Prevalence of abdominal cystic echinococcosis in rural Bulgaria, Romania, and Turkey: a cross-sectional, ultrasound-based, population study from the HERACLES project

Francesca Tamarozzi, Okan Akhan*, Carmen Michaela Cretu*, Kamenna Vutova*, Devrim Akinci, Rossitza Chipeva, Turkmen Ciftci, Corina Manuela Constantin, Massimo Fabiani, Branimir Golemanov, Denisa Janta, Patricia Mihailescu, Marin Muhtarov, Serra Orsten, Marius Petrutescu, Patrizio Pezzotti, Alexandru Cosmin Popa, Loredana Gabriela Popa, Mircea Ioan Popa, Valeri Velev, Mar Siles-Lucas, Enrico Brunetti, Adriano Casulli*

Summary

Background **Cystic echinococcosis is a neglected zoonotic infection that is distributed worldwide and prioritised by WHO for control efforts. The burden of human cystic echinococcosis is poorly understood in most endemic regions, including eastern Europe. We aimed to estimate the prevalence of abdominal cystic echinococcosis in rural areas of Bulgaria, Romania, and Turkey.**

Methods **We did a cross-sectional ultrasound-based survey that recruited volunteers from 50 villages in rural areas of Bulgaria, Romania, and Turkey. These villages were in provinces with annual hospital incidence of cystic echinococcosis within the mid-range for the respective countries. All people who attended a session were allowed to participate if they agreed to be screened. Abdominal ultrasound screening sessions were hosted in public community structures such as community halls, primary health-care centres, schools, and mosques. Lesions were classified using an adapted WHO classification. We reported the prevalence of abdominal cystic echinococcosis adjusted by sex and age through direct standardisation, using the country's rural population as a reference.**

Findings **From July 1, 2014, to Aug 3, 2015, 24 693 individuals presented to screening sessions and 24 687 underwent ultrasound screening. We excluded a further six indivduals due to missing data, leaving 24 681 people in our analysis. Abdominal cystic echinococcosis was detected in 31 of 8602 people screened in Bulgaria, 35 of 7461 screened in Romania, and 53 of 8618 screened in Turkey. The age and sex adjusted prevalence of abdominal cystic echinococcosis was 0·41% (95% CI 0·29–0·58) in Bulgaria, 0·41% (0·26–0·65) in Romania, and 0·59% (0·19–1·85) in Turkey. Active cysts were found in people of all ages, including children, and in all investigated provinces.**

Interpretation **Our results provide population-based estimates of the prevalence of abdominal cystic echinococcosis. These findings should be useful to support the planning of cost-effective interventions, supporting the WHO roadmap for cystic echinococcosis control.**

Funding **European Union Seventh Framework Programme.**

Introduction

Cystic echinococcosis is a chronic and disabling neglected zoonotic infection caused by the larval stage of the tapeworm *Echinococcus granulosus* sensu lato. Human cystic echinococcosis is most prevalent in poor pastoral communities that have close contact with the hosts—usually domestic dogs and sheep.[1] In human beings, the liver is most commonly affected, followed by the lungs. About 60–75% of individuals with hepatic cystic echinococcosis are asymptomatic and can remain so for many years and symptoms, when present, are non-specific.[2] Additionally, some cysts inactivate spontaneously.[2] Unfortunately, no marker is available to predict the development of a cyst toward stability, inactivation, or progression.

Cystic echinococcosis is 100% preventable and is one the seven neglected zoonotic diseases for which WHO advocates concerted control efforts.[3] However, the burden of disease is difficult to measure. Many cases do not reach official statistics, resulting in underestimates and misconceptions about the magnitude of the public health problem.[4] More than 1 million people are estimated to be infected worldwide, with over 1 million disability-adjusted life-years (accounting for under-reporting) lost every year.[5,6] The global costs of cystic echinococcosis per year are estimated at more than US$750 million for human infection and more than $2 billion for livestock infection.[5] However, these estimates rely heavily on modelling, which uses arbitrary assumptions and highly heterogeneous data sources; as a result, the disease burden is probably underestimated.[4,7]

Cystic echinococcosis is highly endemic in western China, central Asia, South America, eastern Europe, the eastern and southern Mediterranean region, and

Lancet Infect Dis 2018

Published Online
May 21, 2018
http://dx.doi.org/10.1016/S1473-3099(18)30221-4

See Online/Comment
http://dx.doi.org/10.1016/S1473-3099(18)30299-8

*Contributed equally

WHO Collaborating Centre for Clinical Management of Cystic Echinococcosis (F Tamarozzi PhD, Prof E Brunetti MD), **Department of Clinical Surgical Diagnostic and Pediatric Sciences, University of Pavia** (F Tamarozzi, Prof E Brunetti), **Division of Tropical and Infectious Diseases, San Matteo Hospital Foundation** (Prof E Brunetti), **Pavia, Italy; Center for Tropical Diseases, Sacro Cuore-Don Calabria Hospital, Negrar, Verona, Italy** (F Tamarozzi); **WHO Collaborating Centre for the Epidemiology, Detection and Control of Cystic and Alveolar Echinococcosis** (F Tamarozzi, A Casulli PhD), **European Reference Laboratory for Parasites and Unit of Foodborne and Neglected Parasitic Diseases** (A Casulli), **Unit of Epidemiology, Biostatistics and Mathematical Modelling** (M Fabiani Dstat, P Pezzotti Dstat), **Department of Infectious Diseases, Istituto Superiore di Sanità, Rome, Italy; Department of Radiology, Faculty of Medicine** (Prof O Akhan MD, Prof D Akinci MD, T Ciftci MD) **and School of Health Services** (S Orsten PhD), **Hacettepe University, Ankara, Turkey; Microbiology** (L G Popa PhD), **Parasitology** (C M Cretu MD), **Surgery** (A C Popa MD), **Carol Davila University of Medicine and Pharmacy, Colentina Clinical Hospital, Bucharest, Romania; Microbiology, Carol**

Davila University of Medicine and Pharmacy, Cantacuzino National Institute for Research, Bucharest, Romania (Prof M I Popa)**; National Institute of Public Health, Bucharest, Romania** (D Janta MD)**; Surgery** (C M Constantin MD), **Parasitology** (M Petrutescu MD), **Eco-Para-Diagnostic** (P Mihailescu BSc), **Colentina Clinical Hospital, Bucharest, Romania; Specialized Hospital for Active Treatment of Infectious and Parasitic Diseases Prof Ivan Kirov, Department of Infectious, Parasitic and Tropical Diseases** (Prof K Vutova PhD, R Chipeva MD, V Velev PhD) **Sofia, Bulgaria; Clinical Centre of Gastroenterology, University Hospital Queen Joanna—Institute for Specialization and Improvement of Medical Doctors, Medical Faculty, Medical University, Sofia, Bulgaria** (B Golemanov MD)**; Colentina Clinical Hospital, Eco-Para-Diagnostic, Bucharest, Romania** (P Mihailescu BSc)**; Multi-Profile Hospital for Active Treatment Kardzhali, Gastroenterology Ward, Kardzhali, Bulgaria** (M Muhtarov PhD)**; and Parasitology Unit, Instituto de Recursos Naturales y Agrobiología de Salamanca, IRNASA-CSIC, Salamanca, Spain** (M Siles-Lucas PhD)

