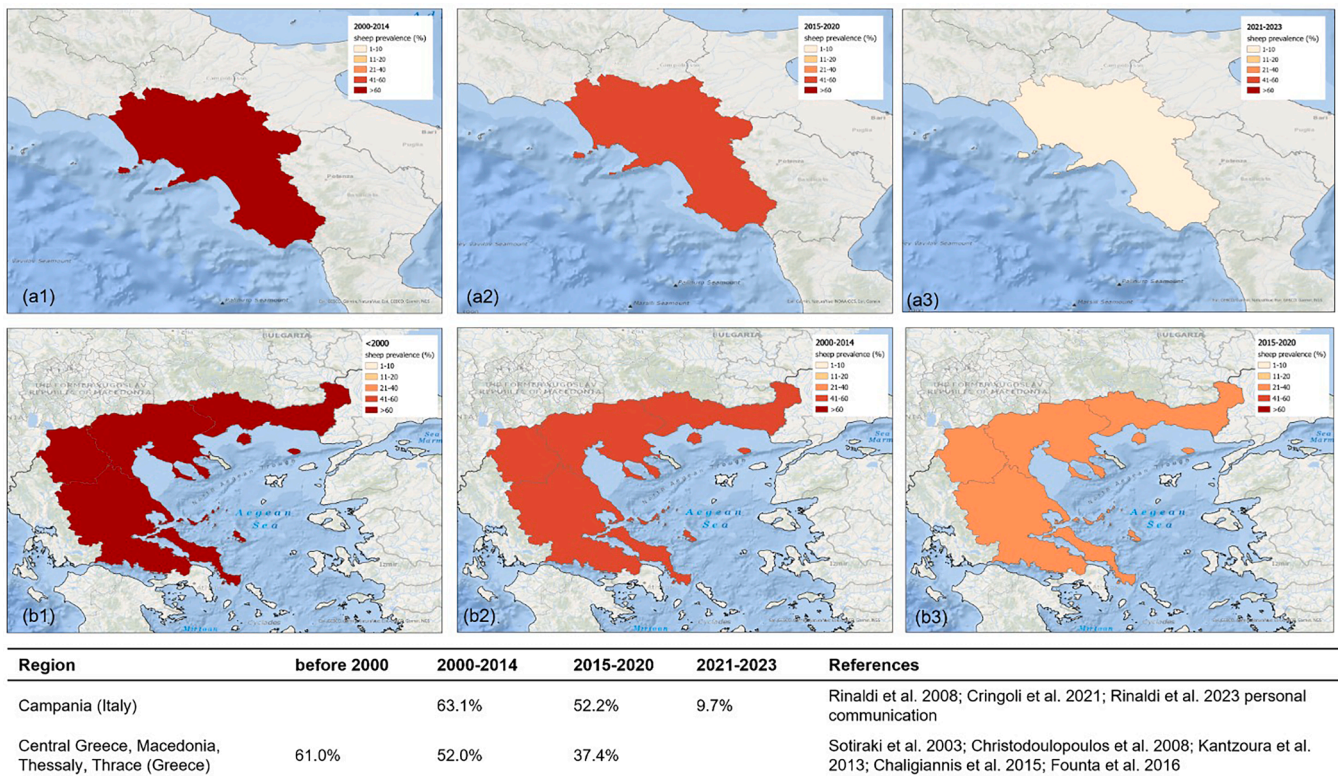
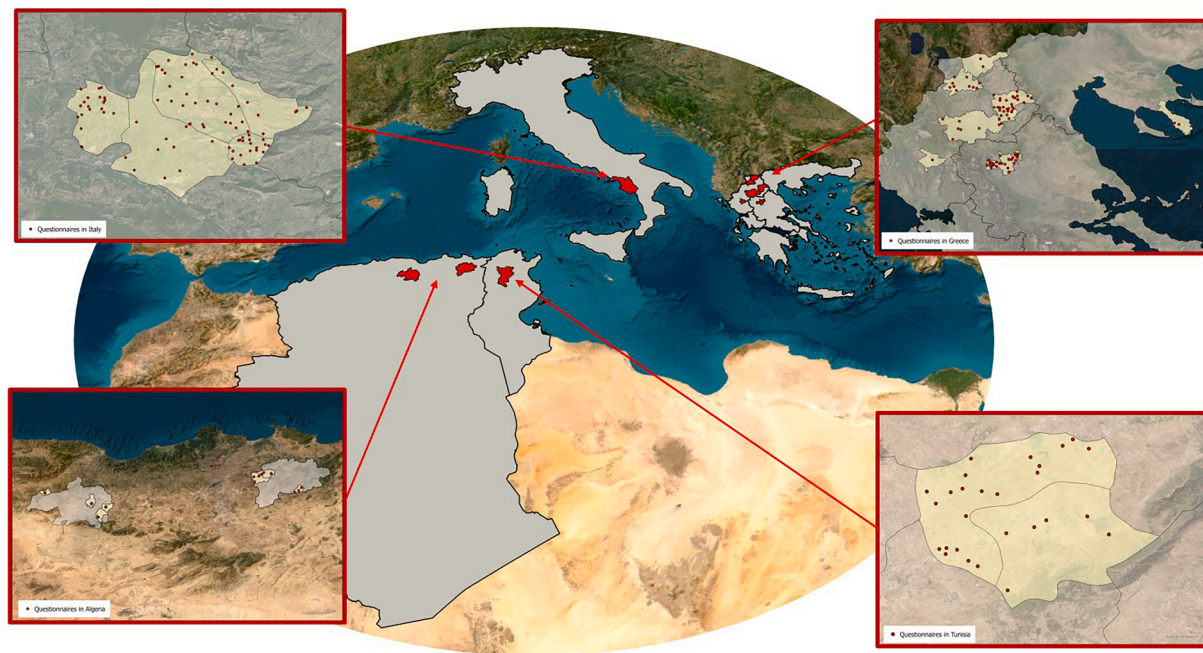


