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

Casulli, Adriano ; Abela-Ridder, Bernadette ; Petrone, Daniele ; Fabiani, Massimo ; Torgerson, Paul R ; Müllhaupt, Beat ; et al

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

Adriano Casulli, Bernadette Abela-Ridder, Daniele Petrone, Massimo Fabiani, Branko Bobić, David Carmena, Barbara Šoba, Enver Zerem, Maria João Gargaté, Gordana Kuzmanovska, Cristian Calomfirescu, Iskra Rainova, Smaragda Sotiraki, Vera Lungu, Balázs Dezsényi, Zaida Herrador Ortiz, Jacek Karamon, Pavlo Maksimov, Antti Oksanen, Laurence Millon, Mario Sviben, Renata Shkjezi, Valbona Gjoni, Ilir Akshija, Urmas Saarma, Paul Torgerson, Viliam Snabel, Daniela Antolova, Damir Muhovic, Hasan Besim, Fanny Chereau, Moncef Belhassen García, François Chappuis, Severin Gloor, Marcel Stoeckle, Beat Müllhaupt, Valerio Manno, Azzurra Santoro*, Federica Santolamazza*

Adriano Casulli, PhD. WHO Collaborating Centre for the Epidemiology, Detection and Control of Cystic and Alveolar Echinococcosis; European Reference Laboratory for Parasites. Department of Infectious Diseases, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy.

Bernadette Abela-Ridder, DVM. Department of Control of Neglected Tropical Diseases, World Health Organization, Avenue Appia 20, 1211 Geneva, Switzerland.

Daniele Petrone, Dstat. Unit of Epidemiology, biostatistics and mathematical modelling, Department of Infectious Diseases, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy.

Massimo Fabiani, Dstat. Unit of Epidemiology, biostatistics and mathematical modelling, Department of Infectious Diseases, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy.

Branko Bobić, PhD. Institute for Medical Research University of Belgrade, National Institute of Republic of Serbia, Dr Subbotića 4, 11000 Beograd, Serbia.

David Carmena, PhD. Parasitology Reference and Research Laboratory, Spanish National Centre for Microbiology, Health Institute Carlos III, Ctra. Majadahonda-Pozuelo Km 2, 28220 Majadahonda, Madrid, Spain.

Barbara Šoba, PhD. Laboratory of Parasitology, Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Zaloška 4, 1000 Ljubljana, Slovenia.

Enver Zerem, PhD. Department of Medical Sciences, The Academy of Sciences and Arts of Bosnia and Herzegovina, Bistrik 7, 71000 Sarajevo, Bosnia and Herzegovina.

Maria João Gargaté, PhD. National Reference Laboratory of Parasitic and Fungal Infections, Department of Infectious Diseases, National Institute of Health Doutor Ricardo Jorge, Avenida Padre Cruz, 1649-016 Lisboa, Portugal.

Gordana Kuzmanovska, MD. Head of the Department of Communicable Diseases Epidemiology, Head of the Institute of Public Health of Republic of North Macedonia, 50 Divizija N-6, 1000 Skopje, Republic of North Macedonia.

Cristian Calomfirescu, programmer. Director of the National Center for Statistics in Public Health, National Institute of Public Health, Str. Doctor Leonte Anastasievici Nr. 1-3 Sector 5, 050463 Bucharest, Romania.

Prof **Iskra Rainova**, MD. Deputy Director, National Center of Infectious and Parasitic Diseases (NCIPD), 26 Yanko Sakazov blvd, 1504 Sofia, Bulgaria.

Smaragda Sotiraki, PhD. Veterinary Research Institute, Hellenic Agricultural Organisation/ELGO-DIMITRA, Campus Thermi 57001 Thessaloniki, Greece.

Vera Lungu, MD. Department for epidemiological surveillance of highly contagious diseases, zoonoses and parasites. National Public Health Agency (NPHA) of the Republic of Moldova. Str. Gheorghe Asachi 67/A, MD 2028 Chisinau, Republic of Moldova.

48 **Balázs Dezsényi**, PhD. Semmelweis University, Department of Anatomy, Histology and Embriology,
49 Tűzoltóutca 58, 1094 Budapest, Hungary.

50 **Zaida Herrador**, PhD. National Centre of Epidemiology, Health Institute Carlos III, C/ Sinesio Delgado
51 nº 6 - Pabellón 12, 28029 Madrid, Spain.

52 **Jacek Karamon**, PhD. Department of Parasitology and Invasive Diseases, National Veterinary
53 Research Institute, Al. Partyzantow 57, 24-100 Pulawy, Poland.

54 **Pavlo Maksimov**, DVM. NRL for echinococcosis, Institute of Epidemiology, Friedrich-Loeffler-
55 Institut, Federal Research Institute for Animal Health, Südufer 10, 17493 Greifswald - Insel Riems,
56 Germany.

57 **Antti Oksanen**, PhD. Finnish Food Authority (FINPAR). Elektroniikkatie 3, 90590 Oulu, Finland.

58 Prof **Laurence Millon**, MD. National Reference Center for Echinococcosis, University Hospital of
59 Besançon, UMR 6249 CNRS Chrono-environnement, University of Bourgogne Franche Comté,
60 France.

61 **Mario Sviben**, PhD. Croatian National Institute for Public Health, National Reference Laboratory for
62 Parasites of Humans, Department of Microbiology, Rockefellerova 7, Zagreb, Croatia. University of
63 Zagreb, School of Medicine, Department of Microbiology and Parasitology, Salata 3, Zagreb, Croatia.

64 **Renata Shkjezi**, PhD. Mother Cabrini – ONLUS Foundation. Via Cogozzo 12, 26866 Sant'Angelo
65 Lodigiano (LO), Italy.

66 **Valbona Gjoni**, PhD. Department of National Reference Laboratories, Institute of Public Health,
67 Aleksander Moisiu Street Nr. 80 Tirana, Albania.

68 **Ilir Akshija**, MD, University Hospital Center, "Mother Teresa", Statistics Department, Rruga e Dibrës
69 372, 1000 Tirana, Albania.

70 Prof **Urmäs Saarma**, PhD. Department of Zoology, Institute of Ecology and Earth Sciences, University
71 of Tartu, Juhan Liivi 2, 50409 Tartu, Estonia.

72 **Paul Torgerson**, PhD. Section of Veterinary Epidemiology, Vetsuisse Faculty, University of Zürich,
73 Winterthurerstrasse 270, 8057 Zürich, Switzerland.

74 **Viliam Šnábel**, PhD. Laboratory of Human Parasitology, Institute of Parasitology of Slovak Academy
75 of Sciences, Hlinkova 3, 040 01 Košice, Slovakia.

76 **Daniela Antolová**, PhD. Laboratory of Human Parasitology, Institute of Parasitology of Slovak
77 Academy of Sciences, Hlinkova 3, 040 01 Košice, Slovakia.

78 **Damir Muhović**, PhD. Department of Gastroenterohepatology, Internal Clinic, Clinical Center of
79 Montenegro, Faculty of Medicine, University of Montenegro, Ljubljanska bb, 81000 Podgorica,
80 Montenegro.

81 Prof **Hasan Besim**, MD. Dept of General Surgery, Near East University Hospital, Near East Boulevard,
82 99138 Nicosia, Cyprus.

83 **Fanny Chereau**, PhD. Infectious Diseases Division, Santé publique France, 94410 Saint-Maurice,
84 France.

85 **Moncef Belhassen-Garcia**, PhD. Internal Medicine Service, Infectious Unit. University Hospital of
86 Salamanca. Institute of Biomedical Research of Salamanca (IBSAL). Research Center for Tropical
87 Diseases of the University of Salamanca (CIETUS). University of Salamanca, Salamanca. Paseo San
88 Vicente SN, 37007 Salamanca, Spain.

89 Prof **François Chappuis**, MD. Division of Tropical and Humanitarian Medicine, Geneva University
90 Hospitals, 4 rue Gabrielle-Perret-Gentil, 1211 Geneva 14, Switzerland.

91 **Severin Gloor**, MD. Department of Visceral Surgery and Medicine, Inselspital, Bern University
92 Hospital, University of Bern, Freiburgstrasse 18, 3010 Bern, Switzerland.

93 **Marcel Stoeckle**, MD. Division of Infectious Diseases and Hospital Epidemiology, University Hospital
94 Basel, University Basel, Petersgraben 4, 4031 Basel, Switzerland.

95 **Beat Müllhaupt**, MD. Gastroenterology and Hepatology, University Hospital Zürich, Rämistrasse
96 100, 8091 Zürich, Switzerland.

97 **Valerio Manno**, Dstat. Statistical Service, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161
98 Rome, Italy.

99 **Azzurra Santoro**, PhD. WHO Collaborating Centre for the Epidemiology, Detection and Control of
100 Cystic and Alveolar Echinococcosis; European Reference Laboratory for Parasites. Department of
101 Infectious Diseases, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy.

102 **Federica Santolamazza**, PhD. WHO Collaborating Centre for the Epidemiology, Detection and
103 Control of Cystic and Alveolar Echinococcosis; European Reference Laboratory for Parasites.
104 Department of Infectious Diseases, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome,
105 Italy.

106

107 * These authors contributed equally to this work

108

109 **Correspondence to:**

110 Adriano Casulli, PhD

111 WHO Collaborating Centre for the Epidemiology, Detection and Control of Cystic and Alveolar
112 Echinococcosis;

113 European Union Reference Laboratory for Parasites (EURLP);

114 ISTITUTO SUPERIORE di SANITÀ (ITALIAN INSTITUTE of HEALTH). Viale Regina Elena, 299, 00161

115 Rome, ITALY

116 adriano.casulli@iss.it

117

118 **KEYWORDS:** Cystic echinococcosis; *Echinococcus granulosus sensu lato*; international public health;
119 incidences and trends; neglected tropical diseases; Europe

120

121 Summary

122 The neglected zoonosis, cystic echinococcosis (CE) affects poor pastoral and rural communities in
123 both low and medium-high income countries. In Europe, it should be regarded as an orphan and
124 rare disease. Although human CE is a notifiable parasitic infectious disease in most European
125 countries, in practice it is largely under-reported by national health systems. To fill this gap, data on
126 the number, incidence and trend of human cases in Europe was extracted by means of systematic
127 review approach from both the scientific and grey literature, accounting for the period of
128 publication 1997–2021. The highest number of human cases at country level was calculated from
129 various data sources to generate a descriptive model of human CE in Europe. This study identified
130 64 376 human CE cases from 40 European countries. Mean annual incidence in Europe was 0.64/100
131 000 during 1997–2020 and 0.50/100 000 during 2017–19.

132 Based on incidence rates and trends detected in this study, the current epicentre of CE in Europe is
133 represented by South-eastern European countries, while historical endemic European
134 Mediterranean countries have recorded a decrease in the number of cases over the time.

135

136 Key messages

- 137 • This study is aiming to shed light on the unrecognized incidence of CE in Europe unveiling its
138 epidemiological impact by providing a quantitative measure of number, incidence and trends of
139 human cases documented within the period 1997–2021.
- 140 • Since human CE cases are generally under-reported and data suffer from uncertainty also due to
141 misdiagnosis, data provided by this study should be considered as a conservative estimate of the
142 real impact of this zoonotic infection historically occurring in Europe.
- 143 • This study identified for the years 2017–19 a mean number of CE cases at least four-fold higher
144 compared to the European Surveillance system data.
- 145 • Decreasing trends have been recorded in most Southern Mediterranean and some Eastern
146 European countries where CE has traditionally been highly prevalent.
- 147 • Increasing trends have been identified in some Eastern and South-eastern European countries but
148 unexpectedly also in most non-endemic countries of Northern and Western Europe.
- 149 • Based on recent incidence rates and trends, the current epicentre of CE in Europe is represented by
150 the Balkan Peninsula.
- 151 • CE in Europe remains a relevant public health issue and findings from this study should be used to
152 support the planning of surveillance and control programmes in Europe according to the WHO
153 2021–2030 roadmap for Neglected Tropical Diseases (NTDs).