Correspondence to:
Dr Adriano Casulli, WHO Collaborating Centre for Clinical Management of Cystic Echinococcosis, Department of Infectious Diseases, Istituto Superiore di Sanità, Rome 00161, Italy
adriano.casulli@iss.it

For more on the **HERACLES project** see http://www.heracles-fp7.eu/

Research in context

Evidence before this study

We searched PubMed and Google Scholar in Oct 16, 2017, with no restrictions on language or year of publication and identified one ultrasound-based population study on cystic echinococcosis due to *Echinococcus granulosus* sensu lato in Bulgaria and six such studies in Turkey, which were done on a limited number of people, geographical area, or age groups. No published ultrasound-based population studies of human cystic echinococcosis in Romania were available. Cretu and colleagues did three ultrasound screening sessions in 2004–09, which included 4176 individuals in three provinces of Romania, but their data have only been presented as congress proceedings. Similar to other neglected tropical diseases, in global estimation projects such as the Global Burden of Disease studies, estimates of the burden of cystic echinococcosis have relied heavily on modelling approaches to fill in data gaps, with arbitrary assumptions and highly heterogeneous data sources. Population-based imaging studies have been done in areas of known high endemicity, often without a rigorous case definition, thus limiting the possibility of extrapolating results to the regional or country level. So far, no studies have estimated the burden of human cystic echinococcosis in eastern Europe.

Added value of this study

We provide estimates of the prevalence of abdominal cystic echinococcosis in the rural population of three countries of eastern Europe and the identification of cyst characteristics. We provide, to our knowledge, the first estimate of the population-based prevalence of abdominal cystic echinococcosis to be based on a large sample with a rigorous case definition, as well as a description of the cyst stage distribution, which could reflect transmission activity.

Implications of all the available evidence

The burden of human cystic echinococcosis is unknown or underestimated in most endemic regions, and control programmes lag behind the WHO roadmap schedule for elimination. This is partly due to difficulties in measuring the real burden of disease, which results in underestimation of the prevalence of cystic echinococcosis. Cystic echinococcosis continues to constitute a public health problem in eastern Europe. Our results will help public health stakeholders investigate the need for control of cystic echinococcosis, including preliminary cost-benefit analyses.

areas of east Africa.[1,5] In endemic areas, the annual incidence of cases reaching medical attention might be more than 30 per 100 000 and prevalence up to 10%.[4,5] Bulgaria reports the highest annual incidence in Europe, with 4·35 officially notified cases per 100 000, compared with the average 0·20 per 100 000 in the European Union and European Economic Area in 2015.[8] In Romania, reported hospital incidence in the first decade of the 2000s was up to 7·2 per 100 000.[9] In 2013, 104 cases were recorded in a single centre (Colentina Teaching Hospital, Bucharest), but only 55 cases were reported in official European statistics at the national level,[8] suggesting substantial under-reporting. In Turkey, data from the Ministry of Health show an incidence of up to 12 per 100 000, mostly based on surgical cases, since 1997.[10,11]

Population surveys might provide more reliable—and partly complementary—data than estimates from hospital-based records and thereby help inform decisions on the need for implementing control programmes. Population-based imaging studies have been done in some areas of high endemicity.[12] However, very few ultrasound-based surveys for cystic echinococcosis have been done in eastern Europe. Only one such study in Bulgaria, in Kardzhali district, has been published.[13] No published studies are available from Romania; Cretu and colleagues[14] did three ultrasound screenings in 2004–09, with a total of 4176 individuals in three provinces of Romania, but these results have been published only as congress proceedings. In Turkey, six studies were done in the Eastern and Central Anatolia and Aegean regions, but only on a small number of people or with restrictions on age groups.[15–20] No estimates of the burden of cystic echinococcosis have so far been made in these three countries, as well as in other endemic eastern European countries. To address this gap, the Human cystic Echinococcosis ReseArch in CentraL and Eastern Societies (HERACLES) project was funded by the European Commission in 2013. This study aims to estimate the prevalence of abdominal cystic echinococcosis, cyst stage distribution, and number of infected individuals in the rural populations of Bulgaria, Romania, and Turkey through ultrasound screening.

Materials and methods

Study design and survey organisation

This was a cross-sectional ultrasound-based survey that recruited volunteers from 50 villages in four districts of Bulgaria, five districts of Romania, and six provinces of Turkey (figure). Provinces, districts, and villages were selected sequentially. First, we identified provinces or districts that reported an average annual hospital incidence of cystic echinococcosis in the mid-range for each country. In Bulgaria and Romania this selection was based on official data from national authorities for 2008–12.[21,22] Recent data were not available for Turkey; provinces across the country were selected on the basis of data from 2001–05.[11] Second, within each province or district, villages were selected where local authorities, who were contacted by the country's project staff, were willing to host the survey. For ethical reasons, ultrasound