Fig. 4. Decreasing trend of sheep prevalence in southern Italy (Campania region) (A1–3) and in central-northern Greece (B1–3) over a period of more than 20 years (Founta et al., 2016; Kantzoura et al., 2013; Rinaldi et al., 2008).



Source: Esri, Maxar, Earthstar Geographics, and the GIS User Community

Fig. 5. The point locations of sheep farms included in the present study in the four pilot areas.

Table 1
Farm characteristics and management system in Algeria, Greece, Italy and Tunisia.

Country	Mean flock size (min-max)	Breed (%)	Production	Flock replacement months (%)	Annual renewal of the herd	Other livestock present (%)	Type of farming (%)
Algeria (no. = 13)	156 (45 – 288)	Crossed (87.5 %) Ouled Jellal (12.5 %)	Meat	No data	40–60 %	Cattle (61.50 %) Goats (38.5 %)	Extensive (7.7 %) Semi-intensive (92.3 %)
Greece (no. = 89)	483 (66–900)	Assaf (1 %) Lacaune (4.5 %) Local improved (93 %)	Milk	May-June (100 %)	10 %	Cattle (3.4 %) Goats (57.3 %)	Extensive (7.8%) Intensive (6.7 %) Semi-intensive (85.4 %)
Italy (no. = 90)	176 (51–320)	Mixed (100 %)	Meat and milk	January (19.0 %) February (57.1 %) March (14.3 %) April (9.5 %)	20–25 %	Goats (80.9 %)	Extensive (100 %)
Tunisia (no. = 27)	141 (40–960)	Barbarine (3.7 %) Western thin-tail (55.5 %) Western thin-tail /Barbarine (37.0 %) Western thin-tail / Sardinian (3.7 %)	Meat and milk	March (77.8 %) March/ April (22.2 %)	30–50 %	Cattle (59.2%) Goats (92.6%) Donkeys (25.9%)	Extensive (3.7%) Intensive (7.4 %) Semi-intensive (88.9%)

Table 2
Descriptive results from the questionnaire on the practices towards CE prevention in Algeria, Greece, Italy and Tunisia.

COUNTRY	Home slaughtering		Uncooked animal viscera eaten by dogs		Handling faeces of dogs		Regular deworming of dogs	
	Yes	No	Yes	No	Leave them where they are	Collect/Burn them	Yes	No
Algeria	84.6 % (11/13)	15.4 % (2/13)	77 % (10/13)	23 % (3/13)	100 % (13/13)	0 % (0/0)	7 % (1/13)	93 % (12/13)
Greece	0% (0/89)	100 % (89/89)	69 % (61/89)	30 % (27/89)*	100 % (89/89)	0 % (0/89)	33 % (30/89)	63 % (56/89)*
Italy	8.8 % (8/90)	91.2 % (82/90)	20.2 % (18/90)	79.8 % (72/90)	100 % (90/90)	0 % (0/90)	71.1 % (64/90)	28.9 % (26/90)
Tunisia	100 % (27/27)	0 % (0/27)	100 % (27/27)	0 % (0/27)	100 % (27/27)	0 % (0/27)	3.7 % (1/27)	96.3 % (26/27)

