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Unveiling the incidences and trends of the neglected zoonosis cystic echinococcosis in Europe: a systematic review from the MEmE project

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The neglected zoonosis cystic echinococcosis affects mainly pastoral and rural communities in both low-income and upper-middle-income countries. In Europe, it should be regarded as an orphan and rare disease. Although human cystic echinococcosis is a notifiable parasitic infectious disease in most European countries, in practice it is largely under-reported by national health systems. To fill this gap, we extracted data on the number, incidence, and trend of human cases in Europe through a systematic review approach, using both the scientific and grey literature and accounting for the period of publication from 1997 to 2021. The highest number of possible human cases at the national level was calculated from various data sources to generate a descriptive model of human cystic echinococcosis in Europe. We identified 64 745 human cystic echinococcosis cases from 40 European countries. The mean annual incidence from 1997 to 2020 throughout Europe was 0·64 cases per 100 000 people and in EU member states was 0·50 cases per 100 000 people. Based on incidence rates and trends detected in this study, the current epicentre of cystic echinococcosis in Europe is in the southeastern European countries, whereas historical endemic European Mediterranean countries have recorded a decrease in the number of cases over the time.

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Introduction

Echinococcosis belongs to the current group of 20 neglected tropical diseases, conditions, or syndromes of global health importance that are endorsed by WHO for their prevention and control.[1,2] The echinococcosis disease group includes cystic, alveolar, and neotropical echinococcosis. Globally, more than 1 million people are estimated to be infected with echinococcosis at any one time.[3] These parasitic diseases are caused by the parasites *Echinococcus granulosus sensu lato* (cystic echinococcosis), which has a worldwide distribution, *Echinococcus multilocularis* (alveolar echinococcosis) present in the northern hemisphere, and *Echinococcus vogeli* (neotropical echinococcosis) and *Echinococcus oligarthra* (neotropical echinococcosis), which are restricted to Mexico, Central America, and South America.[4,5]

In Europe, cystic echinococcosis is mainly transmitted in rural and pastoral communities, where the environment is contaminated by parasitic eggs. In Europe, the lifecycle of *E granulosus s l* involves primarily livestock as intermediate hosts (mainly sheep, cattle, and pigs) and canids as definitive hosts (mainly dogs).[6,7] Similarly, alveolar echinococcosis is mainly transmitted in Europe by wildlife in rural communities, where the environment is contaminated by parasitic eggs. In Europe, the lifecycle of *E multilocularis* involves primarily small rodents as intermediate hosts and canids as definitive hosts (mainly red foxes).[6,8] In both cystic echinococcosis and alveolar echinococcosis, humans act as dead-end hosts with hand-to-mouth and food-borne or water-borne transmission of infective parasite eggs.

Cystic echinococcosis and alveolar echinococcosis are both chronic diseases in humans. Cystic echinococcosis is a disabling disease with a low fatality rate, whereas alveolar echinococcosis is often a life-threatening disease since it causes a tumour-like progression. Within the echinococcosis disease group, cystic echinococcosis is

Key messages

- This study aims to shed light on the unrecognised incidence of cystic echinococcosis in Europe, unveiling its epidemiological effect by providing a quantitative measure of number, incidence, and trends of human cases documented within the period 1997–2021
- Since human cystic echinococcosis cases are generally under-reported and data have uncertainty (partly due to misdiagnosis), data provided in this study should be considered as a conservative estimate of the real impact of this zoonotic infection historically occurring in Europe
- For the years 2017–19, we identified a total number of cystic echinococcosis cases four-fold higher than for The European Surveillance System (TESSy) data
- Decreasing trends have been recorded in most southern Mediterranean and some eastern European countries, where cystic echinococcosis has traditionally been highly prevalent
- Increasing trends have been identified in some eastern and southeastern European countries but, unexpectedly, also in most non-endemic countries of northern and western Europe
- Based on incidence and trends from 2017–19, the current epicentre of cystic echinococcosis in Europe is represented by the Balkan Peninsula
- Cystic echinococcosis in Europe remains a relevant public health issue and findings from this study should be used to support the planning of surveillance and control programmes in Europe according to the WHO 2021–2030 roadmap for neglected tropical diseases

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the most prevalent in Europe, and globally, causing severe morbidity and low mortality among human populations.[5] Cystic echinococcosis mainly affects the liver and the lungs, although the parasite can be localised in any organ or tissue,[9] and is characterised by fluid-filled, isolated, parasitic cysts growing concentrically. Cyst growth might cause compression of neighbouring structures, which in turn is responsible for the insurgence of symptoms (eg, abdominal pain); more severe clinical manifestations can also derive from complications such as cyst rupture or superinfections.

Cystic echinococcosis occurs primarily in pastoral and rural communities, but it is also prevalent in communities in both low-income and upper-middle-income countries, including European ones, where it should be considered a so-called orphan disease (ie, it is rare and therefore has too small of a potential market to attract support and resources).[10] Although human cystic echinococcosis is, in theory, a notifiable infectious disease in most European countries, in practice it is largely under-recorded by national health systems. Several factors account for the underdiagnosis, misdiagnosis, and, consequently, misreporting and under-reporting of cystic echinococcosis cases.[11]

Some biological characteristics of the parasite, such as the delay of months or years between the event of infection and the eventual onset of symptoms, make it impossible to trace back the routes of transmission to attribute the source of infection.[12,13] Moreover, due to this long latency period, the main sources of infection, the pathways of transmission, and the potential risk factors associated with infection are not clear. In addition, outbreaks (ie, occurrences of cystic echinococcosis cases in excess of what would be expected in a defined population) do not exist for this silent, chronic, and long-standing zoonotic infectious disease.[14] Therefore, cystic echinococcosis cases, in the absence of data on the source of infection during the anamnesis, might be misdiagnosed. Moreover, cystic echinococcosis can be asymptomatic or paucisymptomatic for years, and the absence of signs of acute infection for easy case retrieval might contribute to underdiagnosis of cases.

Unlike other parasitic infections, cystic echinococcosis cysts are anatomically isolated in the human body; therefore, triggering a detectable antibody response is variable and depends on several factors such as size, location, number, and stage of the parasitic cysts.[15,16] Thus, serology alone is not a reliable diagnostic tool and, even in combination with imaging, requires experienced personnel for its interpretation, consequently leading to misdiagnosis. Due to the barrier provided by the cyst wall, biomarkers that are useful for diagnosis and prognosis are currently unavailable to detect the direct or indirect presence of the parasite in biological fluids such as blood or urine. Finally, since humans are dead-end hosts infected with the asexual stage of the parasite (metacestode), no eggs or worms are present in faecal samples to support the diagnosis—contrary to what is generally adequate for the diagnosis of other helminths that reside in the human intestine. An exception for the direct detection of this parasite is the *vomica* event in lung cystic echinococcosis, a rare occurrence when part of the ruptured cysts are expelled and can be directly detected in the expectorate. Finally, cystic echinococcosis can be silent for years and when symptoms are present they are unspecific, with no pathognomonic clinical signs related to the presence of cystic echinococcosis cysts. These parasitic characteristics might result in misdiagnosis of cases by less experienced physicians.