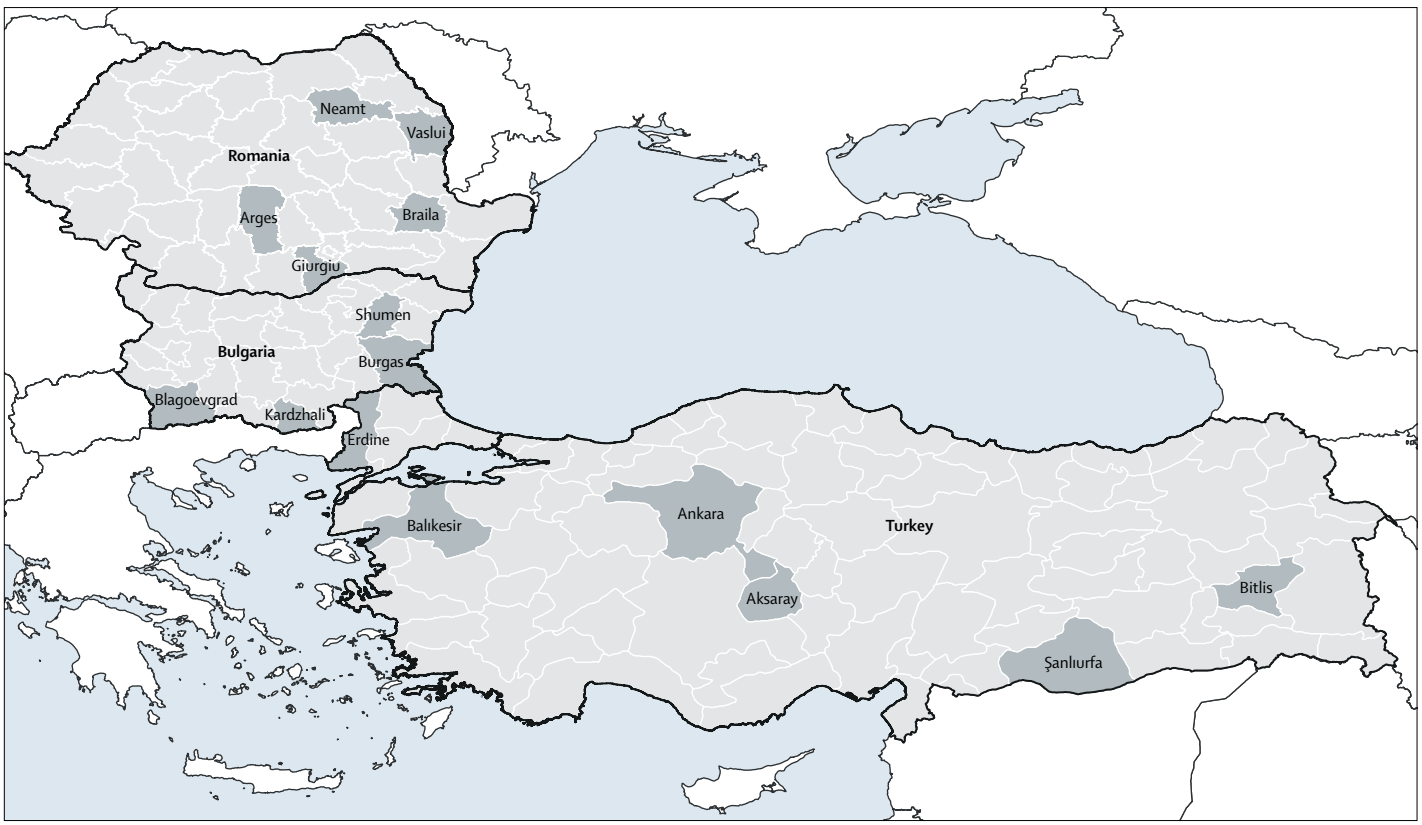

Figure: **Provinces and districts of Bulgaria, Romania, and Turkey included in this study**
Provinces and districts are indicated with their nomenclature of territorial units for statistics codes. In Bulgaria, the rural population was 66 955 in Shumen, 98 897 in Burgas, 126 836 in Blagoevgrad, and 89 135 in Kardzhali. In Romania the rural population was 294 609 in Neamt, 234 499 in Vaslui, 116 900 in Braila, 323 752 in Arges, and 195 663 in Giurgiu. In Turkey, the rural population was 819 006 in Şanlıurfa, 160 667 in Bitlis, 128 198 in Edirne, 467 473 in Balıkesir, 128 487 in Ankara, and 149 656 in Aksaray.

screening was done in a convenience sample of all volunteers of either sex who lived in the targeted provinces, presented to the screening sessions, and provided signed informed consent.

Consent to hold the screening sessions was obtained from local health and civil authorities and community leaders in each village. General information about the infection and the activities of the HERACLES project was provided to local authorities and the general population through meetings, local television and newspaper interviews, advertisements, and informative material (eg, flyers, posters, electronic displays in public squares) distributed through local authorities. Health education on cystic echinococcosis was also provided by the project team during the survey sessions, which were hosted in community public structures such as community hall, primary health-care centres, schools, and mosques.

Ethical approval for the study was granted by the ethics committees of the Specialized Hospital for Active Treatment of Infectious and Parasitic Diseases Prof Ivan Kirov (Sofia, Bulgaria), Colentina Teaching Hospital (Bucharest, Romania), and Hacettepe University Hospital (Ankara, Turkey).

Procedures

Ultrasound scans were done by radiologists and clinicians working in HERACLES project partners' referral centres for cystic echinococcosis, who had long-standing experience in the diagnosis of cystic echinococcosis with ultrasound. Patients with cystic echinococcosis or suspected cystic echinococcosis were offered free transportation to and clinical management at the country's referral hospitals for cystic echinococcosis. A protocol for the diagnosis and clinical management of cystic echinococcosis was adopted for the abdominal ultrasound screening sessions. The protocol was based on the WHO Informal Working Group on Echinococcosis (IWGE) Expert Consensus on clinical management of cystic and alveolar echinococcosis[23] and adapted to the availability of clinical management options in each country. The protocols implemented in each country are provided in the appendix. For ethical reasons, follow-up every 6 months for 2 years was also offered free of charge. The cost for diagnosis and treatment was covered by the project for patients identified during the screening who required medical attention for causes other than cystic echinococcosis but had no access to national health insurance.

See Online for appendix

All lesions visualised on ultrasound as being attributable to cystic echinococcosis were assessed by two sonographers during screening, and images and video files of all cases were re-evaluated by a core team of the project's sonographers for case-definition and cyst staging before the data were analysed. Staging was based on the WHO-IWGE classification,[23] which includes six cyst stages based on ultrasound morphology, grouped into active (CE1–CE2), transitional (CE3a–CE3b), and inactive (CE4–CE5) classes. For the purpose of this study, we applied the more stringent condition that cysts with a visible wall but with no double wall sign were classified as cystic lesions without pathognomonic signs of parasitic aetiology (CL) and regarded as suspect cysts. Furthermore, patients with at least one CE1, CE2, CE3a, or CE3b stage cyst were operationally classified as having active cysts; patients with only CE4 and CE5 cysts were classified as having inactive cysts. This deviation from the WHO-IWGE classification was based on clinical and biological data on the viability of different cystic echinococcosis stages and treatment recommendations;[2,23,24] indeed, the so-called transitional cysts group includes both a viable stage (CE3b) and a stage with unclear viability (CE3a) for which treatment is in any case recommended.[2,23,24]

Because of logistical constraints, only patients who visited the project's country hospitals to be treated for cystic echinococcosis received chest radiography for the detection of possible cystic echinococcosis of the lung. During the field ultrasound surveys, all participants were asked about previous cystic echinococcosis diagnoses and treatments; however, it was not possible to verify the individuals' medical records. Suspect lesions and residual cavities in patients reporting surgical or percutaneous treatment for cystic echinococcosis who presented with ultrasound features suggestive of a relapse were investigated in accordance with the protocol to define the nature of the lesion (appendix).

For our prevalence estimates, we defined patients with cystic echinococcosis in three ways: newly diagnosed cystic echinococcosis, which included all participants diagnosed with abdominal cystic echinococcosis during the ultrasound survey and who had never received previous treatment for cystic echinococcosis; cystic echinococcosis by imaging, which included all participants in the previous group and those with cystic echinococcosis cysts on ultrasound who reported having received previous treatment for cystic echinococcosis; and cystic echinococcosis by imaging or recall, which included all participants in the previous two groups and those who self-reported treatment for cystic echinococcosis but had no cystic echinococcosis cysts detected during the survey (appendix). For the statistical