154

155 Background

156 “Echinococcosis” belongs to the current group of 20 neglected tropical diseases, conditions, or
157 syndromes of global health importance which are endorsed by the World Health Organization
158 (WHO) for their prevention and control.^{1,2} “Echinococcosis” disease group includes cystic (CE),
159 alveolar (AE) and neotropical (NE) echinococcosis. Globally there is estimated to be more than one
160 million people infected at any one time.³ These parasitic diseases are caused by the aetiologic agents
161 *Echinococcus granulosus sensu lato* (CE) which has a worldwide distribution, *Echinococcus*
162 *multilocularis* (AE) present in the Northern hemisphere, and *Echinococcus vogeli* (NE) and
163 *Echinococcus oligarthra* (NE) which are restricted to Mexico, Central and South America.^{4,5}

164 In Europe, CE is mainly transmitted in rural and pastoral communities, where the environment is
165 contaminated by parasitic eggs. In Europe, the life cycle of *Echinococcus granulosus sensu lato*
166 involves primarily livestock intermediate hosts (mainly sheep, cattle and pigs) and canids as
167 definitive hosts (mainly dogs).^{6,7} AE in Europe is mainly transmitted by wildlife in rural communities,
168 where the environment is contaminated by parasitic eggs. In Europe, the life cycle of *Echinococcus*

169 *multilocularis* involves primarily small rodents as intermediate hosts and canids as definitive hosts
170 (mainly red foxes).^{6,8} In both CE and AE, humans act as dead-end hosts with hand-to-mouth and
171 foodborne/waterborne transmission of infective parasite eggs. CE and AE are both chronic diseases
172 in humans. CE is a disabling disease with a low fatality rate, while AE is mostly a life-threatening
173 disease since it causes a tumor-like progression. Within the “echinococcosis” disease group, CE is
174 the most prevalent in Europe, as well as globally, causing severe morbidity and relative low mortality
175 among human populations.⁵ CE mainly affects the liver and the lungs, although the parasite can be
176 localized in any organ or tissue.⁹ CE is characterized by fluid-filled isolated parasitic cysts growing
177 concentrically. Cyst growth might cause compression of neighbouring structures, which in turn is
178 responsible for the insurgence of symptoms (e.g. abdominal pain); more severe clinical
179 manifestations may also derive from complications such as cyst rupture or super-infections.
180 CE occurs in poor pastoral and rural communities, but it is also prevalent in those of medium-high
181 income countries, including European ones, where it should be considered as an orphan and a rare
182 disease.¹⁰ Although human CE, is in theory, a notifiable infectious disease in most European
183 countries, in practice it is largely under-recorded by national health systems. Several factors account
184 for the under-diagnosis, mis-diagnosis and consequently mis-reporting and under-reporting of CE
185 cases.¹¹

186 Some biological characteristics of the parasite, such as the time lag of months or years between the
187 event of infection and the eventual onset of symptoms, make it impossible to trace back the routes
188 of transmission in order to attribute the source of infection.^{12,13} Moreover, due to this long latency
189 period, it is not clear what are the main sources of infection, the pathways of transmission and the
190 potential risk factors associated with odds of infection. In addition, outbreaks, as occurrence of CE
191 cases in excess of what would be expected in a defined population do not exist for this silent, chronic
192 and long-standing zoonotic infectious disease.¹⁴ Therefore CE cases, in absence of data on source of
193 infection during the anamnesis, may be mis-diagnosed. Moreover, CE can be asymptomatic or
194 paucisymptomatic for years with absence of signs of acute infection for easy case retrieval which
195 may contribute to under-diagnosis of cases. Unlike other parasitic infections, CE cysts are
196 anatomically isolated in the human body; therefore, triggering a detectable antibody response is
197 variable and depends on several factors such as size, location, number and stage of parasitic
198 cysts.^{15,16} Therefore, serology alone is not a reliable diagnostic tool, and even in combination with
199 imaging requires experienced personnel for its interpretation, consequently leading to mis-
200 diagnosis. Due to the barrier provided by the cyst wall, biomarkers useful for diagnosis and
201 prognosis are currently unavailable to detect the direct or indirect presence of the parasite in
202 biological fluids such as blood or urine. Finally, since humans are dead-end hosts infected with the
203 asexual stage of the parasite (metacestode), no eggs or worms can be present in the fecal samples
204 to support the diagnosis, contrary to what generally adequate for the diagnosis of other helminths,
205 which reside in the human intestine. An exception for the direct detection of the parasite is the
206 *vomica* event for lung CE, a rare occurrence when part of ruptured cysts is expelled and directly
207 detected in the expectorate. Finally, CE can be silent for years and when symptoms are present,
208 they are unspecific, with no pathognomonic clinical signs related to the presence of CE cysts. These
209 parasitic characteristics may result in mis-diagnosis of cases by less experienced physicians.
210 For all these reasons, imaging techniques, in particular ultrasound, are the main diagnostic tools for
211 human CE, while serology is only supportive for the diagnosis and molecular confirmation is only
212 possible when parasitic cysts, or part of them, are available by interventional procedures.^{10,17} For
213 these reasons, a cyst stage classification has been developed by the WHO Informal Working Group
214 for Echinococcosis (WHO-IWGE).¹⁸ In this context, CE clinical management is currently based on cyst
215 stage specific approach. Cyst-stage specific approaches currently available for the clinical
216 management of CE include parasitostatic drug therapy with benzimidazoles (mainly albendazole,

217 but also mebendazole and, with some uncertainties, praziquantel), percutaneous or surgical
218 interventions and regular ultrasound follow-up without interventions (watch-and-wait).¹⁷
219 The European Union (EU) case-definition mainly accounts for under-reporting of CE, since it is
220 "echinococcosis" and therefore does not provide a distinction between CE and AE, which have
221 different epidemiology and cause two completely different diseases in humans.¹⁹ In this context,
222 most of the EU countries report unspecified "echinococcosis" cases to the ECDC via the European
223 Surveillance System (TESSy).²⁰ Moreover, multicystic stages of CE can be wrongly recorded as AE,
224 therefore leading to mis-diagnosis and consequently mis-reporting and under-reporting. Finally,
225 even if correct CE diagnosis was made and cases attended as outpatients, they are not always
226 captured by hospital discharge records at national level, therefore contributing to under-reporting.
227 The above mentioned regulatory, biological, clinical and diagnostic factors lead to the lack and
228 inadequacy of reporting and consequently to neglect of CE as a public health issue in Europe and
229 worldwide. For this reason, this study conducted within the MEME project
230 (<https://onehealth.ejp.eu/jrp-meme/>) aims at unveiling the historical and current numbers of
231 human CE in Europe by providing quantitative measure from different data-sources of CE human
232 cases reported during last 25 years (1997–2021) at country level in Europe.

233

234 **Methods**

235 Data on incidences and trends of CE in Europe was extracted by means of a systematic review (SR)
236 approach from both scientific and grey literature within the years 1997–2021. Different types of
237 studies were collected from the following data sources: national health reports, national hospital
238 records, TESSy data reports,²¹ and observational studies, such as single- or multi-centre case series,
239 case reports, ultrasound-based cross-sectional studies and the European clinical register on CE
240 (ERCE).¹¹ The main inclusion criterion of this SR was primary data reporting human CE cases in
241 included European countries during the period 1997–2021.

242

243 **Search strategy and selection criteria**

244 This SR is presented, in accordance with the PRISMA guidelines (Appendix, p. 1-2).²² The STN
245 International-Fiz Karlsruhe platform was used for the database search in MEDLINE (PubMed),
246 Embase (Excerpta Medica Database), SciSearch (Science Citation Index) and Google Scholar.²³ In the
247 first round of selection, primary studies published in English between Jan 1, 1997, and Dec 31, 2021
248 were eligible for inclusion. The electronic search strategy was: ("cystic echinococcosis" OR Hydatid*
249 OR echinococcal OR Echinococcus OR E* granulosus OR E* canadensis OR E* equinus OR E* ortleppi)
250 AND (Human OR children OR teenager OR child OR boy OR girl OR young) AND (Europe OR
251 "European Union" OR European) NOT (alveolar OR multilocularis OR E* multilocularis OR
252 "Echinococcus multilocularis" OR "hydatid mole" OR "hydatidiform mole" OR "polycystic kidney
253 disease"). A second search was conducted until Apr 30, 2022 without any language restriction for
254 the identification of papers, reports, datasets, conference abstracts, systematic reviews (where they
255 presented primary data not published elsewhere) and other grey literature from countries in Europe
256 where no data, little data or scattered data were identified in the first search. The articles resulting
257 from these searches and the relevant references cited in these articles were reviewed for additional
258 primary data. Countries (n=40) included in the search were Albania, Austria, Belarus, Belgium,
259 Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France,
260 Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta,
261 Montenegro, the Netherlands, Norway, Poland, Portugal, Republic of Cyprus, Republic of Moldova,
262 Republic of North Macedonia, "Republic of Kosovo", Romania, Serbia, Slovak Republic, Slovenia,
263 Sweden, Switzerland, Spain, United Kingdom and Ukraine. Duplicates between databases were
264 removed and the inclusion or exclusion of data source was carried out by independent researchers.

265 Any disagreement between researchers was resolved by discussion until consensus between the
266 researchers. The initial screening was conducted according to the relevance of the title and abstract
267 according to the focus of this research. Then, the full texts of the selected papers were examined
268 through a second screening stage to assess their eligibility and data was extracted into standardized
269 Microsoft Excel tables. For each included record, the following data were extracted, if available: the
270 reference article, country where the study was conducted, name of the clinical centre, number of
271 CE cases, period, hospital records data (ordinary and day hospitalization), deaths or case fatality
272 rates and nationality of patients. Studies were excluded if they lacked original data (e.g. reviews not
273 containing primary data), in case of duplicated data (e.g. between papers and other records), or
274 concerning the wrong etiologic agent (*E. multilocularis*), or infectious disease (alveolar
275 echinococcosis), or a non-infectious disease (hydatid mole, polycystic kidney disease), or incorrect
276 host (e.g. animal host for CE).