For all these reasons, imaging techniques (in particular, ultrasound) are the main diagnostic tools for human cystic echinococcosis, whereas serology is only supportive for the diagnosis, and molecular confirmation is only possible when parasitic cysts, or part of them, are available by interventional procedures.[10,17] For these reasons, a classification of cyst stage has been developed by the WHO Informal Working Group for Echinococcosis.[18] In this context, cystic echinococcosis clinical management is currently based on an approach specific to the cyst stage. Cyst-stage-specific approaches currently available for the clinical management of cystic echinococcosis include parasitostatic drug therapy with benzimidazoles (mainly albendazole, but also mebendazole and, with some uncertainties, praziquantel), percutaneous or surgical interventions, and regular ultrasound follow-up without interventions (watch-and-wait).[17]

The EU's case definition mainly contributes to under-reporting of cystic echinococcosis, since it is classified only as echinococcosis and therefore does not provide a distinction between cystic echinococcosis and alveolar echinococcosis, which have a different epidemiology and cause two completely different diseases in humans.[19] In this context, most of the EU countries report unspecified echinococcosis cases to the European Centre for Disease Prevention and Control via The European Surveillance System (TESSy).[20] Moreover, multicystic stages of cystic echinococcosis can be wrongly recorded as alveolar echinococcosis, leading to misdiagnosis and, consequently, misreporting and under-reporting. Finally, even if a correct cystic echinococcosis diagnosis was made and individuals were treated as outpatients, they are not always captured by hospital discharge records at the national level and therefore contribute to under-reporting. The previously mentioned regulatory, biological, clinical, and diagnostic factors lead to the absence and inadequacy of reporting and, consequently, to the neglect of cystic echinococcosis as a public health issue in Europe and worldwide. For this reason, this study—done within the MEmE project—aims to unveil the historical and current numbers of human cystic echinococcosis in Europe by providing quantitative measure from different data sources of human cystic echinococcosis cases reported during last 25 years (1997–2021) at the national level in Europe.

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Methods

Data on incidences and trends of cystic echinococcosis in Europe were extracted through a systematic review approach from both scientific and grey literature published in 1997–2021. Different types of studies were collected from data sources: national health reports, national hospital records, TESSy data reports,[21] and observational studies, such as single-centre or multicentre case series, case reports, ultrasound-based cross-sectional studies, and the European clinical register on cystic echinococcosis.[11] The main inclusion criterion of this systematic review was primary data reporting human cystic echinococcosis cases in included European countries during the period 1997–2021.

Search strategy and selection criteria

This systematic review is presented in accordance with the PRISMA guidelines (appendix pp 1–2).[22] The STN International-Fiz Karlsruhe platform was used for the database search in MEDLINE (PubMed), Embase (Excerpta Medica Database), SciSearch (Science Citation Index), and Google Scholar. In the first round of selection, primary studies published in English between Jan 1, 1997, and Dec 31, 2021, were eligible for inclusion. The electronic search terms were (cystic echinococcosis OR Hydatid* OR echinococcal OR *Echinococcus* OR *E* granulosus* OR *E* canadensis* OR *E* equinus* OR *E* ortleppi*) AND (Human OR children OR teenager OR child OR boy OR girl OR young) AND (Europe OR European Union OR European) NOT (alveolar OR multilocularis OR *E* multilocularis* OR *Echinococcus multilocularis* OR hydatid mole OR hydatidiform mole OR polycystic kidney disease). A second search was conducted from Jan 1, 1997 until Oct 10, 2022, without any language restriction for the identification of papers, reports, datasets, conference abstracts, systematic reviews (if they presented primary data not published elsewhere), and other grey literature from countries in Europe where no data, little data, or scattered data were identified in the first search. The articles resulting from these searches, and the relevant references cited in these articles, were reviewed for additional primary data. The 40 countries included in the search were Albania, Austria, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Kosovo, Latvia, Lithuania, Luxembourg, Malta, Moldova, Montenegro, the Netherlands, North Macedonia, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Sweden, Switzerland, Spain, the UK, and Ukraine. Duplicates between databases were removed and the inclusion or exclusion of data sources was done by independent researchers. Any disagreement between researchers was resolved by discussion until there was a consensus between the researchers. The initial screening was done according to the relevance of the title and abstract to the focus of this research. Then, the full texts of the selected papers were examined through a second stage of screening to assess their eligibility, and data were extracted into standardised Microsoft Excel tables. For each record included these data were extracted, if available: the reference article, country where the study was done, name of the clinical centre, number of cystic echinococcosis cases, time period, hospital record data (ordinary and day hospitalisation), deaths or case fatality rates, and nationality of patients. Studies were excluded if they did not contain original data (eg, reviews not containing primary data) or if they duplicated data (eg, between papers and other records), concerned the wrong aetiological agent (eg, *E multilocularis*) or infectious disease (eg, alveolar echinococcosis), or concerned a non-infectious disease (eg, hydatid mole or polycystic kidney disease) or incorrect host (eg, animal host for cystic echinococcosis).

Data curation

The highest number of possible human cases at the national level per year was calculated by summing cases from different data sources with no overlap to generate a descriptive model of human cystic echinococcosis in Europe during the period 1997–2021. Primary data from different data sources (eg, case series) were considered not duplicated for the same time period if they were reported from different clinical centres, recorded by different cystic echinococcosis cohorts (eg, cystic echinococcosis in the liver, lung, or unusual locations), or different clinical management (eg, surgical interventions or percutaneous interventions). In the occurrence of a potential duplication of cases between data sources, the dataset with the lower number of cases was always discharged and not considered. Single case reports were retained for those countries where few data on this disease were retrieved for all or part of the period under consideration (ie, Belgium, Cyprus, Czech Republic, Denmark, France, Ireland, Luxembourg, Poland, Slovenia, Switzerland, and the UK). Unpublished single-centre cohorts were obtained from Bosnia and Herzegovina (n=1; Enver Zerem, unpublished), Cyprus (n=2; Hasan Besim, unpublished), and Switzerland (n=4; Ansgar Deibel and Beat Müllhaupt, unpublished; Marcel Stoeckle, unpublished; François Chappuis, unpublished; Severin Gloor, unpublished) as no data or scanty data were available for the whole period or for a part of it, from both the published literature and official reports. For a few countries (such as Romania and Spain), the number of national cystic echinococcosis cases were calculated from the number of national hospitalisations, because records of cystic echinococcosis cases were not present or were scarce compared with their records on hospitalisations. To avoid case duplication in Romania and Spain from multiple hospitalisations of the same person over time, a decrease correction factor was applied to national hospitalisations. We identified two reference single-centre large cohorts in Bucharest (Romania) and Salamanca (Spain) that recorded both number of cases

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and hospitalisations. Then we used the ratio of cases to hospitalisations from reference cohorts to calculate the number of cases at the national level from national hospitalisations. Unspecified echinococcosis cases were included in the study as cystic echinococcosis cases only for those countries that are non-endemic for human alveolar echinococcosis (ie, Albania, Bosnia and Herzegovina, Bulgaria, Cyprus, Finland, Greece, Ireland, Italy, Kosovo, Montenegro, North Macedonia, Portugal, Serbia, Spain, the UK, and Ukraine).[23] For co-endemic countries for cystic echinococcosis and alveolar echinococcosis (ie, Austria, Belarus, Belgium, Croatia, Czech Republic, Denmark, Estonia, France, Germany, Hungary, Latvia, Lithuania, Luxembourg, Moldova, the Netherlands, Norway, Poland, Slovakia, Slovenia, Sweden, and Switzerland)[23] unspecified echinococcosis cases were excluded and only data reporting cystic echinococcosis were included, with the exception of France, where unspecified cases were attributed to cystic echinococcosis because they had hospital-record characteristics similar to cystic echinococcosis cases.[24] The annual data coverage of this study was calculated as the total number of years in which data were extracted compared with the total number of years included in this study (25 years per 40 included countries) and expressed as percentage. Nationality of patients retrieved from the records included in this systematic review was used as a proxy for the identification of locally acquired and imported cases at the national level, such that nationals were assumed to have been infected in their home country even if they currently resided in a different country.[25]

