Evidence of Low Prevalence of Cystic Echinococcosis in the Catanzaro Province, Calabria Region, Italy

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Abstract. Cystic echinococcosis (CE) is one of the neglected tropical diseases recognized by the WHO. *Echinococcus granulosus sensu lato* affects more than 1 million people worldwide and is responsible for high costs in the healthcare system. A clear knowledge of the prevalence of CE and its clinical characteristics could have an important impact on the approach to its diagnosis and to the public health planning of treatment and control interventions. We performed a prevalence study in four municipalities of Catanzaro Province, South Italy. This area is considered to be at high risk of CE because of ovine breeding. We screened by abdominal ultrasound 2,426 volunteers, four of whom had abdominal CE. Given the need for prevention and control programs for CE in endemic areas of Italy, a detailed mapping of prevalence of CE, to complement data obtained through hospital discharge records, appears imperative.

INTRODUCTION

Cystic echinococcosis (CE) is a zoonotic infection caused by the larval stage of the cestode *Echinococcus granulosus sensu lato*. The parasite life cycle is maintained between canids, mainly dogs, which are definitive hosts harboring the adult stage of the parasite in the intestine, and livestock, mainly sheep, as intermediate hosts.¹ Cystic echinococcosis has a cosmopolitan distribution and is particularly prevalent where sheep raising is practiced.² Worldwide estimates suggest that 1.2 million individuals may be infected, with consistent economic losses for human treatment and animal production.³ The disease is included in the list of neglected tropical diseases for which the WHO advocates control.⁴ Furthermore, in high-income countries, CE may be considered an "orphan" disease as it is perceived as "rare" and not representing a real public health problem.⁵ Mediterranean areas of Europe have always been considered endemic for CE,⁶ and some studies have explored the clinical epidemiology of the disease using different methods. However, epidemiological data on CE are often lacking in both developing and high-income settings.

Studies based on hospital discharge records (HDR) have been performed in several countries.^{7–12} Other studies have analyzed clinical cohorts in single centers.^{13–20} However, hospital-based studies do not capture asymptomatic cases, and HDR do not account for outpatients. Differently, ultrasound-based surveys describe more accurately the epidemiology of CE at population level.^{21,22} Such studies allow for the detection of CE active transmission to humans and can provide

well-grounded estimates of disease prevalence.²² We present the results of an ultrasound population-based survey performed in four municipalities of Catanzaro Province in the Calabria region (Southern Italy), endemic for CE.⁹

METHODS

Study sites, subjects, and community outreach. Because of the unavailability of data on the prevalence of *E. granulosus* infection in animals, target sites were selected on the basis of the ratio between the number of sheep registered in the municipality and the human population, considering municipalities where the population ranged between 2,000 and 7,000 inhabitants. Indeed, the presence of CE in a geographical area has been correlated with the extent of sheep-raising activities, in particular with the density of sheep present in a territory; this has also been shown to correlate with the rates of CE-related hospitalizations.^{23,24} Therefore, we selected our target municipalities among those with the highest presence of previously diagnosed human CE cases as reported in the records of the Department of Infectious Diseases of "Mater Domini" Hospital of Catanzaro. The selected municipalities were Pianopoli (population = 2,613; territory of 24 km²), Tiriolo (population = 3,820; territory 29 km²), Serrastretta (population = 3,082; territory of 41 km²), and Guardavalle (population = 4,463; territory of 60 km²). Figure 1 shows the localization of study sites.

Local communities were informed of the study using printed material (leaflets and posters) displayed in public locations and distributed in cooperation with public health and civil authorities and general practitioners based in the target sites. Public broadcasts through local television networks and press releases were also issued before the start of the screening activities at each site. The screening team, together with civil and health authorities, held a public meeting with communities before starting the work at each site to explain the purpose and

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FIGURE 1. Sites in Calabria region (Italy) included in the study. (A) Map of Italy; the black box frames the province of Catanzaro where the study was conducted. (B) Magnification of the box framing the municipalities of Pianopoli, Tiriolo, Serrastretta, and Guardavalle where the study was carried out, with the localization of screening sites. This figure appears in color at www.ajtmh.org.

implementation of the study and to answer any questions arising from the audience.