	Sample			Reference rural population, 2015		
	Women	Men	Total	Women	Men	Total
Bulgaria						
<20 years	927 (16·1%)	830 (29·0%)	1757 (20·4%)	165 258 (17·1%)	176 246 (18·4%)	341 504 (17·7%)
20–29 years	372 (6·5%)	190 (6·6%)	562 (6·5%)	92 267 (9·5%)	107 974 (11·3%)	200 241 (10·4%)
30–39 years	794 (13·8%)	301 (10·5%)	1095 (12·7%)	103 034 (10·6%)	122 412 (12·8%)	225 446 (11·7%)
40–49 years	1033 (18·0%)	334 (11·7%)	1367 (15·9%)	114 312 (11·8%)	133 987 (14·0%)	248 299 (12·9%)
50–59 years	1224 (21·3%)	484 (16·9%)	1708 (19·9%)	123 387 (12·7%)	137 727 (14·4%)	261 114 (13·6%)
≥60 years	1392 (24·2%)	721 (25·2%)	2113 (24·6%)	370 513 (38·2%)	279 485 (29·2%)	649 998 (33·7%)
Total	5742 (100%)	2860 (100%)	8602 (100%)	968 771 (100%)	957 831 (100%)	1 926 602 (100%)
Romania						
<20 years	993 (19·4%)	693 (29·7%)	1686 (22·6%)	1 033 095 (22·6%)	1 094 626 (23·9%)	2 127 721 (23·3%)
20–29 years	398 (7·8%)	110 (4·7%)	508 (6·8%)	493 721 (10·8%)	584 333 (12·8%)	1 078 054 (11·8%)
30–39 years	656 (12·8%)	188 (8·1%)	844 (11·3%)	582 748 (12·8%)	645 339 (14·1%)	1 228 087 (13·4%)
40–49 years	844 (16·5%)	312 (13·4%)	1156 (15·5%)	599 120 (13·1%)	720 247 (15·8%)	1 319 367 (14·4%)
50–59 years	666 (13·0%)	315 (13·5%)	981 (13·1%)	490 349 (10·7%)	536 800 (11·7%)	1 027 149 (11·2%)
≥60 years	1569 (30·6%)	717 (30·7%)	2286 (30·6%)	1 366 271 (29·9%)	989 383 (21·6%)	2 355 654 (25·8%)
Total	5126 (100%)	2335 (100%)	7461 (100%)	4 565 304 (100%)	4 570 728 (100%)	9 136 032 (100%)
Turkey						
<20 years	1291 (26·9%)	1252 (32·8%)	2543 (29·5%)	3 038 126 (34·0%)	3 202 763 (35·7%)	6 240 889 (34·9%)
20–29 years	485 (10·1%)	322 (8·4%)	807 (9·4%)	1 178 004 (13·2%)	1 258 652 (14·0%)	2 436 656 (13·6%)
30–39 years	755 (15·7%)	534 (14·0%)	1289 (15·0%)	1 115 901 (12·5%)	1 168 183 (13·0%)	2 284 084 (12·8%)
40–49 years	758 (15·8%)	547 (14·3%)	1305 (15·1%)	1 036 607 (11·6%)	1 068 705 (11·9%)	2 105 312 (11·8%)
50–59 years	694 (14·5%)	514 (13·5%)	1208 (14·0%)	970 540 (10·9%)	946 874 (10·6%)	1 917 414 (10·7%)
≥60 years	816 (17·0%)	650 (17·0%)	1466 (17·0%)	1 584 716 (17·8%)	1 317 160 (14·7%)	2 901 876 (16·2%)
Total	4799 (100%)	3819 (100%)	8618 (100%)	8 923 894 (100%)	8 962 337 (100%)	17 886 231 (100%)

Table 1: **Screened populations and reference rural populations, by sex and age group**

analysis, patients with lesions suspected of being attributable to cystic echinococcosis were considered to be cystic echinococcosis-negative.

Statistical analysis

The demographic characteristics of the study sample populations and the 2015 study rural populations,[25–27] were described as numbers and percentages. For each country, the overall and province-specific prevalences of cystic echinococcosis infection were adjusted with direct standardisation by sex and age group based on the respective country's rural population in 2015 as a reference. Age groups were defined so they included cases within each age and sex stratum. Differences in cystic echinococcosis prevalence among provinces were assessed with the Pearson χ^2 test corrected for the sampling design with the second-order correction of Rao and Scott and converted into an *F* statistic. The test was done with the observed and expected frequencies calculated by weighting data according to the relative age and sex distribution of the reference population. To allow a comparison with other European countries, we also adjusted the overall cystic echinococcosis prevalence, using the 2013 European population by sex and age as a standard reference.[28] For each country, the number of people infected with cystic echinococcosis in the population was estimated by multiplying the adjusted prevalence by the 2015 rural population size for the respective countries. All estimates were presented with 95% CIs calculated with the logit transformation and accounting for the increased variance due to the sampling design through the Taylor linearisation method.

We also estimated the sex-specific and age group-specific prevalence of cystic echinococcosis and the proportion of active cysts in individuals who had never been treated for cystic echinococcosis. We used multivariable logistic models to assess the association of demographic variables with cystic echinococcosis infection and cyst activity, with random effects included in the models to account for clustering at the village and patient levels, respectively. We used adjusted odds ratios (OR) with 95% CI to describe the strength of these associations. We set the statistical significance level at a two-sided p value less than 0·05. We did the statistical analyses with Stata/MP version 14.2.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From July 1, 2014, to Aug 3, 2015, 24693 individuals presented to the study sessions, including 8602 in Bulgaria, 7467 in Romania, and 8624 in Turkey. Data from 12 individuals were excluded from the analysis because of refusal to undergo the ultrasound examination (six participants in Romania) and missing age information (six participants in Turkey). Of the 24681 individuals analysed, median age was 46 years (IQR 27–59) in Bulgaria, 45 years (24–63) in Romania, and 37 years (15–53) in Turkey. The demographic distribution of the screened and analysed population and of the general resident rural population of the study areas is detailed in table 1. Participants represented between 1·1% (4155 of 89135 individuals) and 4·7% (4155 of 89135) of the resident population of each selected province in Bulgaria, between 0·5% (1648 of 323752) and 1·1% (1253 of 116900) in Romania, and between 0·1% (847 of 819006) and 2·1% (3122 of 149656) in Turkey (appendix).

The number of individuals with abdominal cystic echinococcosis detected during the surveys and the crude prevalence of infection are shown in table 2. When adjusting for age and sex by direct standardisation, the prevalence of abdominal cystic echinococcosis by imaging was 0·41% (95% CI 0·29–0·58) in Bulgaria, 0·41% (0·26–0·65) in Romania, and 0·59% (0·19–1·85) in Turkey (table 2). Most cases were diagnosed for the first time during the screening sessions (table 2). Cystic echinococcosis prevalence by sex and age groups varied between countries (table 3). In all countries, prevalence was not significantly different between men and women, for both new diagnoses and cystic echinococcosis

	Newly diagnosed cystic echinococcosis	Cystic echinococcosis by imaging
Bulgaria		
Abdominal cystic echinococcosis detected/ participants screened	17/8602	31/8602
Crude prevalence	0·20% (0·14–0·28)	0·36% (0·26–0·50)
Standardised prevalence		
Reference Bulgarian rural population, 2015	0·21% (0·15–0·29)	0·41% (0·29–0·58)
Reference European population, 2013	0·20% (0·15–0·28)	0·39% (0·28–0·56)
Romania		
Abdominal cystic echinococcosis detected/ participants screened	29/7461	35/7461
Crude prevalence	0·39% (0·24–0·63)	0·47% (0·28–0·79)
Standardised prevalence		
Reference Romanian rural population, 2015	0·35% (0·23–0·54)	0·41% (0·26–0·65)
Reference European population, 2013	0·37% (0·24–0·56)	0·42% (0·27–0·67)
Turkey		
Abdominal cystic echinococcosis detected/ participants screened	46/8618	53/8618
Crude prevalence	0·53% (0·19–1·50)	0·61% (0·20–1·89)
Standardised prevalence		
Reference Turkish rural population, 2015	0·51% (0·18–1·49)	0·59% (0·19–1·85)
Reference European population, 2013	0·59% (0·20–1·75)	0·67% (0·21–2·13)

Data are n/N or % (95% CI). Standardised prevalence is directly standardised by age and sex using the 2015 rural population of each country or the 2013 European population as the reference.