Statistical analysis

To ensure the homogeneity of the methodological approach, the incidence rates were not collected as reported in the data sources but recalculated at the national level. Average annual incidence rates were calculated as the total number of likely new cases of cystic echinococcosis recorded in a given period per 100 000 inhabitants. Population national statistics derived from The World Bank were used as denominator for incidence rates calculation.[26] The average annual incidence was calculated for both the whole period that data were eventually available (1997–2020), as the best evidence of cystic echinococcosis cases at a national level, and for the latest period (2017–19), as a proxy for the current epidemiological situation. Incidence for the whole period was calculated until 2020, since 2021 data were scarce and incomplete for most of the countries (mainly due to the ongoing national notifications in 2022 for 2021, and due to the effect of the COVID-19 pandemic on cystic echinococcosis notification in 2020 and 2021), therefore affecting total rates. Data from 2020 were included because the single year of decreasing trends did not affect the total incidence for the 25-year data collection. For the incidence trends during 2017–19, we excluded 2020 and 2021 data as they were affecting rates calculated for the shorter 3-year period. Due to insufficient data in some low endemic countries (ie, countries in which endemicity is suspected or low and sporadic),[27] published case reports were included in the incidence calculation for Cyprus, the Czech Republic, Ireland, Luxembourg, and Slovenia.

The time-trend analysis of cystic echinococcosis cases at the national level was done until 2019, with a subset of data from the most representative data sources (ie, official records such as national reports or TESSy data), which are expected to remain the same over time in terms of methodology and collection, without introducing a selection bias (ie, we did not consider data from single-centre or multicentre case series published in the literature). Due to scarce data in some low endemic countries, published case reports were included in trends analysis for the Czech Republic. We analysed the time trend of cystic echinococcosis cases for each country using log-linear regression models. To allow for the models' convergence, we imputed 0·1 cases when 0 cases had been reported. On the basis of the models' parameters, we predicted the number of cases for the years 2020–24 and estimated the 95% prediction intervals using the forecast standard error. The antilog of the fitted and forecasted estimates were plotted for each country, together with the observed number of cases. All analyses were done with RStudio 2021.09.0 under R version 4.1.2.

Results

A total of 1724 publications were identified through the first literature search, of which 545 were duplicated between databases and therefore excluded (appendix p 3). The remaining 1179 papers were assessed for eligibility. Subsequently, 548 papers were excluded by checking the title and abstract, and the text of 631 papers was assessed for inclusion criteria, of which 352 full-text papers were excluded because they did not contain relevant data for this systematic review. Additional extended searches at a national level without any language restrictions identified 232 additional records for inclusion. Finally, a total of 511 records from the two searches were included in the systematic review for data extraction (appendix pp 4–30).

For Europe, this systematic review had an annual data coverage of 87·4% within the considered period (1997–2021), with a mean of 21·9 years (95% CI 21·3–22·3) of data coverage per country, including case reports (table 1, appendix pp 31–36). Without case reports, the annual data coverage was 84·2%. The annual data coverage for the 27 EU member states was 87·7%, with a mean of 21·9 years (95% CI 21·3–22·5) per member state (table 1, appendix pp 31–36). Data extraction during this period identified a total of 64 745 human cystic echinococcosis cases from 40 European countries and 54 244 cases from the 27 EU member states (figure 1, table 1). Bulgaria, Italy, Romania, and Spain accounted for 67·4% (n=43 653) of the total cystic echinococcosis

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	Total cystic echinococcosis cases, N (1997–2021)	Years in which data were extracted (1997–2021)	Total years of extracted data	Average annual cystic echinococcosis cases, N (2017–19)	Range (min–max) of the annual cystic echinococcosis cases (2017–19)	Years in which data were extracted (2017–19)	Average cystic echinococcosis cases predicted for 2023, N*	95% prediction interval for 2023*	Cystic echinococcosis hospital records (1997–2021)	Period covered by hospital records	Total years covered by hospital records	Cystic echinococcosis deaths	Case fatality rate	Unspecified echinococcosis deaths†
Albania	1529	1997–2021	25	84	34–114	2017–19	46	16 to 132	..	..	..	1	0·3%	..
Austria	527	1997–2021	25	29	16–40	2017–19	9	1 to 48	..	..	..	..	..	..
Belarus	182	1997–2018	19	13	13–13	2018	45	9 to 216	..	..	..	..	..	..
Belgium	166	1997–2021	19	10	9–12	2017–19	12	4 to 32	..	..	..	..	..	..
Bosnia and Herzegovina	624	1997–2021	25	13	11–15	2017–19	9	3 to 24	..	..	..	..	..	..
Bulgaria	9739	1997–2021	25	206	193–218	2017–19	160	110 to 233	16 843	1997–2021	25	187	2·40%	..
Croatia	408	1997–2021	25	9	4–15	2017–19	7	3 to 17	..	..	..	1	0·3%	..
Cyprus	57	1997–2021	25	2	0–5	2017–19	0	0 to 1	..	..	..	..	..	..
Czech Republic	28	2003–20	17	1	1–1	2017–19	1	1 to 1	..	..	..	..	..	..
Denmark	140	2000–17	13	13	9–20	2012–14	26	2 to 291	..	..	..	..	..	..
Estonia	4	1997–2021	25	0	0–1	2018–20	0	0 to 1	..	..	..	..	..	..
Finland	54	1997–2021	25	5	1–8	2017–19	5	0 to 98	..	..	..	..	..	..
France	3873	1997–2021	24	226	220–232	2017–19	194	163 to 231	6062	2005–2020	16	85‡	2·39%	..
Germany	1578	2001–21	21	89	86–93	2017–19	122	64 to 234	..	..	..	..	..	145
Greece	502	1998–2021	24	11	7–15	2017–19	8	2 to 25	..	..	..	3	0·59%	..
Hungary	144	2000–20	21	8	6–11	2017–19	26	0 to >500	..	..	..	1	0·694%	..
Iceland	0	2013–20	8	0	0–0	2017–19	0	0 to 0	..	..	..	..	..	..
Ireland	15	2003–21	19	1	0–2	2017–19	1	0 to 42	..	..	..	1	7·14%	..
Italy	15 489	1997–2021	25	386	281–464	2017–19	221	173 to 282	24 651	1997–2021	25	132	0·92%	..
Kosovo	363	1997–2018	22	2	1–2	2017–18	0	0 to 30	..	..	..	..	..	..
Latvia	147	1999–2021	23	4	4–5	2017–19	6	0 to 176	..	..	..	1	0·76%	13
Lithuania	332	1997–2021	25	20	11–30	2017–19	47	8 to 272	..	..	..	..	..	1
Luxembourg	8	2007–20	8	1	0–2	2017–19	5	0 to >500	..	..	..	..	..	..
Malta	1	2015–20	6	0	0–0	2017–19	0	0 to 0	..	..	..	..	..	..
Moldova	3214	1997–2021	25	46	40–53	2017–19	52	21 to 128	..	..	..	41	1·28%	..
Montenegro	120	1997–2020	24	4	3–5	2017–19	10	0 to 335	..	..	..	..	..	..
Netherlands	915	1997–2020	23	44	41–48	2017–19	37	20 to 67	..	..	..	..	..	..
North Macedonia	538	1997–2021	25	29	21–37	2017–19	42	15 to 119	1652	2008–2020	13	22	5·30%	..
Norway	90	1999–2020	22	6	5–7	2017–19	14	1 to 200	..	..	..	1	1·11%	..
Poland	590	1997–2021	23	22	17–27	2017–19	10	3 to 33	704	2001–2020	..	..	..	33
Portugal	502	1997–2021	25	20	16–28	2017–19	20	7 to 56	..	..	..	..	..	..
Romania	7750	1998–2021	24	317	314–320	2017–19	197	149 to 260	20 400	2006–2020	15	261	1·58%	..
Serbia	1311	1997–2019	23	56	30–74	2017–19	61	33 to 112	..	..	..	11	0·84%	..
Slovakia	101	1997–2021	25	3	2–3	2017–19	3	0 to 97	..	..	..	..	..	..