Ultrasound screening. Public locations (e.g., town halls) provided by civil authorities were used as settings for the screenings. For practical reasons, convenience sampling was conducted on subjects voluntarily participating in the study, with the sole exclusion criteria of children younger than 5 years. Before enrollment, participants were given a brief overview of CE and information about the scope of the study, the execution of the abdominal ultrasound with the implications and limits of a screening activity, and the voluntary, free-of-charge nature of their participation.

Written informed consent was obtained from adult participants. In the case of minors or subjects who were not able to willingly provide consent, this was granted by their parents or legal guardians. Abdominal ultrasound examinations were conducted with four portable machines: Sonosite M-Turbo, Sonosite 180 plus (Fujifilm, Japan), Logiq V2 (General Electric, Boston, MA), and Z-6 (Mindray, China). Examinations were performed by physicians trained in general abdominal ultrasound and proficient in the diagnosis and staging of CE cysts according to the WHO Informal Working Group on Echinococcosis (IWGE) classification²⁵. Images and video files of any lesion found during the examinations were recorded using an anonymized patient identification code and electronically stored. Participants were systematically asked if they had undergone any imaging examination in the 5 years before this screening and if they had received any previous diagnosis or treatment for CE.

Participants diagnosed with any medically relevant findings were provided with a written report and iconographic material, and referred for further clinical management to local national health centers liaising with the staff of the Department of Infectious Diseases of the University of Catanzaro. Individuals with CE were managed according to the WHO-IWGE Expert consensus for the clinical management of CE.²⁵

Sample size. The minimum sample size of 1,522 subjects was calculated based on an estimated prevalence of 1% with a precision of 0.5% and 95% confidence level. For ethical reasons, participation to the screening was not denied to all subjects fulfilling the inclusion criteria who presented to the screening site, even after reaching an adequate sample size.

Ethical statement. The study was approved by the Ethics Committee of the Policlinico San Matteo Hospital Foundation, Pavia, Italy (prot. N. 20180060669). Data and images were pseudonymized and stored, and analyses were carried out in accordance with Italian legislation on personal data protection.

RESULTS

A total of 2,426 volunteers were screened in 28 days. Of these, 2,147 (88.5%) were residents in the target municipalities, while 279 (11.5%) came from villages within a few kilometers. Table 1 shows the number of the investigated population in screening sites. Among the total population screened, 1,506 (62.07%) were females and the median age was 51 (range, 5–91) years; 1,471 (60.6%) participants reported having undergone imaging examinations in the 5 years before the ultrasound performed as part of this study. CE cysts were found in four individuals (0.16%); in all cases, they were single hepatic cysts in inactive stage (CE4).²⁵ In all cases, the cysts were already known by the participant, and in two cases surgery had been proposed at diagnosis, notwithstanding the uncomplicated inactive stage. Five subjects (0.2%) reported previous surgery for CE, and no new abdominal CE cysts were detectable during the screening examination. Three participants (0.1%), two of whom having a family history of CE, reported having a lesion suspect of CE, which was subsequently disproved, with a final diagnosis of unspecific liver calcifications in two cases, and multiple simple biliary and renal cysts in the other. Non-CE focal lesions found during the screening are detailed in Table 2.

DISCUSSION

The characteristics of CE make it difficult to clarify its epidemiology and burden in many regions of the world.²⁶ Southern regions and islands of Italy are considered endemic for CE.⁹ However, although notification of all CE cases in Italy is mandatory, de facto only hospitalized cases with a primary or secondary diagnosis of CE are notified to the Italian Ministry of Health through HDR. Therefore, the only available data in Italy refer to the incidence of hospitalized CE cases, which represent only a fraction of the infected population. Moreover, HDR are burdened by inaccuracy and incompleteness.⁹

TABLE 1

Number of people screened and total resident population in the study sites in Catanzaro Province, Calabria region, Italy

Study site	Number screened	Total population	%
Pianopoli	544	2,613	20.8
Serrastretta	590	3,082	19.1
Tiriolo	457	3,820	11.9
Guardavalle	556	4,463	12.4
Total*	2,147	13,798	15.3

*Another 279 coming from municipalities adjacent to the target sites were also included, bringing the total number of enrolled subjects to 2426.