Table 2: **Prevalence of abdominal cystic echinococcosis**

	Newly diagnosed cystic echinococcosis				Cystic echinococcosis by imaging			
	Cases/participants screened (%)	Standardised prevalence* (95% CI)	Odds ratio (95% CI)	p value	Cases/participants screened	Standardised prevalence*% (95% CI)	Odds ratio (95% CI)	p value
Bulgaria								
Age (years)			1·01 (0·77–1·31)	0·9448			1·02 (0·86–1·21)	0·8004
<20	3/1757 (0·17%)	0·19% (0·08–0·42)			6/1757 (0·34%)	0·36% (0·18–0·75)		
20–29	2/562 (0·36%)	0·41% (0·10–1·67)			3/562 (0·53%)	0·69% (0·23–2·07)		
30–39	3/1095 (0·27%)	0·30% (0·11–0·82)			4/1095 (0·37%)	0·48% (0·13–1·69)		
40–49	1/1367 (0·07%)	0·04% (0·01–0·34)			3/1367 (0·22%)	0·25% (0·06–0·99)		
50–59	3/1708 (0·18%)	0·19% (0·06–0·58)			6/1708 (0·35%)	0·44% (0·22–0·90)		
≥60	5/2113 (0·24%)	0·20% (0·08–0·51)			9/2113 (0·43%)	0·37% (0·23–0·60)		
Sex								
Female	11/5742 (0·19%)	0·22% (0·14–0·35)	1		18/5742 (0·31%)	0·37% (0·27–0·51)	1	
Male	6/2860 (0·21%)	0·20% (0·12–0·32)	1·11 (0·57–2·16)	0·7292	13/2860 (0·45%)	0·45% (0·28–0·71)	1·53 (0·98–2·40)	0·0592
Total	17/8602 (0·20%)	0·21% (0·15–0·29)			31/8602 (0·36%)	0·41% (0·29–0·58)		
Romania								
Age (years)			1·30 (1·10–1·53)	0·0027			1·27 (1·08–1·49)	0·0046
<20	1/1686 (0·06%)	0·07% (0·01–0·63)			2/1686 (0·12%)	0·12% (0·03–0·52)		
20–29	1/508 (0·20%)	0·12% (0·01–0·92)			1/508 (0·20%)	0·12% (0·01–0·92)		
30–39	4/844 (0·47%)	0·29% (0·11–0·78)			4/844 (0·47%)	0·29% (0·11–0·78)		
40–49	6/1156 (0·52%)	0·44% (0·17–1·15)			7/1156 (0·61%)	0·50% (0·18–1·38)		
50–59	2/981 (0·20%)	0·33% (0·10–1·12)			4/981 (0·41%)	0·48% (0·17–1·29)		
≥60	15/2286 (0·66%)	0·71% (0·40–1·24)			17/2286 (0·74%)	0·78% (0·44–1·37)		
Sex								
Female	18/5126 (0·35%)	0·34% (0·17–0·68)	1		24/5126 (0·47%)	0·44% (0·22–0·91)	1	
Male	11/2335 (0·47%)	0·37% (0·23–0·61)	1·32 (0·57–3·06)	0·5031	11/2335 (0·47%)	0·37% (0·23–0·61)	1·00 (0·43–2·31)	0·9962
Total	29/7461 (0·39%)	0·35% (0·23–0·54)			35/7461 (0·47%)	0·41% (0·26–0·65)		
Turkey								
Age (years)			1·28 (1·13–1·45)	0·0019			1·26 (1·13–1·41)	0·0018
<20	5/2543 (0·20%)	0·19% (0·06–0·60)			6/2543 (0·24%)	0·23% (0·06–0·80)		
20–29	5/807 (0·62%)	0·74% (0·20–2·75)			7/807 (0·87%)	0·94% (0·28–3·14)		
30–39	6/1289 (0·47%)	0·42% (0·10–1·78)			7/1289 (0·54%)	0·52% (0·12–2·24)		
40–49	7/1305 (0·54%)	0·54% (0·20–1·41)			7/1305 (0·54%)	0·54% (0·20–1·41)		
50–59	8/1208 (0·75%)	0·73% (0·38–1·38)			11/1208 (0·91%)	0·87% (0·38–2·00)		
≥60	14/1466 (0·95%)	0·95% (0·21–4·20)			15/1466 (1·02%)	1·01% (0·21–4·67)		
Sex								
Female	32/4799 (0·67%)	0·64% (0·18–2·18)	1		38/4799 (0·79%)	0·77% (0·21–2·82)	1	
Male	14/3819 (0·37%)	0·39% (0·17–0·93)	0·58 (0·28–1·23)	0·1319	15/3819 (0·39%)	0·42% (0·17–1·04)	0·53 (0·25–1·12)	0·0840
Total	46/8618 (0·53%)	0·51% (0·18–1·49)			53/8618 (0·61%)	0·59% (0·19–1·85)		

Odds ratios were adjusted for sex and age and derived from multilevel logistic models. The odds ratio for age indicates the change of odds per 10-year increase in age.
*Directly standardised by age and sex, using the 2015 rural population of each country as a reference.

***Table 3*: Prevalence of abdominal cystic echinococcosis by age and sex**

diagnoses by imaging. Independently of sex, the prevalence of new diagnoses and cystic echinococcosis by imaging steadily increased with age in Romania and Turkey (table 3). We detected no statistically significant association between age and abdominal cystic echinococcosis in Bulgaria. Standardised cystic echinococcosis prevalence did not differ significantly among provinces in Bulgaria and Romania, but did differ significantly among Turkish provinces (p=0·0103 for new diagnoses and p=0·0011 for cystic echinococcosis by imaging; appendix).

We detected 49 abdominal echinococcosis cysts (1·58 cysts per patient; 44 in the liver; 23 newly diagnosed) in Bulgaria, 43 cysts (1·23 cysts per patient; 40 in the liver; 33 newly diagnosed) in Romania, and 66 cysts (1·25 cysts per patient; 64 in the liver; 59 newly diagnosed) in Turkey. No lung cysts were detected in patients with abdominal cystic echinococcosis who received chest radiography (ten patients in Bulgaria, 31 in Romania, and seven in Turkey). In Bulgaria, within the newly diagnosed cystic echinococcosis group, 14 (61%) of 23 cysts were

inactive and ten (59%) of 17 patients had only inactive cysts, whereas in Romania, 18 (55%) of 33 cysts were inactive and 16 (55%) of 29 patients had only inactive cysts, and in Turkey, 40 (68%) of 59 cysts and 31 (67%) of 53 patients had only inactive cysts. Of patients with identifiable abdominal cystic echinococcosis on ultrasound surveys who reported a history of treatment for cystic echinococcosis, active cysts were detected in six (43%) of 14 patients in Bulgaria, one (17%) of six patients in Romania, and two (29%) of seven patients in Turkey. Because of the lack of medical documentation, it was not possible to infer whether these active cysts were the result of new infections or relapses. The sex-standardised and age-standardised prevalence of infection with active and inactive cysts is available in the appendix. We did not detect significant differences in the proportions of active cysts between provinces within countries (appendix). The stage distributions of the cysts by sex and age groups in the newly diagnosed cystic echinococcosis group is shown in the appendix. There was no significant association between cyst activity and demographic variables (appendix); newly diagnosed active cysts were also detected in children younger than 10 years (one child in Bulgaria, one in Romania, and two in Turkey). However, the patterns of cyst stage distribution by age and sex differed between countries (appendix). Details of cystic lesions suspected of being attributable to cystic echinococcosis and other incidental findings of medical relevance are also provided in the appendix.