277 278 **Data curation**

279 The highest number of human cases at country level per year was calculated by summing cases from
280 the different data sources with no overlapping to generate a descriptive model of human CE in
281 Europe during the period 1997–2021. Primary data from different data sources (e.g. case series)
282 were considered not duplicated at the same time period when they were reported from different
283 clinical centres, or recorded by different CE cohorts (e.g. liver CE, lung CE, unusual locations) or
284 different clinical management (e.g. surgical interventions, percutaneous interventions). In case of
285 potential duplication of cases between data sources, the dataset with the lower number of cases
286 was always discharged and not considered. Single case-reports were retained for those countries
287 where little data on this disease was retrieved for all or part of the period under consideration (i.e.
288 Belgium, Czech Republic, Denmark, France, Ireland, Luxembourg, Poland, Republic of Cyprus,
289 Slovenia, Switzerland and United Kingdom). Unpublished single centre cohorts were obtained from
290 Bosnia-Herzegovina (n=1), the Republic of Cyprus (n=2) and Switzerland (n=4) where no data or
291 scanty data were available for the whole period or for a part of it, from both the published literature
292 and official reports. For a few countries, such as Romania and Spain, the number of national CE cases
293 were calculated from the number of national hospitalizations since records of CE cases were not
294 present or were scarce, compared to their hospitalizations. To avoid cases duplication in Romania
295 and Spain from multiple hospitalizations of the same person over time, a decrease correction factor
296 was applied to national hospitalizations. In fact, we identified two reference single centre large
297 cohorts in Bucharest and Salamanca which recorded both number of cases and hospitalizations.
298 Then we used the ratio of cases/hospitalizations from reference cohorts to calculate the number of
299 cases at national level from national hospitalizations. Unspecified “echinococcosis” cases were
300 included in the study as CE cases, only for those countries that are non-endemic for human AE (i.e.
301 Albania, Bosnia-Herzegovina, Bulgaria, Republic of Cyprus, Finland, Greece, Ireland, Italy,
302 Montenegro, Portugal, Republic of Cyprus, Republic of Kosovo, Republic of North Macedonia,
303 Serbia, Spain, United Kingdom and Ukraine).²⁴ For co-endemic countries for CE and AE (i.e. Austria,
304 Belarus, Belgium, Croatia, Czech Republic, Denmark, Estonia, France, Germany, Hungary, Latvia,
305 Lithuania, Luxembourg, the Netherlands, Norway, Poland, Republic of Moldova, Slovak Republic,
306 Slovenia, Sweden and Switzerland)²⁴ unspecified “echinococcosis” cases were excluded and only
307 data reporting CE were included with the exception of France where unspecified cases were
308 attributed to CE since they had hospital records characteristics similar to CE cases.²⁵ The annual data
309 coverage of this study was calculated as the total number of years in which data were extracted
310 compared to the total number years included in this study (25 years per 40 included countries) and
311 expressed as percentage. Nationality of patients retrieved from the records included in this SR was
312 used as a proxy for the identification of locally acquired and imported cases at country level.²⁶

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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 country level. Average annual incidence rates were calculated as the total number of likely new cases of CE recorded in a given period per 100 000 inhabitants. Population national statistics derived from the “World Bank – Population, total” were used as denominator for incidence rates calculation.²⁷ The average annual incidence rates were calculated for both the whole period where data was eventually available (1997–2020) as the best evidence of CE cases at country level and for the recent period (2017–19) as a proxy of the current epidemiological scenario. Incidence rates for the whole period were 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 for the impact of COVID-19 pandemic on CE notification in 2020 and 2021), therefore affecting total rates. Data from 2020 were included since the single year of decreasing trends did not affect the total incidence rates for the 25-year data collection. For as concern the recent incidence trends 2017–2019, we excluded 2020 and 2021 data since they were affecting rates calculated for a shorter period of 3 years. Due to scanty data in some low endemic countries, published case reports were included in the incidence rates calculation for the Czech Republic, Ireland, Luxembourg, the Republic of Cyprus and Slovenia.

The time trend analysis of CE cases at country level was conducted until 2019 using a subset of data from the most representative data-sources (i.e. official records such as national reports or the European Surveillance System data), which are expected to remain the same over time in terms of methodology and collection, without introducing a selection bias (i.e. we did not consider data from single- or multi-centre case series published in the literature). Due to scanty data in some low endemic countries, published case reports were included in trends analysis for the Czech Republic. We analyzed the time trend of CE cases for each country using log-linear regression models. To allow for the models convergence, we imputed 0.1 cases where 0 cases had been reported. Based on the models’ parameters, we predicted the number of cases for the years 2020–2024 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 performed using RStudio 2021.09.0 under R version 4.1.2.²⁸

Results

A total of 1724 publications were identified by the first literature search of which, 545 were duplicated between databases and therefore were excluded. Remaining papers assessed for eligibility were 1179. Subsequently, 548 papers were excluded by checking the title and abstract and the text of 631 papers were assessed for inclusion criteria of which 352 full text papers were excluded because they did not contain relevant data for this SR. Additional extended searches at country level without any language restriction identified 231 additional records for inclusion. Finally, a total of 510 records resulting from the two searches were included in the SR for data extraction (Appendix, p. 3 and p. 4-30).

The annual data coverage of this SR was 86% within the considered period (1997–2021), with a mean of 21.5 years (95% confidence intervals 20.9-22.0) data coverage per country, including case-reports (Table 1; Appendix, p. 31-33 and 34-36). Without case reports, the annual data coverage was 82.5%. Data extraction during this period identified a total of 64 376 and 53 875 human CE cases from 40 European countries and from the 27 European Union member states, respectively (Figure 1; Table 1). Bulgaria, Italy, Romania and Spain accounted for 67.4% (n=43 367) of the total CE cases (Figure 1; Table 1). National hospital records were available only from eight European countries (Bulgaria, France, Italy, Poland, Republic of North Macedonia, Romania, Spain and United Kingdom),

361 in which 83 033 hospitalizations were recorded, with an annual data coverage of 12.3% within the
362 considered period (Table 1).^{25,29,30} Only three published cross-sectional studies by ultrasound
363 population-based surveys were identified in Europe.^{31,32,33} One of these cross-sectional studies, at
364 large scale, estimated around 8000 and 37 000 CE infections in rural endemic areas of Bulgaria and
365 Romania, respectively, during the period 2014–15.³² Data from these surveys, as from ERCE clinical
366 register, were extracted but not useful for any final calculation on numbers, incidence rates or
367 trends of CE.^{11,31,32,33}

368 An average of 2101 (range 1801–2360) and 1716 (range 1519–1897) new CE cases per year were
369 recorded at European countries and EU level during 2017–2019, respectively, before the COVID–19
370 pandemic compromised the notification of CE cases (Table 1).¹³ An estimate of 1756 (95% prediction
371 intervals 1072 to >5323) and 1361 (95% PI 903 to >3823) new CE cases per year are expected in
372 2023 at European countries and EU level, respectively, based on predicted time trend analysis during
373 1997–2019 (Table 1).

374 CE deaths were recorded in 16 countries (40%) in a total of 895 cases during the considered period,
375 corresponding to a hospitalized case fatality rate (CFR) of 1.39% (Table 1). In addition, 192 deaths
376 were reported as “echinococcosis” from 4 countries (e.g. Germany, Latvia, Lithuania and Poland),
377 where it was not possible to differentiate CE from AE deaths (Table 1).

378 Mean annual incidence at European countries and EU level in the period 1997–2020 were 0.64/100
379 000 and 0.50/100 000, respectively. As indicated by WHO, high endemicity areas for CE (1–5/100
380 000)³² in the period 1997–2020 were identified in eight European countries: Albania (2.25/100 000),
381 Bosnia-Herzegovina (1.00/100 000), Bulgaria (5.32/100 000), Italy (1.21/100 000), Republic of
382 Moldova (4.65/100 000), Republic of North Macedonia (1.08/100 000), Romania (2.16/100 000) and
383 Spain (1.00/100 000) (Table 2; Figure 2). Mean annual incidences at European countries and EU level
384 during the recent period 2017–19 were 0.46/100 000 and 0.35/100 000, respectively. During the
385 recent period (2017–19), high endemicity areas for CE³⁴ were identified in five European countries:
386 Albania (2.94/100 000), Bulgaria (2.93/100 000), Republic of Moldova (1.70/100 000), Republic of
387 North Macedonia (1.41/100 000) and Romania (1.63/100 000) (Table 2; Figure 3).

388 The annual data coverage for analysis of trends was 74.8% within the considered period (1997–
389 2019), with an average of 17.2 years (95% CI 16.5–17.8) data coverage per country (Appendix, p. 31–
390 33 and 34–36). Considering the observed annual incidences and those predicted by the model, a
391 general decrease in the number of human CE cases has been identified in Europe from 1997 to 2020
392 (Figure 4). In particular, the statistically significant decreasing trends were detected in most
393 Southern and some Eastern European countries where the disease has traditionally been highly
394 prevalent, such as Bosnia-Herzegovina, Bulgaria, France, Greece, Italy, Republic of Moldova,
395 Romania, Spain and Ukraine, but also in Croatia, the Czech Republic and Poland (Figure 4; Table 2).
396 Mostly statistically significant increasing trends were detected in Eastern and South-eastern
397 European countries (Balkans and Southern Baltics) such as Belarus, Montenegro, the Republic of
398 North Macedonia, Serbia, Slovenia and Lithuania (Figure 4; Table 2). Mostly statistically significant
399 increasing trends were also detected in most non-endemic Northern (Scandinavia) and Western
400 European countries such as Finland, Germany, Norway, Sweden and Switzerland (Figure 4; Table 2).
401 Malta has reported one presumably imported case and Iceland has never documented CE cases in
402 the last 25 years. A synthesis of CE endemicity and whether these CE cases at country level should
403 be considered as locally acquired, imported or both, was reported in Table 2, where low incidences
404 in non-endemic countries were commonly associated only with imported cases.

405 Taking into account both the recent incidences and trends, CE remains a relevant public health issue
406 in the Mediterranean European (Italy and Spain) and Eastern and South-eastern European countries
407 (Albania, Bosnia-Herzegovina, Bulgaria, Montenegro, Republic of Moldova, Republic of North
408 Macedonia, Serbia and Romania) (Figure 1). Such incidence and trends are decreasing in the

409 Mediterranean area, while they remain stable or increasing in the Southern Baltic and in Balkan
410 Peninsula. This latter area should be considered as the current focus of CE in Europe (Figure 2; Figure
411 3; Figure 4).

412

413 Discussion

414 This study provided for the first time a conservative estimate of the number of cases, incidence rates
415 and trends of human CE at country level in 40 selected European countries. This research identified
416 around 65 000 human CE cases in Europe during last 25 years with a mean annual incidence of
417 0·64/100 000 with different trends in some endemic or not macro-areas (i.e. Balkan, Mediterranean,
418 Scandinavian countries). The reliability of the results from this retrospective CE European-scale SR
419 depends on the extent to which potential sources of bias have been avoided both in the
420 methodology and the content of the data source used. In this study, such biases were minimized by
421 verifying data, whenever possible with national experts and requesting co-authors to review results
422 and conclusions. In this context, it is worth listing the limitations of this research that may have
423 biased the outcome of this study, resulting in an overestimation or a more likely underestimation
424 of the effect. In particular, we are mainly referring to the sampling bias, misclassification bias and
425 publication bias that could have generated type 1 (false positive CE findings) or type 2 (false negative
426 CE findings) errors.

427 It should be noticed that the four main data-sources used in this study (i.e. national reports, hospital
428 records, the European surveillance system data reports and single- or multi-centre case series) may
429 provide different evidence on number of CE cases, depending on the health-setting of the
430 investigated country.

431

432 Potential bias which may lead to over-estimation

433 Generally speaking, published or unpublished single- or multi-centre case series usually provide the
434 most reliable evidence of the number of human CE cases, both in the absence and presence of
435 national data (i.e. Austria, Belgium, Czech Republic, Bosnia-Herzegovina, Latvia, Norway, Republic
436 of Cyprus, Republic of Kosovo, Serbia and Switzerland).³⁵⁻³⁹ The limitation is that single- or multi-
437 centre case series are scarce and therefore fragmented over time and cannot be used to calculate
438 trends. Moreover, single- or multi-centre case series may introduce sampling bias, as it is not always
439 possible to disaggregate duplicated cases with other data-sources in a given period or to eliminate
440 misdiagnosed cases. This study assumes that even if some cases were wrongly duplicated or
441 diagnosed, as a whole they cannot overestimate the under-recorded condition of CE. Finally, single-
442 or multi-centre case series were recorded mainly at the beginning of the study period and may
443 therefore lead to an under-estimation of CE incidences calculated for the last period (2017–19) if
444 compared to the period as a whole (1997–2020).