(Table 1 continues on next page)

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	Total cystic echinococcosis cases, N (1997–2021)	Years in which data were extracted (1997–2021)	Total years of extracted data	Average annual cystic echinococcosis cases, N (2017–19)	Range (min–max) of the annual cystic echinococcosis cases (2017–19)	Years in which data were extracted (2017–19)	Average cystic echinococcosis cases predicted for 2023, N*	95% prediction interval for 2023*	Cystic echinococcosis hospital records (1997–2021)	Period covered by hospital records	Total years covered by hospital records	Cystic echinococcosis deaths	Case fatality rate	Unspecified echinococcosis deaths†
(Continued from previous page)														
Slovenia	104	1997–2021	25	2	1–3	2017–19	4	1 to 11	..	..	..	..	..	..
Spain	10 675	1997–2021	25	260	256–264	2017–19	200	174 to 229	17 893	1997–2020	24†	145	1·36%	..
Sweden	395	1997–2021	25	27	24–30	2017–19	40	18 to 86	..	..	..	..	..	..
Switzerland	166	1997–2021	25	10	7–14	2017–19	12	6 to 27	..	..	..	..	..	..
UK	211	1997–2020	24	4	3–4	2017–19	12	4 to 39	227	2005–09	5	2	0·67%	..
Ukraine	2153	2000–13	14	118	114–125	2011–13	92	61 to 138	..	..	..	..	..	..
EU	54 244	1997–2021	592	1716	1519–1897	2017–19	1361	903 to >3823	79 787	..	105	816	1·51%	192
European countries	64 745	1997–2021	874	2101	1801–2360	2017–19	1756	1072 to >5323	88 432	..	123	895	1·39%	192

*Time-trend prediction for 2023 is based on the subset of data from 1997 to 2019 (appendix p 31–33). †It was not possible to differentiate cystic echinococcosis from alveolar echinococcosis deaths. ‡It is not possible to ascertain whether patients with cystic echinococcosis died as a result of cystic echinococcosis or because of other comorbidities.

Table 1: **Number of cases, hospitalisations, and deaths of human cystic echinococcosis at a national level during 1997–2021**

cases in Europe (figure 1; table 1). National hospital records were available only from eight European countries (Bulgaria, France, Italy, North Macedonia, Poland, Romania, Spain, and the UK), in which 83 432 hospitalisations were recorded, with an annual data coverage of 12·3% within the considered period (table 1).[24,28,29] Only three published cross-sectional studies that used ultrasound population-based surveys were identified in Europe.[30–32] One of these large-scale, cross-sectional studies estimated approximately 8000 cystic echinococcosis infections in rural endemic areas of Bulgaria and 37 000 cystic echinococcosis infections in rural endemic areas of Romania during the period 2014–15.[31] Data from these surveys, as from the European Clinical Register on cystic echinococcosis, were extracted but not useful for any final calculation on numbers, incidence rates, or trends of cystic echinococcosis.[11,30–32]

An average of 2101 (range 1801–2360) new cystic echinococcosis cases per year were recorded throughout European countries and 1716 (1519–1897) throughout EU member states during 2017–19, before the COVID–19 pandemic compromised the notification of cystic echinococcosis cases (table 1).[13] In 2023, an estimated 1756 (95% prediction intervals 1072 to >5323) new cystic echinococcosis cases per year are expected throughout European countries and 1361 (903 to >3823) within EU member states, based on predicted time-trend analysis during 1997–2019 (table 1).

Cystic echinococcosis deaths were recorded in 16 (40%) countries, in a total of 895 cases during the considered period, corresponding to a hospitalised case fatality rate of 1·39% (table 1). In addition, 192 deaths were reported as echinococcosis from four countries (Germany, Latvia, Lithuania, and Poland), where it was not possible to differentiate cystic echinococcosis from alveolar echinococcosis deaths (table 1).

Mean annual incidence was 0·64 per 100 000 people in European countries and 0·50 per 100 000 people in only EU countries for the period 1997–2020. As defined by WHO, high endemicity areas for cystic echinococcosis (one to five cases per 100 000 people)[31] in the period 1997–2020 were identified in eight European countries: Albania (2·25 per 100 000), Bosnia and Herzegovina (1·00 per 100 000), Bulgaria (5·33 per 100 000), Italy (1·21 per 100 000), Moldova (4·65 per 100 000), North Macedonia (1·08 per 100 000), Romania (2·16 per 100 000), and Spain (1·00 per 100 000; table 2; figure 2). Mean annual incidences during the period 2017–19 were 0·46 cases per 100 000 people for European countries and 0·35 per 100 000 people for EU countries. During the 2017–19 period, high endemicity areas for cystic echinococcosis[27] were identified in five European countries: Albania (2·94 per 100 000), Bulgaria (2·93 per 100 000), Moldova (1·70 per 100 000), North Macedonia (1·41 per 100 000), and Romania (1·63 per 100 000; table 2; figure 3).

The annual data coverage for analysis of trends was 74·8% within the considered period (1997–2019), with an

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average of 17·2 years (95% CI 16·5–17·8) data coverage per country (appendix pp 32). Considering the observed annual incidences and those predicted by the model, a general decrease in the number of human cystic echinococcosis cases has been identified in Europe from 1997 to 2020 (figure 4). In particular, the significant decreasing trends were detected in most southern and some eastern European countries where the disease has traditionally been highly prevalent, such as Bosnia and Herzegovina, Bulgaria, France, Greece, Italy, Moldova, Romania, Spain, and Ukraine, but also in Croatia, the Czech Republic, and Poland (figure 4; table 2). Mostly, significant increasing trends were detected in eastern and southeastern European countries (the Balkans and the southern Baltics), such as Belarus, Montenegro, North Macedonia, Serbia, Slovenia, and Lithuania but also in most non-endemic northern (Scandinavia) and western European countries, such as Finland, Germany, Norway, Sweden, and Switzerland (figure 4; table 2). Malta has reported one presumably imported case and Iceland has never documented a cystic echinococcosis case in the last 25 years. A synthesis of cystic echinococcosis endemicity and whether these cystic echinococcosis cases at a national level should be considered as locally acquired, imported, or both was reported in table 2, when low incidences in non-endemic countries were commonly associated only with imported cases.

Taking into account both the latest incidences and trends, cystic echinococcosis remains a relevant public health issue in the Mediterranean European (Italy and Spain) and eastern and southeastern European countries (Albania, Bosnia and Herzegovina, Bulgaria, Montenegro, Moldova, North Macedonia, Serbia, and Romania; figure 1). Such incidences and trends are decreasing in the Mediterranean area, but they remain stable or increasing in the southern Baltic area and in the Balkan Peninsula. The Balkan Peninsula should be considered as the current focus of cystic echinococcosis in Europe (figure 2–4). The individual country results are reported in the Appendix.