Using the age-standardised and sex-standardised prevalence values shown in table 2 and the reference rural population sizes of each country in 2015, we estimated that the number of individuals who might currently be infected with cystic echinococcosis was 7872 (95% CI 5520–11 220) in rural Bulgaria, 37 229 (23 405–59 166) in rural Romania, and 106 237 (33 829–330 751) in rural Turkey (appendix). Of these people, 3374 (42·9%) in Bulgaria, 15 004 (40·3%) in Romania, and 34 798 (32·8%) in Turkey may harbour cysts in active stage (appendix).

The number of individuals who reported having been treated for cystic echinococcosis in the past and did not show echinococcal lesions on ultrasound was 50 in Bulgaria, 35 in Romania and 44 in Turkey. In our cohort, 25 (50%) of these 50 individuals in Bulgaria had been treated less than 5 years earlier, which was also the case for 13 (37%) of the 35 individuals in Romania, and ten (23%) of the 44 individuals in Turkey. Complete results, including data from survey participants reporting a history of previous treatment for cystic echinococcosis are provided in the appendix.

Discussion

WHO advocates control of cystic echinococcosis.[3] Previous successful control and eradication programmes have been done in geographically small territories, mainly islands, and new tools have become available during past 25 years, including the recombinant EG95 vaccine for sheep, coproantigen detection in dogs, portable ultrasound machines, and mathematical modeling.[29] Incorporation of measures such as regular dog deworming with praziquantel, culling of aged sheep, and sheep vaccination into control and eradication programmes could substantially reduce the time required to interrupt transmission from 20 years or more, as generally estimated, to as little as 5–10 years.[30]

However, patients with cystic echinococcosis would continue to be detected for many decades after transmission is halted. In this context, active case detection might decrease the burden of disease in humans requiring treatment, but more extensive and accurate mapping of the distribution of cystic echinococcosis in humans and animals is needed. Population-based imaging studies have been done in some high endemicity areas in several countries;[4] however, the few data available are insufficient to extrapolate results to wider areas. Therefore, we encourage the use of active case detection in rural endemic areas, with rigorous cystic echinococcosis case definition by ultrasound screening. Accurate assessments of prevalence would enable policy makers to implement cost-effective targeted interventions.

Human cystic echinococcosis is endemic in eastern Europe; however, the number of infected people in each country has never been estimated. We estimated that around 151 000 people living in rural Bulgaria, Romania, and Turkey might be infected with abdominal cystic echinococcosis. Around a third of them might have active infection. Although we could not verify patients' reports, including cystic echinococcosis by recall increased the estimated number of cases by almost threefold in rural Bulgaria and almost double in Romania and Turkey (appendix). The frequency of a history of infection is important because patients treated for cystic echinococcosis require many years of follow-up to detect relapses, which mostly occur within 5 years after intervention.[31]

Differences between the number of previously undiagnosed infections versus treated infections highlight the proportion of cystic echinococcosis cases captured by national health systems. These figures might provide valuable information to national health authorities for estimation of cystic echinococcosis-related health expenses. Our data suggest that a higher proportion of participants with cystic echinococcosis who attended screening in Bulgaria had accessed the health system compared with participants attending screening in Romania and Turkey, although whether the reason for seeking care was primarily related to cystic echinococcosis was not investigated.

It is plausible that newly diagnosed individuals were asymptomatic, or at least did not have severe enough symptoms to seek medical attention, although participants were not asked about symptoms. In Turkey and Romania, alveolar echinococcosis is also present,[1,32] and some people without lesions on ultrasound might

have erroneously reported treatment for alveolar echinococcosis as treatment for cystic echinococcosis. However, the prevalence of alveolar echinococcosis in Turkey and Romania is much lower than that of cystic echinococcosis.[1,32] In Bulgaria, although *Echinococcus multilocularis* has been reported in animal hosts, convincing evidence of the presence of alveolar echinococcosis in humans is lacking.[1]

To give a better insight into transmission dynamics, we evaluated the cyst stage distribution in individuals with no previous treatment for cystic echinococcosis. Among these individuals, active cysts, which could reflect continuing transmission,[33,34] were found in children younger than 10 years. Furthermore, newly diagnosed active cysts were found in all investigated provinces, with the exception of Kardzhali district in Bulgaria, including areas of Turkey where Shafi'i people live, a Muslim population who strictly avoid contact with dogs. In all countries, cyst activity and demographic variables were not significantly associated, and active cysts were found across different ages, as reported previously.[35,36] However, cyst stage distribution by age and sex showed different patterns in each country. This could be due to exposure differences related to social habits or different access to the health system by age and sex in different countries and regions. These results, taken together, support the hypothesis that environmental contamination is likely to be the main source of cystic echinococcosis transmission[35–37] and that control measures might benefit the whole resident population, given that infection can occur at all ages.[38] Finally, most of the echinococcosis cysts detected were inactive, as has also observed elsewhere,[35,36] which is in line with observations that cysts tend to evolve spontaneously towards inactivation.[34,39] Thus, stage-specific management is needed to avoid overtreatment, especially for individuals with asymptomatic spontaneously inactivated cysts,[23] which rarely reactivate.[34,40,41]

The burden of cystic echinococcosis has generally been estimated with highly heterogeneous and incomplete data sources, including hospital reports, and relying strongly on modelling.[7] Estimates based on hospital records are likely to miss many asymptomatic or mildly symptomatic cases, which our results suggest might constitute most patients. Cross-sectional studies based on population ultrasound surveys might provide more reliable and complementary data. In Romania, 31 cases in 2014, and 18 cases in 2015, were officially reported to European authorities.[8] In the same years, 35 individuals with abdominal cystic echinococcosis were identified by ultrasound screening within the HERACLES project, which examined around 0·1% of the Romanian rural population. Thus, estimates from hospital data might underestimate the true value by 700 fold, seven times higher than what was estimated by Budke and colleagues.[4] However, in Bulgaria the underestimate might be only tenfold: 302 and 313 cases were reported officially in 2014, and 2015, respectively, and 31 cases were identified during screening, which examined around 0·5% of the rural population of Bulgaria. Unfortunately, no data are available for Turkey, to calculate similar proportions.

Previous population-based studies have been limited by their limited geographical range, focusing on areas with high endemicity,[4,6] and the absence of a rigorous case definition. We applied a rigorous case definition, cyst staging, and reappraisal of detected cases, and worked in provinces considered to have mid-range endemicity.[21,22] This approach could underestimate the prevalence of disease since early cystic echinococcosis infections detected in our study as CL might have been excluded and cystic echinococcosis of the lung could not be investigated by ultrasound. In a cohort from Turkana (Kenya) and Morocco, 11 (42%) of 26 CL lesions were still classified as CL on a second ultrasound follow-up.[34] In our study, in Turkey, where the cause of all CLs detected during the survey could be evaluated with diagnostic puncture, no lesions were due to early cystic echinococcosis (appendix). This approach, unfortunately, was not possible in Bulgaria and Romania; however, among patients with CLs who adhered to the ultrasound follow-up, none of these lesions developed the pathognomonic features of echinococcosis cysts.