445 Other relevant data-sources to discuss are national reports on CE cases and national hospital records
446 reporting the number of hospitalizations generated by single cases. For Italy, number of reported
447 national CE cases was 62·50% of the national hospitalizations that they generated (reporting both
448 ordinary and day hospitalization) (Appendix, p. 4-30). For Bulgaria and the Republic of North
449 Macedonia, numbers of national CE cases were 46·44% and 22·46% of national hospitalizations
450 (reporting only ordinary hospitalization), respectively (Appendix, p. 4-30). Such figure from these
451 three highly endemic countries suggests that sequelae and in the end an improper clinical
452 management, may increase the disease burden of CE.^{18,40} Such morbidity should be taken in account
453 for further research on the clinical burden of disease at country level.

454 For Romania and Spain, only hospitalized cases were available. For Romania, a single reference
455 centre from Bucharest reported 1038 cases (representing 29·56% of hospitalizations) that
456 generated 3511 hospitalizations during the period 2006–2010 (Colentina Clinical Hospital, Carol

457 Davila University of Medicine and Pharmacy, Bucharest) (Appendix, p. 4-30). For Spain, a single
458 reference centre from Salamanca recorded 659 cases (representing 59·48% of hospitalizations) that
459 generated 1108 hospitalizations during the period 1998–2021 (Centro de Investigación de
460 Enfermedades Tropicales de la Universidad de Salamanca, Hospital Universitario de Salamanca)
461 (Appendix, p. 4-30). Such ratios (cases/hospitalizations) from Bucharest and Salamanca reference
462 cohorts were used to calculate number of CE national cases from national hospitalizations. It should
463 also be stressed that, as previously discussed for Italy, CE reporting based solely on hospital records
464 have some drawbacks and are inadequate to capture all cases, as most of CE cases in some settings
465 are diagnosed and clinically managed in an outpatient setting.⁴¹
466

467 **Potential bias which may lead to under-estimation**

468 For as concern sampling selection bias, single- or multi-centre case series were recorded mainly at
469 the beginning of the considered period and may therefore lead to an under-estimation of CE
470 incidences calculated for the last period (2017–19) if compared to the period as a whole (1997–
471 2020). Another major source of bias leading to under-estimation is unspecified “echinococcosis”
472 cases which, given the highest number of CE compared to AE cases, mainly affect CE notification. In
473 fact, around 200 000 and 18 000 new cases per year of CE and AE are globally estimated,
474 respectively, with 91% of AE cases occurring in China and around 1600 cases in Europe, Central Asia
475 and Russia.^{5,34,42,43} According to this numerical proportion, for every human AE infection, between
476 10 and 20 CE infections can be expected, particularly in Europe but also worldwide. It should be
477 stressed that even if AE infections represent a small proportion of “echinococcosis” infections, they
478 can be more represented in the reporting systems due to the severity of this clinical condition. In
479 this scenario, during the years 2013–2020 the European surveillance system data reports recorded
480 6269 cases of “echinococcosis”, of which 3240 were CE cases (52·16%), 1012 AE cases (16·14%) and
481 1987 (31·70%) unspecified “echinococcosis”.^{24,44,45} In this study, unspecified “echinococcosis” from
482 TESSy were only considered for those countries that are endemic only for CE and not for AE or not
483 endemic for both the diseases. Due to unspecified “echinococcosis” cases, the European
484 surveillance system data reports is not, as in case of some national reports, a perfect tool to capture
485 all CE cases, although in recent years a huge improvement in the notification has been undertaken
486 by EU member states to distinguish between these two parasitic diseases.^{24,44,45} For instance, Italy
487 has never reported any case to the European surveillance system, irrespective of the huge disease
488 burden documented by hospital records.³⁰ For these reasons, the current study identified between
489 2017–19 an average number of CE cases at least four-fold higher than the same 31 countries
490 reported in the European Surveillance system data (1736 versus 423 cases) (Table 1).²⁴ It should be
491 noted that AE can be misdiagnosed as CE. In a retrospective sentinel case series from endemic
492 Germany, AE was mistaken for CE in 12 out of 26 cases. AE non-endemic Mediterranean countries,
493 such as Italy and Spain, have reported hundreds of AE cases that were most likely misdiagnosed
494 with multicystic CE (mainly CE2 and CE3b according to the WHO-IWGE cyst stage
495 classification).^{29,30,46}

496 Concerning the calculation of trends at the country level, a subset of data not containing case-series
497 were analysed until 2019, before the COVID–19 pandemic (Appendix, p. 31-33). A 56·12% decrease
498 of cases has been noticed between notification rates for 2020 (242 CE cases) compared to the
499 average of cases in 2016–19 (mean of 431 CE cases).²⁴ These data suggest that the COVID–19
500 pandemic has adversely affected the availability of general surgery. This may have resulted in the
501 postponement of hospital admission for CE cases, and hence reduction in reporting of CE to the
502 European surveillance systems.²⁴

503 In addition to the under-reported and misdiagnosed CE patients, there are the undiagnosed CE
504 cases, as was evidenced as a large research-based cross-sectional ultrasound survey conducted in

505 Bulgaria and Romania.³² This active search of CE carriers aiming at the detection of asymptomatic
506 cases in rural areas identified a prevalence of 0·41% in both countries. This resulted in an estimated
507 total of 45 000 people that may be infected with *E. granulosus s.l.* Extrapolating this estimated
508 prevalence to the top five countries with the highest incidence rates (Albania, Bulgaria, Republic of
509 Moldova, Republic of North Macedonia and Romania), the current number of cases that could be
510 infected in rural areas of Europe at any given time would be higher than that recorded in the present
511 study.

512 For case fatality rates (CFR), the data sources from two out of 16 recording countries such as France
513 and Spain are mainly based on national hospital records which, unlike the case series or the national
514 institute of statistics data, cannot ascertain whether CE was the cause of death or resulted from
515 other comorbidities (Appendix, p. 4-30).^{25,29} Nevertheless, the CFR at European level identified in
516 this study is consistent both with national data not derived from hospitalizations (Table 1) and with
517 other cohorts from the literature.^{3,47-49} As for locally acquired versus imported cases, it should also
518 be noted that documented human CE cases in non-endemic countries with no travel history abroad
519 (e.g. Germany) suggest that some infections may be locally acquired through food traded from
520 endemic countries or by direct contact with dogs that had travelled abroad.⁵⁰ Finally, imported cases
521 may present an important contribution to CE health burden at country level, even in endemic
522 countries such as Italy, which recorded 13·6% all documented cases during the period 2001–14 were
523 in foreign patients.³⁰

524 Most of these biases, including the annual data extraction from this study that do not cover the
525 whole period, mainly contribute to an under-estimation of this neglected zoonotic disease in
526 Europe. Finally, a recent study was attempting to collect human CE incidence data from the
527 literature and to calculate pooled prevalences on animal CE in the Mediterranean and Balkan
528 countries. Such study, that was not recalculating incidences rates at country level, confirmed that
529 Italy, Spain and Eastern Europe are the most affected areas for human CE.⁵¹

530

531 **Conclusion**

532 CE remains endemic and under the radar in many regions of Europe. However, there appears to be
533 a general decrease in incidences with variable trends at country level. With few exceptions, most of
534 endemic Southern and some Eastern European countries, where the disease has traditionally been
535 highly prevalent, have reported a decreasing trend in human CE cases. Such a decrease may be
536 explained due to the increased hygiene over time, the rural-to-urban migration at country level, a
537 decrease in the sheep populations over the time, increase in intensive farming and the
538 implementation of national control programmes.⁵² On the other hand, increasing trends have been
539 unexpectedly identified in most non-endemic Northern (Scandinavia), Western European and
540 southern Baltic countries. Such a trend (corresponding to hundreds of cases) may be due to an
541 increase of migration from endemic countries (in particular from Northern Africa, Middle East,
542 Southern America and Central Asia), international travel and increasing interest among physicians.
543 Based on recent incidence data and trends detected in Eastern and South-eastern European
544 countries, the Balkans should be considered the current epicentre of CE in Europe.

545 Finally, we encourage ultrasound population-based surveys for the active search of CE carriers in
546 highly endemic areas of Europe, especially in the Balkan Peninsula. To provide a more reliable
547 picture of the health burden of the disease in Europe, more accurate collection of epidemiological
548 and clinical data is needed, which will provide a statistically sound case series for an evaluation of
549 the cost-effectiveness of interventions. The findings from this study coupled with other studies on
550 potential risk factors increasing odds of infection for human CE,⁵³ should be used to support the
551 planning of surveillance and control of human and animal CE in Europe by the One-Health approach,
552 according to the WHO 2021–2030 roadmap for Neglected Tropical Diseases.

553

554 Contributors

555 AC conceived the study, extracted the data, performed statistical analysis, interpreted the results
556 and wrote the paper. FS and AS extracted and interpreted the data in the first round. DP and MF
557 performed time trends statistical analysis. BAR, DP, MF, BB, DC, BŠ, EZ, MJG, GK, CC, IR, SS, VL, BD,
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559 extracted and interpreted the data in the second round. All authors reviewed the article, and
560 approved submission. AC received funding for this study.

561

562 Declaration of interests

563 All authors declare no competing interests.

564

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577

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705

706 **Figures & Tables**

707

708 **Table 1.** Number of cases, hospitalizations and deaths of human cystic echinococcosis at country
709 level within 1997–2021.

710

711 **Table 2.** Average annual incidence rates and endemicity at country level for the years 1997–2020
712 and 2017–19.

713

714 **Figure 1.** Number of documented human cystic echinococcosis cases in Europe at country level
715 within the years 1997–2021 (n=64 376).

716

717 **Figure 2.** Mean annual incidence intervals (expressed as number of cases per 100 000 people) of
718 documented human cystic echinococcosis cases in Europe at country level within 1997–2020. Dark
719 red countries considered as high endemicity areas for CE (1–5/100 000).

720

721 **Figure 3.** Mean annual incidence intervals (expressed as number of cases per 100 000 people) of
722 documented human cystic echinococcosis cases in Europe at country level during the recent period
723 2017–19. Dark red countries considered as high endemicity areas for CE (1–5/100 000).

724

725 **Figure 4.** Time trend analysis of the number of human cystic echinococcosis cases at country level
726 (observed cases and predicted cases for the years 2020–2024). * Statistically significant time trend
727 (p<0.05).

Table 1

Table 1. Number of cases, hospitalizations and deaths of human cystic echinococcosis at country level within the years 1997–2021.