*missing questionnaire replies.

limitation of this questionnaire-based survey was the lower number of responses from Algeria and Tunisia than from the other two European countries. This bias should be considered to avoid inaccurate interpretations of data in the present study. The sheep farms in the four Mediterranean countries shared common features such as large flock sizes and the widespread use of extensive or semi-intensive sheep

farming, which were identified as risk factors associated with CE infection (Garippa et al. 2004; Zeng et al. 2020). In contrast, the four pilot areas showed differences in their management systems, especially regarding production (milk or meat), the percentage of annual sheep renewal (from 10 % in Greece to 40–60 % in Algeria) and the timing of renewal, which is crucial information for the design of lamb vaccination

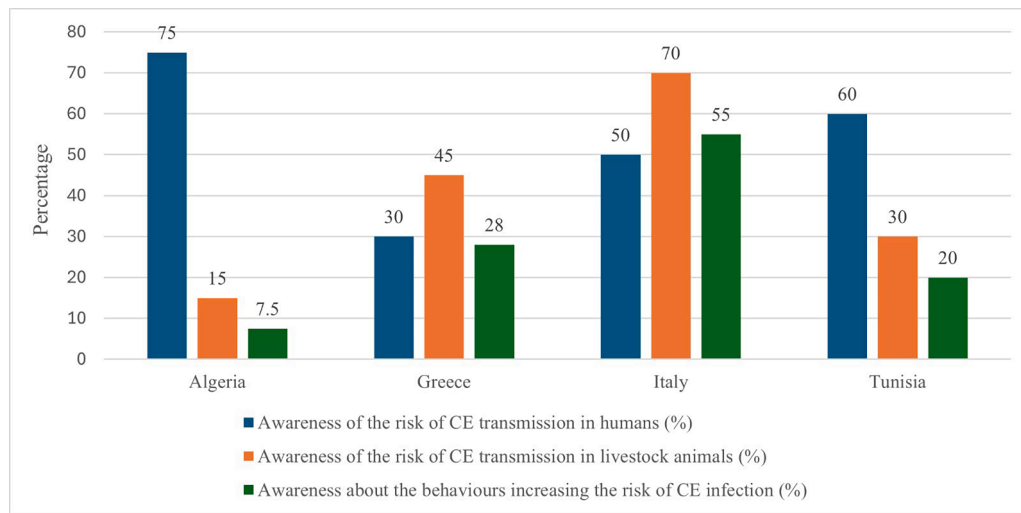


Fig. 6. Awareness of cystic echinococcosis among livestock farmers.

programmes in each country.

In this survey, farmers were asked about potentially risky practices, specifically those associated with dog management in their households or farms. The most common practices identified were the improper disposal of dead animals, farmers' carelessness in treating their farm dogs with anthelmintics, and the presence of stray dogs around the farms. The majority of interviewees did not de-worm their dogs or treated them with ineffective drugs or dosing. Praziquantel has demonstrated high and reliable efficacy against mature and immature adult stages of taeniid cestodes in the intestine and it has been widely and successfully used for deworming dogs in control campaigns against *E. granulosus* infections in canids (Lightowlers et al. 2021). To achieve effective control programmes, praziquantel treatment should be repeated at least every 6 weeks, corresponding to the prepatent period of *E. granulosus* (Torgerson and Budke, 2003). In Morocco, it was demonstrated that 4-monthly treatment of owned dogs with praziquantel was insufficient to have an impact on *E. granulosus* transmission (Amarir et al. 2021). Another risk factor identified during the questionnaire survey was that most of the farmers indicated feeding uncooked viscera to their dogs. Similar findings have been documented in other endemic CE settings (Abdulhameed et al. 2018; Avila et al. 2022). These results are consistent with previous findings, which concluded that feeding dogs raw offal is a significant risk factor for increasing the risk of public infection with this parasite (Haleem et al. 2018).

As for another study conducted in Iraq, all the farmers revealed that they do not remove dog faeces from the farm ground (Abdulhameed et al. 2018). This represents a high source of infection for humans as well as for animals, since *Echinococcus* eggs can remain viable in outdoor conditions for long periods of time (Alvarez Rojas et al. 2018). Most farmers declared a high presence of stray dogs around their farms. This is a risk factor associated with the spread of CE (Rong et al. 2018), making the control of stray dogs necessary (El Berbri et al. 2020).