Several limitations might have affected our prevalence estimates. The voluntary participation could have introduced self-selection bias, which could have affected prevalence estimates in either direction.[4] Physical inability of severely symptomatic patients to participate or lack of interest in the survey among individuals who have already been diagnosed might result in an underestimation. Conversely, individuals who have previously been treated for cystic echinococcosis might have increased interest in participating in screening and receiving a free check-up. Moreover, the health education materials and advertisements for screening might have encouraged people to participate, especially if they had symptoms, thus skewing the estimate toward an overestimation. However, most participants with cystic echinococcosis did not attend the follow-up offered; therefore, we think the latter scenario is unlikely. Finally, the generalisability of our results might be limited by the small number of villages investigated within each province. Only villages where local authorities were willing to host the survey participated, but whether this was due to a perception of cystic echinococcosis as a potential health problem for their communities was not investigated and might warrant attention in similar studies in the future. Overall, this approach probably led to a conservative estimate of infection prevalence in rural areas at the country level. Further studies might be needed to address infection prevalence in urban and peri-urban areas.

Cystic echinococcosis continues to constitute a public health problem in endemic rural areas. Our results

should be of useful for raising awareness among physicians of the presence of this infection—and thus its inclusion in the differential diagnosis of suggestive lesions in patients coming from endemic areas—and encourage improvement of case notification and cost-benefit analyses in public health interventions. An underestimate of cystic echinococcosis prevalence could give the impression that control programmes are not working if enhanced surveillance occurs during control efforts and therefore more extensive and accurate mapping of the distribution of cystic echinococcosis in humans and animals is needed to comply with the WHO roadmap schedule for cystic echinococcosis elimination, which envisages infection control in selected countries.[3] Evaluation of only those cases of cystic echinococcosis that reach medical attention is inadequate to this aim, as such cases represent only a small proportion of infections in endemic areas; furthermore, not all cases in hospital reports are included in official statistics, as also noted in other European countries.[42–44] This lack or inadequacy of reporting leads to neglect of cystic echinococcosis as a public health issue, since it suggests that the infection is uncommon and therefore deserving of little attention and monitoring.

Although cystic echinococcosis is usually benign and care must be taken to avoid overtreatment,[45] serious complications of infection can occur and no marker is available to predict them. People with cystic echinococcosis have lower quality of life compared with ultrasound-negative controls, even before diagnosis.[45] Some localisations, such as osseous infiltration, are devastating for patients. Unfortunately, the chronicity and heterogeneity of presentation of the infection make it almost impossible to implement large prospective clinical trials to gather evidence-based information for clinical management. A first step to overcome these problems is the European Register of Cystic Echinococcosis (ERCE),[46] an international prospective online register of human cystic echinococcosis cases visited by clinicians in all settings, with clinical data captured in a standardised manner. However, such initiatives based on voluntary adherence and the goodwill of clinicians are not enough. With the aim of improving surveillance of cystic echinococcosis, we encourage international agencies (eg, EFSA, ECDC, and WHO) to lobby the European Commission to champion new health policies for the notification of human and animal cystic echinococcosis.

Contributors

FT, OA, CMCr, KV, EB, and AC designed the study. FT, OA, CMCr, KV, DA, RC, TC, CMCo, BG, DJ, PM, MM, SO, MP, ACP, LGP, MIP, VV, MS-L, and AC coordinated and implemented the fieldwork and data collection. FT, OA, CMCr, KV, FT, MF, PP, and AC analysed and interpreted the data. FT, MF and AC wrote the paper. All authors had access to the clinical study report, reviewed the Article, and approved submission.

Declaration of interests

We declare no competing interests.

Acknowledgments

This work was supported by the European Union Seventh Framework Programme (FP7) under the HERACLES project (grant agreement number 602051). The funding body had no involvement in the conception, preparation and writing of the manuscript, in the viewpoints expressed, nor in the decision to submit this Article. We are grateful to Prof Thomas Junghanss (Head of the Section of Clinical Tropical Medicine at Heidelberg University Hospital and Chair of the WHO Informal Working Group on Echinococcosis), Bernadette Abela-Ridder (Team Leader, Neglected Zoonotic Diseases, Department of the Control of Neglected Tropical Diseases, WHO), and Johanna Takkinen (Head of Disease Programme Food- and Waterborne Diseases and Zoonoses, European Centre for Disease Prevention and Control) for supporting this research. We are also thankful to Iskra Rainova (Department of Parasitology and Tropical Medicine, National Centre of Infectious and Parasitic Diseases, Sofia, Bulgaria) for help with retrieving official human data from Bulgaria. We also thank the students who volunteered to help during the fieldwork: Madalina Preda, Adelina Silvana Gheorghe, Andrei Capraru, and Luca Stan Sion.

References

1 Deplazes P, Rinaldi L, Alvarez Rojas CA, et al. Global distribution of alveolar and cystic echinococcosis. *Adv Parasitol* 2017; **95:** 315–493.
2 Junghanss T, da Silva AM, Horton J, Chiodini PL, Brunetti E. Clinical management of cystic echinococcosis: state of the art, problems, and perspectives. *Am J Trop Med Hyg* 2008; **79:** 301–11.
3 WHO. Neglected tropical diseases. http://www.who.int/echinococcosis/en/ (accessed March 1, 2017).
4 Budke CM, Carabin H, Ndimubanzi PC, et al. A systematic review of the literature on cystic echinococcosis frequency worldwide and its associated clinical manifestations. *Am J Trop Med Hyg* 2013; **88:** 1011–27.
5 WHO Department of Control of Neglected Tropical Diseases. Intergrating neglected tropical diseases into global health and development: fourth WHO report on neglected tropical diseases 2017. Geneva: World Health Organization, 2017.
6 Budke CM, Deplazes P, Torgerson PR. Global socioeconomic impact of cystic echinococcosis. *Emerg Infect Dis* 2006; **12:** 296–303.
7 Herricks JR, Hotez PJ, Wanga V, et al. The global burden of disease study 2013: What does it mean for the NTDs? *PLoS Negl Trop Dis* 2017; **11:** e0005424.
8 EFSA, ECDC. The European Union summary report on trends and sources of zoonoses, zoonotic agents and food-borne outbreaks in 2015. *EFSA J* 2016; **14:** 4634.
9 Tirnea L, Neghina R, Siko-Barabasi S, et al. Epidemiological and medico-social aspects of human hydatidosis in Timis county, Romania. *Revista de Igiena si Sanitate Publica* 2009; **59:** 26–35.
10 Gonlugur U, Ozcelik S, Gonlugur TE, et al. The retrospective annual surgical incidence of cystic echinococcosis in Sivas, Turkey. *Zoonoses Public Health* 2009; **56:** 209–14.
11 Yazar S, Ozkan AT, Hokelek M, et al. Cystic echinococcosis in Turkey from 2001–2005. *Turkiye Parazitol Derg* 2008; **32:** 208–20 (in Turkish).
12 Macpherson CN, Bartholomot B, Frider B. Application of ultrasound in diagnosis, treatment, epidemiology, public health and control of *Echinococcus granulosus* and *E. multilocularis*. *Parasitology* 2003; **127** (suppl)**:** S21–35.
13 Muhtarov M. First portable ultrasond based screening study in Bulgaria on the prevalence of cystic echinococcosis in Kardzhali district. *Trakia J Sci* 2014; **12** (suppl 1)**:** 170–74.
14 Cretu C, Brunetti E, Macpherson CN, et al. Ultrasound screenng for echinococcosis, a useful method to detect the disease in rural endemic areas. 24th World Congress on Hydatidosis; Urumqi, China; Sept 14–18, 2011. Abstract OII-7.
15 Bakal U, Kazez A, Akyol M, Kocakoc E, Simsek S. A portable ultrasound based screening study on the prevalence and risk factors of cystic echinococcosis in primary school children in East Turkey. *Acta Trop* 2012; **123:** 91–95.
16 Ertabaklar H, Dayanir Y, Ertug S. Research to investigate human cystic echinococcosis with ultrasound and serologic methods and educational studies in different provinces of Aydin/Turkey. *Turkiye Parazitol Derg* 2012; **36:** 142–46 (in Turkish).
17 Kilimcioglu AA, Girginkardesler N, Korkmaz M, et al. A mass screening survey of cystic echinococcosis by ultrasonography, western blotting, and ELISA among university students in Manisa, Turkey. *Acta Trop* 2013; **128:** 578–83.