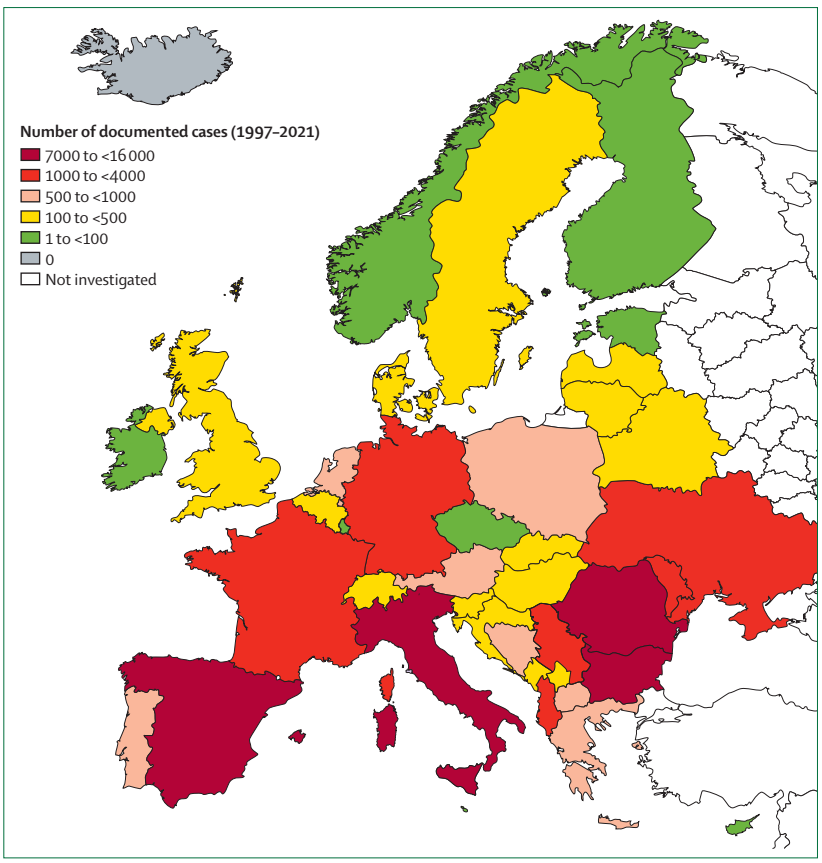

Figure 1: **Number of documented human cystic echinococcosis cases in Europe at the national level during 1997–2021 (n=64 745)**
Numbers of cases were seemingly clustered within discrete ranges, which drove the categorisation of countries and resulted in some substantial gaps between ranges (ie, red and dark red countries).

Discussion

To our knowledge, this systematic review is the first to provide a conservative estimate of the number of cases, incidence, and trends of human cystic echinococcosis at a national level in 40 selected European countries. This systematic review identified approximately 65 000 human cystic echinococcosis cases in Europe during the past 25 years, with a mean annual incidence of 0·64 cases per 100 000 people and different trends in both some endemic and non-endemic macro-areas (ie, Balkan, Mediterranean, and Scandinavian countries). The reliability of the results from this retrospective, European-scale systematic review depends on the extent to which potential sources of bias have been avoided both in the methods and the content of the data source used. In this study, such biases were minimised by verifying data, whenever possible, with national experts and requesting that coauthors review results and conclusions. In this context, it is worth listing the limitations of this research that might have biased the outcome of this study, resulting in an overestimation or, more likely, an underestimation of the rates. In particular, we are mainly referring to the sampling bias, misclassification bias, and publication bias that could have generated type 1 (false-positive cystic echinococcosis cases) or type 2 (false-negative cystic echinococcosis cases) errors.

Of note, the four main data sources used in this study (ie, national reports, hospital records, TESSy data reports, and single-centre or multicentre case series) might provide different evidence on the number of cystic echinococcosis cases, depending on the health setting of the investigated country.

Potential bias which can lead to overestimation

Generally speaking, published or unpublished single-centre or multicentre case series usually provide the most reliable evidence on the number of human cystic echinococcosis cases (ie, for Austria, Belgium, Bosnia and Herzegovina, Cyprus, Czech Republic,

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	Mean annual incidence* (1997–2020)	Period analysed	Endemicity† (1997–2020)	Mean annual incidence* (2017–19)	Period analysed	Endemicity† (2017–19)	Assumed origins of cases‡
Albania	2·25	2003–20	High endemicity	2·94	2017–19	High endemicity	Majority locally acquired
Austria	0·25	1997–2020	Present	0·33	2017–19	Present	Most imported; some locally acquired
Belarus	0·10	1997–2018	Present	0·14	2018	Present	Majority locally acquired
Belgium	0·08	2005–20	Rare or sporadic	0·09	2017–19	Rare or sporadic	Majority imported; 1 locally acquired
Bosnia and Herzegovina	1·00	1997–2020	High endemicity	0·38	2017–19	Present	Majority locally acquired
Bulgaria	5·33	1997–2020	High endemicity	2·93	2017–19	High endemicity	Majority locally acquired
Croatia	0·39	1997–2020	Present	0·21	2017–19	Present	All locally acquired
Cyprus	0·22	1997–2020	Rare or sporadic	0·20	2017–19	Rare or sporadic	Both locally acquired/imported
Czech Republic	0·02	2003–20	Rare or sporadic	0·01	2018; 2020	Rare or sporadic	Majority imported; 1 locally acquired
Denmark	0·23	2004–14	Suspected	0·17	2013–14§	Suspected	All imported
Estonia	0·01	1997–2020	Suspected	0·02	2017–20	Suspected	Most locally acquired but also imported
Finland	0·04	1998–2020	Rare or sporadic	0·08	2017–19	Rare or sporadic	Majority imported; 1 locally acquired
France	0·37	2005–20	Present	0·34	2017–19	Present	Most imported; some locally acquired
Germany	0·09	2001–20	Rare or sporadic	0·11	2017–19	Rare or sporadic	All imported; few seems locally acquired
Greece	0·20	1998–2020	Present	0·10	2017–19	Present	Majority locally acquired
Hungary	0·07	2000–20	Present	0·08	2017–19	Present	Majority locally acquired; some imported
Iceland	0·00	2013–20	Probably absent	0·00	2013–21	Probably absent	No cases
Ireland	0·02	2003–20	Suspected	0·02	2017–19	Suspected	All cases imported; 1 possibly locally acquired
Italy	1·21	2001–20	High endemicity	0·64	2017–19	Present	Most locally acquired but also imported
Kosovo	0·93	1997–2018	Present	0·18	2012–18	Present	Majority locally acquired
Latvia	0·28	1999–2020	Rare or sporadic	0·22	2017–19	Rare or sporadic	Most locally acquired but also imported
Lithuania	0·43	1997–2020	Present	0·71	2017–19	Present	Most locally acquired but also imported
Luxembourg	0·17	2007–20	Suspected	0·16	2017–19	Suspected	All imported
Malta	0·00	2015–20	Probably absent	0·00	2017–19	Probably absent	All imported
Moldova	4·65	1997–2020	High endemicity	1·70	2017–19	High endemicity	Majority locally acquired
Montenegro	0·81	1997–2020	Present	0·64	2017–19	Present	Majority locally acquired
Netherlands	0·24	1997–2020	Suspected	0·26	2017–19	Suspected	All imported
North Macedonia	1·08	1997–2020	High endemicity	1·41	2017–19	High endemicity	Majority locally acquired; some imported
Norway	0·09	2000–20	Suspected	0·12	2017–19	Suspected	All imported
Poland	0·07	2001–20	Present	0·06	2017–19	Present	Majority locally acquired
Portugal	0·19	1997–2020	Present	0·20	2017–19	Present	Majority locally acquired
Romania	2·16	2008–20	High endemicity	1·63	2017–19	High endemicity	Majority locally acquired
Serbia	0·78	1997–2019	Present	0·80	2017–19	Present	Majority locally acquired
Slovakia	0·07	1997–2020	Rare or sporadic	0·05	2017–19	Rare or sporadic	Most locally acquired but also imported
Slovenia	0·21	1997–2020	Rare or sporadic	0·14	2018–19	Rare or sporadic	Both locally acquired/imported
Spain	1·00	1997–2020	High endemicity	0·56	2017–19	Present	Most locally acquired but also imported
Sweden	0·21	2004–20	Suspected	0·27	2017–19	Suspected	All imported
Switzerland	0·08	1997–2020	Suspected	0·16	2017–19	Suspected	All imported
UK	0·02	1997–2019	Rare or sporadic	0·01	2017; 2019	Rare or sporadic	Majority imported; 5 locally acquired
Ukraine	0·33	2000–13	Present	0·26	2011–13§	Present	Majority locally acquired
EU	0·50	..	..	0·35	..	..	..
European countries	0·64	..	..	0·46	..	..	..