The results of the present study also revealed that most farmers are unfamiliar with CE and its transmission from dogs to humans and livestock. Therefore, these findings highlight the need to strengthen health education strategies among livestock farmers and rural communities (Haleem et al. 2018). An effective strategy to control CE should also include monitoring and surveillance systems in animals and humans through a One Health approach (Prata et al. 2022). Current surveillance data highlighting disease hotspots could in fact be used to identify areas which require the implementation of control measures (Entezami et al. 2022). Continuous updating of maps, or the use of dynamic mapping (Castronovo et al. 2009), on CE distribution at global and local level can improve the spatio-temporal targeting of control measures and to

enhance the cost-effectiveness of integrated disease control programmes for *E. granulosus* in definitive and intermediate hosts (Deplazes et al. 2017). However, it is important to consider that estimating the real prevalence, incidence and burden of CE can be challenging. This is due to the uneven distribution of CE within transmission areas, a high proportion of asymptomatic infected individuals and symptomatic patients living in resource-poor areas with logistical and/or economic constraints, lack of accurate diagnostic tests and the underreporting of diagnosed cases (Rossi et al. 2016). Furthermore, cases of human echinococcosis are often not identified to the species level, which poses challenges in regions where cystic and alveolar echinococcosis are co-endemic (Schurer et al. 2019). Improving the reporting system and raising awareness among governments and health ministries is the next essential step in defining the global health burden and distribution of CE (Alvi et al. 2023).

Since the mid-19th century, the public health importance of CE has been recognized and considerable efforts have been made to reduce or eliminate the disease (Craig et al. 2017; Larrieu et al. 2019; Cringoli et al. 2021). However, despite the implementation of control initiatives in several countries, CE still remains a problem in Mediterranean areas, although a decreasing trend has been recorded in most southern Mediterranean and some eastern European countries, where cystic echinococcosis has traditionally been highly prevalent (Casulli et al. 2023). Over the years, a decreasing trend in the number of CE cases was observed in ruminants in southern Europe, especially in central-southern Italy (Campania region), where updated reports on the endemic status of this area showed a prevalence value of 9.7 % in sheep (Rinaldi et al. 2023, personal communication), which is lower than that observed in prior epidemiologic investigation in the same study areas (52.5 %) (Cringoli et al. 2021). By comparing available prevalence data, including in the macro-area of central-northern Greece, a decrease of CE prevalence emerged. However, it is necessary to interpret this result with caution, since the maps were generated on the basis of an average of the prevalence referred to different areas (Central Greece, Macedonia, Thessaly and Thrace) and, within each of these, the trend of the prevalence data should be analysed more closely.

This decline in southern Europe could be attributed to the implementation of the European Union (EU)'s legal requirements. The EU system for monitoring and collection of information on zoonoses, including echinococcosis, is based on the Zoonoses Directive 2003/99/EC1, which obliges EU Member States (MS) to collect relevant and, when applicable, comparable data on zoonoses, zoonotic agents, antimicrobial resistance and food-borne outbreaks. CE is notifiable in most countries in Europe. Active surveillance is mandatory in all countries by visual

inspection of cysts in liver and lungs during meat inspection of ruminants, horses, and other susceptible animals, according to European Regulation 2019/627 (Commission Regulation (EU), 2019) (van der Giessen et al. 2021). In addition to that, in southern Italy (Conchedda et al. 2012; Cringoli et al. 2021) as well as in Greece (Sotiraki et al. 2003), control programmes against CE have been implemented for several years. Furthermore, since 2020 the regional authorities of Campania (Southern Italy) have developed a specific regulation undertaken and managed by the Veterinary Regulation Department on which the procedures and tools adopted during the integrated control programme developed and implemented by Cringoli et al. (2021) must be used regionally to target interventions aimed at further controlling CE in animals and humans. These results highlight how CE may be effectively controlled by adopting an integrated approach but a comprehensive consideration including the political level may have higher impact on this zoonosis (Rong et al. 2021).

5. Conclusions

Data obtained through the farmer questionnaire and the update of the epidemiological situation highlight that CE is still a very serious problem in Mediterranean areas. Raising awareness among farmers about the disease and the behaviours that contribute to the persistence of CE is necessary to properly control its spread. Furthermore, efforts are needed to identify potential diagnostic targets and therapeutic candidates against CE in order to reduce the spread of this disease. Future perspectives could include the development of innovative strategies based on RNA technology, which has recently proven to be effective in treating various infectious diseases, to improve CE control programmes.

Availability of data and materials

Not applicable.

Author statement

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

Consent for publication

All the authors consent the publication of the manuscript.

Ethic approval and consent to participate

This study received institutional approval from the Ethical Animal Care and Use Committee of the University of Naples Federico II (Protocol No. PG/2021/0058962).

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Supplementary materials

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