COUNTRY	Total CE cases [1997-2021]	Years in which data was extracted [1997-2021]	Total Years	Average annual N of CE cases [2017-19]	Range of the annual N of CE cases [2017-19] (min max)	Years in which data was extracted [2017-19]	Average N of CE cases predicted for 2023 *	95% prediction interval for 2023 *	CE Hospital records [1997-2021]	Period covered	Total Years	CE deaths **	Case Fatality Rate	Unspecified "echinococcosis" deaths ***
Albania	1529	1997-2021	25	84	(34 114)	2017-2019	46	16 132				1	0.3%	
Austria	503	1997-2020	24	29	(16 40)	2017-2019	9	1 48						
Belarus	182	1997-2018	19	13	(13 13)	2018	45	9 216						
Belgium	156	1997-2021	19	10	(9 12)	2017-2019	12	4 32						
Bosnia-Herzegovina	624	1997-2021	25	13	(11 15)	2017-2019	9	3 24						
Bulgaria	9733	1997-2021	25	206	(193 218)	2017-2019	160	110 233	16 843	1997-2021	25	187	2.40%	
Croatia	408	1997-2021	25	9	(4 15)	2017-2019	7	3 17				1	0.3%	
Czech Republic	28	2003-2020	17	1	(1 1)	2017-2019	1	1 1						
Denmark	140	2000-2017	13	13	(9 20)	2012-2014	26	2 291						
Estonia	4	1997-2021	25	0	(0 1)	2018-2020	0	0 1						
Finland	53	1997-2021	25	5	(1 8)	2017-2019	5	0 98						
France	3873	1997-2021	24	226	(220 232)	2017-2019	194	163 231	6062	2005-2020	16	85	2.39%	
Germany	1578	2001-2021	21	89	(86 93)	2017-2019	122	64 234				0?		145
Greece	498	1998-2020	23	11	(7 15)	2017-2019	8	2 25				3	0.59%	
Hungary	144	2000-2020	21	8	(6 11)	2017-2019	26	0 >500				1	0.694%	
Iceland	0	2013-2020	8	0	(0 0)	2017-2019	0	0 0						
Ireland	14	2003-2020	18	1	(0 2)	2017-2019	1	0 42				1	7.14%	
Italy	15 243	1997-2020	24	386	(281 464)	2017-2019	221	173 282	24 252	1997-2020	25	132	0.92%	
Latvia	132	1999-2020	22	4	(4 5)	2017-2019	6	0 176				1	0.76%	13
Lithuania	330	1997-2020	24	20	(11 30)	2017-2019	47	8 272				0?		1
Luxembourg	8	2007-2020	8	1	(0 2)	2017-2019	5	0 >500						
Malta	1	2015-2020	6	0	(0 0)	2017-2019	0	0 0						
Montenegro	120	1997-2020	24	4	(3 5)	2017-2019	10	0 335						
The Netherlands	915	1997-2020	23	44	(41 48)	2017-2019	37	20 67						

Norway	90	1999-2020	22	6	(5	7)	2017-2019	14	1	200			1	1.11%		
Poland	578	1997-2020	22	22	(17	27)	2017-2019	10	3	33	704	2001-2020	0?		33	
Portugal	502	1997-2021	25	20	(16	28)	2017-2019	20	7	56						
Republic of Cyprus	57	1997-2021	25	2	(0	5)	2017-2019	0	0	1						
Rep. of Kosovo	363	1997-2018	22	2	(1	2)	2017-2018	0	0	30						
Rep. of Moldova	3214	1997-2021	25	46	(40	53)	2017-2019	52	21	128			41	1.28%		
Rep. of North Macedonia	538	1997-2021	25	29	(21	37)	2017-2019	42	15	119	1652	2008-2020	13	22	5.30%	
Romania	7749	1998-2020	23	317	(314	320)	2017-2019	197	149	260	20 400	2006-2020	15	261	1.58%	
Serbia	1311	1997-2019	23	56	(30	74)	2017-2019	61	33	112			11	0.84%		
Slovak Republic	99	1997-2020	24	3	(2	3)	2017-2019	3	0	97						
Slovenia	104	1997-2021	25	2	(1	3)	2017-2019	4	1	11						
Spain	10 642	1997-2020	24	260	(256	264)	2017-2019	200	174	229	17 893	1997-2020	24	145	1.36%	
Sweden	383	1997-2020	24	27	(24	30)	2017-2019	40	18	86						
Switzerland	166	1997-2021	25	10	(7	14)	2017-2019	12	6	27						
United Kingdom	211	1997-2020	24	4	(3	4)	2017-2019	12	4	39	227	2005-2009	5	2	0.67%	
Ukraine	2153	2000-2013	14	118	(114	125)	2011-2013	92	61	138						
EUROPEAN UNION	53 875		579	1716	(1519	1897)		1361	903	>3823	79 388		105	816	1.52%	192
EUROPEAN COUNTRIES	64 376		860	2101	(1801	2360)		1756	1072	>5323	88 033		123	895	1.39%	192

* Time trend prediction for 2023 based on the subset of data from 1997 to 2019 reported in **Appendix** (p. 31-33); ** For France and Spain it cannot be possible to ascertain whether CE patients deceased as a result of CE or for other comorbidities; *** It could not be possible to differentiate cystic from alveolar echinococcosis deaths.

Table 2. Average annual incidence rates and endemicity at country level for the periods 1997–2020 and 2017–19.

COUNTRY	Mean annual incidence * [1997-2020]	Period analyzed	Endemicity ** [1997-2020]	Mean annual incidence * [2017-19]	Period analyzed	Endemicity ** [2017-19]	Comment on CE cases imported or not *
Albania	2.25	2003-2020	High endemicity	2.94	2017-2019	High endemicity	Majority LA
Austria	0.25	1997-2020	Present	0.33	2017-2019	Present	Most Im; some LA
Belarus	0.10	1997-2018	Present	0.14	2018	Present	Majority LA
Belgium	0.08	2005-2020	Rare/Sporadic	0.09	2017-2019	Rare/Sporadic	Majority Im; 1 LA
Bosnia-Herzegovina	1.00	1997-2020	High endemicity	0.38	2017-2019	Present	Majority LA
Bulgaria	5.33	1997-2020	High endemicity	2.93	2017-2019	High endemicity	Majority LA
Croatia	0.39	1997-2020	Present	0.21	2017-2019	Present	All LA
Czech Republic	0.02	2003-2020	Rare/Sporadic	0.01	2018; 2020	Rare/Sporadic	Majority Im; 1 LA
Denmark	0.23	2004-2014	Suspected	0.17	2013-2014 [§]	Suspected	All Im
Estonia	0.01	1997-2020	Suspected	0.02	2017-2020	Suspected	Most LA but also Im
Finland	0.04	1998-2020	Rare/Sporadic	0.08	2017-2019	Rare/Sporadic	Majority Im; 1 LA
France	0.37	2005-2020	Present	0.34	2017-2019	Present	Most Im; some LA
Germany	0.09	2001-2020	Rare/Sporadic	0.11	2017-2019	Rare/Sporadic	All Im; few seems LA
Greece	0.20	1998-2020	Present	0.10	2017-2019	Present	Majority LA
Hungary	0.07	2000-2020	Present	0.08	2017-2019	Present	Majority LA; some Im
Iceland	0.00	2013-2020	Probably absent	0.00	2013-2021	Probably absent	No cases
Ireland	0.02	2003-2020	Suspected	0.02	2017-2019	Suspected	All cases Im; 1 possibly LA
Italy	1.21	2001-2020	High endemicity	0.64	2017-2019	Present	Most LA but also Im
Latvia	0.28	1999-2020	Rare/Sporadic	0.22	2017-2019	Rare/Sporadic	Most LA but also Im
Lithuania	0.43	1997-2020	Present	0.71	2017-2019	Present	Most LA but also Im
Luxembourg	0.17	2007-2020	Suspected	0.16	2017-2019	Suspected	All Im
Malta	0.00	2015-2020	Probably absent	0.00	2017-2019	Probably absent	All Im
Montenegro	0.81	1997-2020	Present	0.64	2017-2019	Present	Majority LA
The Netherlands	0.24	1997-2020	Suspected	0.26	2017-2019	Suspected	All Im
Norway	0.09	2000-2020	Suspected	0.12	2017-2019	Suspected	All Im
Poland	0.07	2001-2020	Present	0.06	2017-2019	Present	Majority LA
Portugal	0.19	1997-2020	Present	0.20	2017-2019	Present	Majority LA
Republic of Cyprus	0.22	1997-2020	Rare/Sporadic	0.20	2017-2019	Rare/Sporadic	Both LA/Im

Republic of Kosovo	0.93	1997-2018	Present	0.18	2012-2018	Present	Majority LA
Republic of Moldova	4.65	1997-2020	High endemicity	1.70	2017-2019	High endemicity	Majority LA
Republic of North Macedonia	1.08	1997-2020	High endemicity	1.41	2017-2019	High endemicity	Majority LA; some Im
Romania	2.16	2008-2020	High endemicity	1.63	2017-2019	High endemicity	Majority LA
Serbia	0.78	1997-2019	Present	0.80	2017-2019	Present	Majority LA
Slovak Republic	0.07	1997-2020	Rare/Sporadic	0.05	2017-2019	Rare/Sporadic	Most LA but also Im
Slovenia	0.21	1997-2020	Rare/Sporadic	0.14	2018-2019	Rare/Sporadic	Both LA/Im
Spain	1.00	1997-2020	High endemicity	0.56	2017-2019	Present	Most LA but also Im
Sweden	0.21	2004-2020	Suspected	0.27	2017-2019	Suspected	All Im
Switzerland	0.08	1997-2020	Suspected	0.16	2017-2019	Suspected	All Im
United Kingdom	0.02	1997-2019	Rare/Sporadic	0.01	2017; 2019	Rare/Sporadic	Majority Im; 5 LA
Ukraine	0.33	2000-2013	Present	0.26	2011-2013 [§]	Present	Majority LA
EUROPEAN UNION	0.50			0.35			
EUROPEAN COUNTRIES	0.64			0.46			

* Expressed as number of CE cases per 100 000 population living in the considered country; ** Definitions modified from “Working to overcome the global impact of neglected tropical diseases: first WHO report on neglected tropical diseases. World Health Organization. <https://apps.who.int/iris/handle/10665/44440>”. **Probably absent:** Countries or territories with no confirmed identifications or reports of *E. granulosus s.l.* in indigenous domestic or wild animal populations. Human CE has not been reported. **Suspected:** *E. g. s.l.* may not be recorded in official data or publications. but may occur in wildlife and possibly at low prevalence in domestic animals. Human CE appears not to occur. **Rare/Sporadic:** *E. g. s.l.* has been recorded at low prevalence in domestic animals and may be transmitted in wildlife populations. Human CE cases are only occasionally reported. **Present:** *E. g. s.l.* is known to be endemic in at least some areas of the country. Domestic animal (and possibly wildlife) and human CE occur regularly. **High endemicity:** *E. g. s.l.* prevalence in dogs exceeds 5-10% and where the prevalence of human CE is greater than 1-5 cases/100 000 inhabitants annually; *** Locally acquired (LA) and/or Imported (Im) cases based on **Appendix** (p. 4-31). “Majority”, “Most” and “Both” were reported when documented CE cases were >90%, >70% and ≈50%, respectively; § Denmark and Ukraine did not report data on CE during the years 2017-2019. As a measure of the recent trends last available data were used.