*Expressed as the number of cystic echinococcosis cases per 100 000 people living in the considered country. †Definitions modified from WHO.[27] Probably absent means countries or territories with no confirmed identifications or reports of *Echinococcus granulosus sensu lato* in indigenous domestic or wild animal populations; human cystic echinococcosis has not been reported. Suspected means *E granulosus s l* might not be recorded in official data or publications but could occur in wildlife and possibly at low prevalence in domestic animals; human cystic echinococcosis appears not to occur. Rare or sporadic means *E granulosus s l* has been recorded at low prevalence in domestic animals and could be transmitted in wildlife populations; human cystic echinococcosis cases are only occasionally reported. Present means *E granulosus s l* is known to be endemic in at least some areas of the country; domestic animal (and possibly wildlife) and human cystic echinococcosis occurs regularly. High endemicity means *E granulosus s l* prevalence in dogs exceeds 5–10% and the prevalence of human cystic echinococcosis is greater than one to five cases per 100 000 inhabitants annually. ‡Locally acquired and imported cases based on the appendix (p 4–30); documented cystic echinococcosis cases were reported as majority (>90%), most (>70%), and both (approximately 50%). §Denmark and Ukraine did not report data on cystic echinococcosis during the years 2017–19; as a measure of the latest trends, last available data were used.

Table 2: **Average annual incidence rates and endemicity at the national level for the periods 1997–2020 and 2017–19**

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Kosovo, Latvia, Norway, Serbia, and Switzerland), both in the absence and presence of national data.[33–37] The limitation is that single-centre or multicentre case series are scarce and, therefore, fragmented over time and cannot be used to calculate trends. Moreover, single-centre or multicentre case series could introduce a sampling bias, as duplicated cases cannot always be disaggregated with other data sources in a given period nor can we eliminate misdiagnosed cases. This study assumes that, even if some cases were wrongly duplicated or diagnosed, as a whole, these case series cannot overestimate the under-recorded condition of cystic echinococcosis. Finally, single-centre or multicentre case series were recorded mainly at the beginning of the study period and might therefore lead to an underestimation of cystic echinococcosis incidences calculated for the latest period (2017–19) compared with the entire period (1997–2020).

Other relevant data sources to discuss are national reports on cystic echinococcosis cases and national hospital records, reporting the number of hospitalisations generated by single cases. For Italy, there were 100 hospitalisations reported for every 62·5 national cystic echinococcosis cases (reporting both ordinary and day hospitalisation), meaning that for every case of cystic echinococcosis there were 1·6 hospitalisations (appendix pp 4–30). For Bulgaria, each cystic echinococcosis cases resulted in an average of 2·2 hospitalisations, and for North Macedonia each case resulted in 4·5 hospitalisations (reporting only ordinary hospitalisation; appendix pp 4–30). Such rates of hospitalisation from these three highly endemic countries suggests that sequelae and improper clinical management might increase the disease burden of cystic echinococcosis.[18,38] Such morbidity should be taken in account for further research on the clinical burden of disease at the national level.

For Romania and Spain, only hospitalised cases were available. For Romania, a single reference centre (Colentina Clinical Hospital, Carol Davila University of Medicine and Pharmacy, Bucharest) reported 1038 cases (representing 29·56% of hospitalisations) that generated 3511 hospitalisations during the period 2006–10 (appendix pp 4–30). For Spain, a single reference centre (Centro de Investigación de Enfermedades Tropicales de la Universidad de Salamanca, Hospital Universitario de Salamanca, Salamanca) recorded 659 cases (representing 59·48% of hospitalisations) that generated 1108 hospitalisations during the period 1998–2021 (appendix pp 4–30). Such ratios (cases to hospitalisations) from the Bucharest and Salamanca reference cohorts were used to calculate number of national cystic echinococcosis cases from national hospitalisations. It should also be stressed that, as previously discussed for Italy, cystic echinococcosis reporting based solely on hospital records has some drawbacks and is inadequate to capture all cases, as most cystic echinococcosis cases in some national health settings are diagnosed and clinically managed in an outpatient setting.[39]

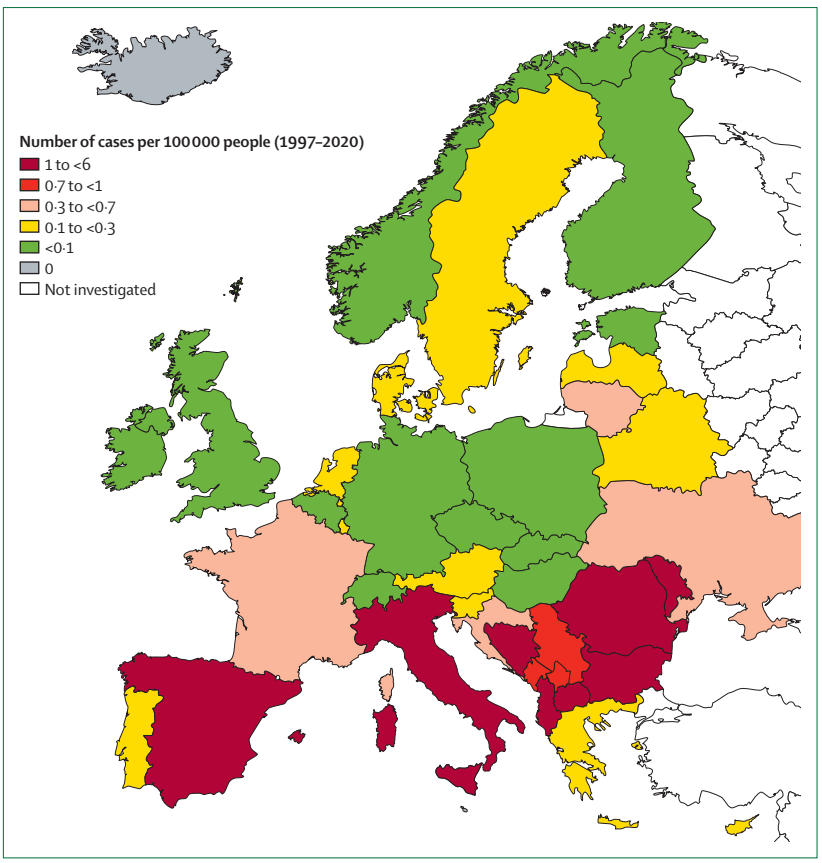

Figure 2: **Mean national annual incidence intervals (expressed as number of cases per 100 000 people) of documented human cystic echinococcosis cases in Europe within the years 1997–2020**
Dark red countries are considered as high endemicity areas for cystic echinococcosis (one to six cases per 100 000 people).