18 Kilimcioglu AA, Ozkol M, Bayindir P, Girginkardesler N, Ostan I, Ok UZ. The value of ultrasonography alone in screening surveys of cystic echinococcosis in children in Turkey. *Parasitol Int* 2006; **55:** 273–75.

19 Ok UZ, Ozkol M, Kilimcioglu AA, et al. A province-based study using sampling method to investigate the prevalence of cystic echinococcosis among primary school children in Manisa, Turkey. *Acta Trop* 2007; **103:** 116–22.

20 Yazar S, Yaman O, Cetinkaya F, Sahin I. Cystic echinococcosis in Central Anatolia, Turkey. *Saudi Med J* 2006; **27:** 205–09.

21 INSP. National Institute of Public Health. http://www.insp.gov.ro (accessed Dec 12, 2013).

22 NCPID. Ministry of Health, National Center of Infectious and Parasitic Diseases, Sofia, Bulgaria. http://www.ncipd.org/index.php?lang=en accessed Dec 12, 2013).

23 Brunetti E, Kern P, Vuitton DA, Writing Panel for the WHO-IWGE. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. *Acta Trop* 2010; **114:** 1–16.

24 Hosch W, Junghanss T, Stojkovic M, et al. Metabolic viability assessment of cystic echinococcosis using high-field 1H MRS of cyst contents. *NMR Biomed* 2008; **21:** 734–54.

25 Turkish Statistical Institute. Social structure and gender statistics. http://www.turkstat.gov.tr/VeriBilgi.do?alt_id=1068 (accessed March 21, 2017).

26 National Institute of Statistics. http://www.insse.ro/cms/en (accessed March 18, 2017).

27 Republic of Bulgaria National Statistical Institute. Population by districts, age, place of residence and sex. http://www.nsi.bg/en/content/6708/population-districts-age-place-residence-and-sex (accessed March 15, 2017).

28 ISD Scotland. GPD Support. Population. http://www.isdscotland.org/Products-and-Services/GPD-Support/Population/Standard-Populations/ (accessed March 22, 2017).

29 Craig PS, Hegglin D, Lightowlers MW, Torgerson PR, Wang Q. Echinococcosis: control and prevention. *Adv Parasitol* 2017; **96:** 55–158.

30 Craig PS, McManus DP, Lightowlers MW, et al. Prevention and control of cystic echinococcosis. *Lancet Infect Dis* 2007; **7:** 385–94.

31 Prousalidis J, Kosmidis C, Anthimidis G, Kapoutzis K, Karamanlis E, Fachantidis E. Postoperative recurrence of cystic hydatidosis. *Can J Surg* 2012; **55:** 15–20.

32 Snabel V, Calma C, Georgescu SO, et al. Genetic survey of alveolar and cystic echinococcoses in Romania: first molecular evidence of *Echinococcus multilocularis* in humans in the country. *Helminthologia* 2017; **54:** 189–98.

33 Rogan MT, Hai WY, Richardson R, Zeyhle E, Craig PS. Hydatid cysts: does every picture tell a story? *Trends Parasitol* 2006; **22:** 431–38.

34 Solomon N, Kachani M, Zeyhle E, Macpherson CNL. The natural history of cystic echinococcosis in untreated and albendazole-treated patients. *Acta Trop* 2017; **171:** 52–57.

35 Chebli H, Laamrani El Idrissi A, Benazzouz M, et al. Human cystic echinococcosis in Morocco: ultrasound screening in the Mid Atlas through an Italian-Moroccan partnership. *PLoS Negl Trop Dis* 2017; **11:** e0005384.

36 Tamarozzi F, Hou A, Morales ML, et al. Prevalence and risk factors for human cystic echinococcosis in the Cusco region of the Peruvian highlands diagnosed using focused abdominal ultrasound. *Am J Trop Med Hyg* 2017; **96:** 1472–77.

37 Possenti A, Manzano-Roman R, Sanchez-Ovejero C, et al. Potential risk factors associated with human cystic echinococcosis: systematic review and meta-analysis. *PLoS Negl Trop Dis* 2016; **10:** e0005114.

38 Beard TC. Evidence that a hydatid cyst is seldom "as old as the patient". *Lancet* 1978; **2:** 30–32.

39 Romig T, Zeyhle E, Macpherson CN, Rees PH, Were JB. Cyst growth and spontaneous cure in hydatid disease. *Lancet* 1986; **1:** 861.

40 Piccoli L, Tamarozzi F, Cattaneo F, et al. Long-term sonographic and serological follow-up of inactive echinococcal cysts of the liver: hints for a "watch-and-wait" approach. *PLoS Negl Trop Dis* 2014; **8:** e3057.

41 Stojkovic M, Rosenberger KD, Steudle F, Junghanss T. Watch and wait management of inactive cystic echinococcosis—does the path to inactivity matter—analysis of a prospective patient cohort. *PLoS Negl Trop Dis* 2016; **10:** e0005243.

42 Piseddu T, Brundu D, Stegel G, et al. The disease burden of human cystic echinococcosis based on HDRs from 2001 to 2014 in Italy. *PLoS Negl Trop Dis* 2017; **11:** e0005771.

43 Herrador Z, Siles-Lucas M, Aparicio P, et al. Cystic Echinococcosis epidemiology in spain based on hospitalization records, 1997–2012. *PLoS Negl Trop Dis* 2016; **10:** e0004942.

44 van Cauteren D, Millon L, de Valk H, Grenouillet F. Retrospective study of human cystic echinococcosis over the past decade in France, using a nationwide hospital medical information database. *Parasitol Res* 2016; **115:** 4261–65.

45 Budke CM, Jiamin Q, Zinsstag J, Qian W, Torgerson PR. Use of disability adjusted life years in the estimation of the disease burden of echinococcosis for a high endemic region of the Tibetan plateau. *Am J Trop Med Hyg* 2004; **71:** 56–64.

46 Rossi P, Tamarozzi F, Galati F, et al. The first meeting of the European Register of Cystic Echinococcosis (ERCE). *Parasit Vectors* 2016; **9:** 243.