Figure 1. number of cases 1997-2021

[Click here to access/download;Figure;Fig 1 N cases_1997_2021.tif](#)

(1997-2021)

- 7,000 < N < 16,000
- 1,000 ≤ N < 4,000
- 500 ≤ N < 1,000
- 100 ≤ N < 500
- 1 ≤ N < 100
- N = 0
- Not investigated

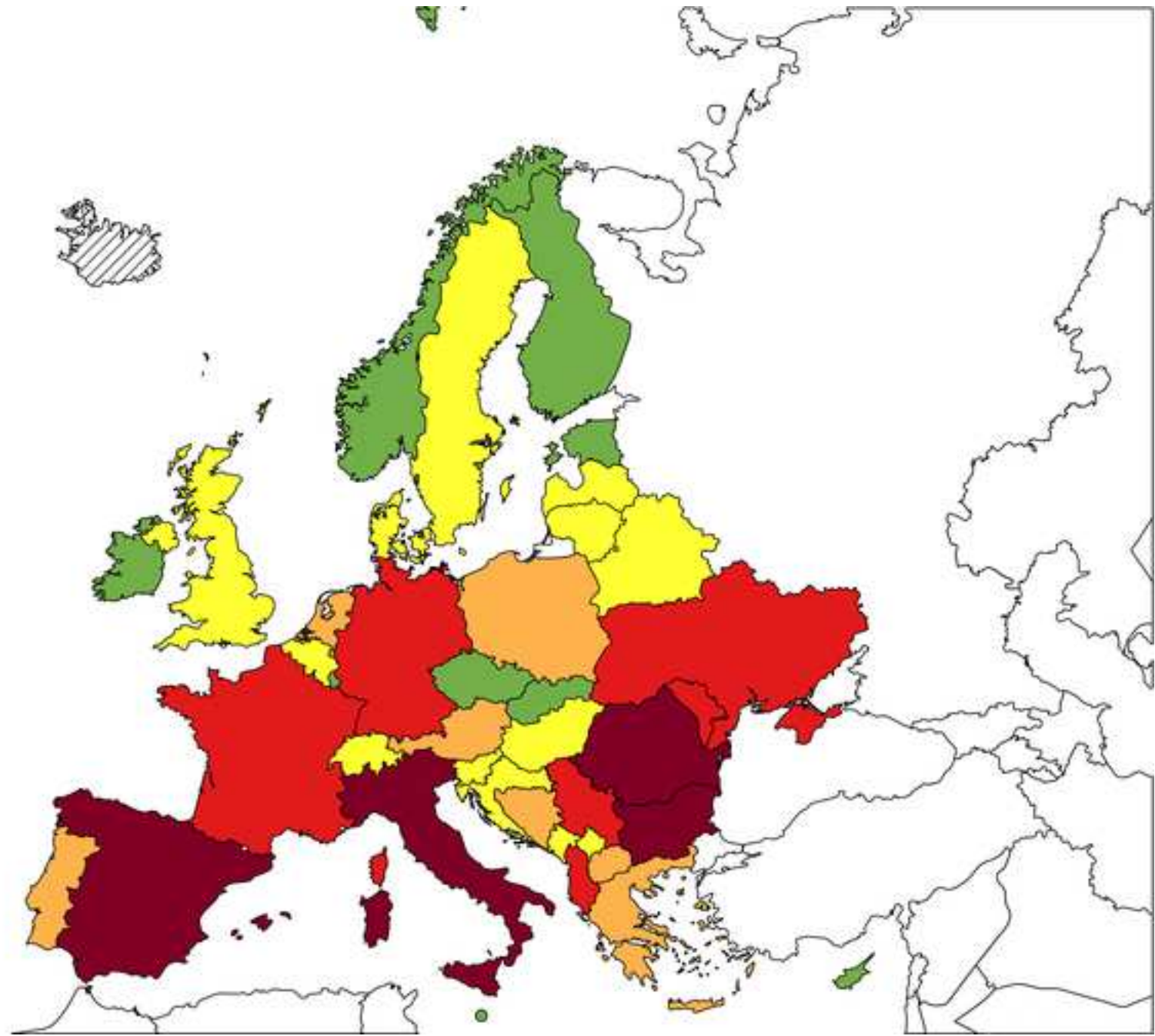


Figure 2. Incidence 1997-2020

[Click here to access/download;Figure;Fig 2 Incidence_1997_2020.tif](#)

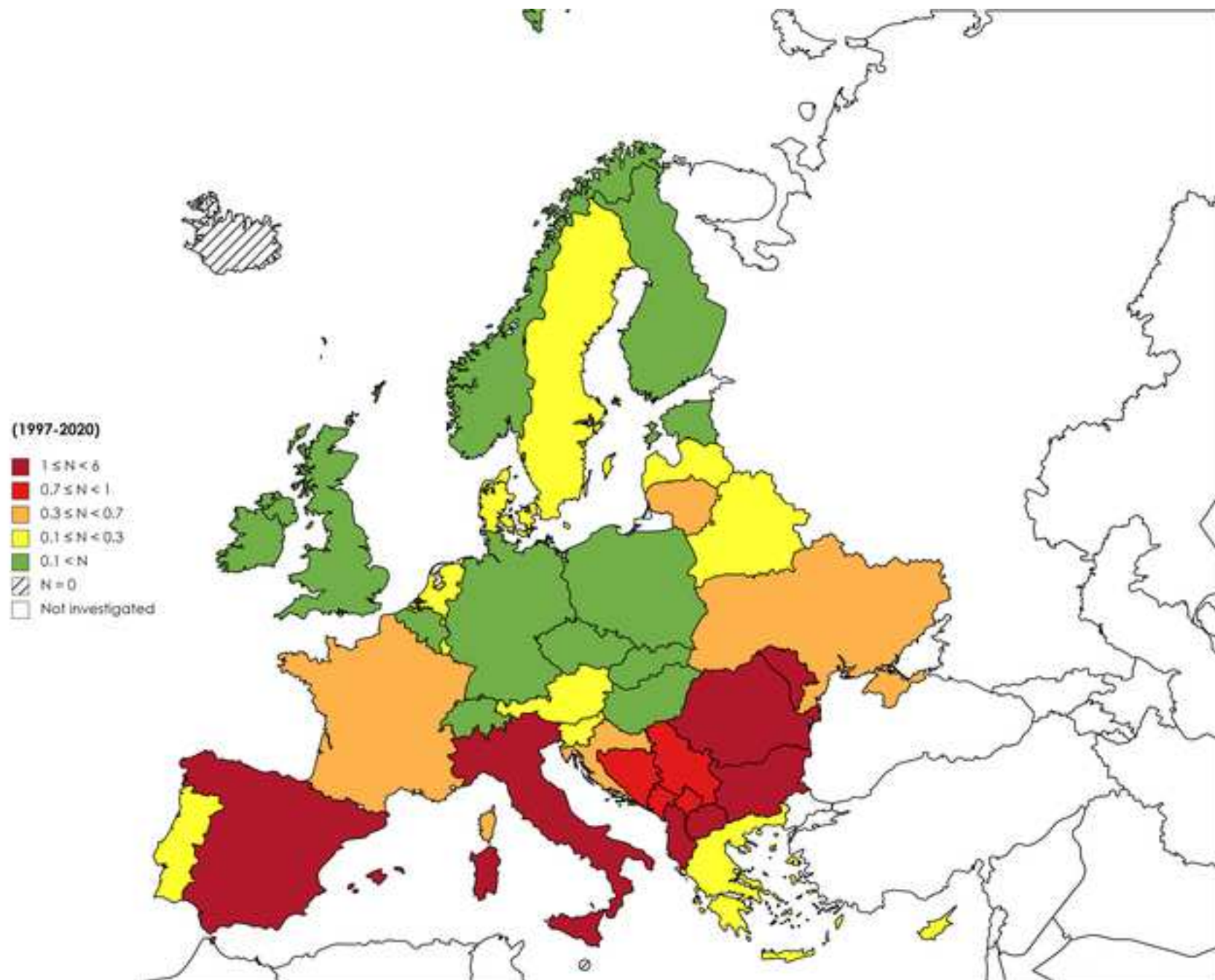


Figure 3. Incidence 2017-19

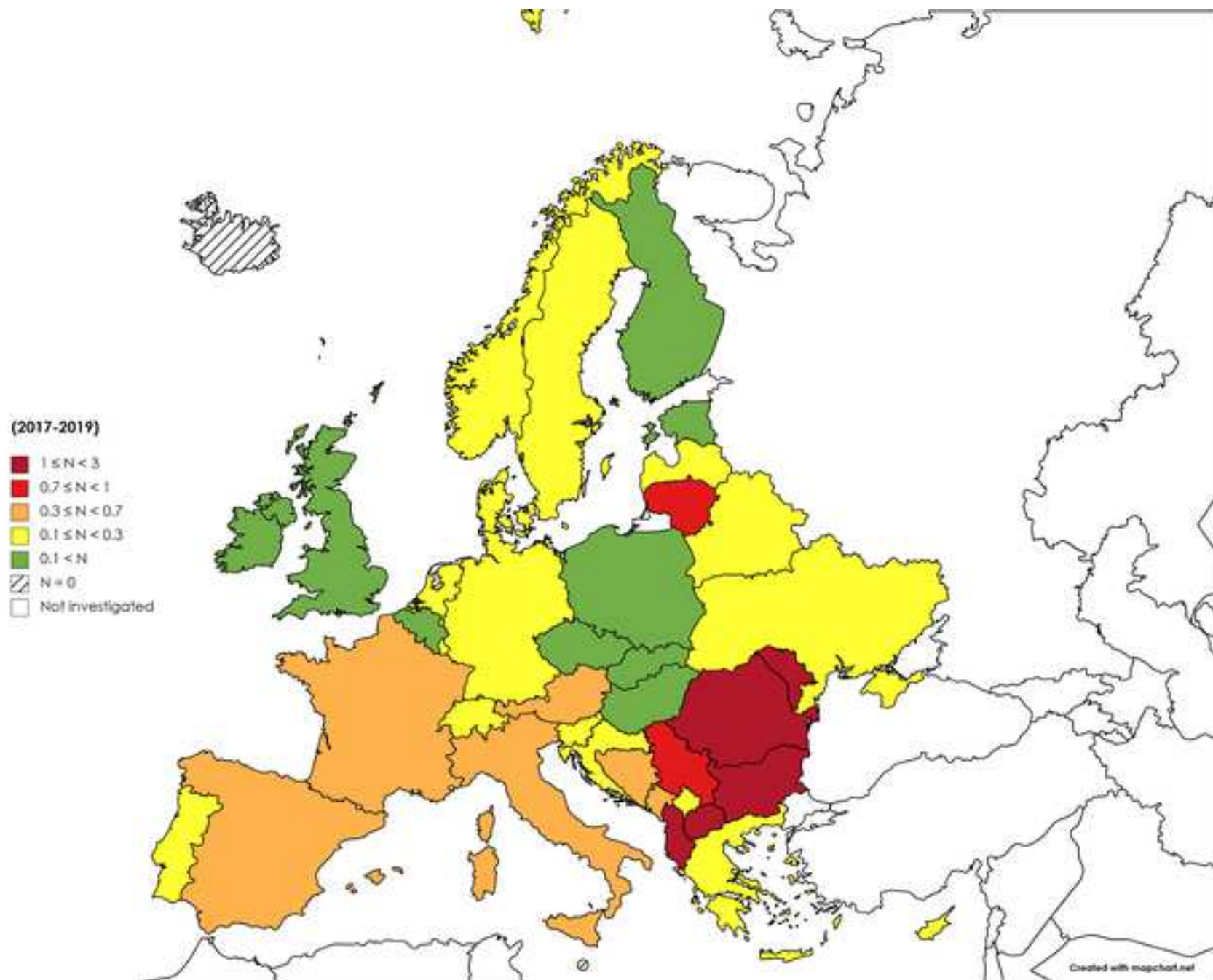
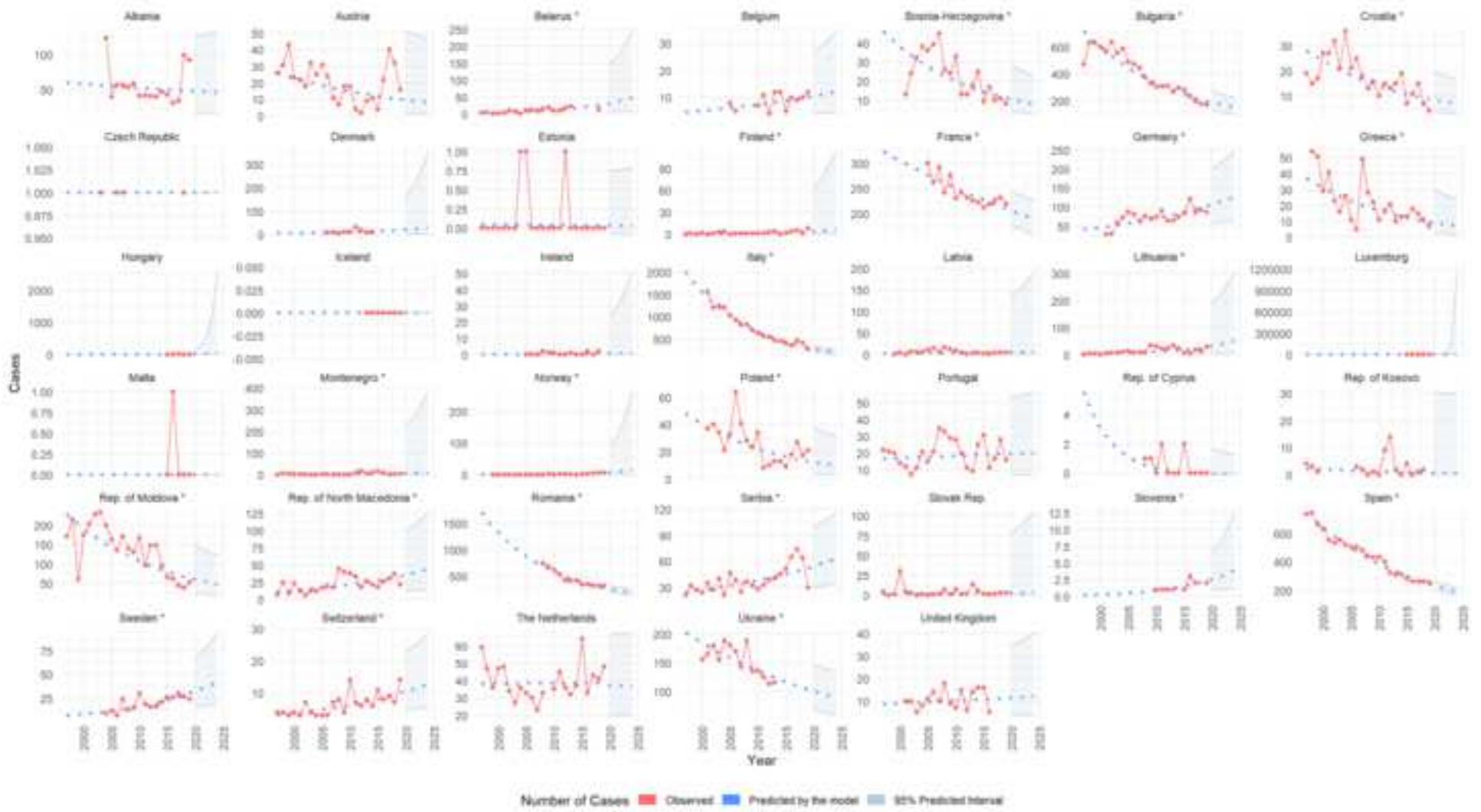