Potential bias which can lead to underestimation

For sampling selection bias, single-centre or multicentre case series were recorded mainly at the beginning of the considered period and might, therefore, lead to an underestimation of cystic echinococcosis incidences in the last period (2017–19) compared with the entire period (1997–2020).

Another major source of bias is the unspecified echinococcosis cases which, given the higher number of cystic echinococcosis cases than alveolar echinococcosis cases, is most likely to affect cystic echinococcosis estimates. In fact, approximately 200 000 new cases per year of cystic echinococcosis and 18 000 new cases per year of alveolar echinococcosis are estimated globally, with 91% of alveolar echinococcosis cases occurring in China and around 1600 cases in Europe, central Asia, and Russia.[5,27,40,41] According to this numerical proportion, for every human alveolar echinococcosis infection, 10–20 cystic echinococcosis infections can be expected, particularly in Europe but also worldwide. Notably, even

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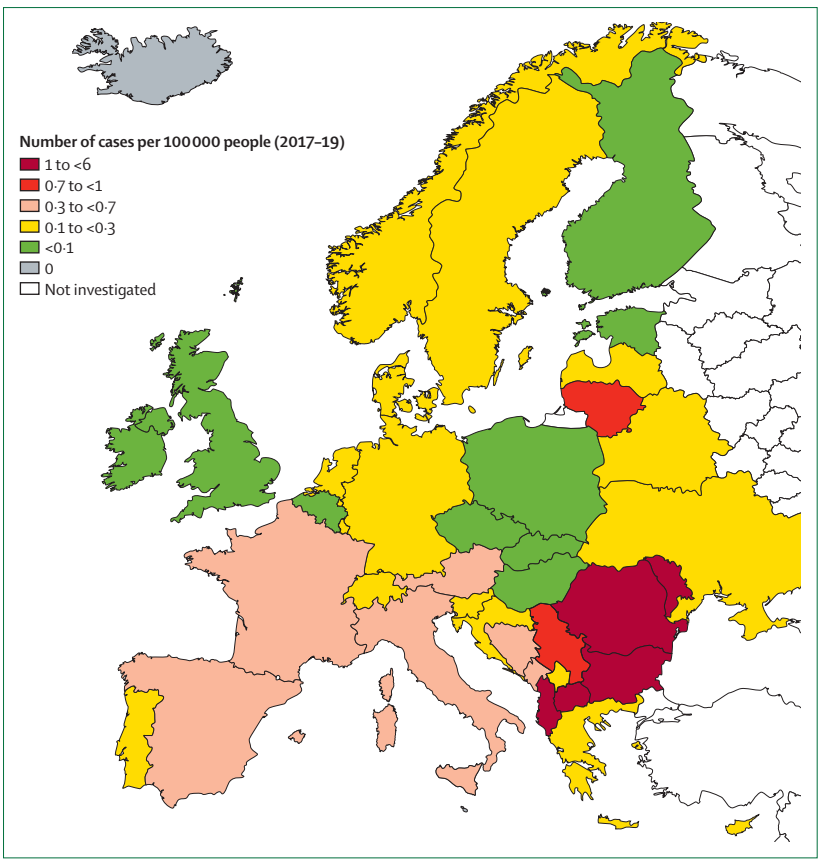

Figure 3: **Mean national annual incidence intervals (expressed as number of cases per 100 000 people) of documented human cystic echinococcosis cases in Europe during the period 2017–19**
Dark red countries considered as high endemicity areas for cystic echinococcosis (one to six cases per 100 000 people).

if alveolar echinococcosis infections represent a small proportion of general echinococcosis infections in Europe, alveolar echinococcosis infections are likely to be more represented in the reporting systems due to the severity of this clinical condition. In this scenario, during the years 2013–20, TESSy data recorded 6269 cases of echinococcosis, of which 3240 (51·68%) were cystic echinococcosis cases, 1012 (16·14%) alveolar echinococcosis cases, and 1987 (31·70%) unspecified echinococcosis.[23,42,43] In this systematic review, unspecified echinococcosis cases from TESSy were only included for those countries that are exclusively endemic for cystic echinococcosis, but not those endemic for alveolar echinococcosis or for both diseases. Due to these unspecified echinococcosis cases, TESSy data reports are not a perfect tool to capture all cystic echinococcosis cases, as is the case for some national reports, although a huge improvement in the notification has been undertaken by EU member states to distinguish between these two parasitic diseases.[23,42,43] For instance, Italy has never reported any case to TESSy, irrespective of the huge disease burden documented by hospital records.[29] For these reasons, the current study was able to identify a total number of cystic echinococcosis cases four-fold higher than the same EU member states reported in TESSy data (5106 cases *vs* 1251 cases) in 2017–19 (appendix p 31).[23]

Of note, alveolar echinococcosis can be misdiagnosed as cystic echinococcosis. In a retrospective sentinel case series from endemic Germany, alveolar echinococcosis was mistaken for cystic echinococcosis in 12 of 26 cases. Mediterranean countries that are non-endemic for alveolar echinococcosis, such as Italy and Spain, have reported hundreds of alveolar echinococcosis cases that were most likely people misdiagnosed with multicystic cystic echinococcosis (mainly CE2 and CE3b according to the WHO Informal Working Group for Echinococcosis cyst-stage classification).[28,29,44]

For the calculation of trends at the national level, a subset of data not containing case series was analysed until 2019, before the COVID-19 pandemic (appendix pp 31–33). There was a 56·12% decrease of notification rates for 2020 (242 cystic echinococcosis cases) compared with the average cases in 2016–19 (mean 431 cystic echinococcosis cases).[23] These data suggest that, as the COVID-19 pandemic has adversely affected the availability of general surgery, this might have resulted in the postponement of hospital admission for cystic echinococcosis cases and hence reduction in reporting of cystic echinococcosis to TESSy.[23]

In addition to the under-reported and misdiagnosed patients with cystic echinococcosis, there are also undiagnosed cystic echinococcosis cases, as was evidenced in a large research-based, cross-sectional, ultrasound survey conducted in Bulgaria and Romania.[31] This active search for cystic echinococcosis carriers aiming to detect asymptomatic cases in rural areas identified a prevalence of 0·41% in both countries. This value resulted in an estimated total of 45 000 people that might be infected with *E granulosus s l.* Extrapolating this estimated prevalence to the top five countries with the highest incidences (Albania, Bulgaria, Moldova, North Macedonia, and Romania), the current number of people that could be infected in rural areas of Europe at any given time would be higher than that recorded in the present study.