TABLE 2

Non-Cystic echinococcosis focal lesions found during the screening in Catanzaro Province, Italy

Diagnosis	Organ	N	%
Cystic echinococcosis	Liver	4	0.16
Hemangioma	Liver	61	2.51
Simple cyst	Liver	115	4.74
Calcification	Liver	36	1.48
Focal liver lesion of suspected malignant origin*	Liver	5	0.2
Angiomyolipoma	Kidney	21	0.86
Simple cyst	Kidney	295	12.1
Suspect kidney cancer*	Kidney	4	0.16
Hemangioma	Spleen	3	0.12
Simple cyst	Spleen	7	0.28
Suspect simple cyst*	Pancreas	7	0.28
Fibroma	Uterus	63	2.59
Suspect sarcoma*	Uterus	3	0.12
Simple cyst	Ovary	62	2.55
Suspect bladder cancer*	Bladder	1	0.04

*All patients with suspect lesions were referred for second-level investigation as appropriate (e.g., RMN of the abdomen for pancreatic cysts).

Based on HDR, the Calabria region shows an annual incidence of 2.6 cases/100,000 population. As such, it ranks as the fifth most endemic region in Italy.⁹ However, no precise animal data on CE infection are available, as no systematic surveillance at abattoirs, especially for small ruminants, is carried out in Italy.²³ Recent work has used data modeling to estimate the prevalence of animal infection in Calabria, resulting in very low figures.²³

In this epidemiological context, we decided to carry out an ultrasound-based survey in four villages in the Catanzaro Province of Calabria. Such studies can provide more accurate estimates of disease prevalence and information on the presence of ongoing transmission.^{21,22,27} Incidence of CE in the selected province, according to data derived from HDR, is 2–4 cases/100,000 population.⁹ In our study, the prevalence of abdominal CE by ultrasound was 0.16%, far lower than what found in studies carried out in Morocco, Turkey, Bulgaria, and Romania, all areas where CE is considered as endemic as in Southern Italy.^{22,28} Also, we could not find cysts in active stages, which arguably indicates the lack of active transmission in the surveyed areas. The percentage of the resident population screened in the target municipalities (Table 1) allows us to confidently state that the four villages present a low prevalence of human CE. However, our screening included 0.7% of the whole population of the Catanzaro Province. Therefore, we cannot generalize our results to the whole province or region.

Interestingly, we did find cases misdiagnosed as CE and individuals with asymptomatic inactive CE cysts to whom unnecessary invasive treatment was proposed, contrary to what recommended by the WHO-IWGE.²⁵ This highlights the well-known problem of poor knowledge of CE, its diagnosis, and clinical management outside referral centers, with attendant unnecessary risks for the patients and private and/or public health costs, especially when surgical management is applied indiscriminately.^{16,29–31} It is also interesting that 60% of volunteers presenting to our screening sites reported having already undergone a radiological examination able to detect CE in the 5 years before the screening. On the one hand, this may indicate a self-selection bias in our studied population, as it is possible that people more keen on undergoing medical checkups were also keener on taking advantage of the study screening. On the other hand, this also suggests that

in settings where access to health care is available, such as in the case of the Italian universal coverage health system, a likely large proportion of the potentially infected population is and can be captured by the health system. In such context, a surveillance, based on the notification of all CE cases, is feasible, while population screening campaigns may have a less important role than in resource-poor settings. In line with this observation, a previous study looked at the rate of CE patients diagnosed in 19 ultrasound units in Italy, reporting a prevalence of CE of 0.7% over their studied cohort.³² In the last few years, the European Register of Cystic Echinococcosis (ERCE) has been set up.³⁴ At the time of this publication, the total number of cases recorded in the ERCE from European centers was superior to the number of cystic and alveolar echinococcosis cases annually notified across Europe since the existence of the registry, and the total number of cases, including those entered by non-European centers, was more than 2,000 (P. Rossi, personal communication³⁴). The ERCE, therefore, can be a valuable starting platform to implement a notification system of both inpatient and outpatient CE cases and a standardized case retrieval for observational clinical research.

To conclude, our survey suggests a low prevalence of human CE in the investigated areas, with likely absent or low-level ongoing transmission, in a region traditionally considered highly endemic for CE. The result of this survey, together with 60% of its participants declaring having undergone imaging examinations in the 5 years before this study and HDR data reporting CE cases in this area, suggests that the Italian universal coverage health system is capturing a large proportion of subjects with CE, but these data fail to reach the official statistics. In this context, where virtuous health systems are in place, CE should be regarded as an orphan disease and patients should be managed by interdisciplinary teams in referral centers, thus avoiding the malpractice of surgery in inactive cysts. Surveillance activities are needed to better map, at both human and animal levels, the endemic areas for CE in Italy, to optimize public health policies on human and animal infection.

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