Figure 4. Time trend analysis 1997-2019

[Click here to access/download;Figure;Fig 4 trends.png](#)

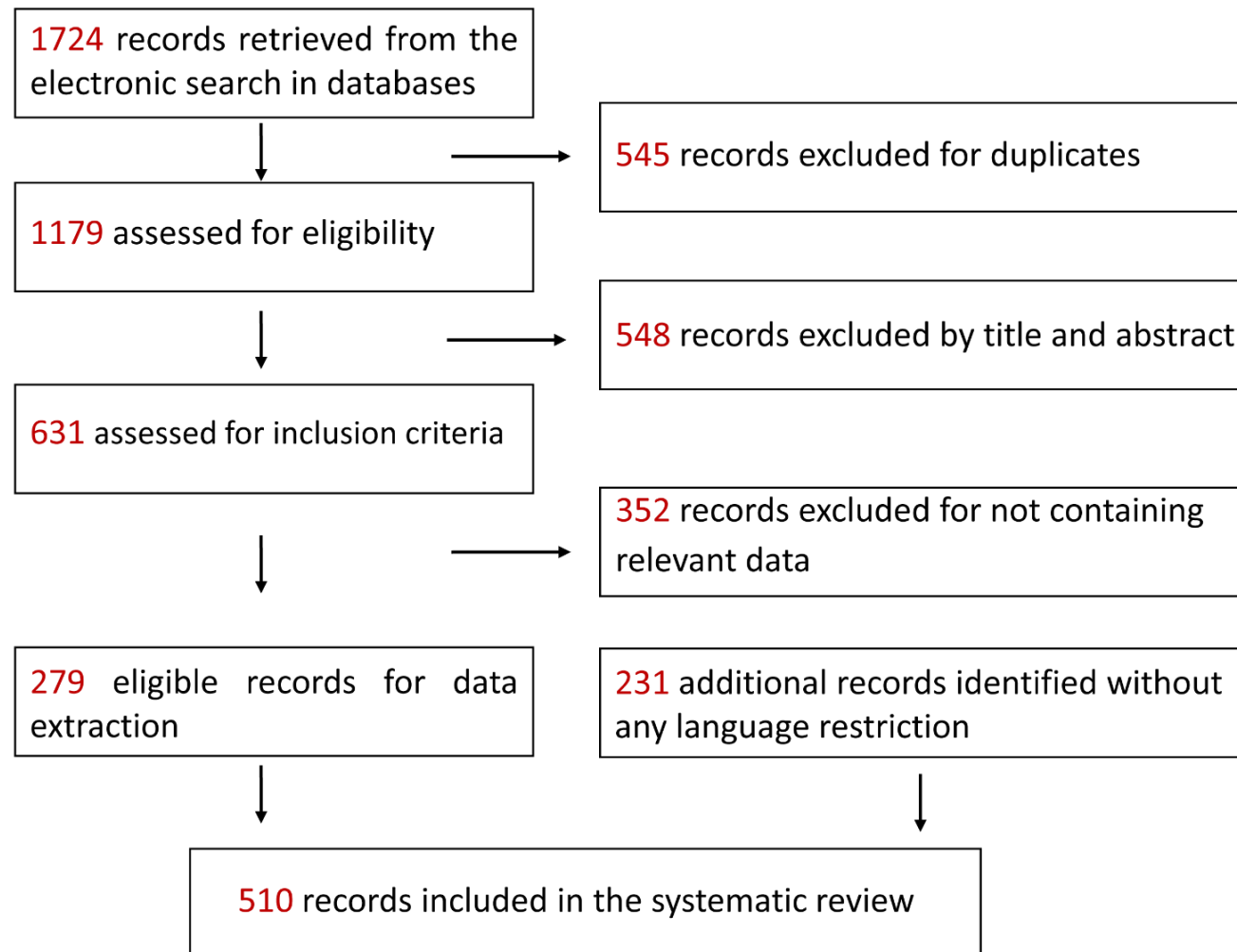


SUPPLEMENTARY file 1. PRISMA 2020 checklist.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1-2
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	120-133
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	179-223
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	223-231
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	242-263
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	234-240
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	243-257
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	262-271
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	262-271
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	268-275
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	268-275
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	264-271
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	280-310
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	268-275
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	329-340
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	266-271
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	329-340
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	na
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	na
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	335-340
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	na
RESULTS			

Section and Topic	Item #	Checklist item	Location where item is reported
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Appendix (Supp. file 2)
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	343-350
Study characteristics	17	Cite each included study and present its characteristics.	Appendix (Supp. file 2)
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	na
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Appendix (Supp. file 2)
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	na
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	366-409
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	na
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	na
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	na
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	na
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	412-418
	23b	Discuss any limitations of the evidence included in the review.	418-428
	23c	Discuss any limitations of the review processes used.	420-424
	23d	Discuss implications of the results for practice, policy, and future research.	425-428
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	563-566
Competing interests	26	Declare any competing interests of review authors.	560
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Appendix (Supp. files 3-4); Tables 1-2.

SUPPLEMENTARY file 2. Flow chart with article selection.



SUPPLEMENTARY file 4. Data source of human cystic echinococcosis cases that have been used for: A) the calculation of the total number of cases and incidence trends within the years 1997–2021, and B) time trends analysis within the years 1997–2019, at country level.

A) DATA SOURCE FOR THE CALCULATION OF THE TOTAL NUMBER OF CASES AND INCIDENCE TRENDS *

COUNTRY	Data sources §	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
Albania	1,4	25	33	42	41	61	64	163	124	40	57	57	54	59	41	42	41	40	47	43	31	34	114	105	93	78
Austria	1,3,4	26	31	43	23	22	18	32	25	31	24	11	7	18	18	4	8	17	13	4	22	40	32	16	18	
Belarus	4	4	5	1	2	4	11	8	2	11	12	10	15	20	10	10	18	22	4				13			
Belgium	1,3,4,5	1	1				2	1		8	5			35	7	11	4	12	12	5	10	9	10	12	10	1
Bosnia-Herzegovina	1,4	11	14	18	108	23	24	32	38	36	39	45	26	24	33	13	13	18	25	14	17	15	12	11	7	8
Bulgaria †	1,2,3	473	632	632	600	567	642	557	590	492	476	461	386	323	291	307	320	278	302	313	296	218	206	193	95	83
Croatia	1	a19	15	17	27	27	32	21	36	21	25	18	13	16	10	15	13	15	19	7	11	15	7	4	3	2
Czech Republic	3,4,5							1		10	1	1	11				2						1		1	
Denmark	1,5				1				8	15	10	9	5	11	10	31	20	9	10				1			
Estonia	1,3,4	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0	1	0
Finland	1	0	1	0	2	0	1	3	4	0	1	1	1	1	1	1	3	4	0	2	4	5	1	8	4	5
France †	2,4,5	2	2	0	2	1	6		1	301	262	293	242	277	230	243	232	227	223	212	219	227	232	220	196	23
Germany	1					29	30	59	73	88	81	62	76	70	74	90	64	65	74	85	122	86	93	87	81	89
Greece	1,3		54	51	29	41	23	16	26	11	5	49	28	22	11	17	21	10	13	13	18	15	11	7	7	
Hungary	1				112															2	3	11	6	6	4	
Iceland	3																	0	0	0	0	0	0	0	0	
Ireland	1,5							1	1	0	0	0	2	1	1	0	0	1	0	0	2	0	2	1	2	
Italy †	2,4	133	365	280	104	1564	1209	1252	1207	1034	935	818	833	707	636	565	553	473	458	404	360	464	414	281	194	
Latvia	3,4											116										1	4	5	4	2
Lithuania	1,3	1	5	4	1	7	9	8	11	13	9	8	8	35	32	23	24	34	24	9	5	19	11	30	0	
Luxembourg	3,5											1				1				0	0	2	0	1	3	
Malta	3																			0	1	0	0	0	0	
Montenegro	1	0	8	6	3	3	3	2	1	3	3	2	0	1	0	9	19	5	11	17	10	3	4	5	2	
The Netherlands	1,4	59	47	36	47	48	34	27	36	33	30	23	33		35	45	36	32	37	64	33	43	41	48	48	
Norway	1,4														90											
Poland	1,3,4,5	78		1		37	40	34	21	33	64	41	28	23	34	8	10	13	13	9	18	27	17	21	8	
Portugal	1,4	22	21	20	14	12	7	11	21	15	21	35	33	29	28	20	11	9	25	31	11	17	28	16	21	24