For case fatality rates, the data sources from two of 16 recording countries (France and Spain) are mainly based on national hospital records that, unlike the case series or the National Institute of Statistics data, cannot ascertain whether cystic echinococcosis was the cause of death or whether death resulted from other comorbidities (appendix pp 4–30).[24,28] Nevertheless, the European-level case fatality rate identified in this study is consistent both with national data not derived from hospitalisations (table 1) and with other cohorts from the literature.[3,45–47] As for locally acquired cases versus imported cases, it should also be noted that documented human cystic echinococcosis cases in non-endemic countries for patients with no travel history abroad (eg, patients in Germany) suggest that some infections might be locally acquired through

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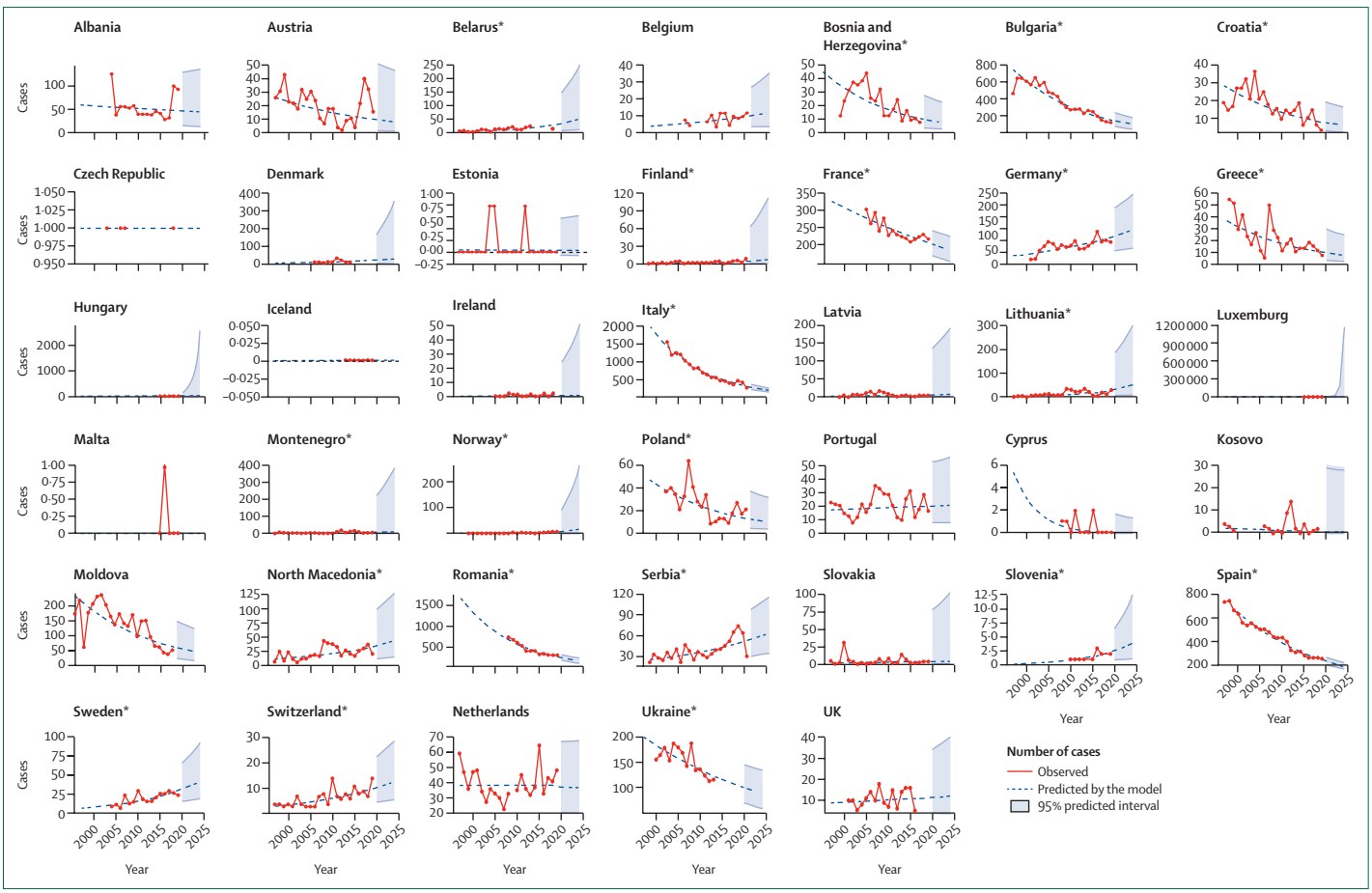

Figure 4: **Time-trend analysis of the number of human cystic echinococcosis cases at the country level (observed cases and predicted cases for the years 2020–24)**
*Significant time trend (p<0·05).

food from endemic countries or by direct contact with dogs that have travelled abroad.[48] Finally, imported cases could present an important contribution to the cystic echinococcosis health burden at a national level, even in endemic countries such as Italy, which recorded that 13·6% of all documented cases during the period 2001–14 were in foreign patients.[29]

Most of these biases, including the annual data extraction from this study that does not cover the whole period, mainly contribute to an underestimation of this neglected zoonotic disease in Europe. Finally, a 2020 study[49] collected human cystic echinococcosis incidence data from the literature and calculated pooled prevalences on animal cystic echinococcosis in the Mediterranean and Balkan countries. This study, which was not recalculating incidences at the national level, also found that Italy, Spain, and Eastern Europe are the most affected areas for human cystic echinococcosis.

Conclusion

Cystic echinococcosis remains endemic and neglected in many regions of Europe. However, there appears to be a general decrease in incidences, with variable trends at the national level. With few exceptions, most of the endemic southern, and some eastern, European countries, where the disease has traditionally been highly prevalent, have reported a decrease in human cystic echinococcosis cases. Such a decrease could be due to the increasing hygiene, the rural-to-urban migration at a national level, a decrease in sheep populations, an increase in intensive farming, and the implementation of national control programmes.[50] By contrast, increases have been unexpectedly identified in most non-endemic northern (Scandinavia) and western European countries and southern Baltic countries. Such a trend (corresponding to hundreds of cases) might be due to an increase of migration from endemic countries (in particular from northern Africa, the Middle East, southern America, and central Asia), international travel, and increasing knowledge among physicians. On the basis of the latest incidence data and trends detected in eastern and southeastern European countries, the Balkans should be considered the current epicentre of cystic echinococcosis in Europe.

Finally, we encourage ultrasound, population-based surveys for the active search of cystic echinococcosis carriers in highly endemic areas of Europe, especially in

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the Balkan peninsula. To provide a more reliable picture of the health burden of the disease in Europe, a more accurate collection of epidemiological and clinical data is needed, which will provide a statistically sound case series for the evaluation of the cost-effectiveness of interventions. The findings from this systematic review, coupled with other studies on potential risk factors increasing the likelihood of infection for human cystic echinococcosis,[51] should be used to support the planning of surveillance and control of human and animal cystic echinococcosis in Europe through the One Health approach, according to the WHO 2021–2030 roadmap for Neglected Tropical Diseases.[1]

Contributors

AC conceived the study, extracted the data, performed statistical analyses, interpreted the results, and wrote the paper. FS and AS extracted and interpreted the data in the first round. DP and MF performed time-trends statistical analyses. BA-R, DP, MF, BB, DC, BŠ, EZ, MJG, GK, CC, IR, SS, VL, BD, ZH, JK, PM, AO, LM, MSv, RS, VG, IA, US, PT, DA, VŠ, DM, HB, FChe, MBG, FCha, SG, MSt, BM, and VM extracted and interpreted the data in the second round. All authors reviewed the article and approved submission.

Declaration of interests

We declare no competing interests.

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