Republic of Cyprus	3,4,5	8	3	4	2	2	2	2	1	1	6	4	1	1	0	2	0	1	0	2	3	2	5	0	4	1
Rep. of Kosovo	1,4	4	3	163		164										22			0	4	0	1	2			
Rep. of Moldova	1	171	214	62	175	203	228	233	200	162	135	171	140	131	167	97	148	149	96	67	63	45	40	53	30	34
Rep. of North Macedonia †	1	7	25	9	23	12	6	12	12	17	19	17	44	39	38	33	18	27	21	18	26	30	37	21	19	8
Romania †	2,4		333	281	39	45	387	23	239	315	244	256	747	677	618	534	418	408	412	339	346	320	316	314	137	
Serbia	1,4	21	820												28	33	39	40	45	52	65	74	64	30		
Slovak Republic	3,4	4	0	1	31	5	3	0	1	0	1	2	7	1	8	1	2	14	6	2	1	2	3	3	1	
Slovenia	1,4,5	98						1	1									1					3	1	1	2
Spain †	2	739	745	664	633	558	538	557	524	504	507	482	441	433	434	403	322	310	312	281	262	264	261	256	211	
Sweden	1,4	7	7	5	3	8	14	4	9	12	7	24	13	15	30	19	16	16	21	26	26	30	27	24	20	
Switzerland	4	4	4	3	4	3	7	4	3	3	3	7	8	4	14	7	6	8	6	11	8	9	7	14	8	11
United Kingdom	1,2,3,4,5	1	3	1	1	10	10	5	8	11	14	10	18	9	7	15	7	14	25	26	5	4	3	3	1	
Ukraine	2				156	165	180	155	188	181	170	143	188	135	137	125	114	116								

B) SUBSET OF DATA USED FOR THE CALCULATION OF TIME TRENDS *,**

COUNTRY	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Albania								124	40	57	57	54	59	41	42	41	40	47	43	31	34	99	92
Austria	26	31	43	23	22	18	32	25	31	24	11	7	18	18	4	2	9	11	4	22	40	32	16
Belarus	4	5	1	2	4	11	8	2	11	12	10	15	20	10	10	18	22					13	
Belgium									8	5				7	11	4	12	12	5	10	9	10	12
Bosnia-Herzegovina					13	24	32	38	36	39	45	26	24	33	13	13	18	25	9	17	10	11	8
Bulgaria †	473	632	632	600	567	642	557	590	492	476	443	376	329	305	310	312	266	296	283	237	196	178	168
Croatia	19	15	17	27	27	32	21	36	21	25	18	13	16	10	15	13	15	19	7	11	15	7	4
Czech Republic							1			1	1											1	
Denmark								8	15	10	9	5	11	10	31	20	9	10					
Estonia	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Finland	0	1	0	2	0	1	3	4	0	1	1	1	1	1	1	3	4	0	2	4	5	1	8
France									301	262	293	242	277	230	243	232	227	223	212	219	227	232	220
Germany					29	30	59	73	88	81	62	76	70	74	90	64	65	74	85	122	86	93	87
Greece		54	51	29	41	23	16	26	11	5	49	28	22	11	17	21	10	13	13	18	15	11	7
Hungary																			2	3	11	6	6
Iceland																0	0	0	0	0	0	0	0
Ireland									0	0	0	2	1	1	0	0	1	0	0	2	0	2	
Italy					1564	1209	1252	1207	1034	935	818	833	707	636	565	553	473	458	404	360	464	414	281
Latvia			0	4	0	7	7	6	11	14	6	17	12	9	4	1	3	4	2	1	4	5	4
Lithuania	1	5	4	1	7	9	8	11	13	9	8	8	35	32	23	24	34	24	9	5	19	11	30

Luxembourg																			0	0	2	0	1
Malta																			0	1	0	0	0
Montenegro	0	8	6	3	3	3	2	1	3	3	2	0	1	0	9	19	5	11	17	10	3	4	5
The Netherlands	59	47	36	47	48	34	27	36	33	30	23	33		35	45	36	32	37	64	33	43	41	48
Norway			0	0	0	0	0	0	1	0	0	0	4	1	3	2	2	0	2	3	5	7	7
Poland					37	40	34	21	33	64	41	28	23	34	8	10	13	13	9	18	27	17	21
Portugal	22	21	20	14	12	7	11	21	15	21	35	33	29	28	20	11	9	25	31	11	17	28	16
Republic of Cyprus												1	1	0	2	0	0	0	2	0	0	0	0
Rep. of Kosovo	4	3	1							3	2	0	1	0	9	14	2	0	4	0	1	2	
Rep. of Moldova	171	214	62	175	203	228	233	200	162	135	171	140	131	167	97	148	149	96	67	63	45	40	53
Rep. of North Macedonia	7	25	9	23	12	6	12	12	17	19	17	44	39	38	33	18	27	21	18	26	30	37	21
Romania												747	677	618	534	418	408	412	339	346	320	316	314
Serbia	21	32	27	24	35	27	40	21	47	38	25	37	32	28	33	39	40	45	52	65	74	64	30
Slovak Republic	4	0	1	31	5	3	0	1	0	1	2	7	1	8	1	2	14	6	2	1	2	3	3
Slovenia														1	1	1	1		1	3	2		2
Spain	739	745	664	633	558	538	557	524	504	507	482	441	433	434	403	322	310	312	281	262	264	261	256
Sweden								9	12	7	24	13	15	30	19	16	16	21	26	26	30	27	24
Switzerland	4	4	3	4	3	7	4	3	3	3	7	8	4	14	7	6	8	6	11	8	9	7	14
United Kingdom					10	10	5	8	11	14	10	18	9	7	15	6	14	16	16	5			
Ukraine				156	165	180	155	188	181	170	143	188	135	137	125	114	116						

* Bibliographic references used for the data extracted in these tables are reported at country level in Supplementary file 3 (p. 4-30) and Supplementary file 5 (p. 34-36); ** Data source for trends calculation were based on national reports or the European Surveillance System data, which are expected to remain the same over time without introducing a selection bias. Due to scanty data, case reports were only included in trends analysis for the Czech Republic and Estonia; § Data sources used at country level were: 1) national health reports, 2) national hospital records, 3) European Surveillance System TESSy, 4) single- multi-centre case series, 5) single-centre case report; † Hospital records related to echinococcosis (ICD-10 codes B67.0 to B67.4 and B67.8 to B67.9; ICD-9 codes 122.0 to 122.4, 122.8 and 122.9) from Bulgaria (period 1997–2021), France (2005–2020) Italy (2001–2020), Rep. of North Macedonia (1997–2021), Romania (2007–2020) and Spain (1997–2020) were extracted from the national hospital information systems and analyzed following the methodology described in Van Cauteren et al. (2016), Piseddu et al. (2017) and Herrador et al. (2016) (Supplementary file 3, p. 4-30).

SUPPLEMENTARY file 5. References used at country level per year for data analysis. Numbers reported in this table refer to Supplementary file 3 reference list (p. 4-30).

COUNTRY	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	
Albania	3, 4, 5	3, 4, 5	3, 4, 5	3	3	3	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1,2	1, 2	1, 2	2, 3	
Austria	7	7	7	7	7	7	7	7	9	10	11	12	13	14	15	8	8	8	19	20	21	22	504, 505	504, 505		
Belarus	27	27	27	27	27	27	27	27	27	27	27	27	27	25	25	27	27	26				24				
Belgium	28	29				30	31		36	36			53	50	50	50	50	50	50	50	50	50	504, 505	504, 505	42	
Bosnia-Herzegovina	95	56, 95	56	54, 56, 57, 95	56, 57	66	66	66	66, 81	67, 82	68, 83	68, 84	69, 85	70, 86	71, 87	72, 88	73, 89	74, 90		76, 92				80	8	
Bulgaria	96	96	96	96	96	96	96	96	96	96	96	508	508	508	508	508	507	506, 507	506	504, 505	504, 505	504, 505	504, 505	504, 505	504, 505	96
Croatia	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106
Czech Republic							114			112, 113	112, 113, 115	112, 113	112, 113	112	112	110, 112	112					504, 505		504, 505		
Denmark				128				122	123	124	125	126	127	127	127	127	125	127				121				
Estonia								129, 131	129, 131							130								504, 505		
Finland	132	132	132	132	132	132	132	132	132	132	132	132	132	132	132	132	132	132	132	132	132	132	132	132	132	
France	137, 150	148, 149		146, 147	138			139	135	135	135	135	135	135	135	135	135	135	135	135	135	135	135	135	135	156
Germany					158	158	158	158	158	158	158	158	158	158	158	158	158	158	158	158	158	158	158	158	158	158
Greece		169	169	169	169	169	169	169	169	169	169	508	508	508	508	508	507	506, 507	506	504, 505	504, 505	504, 505	504, 505	504, 505	504, 505	
Hungary				181, 184	181, 184	181, 184	181, 183, 184	181, 183, 184	181, 183, 184	181, 183, 184	181, 183, 184	181, 183, 184	181, 183, 184	181, 183, 184	181, 183, 184	181, 183, 184	181, 183, 184	181, 183, 184	183, 184	183, 184	182, 183	182, 183	182, 183	182, 183	182, 183	
Iceland																507	506, 507	506	504, 505	504, 505	504, 505	504, 505	504, 505	504, 505		
Ireland							186	187	185	185	185	185	185	185	185	185	185	185	185	185	185	185	188	189, 190		

Italy	196, 197, 198, 199	195, 196, 197, 198, 199	195, 196, 197, 198, 199	195, 196, 197, 198, 199	193	193	193	193	193	193	193	193	193	193	193	193	193	193	193	193	193	193	193		
Latvia			222, 223, 224	222, 223, 225	222, 223, 226	222, 223, 227	222, 223, 228	222, 223, 229	222, 223, 230	222, 223, 231	222, 223, 232	222, 223, 233	222, 223, 234	222, 223, 235	222, 223, 236	222, 223, 237	222, 223, 238, 507	222, 223, 239, 506	222, 223, 240, 506	504, 505	504, 505	504, 505	504, 505	504, 505	
Lithuania	225	225	225	225	225	225	225	225	225	225	225	225	225	225	225	225	225	225	506	504, 505	504, 505	504, 505	504, 505	504, 505	
Luxembourg											228				53			506	504, 505	504, 505	504, 505	504, 505	504, 505	504, 505	
Malta																			229, 504, 505						
Montenegro	230	230	230	230	230	230	230	230	230	231	232	233	234	235	235	236	237	238	239	240	241	243	244	245	
The Netherlands	246	246	246	246	246	246	246	246	246	246	146, 248	246, 248	249	250	251	252	253	254	255	256	257	258	259	260	
Norway	262	263	264	261, 265	261, 266	261, 267	261, 268	261, 269	261, 270	261, 271	261, 272	261, 273	261, 274	261, 275	261, 276	261, 277	261, 278	261, 279	261, 280	261, 281	261, 282	261, 283	261, 284	261, 285	
Poland	302, 303, 305		304		287	288	289	290	291	292	293	294	295	296	297, 298	301	507	506, 507	506	504, 505	504, 505	504, 505	504, 505	504, 505	
Portugal	307	307	307	307	307	307	307	307, 308	307, 308	307, 308	307, 308	306, 307	306	306	306	306	306	308	308	308	308	308	308	308	
Republic of Cyprus	312	312	312	312	312	312	312	312	312	312	312	312	508	508	508	311, 508	508	313	506, 507	311, 506	309, 310	309, 310	309, 310	309, 310	
Rep. of Kosovo	320	320	318		316											317		321	322	323	324	325			
Rep. of Moldova	327	327	327	327	327	327	327	327	327	327	327	327	327	327	330	330	330	330	330	330	330	330	330	330	
Rep. of North Macedonia	342	342	342	342	342	342	342	342	342	342	342	342	342	342	342	342	342	342	342	342	342	342	342	342	
Romania		357	357	357, 358, 365	357, 358, 365	357, 358, 365, 366	357, 358, 365, 366	357, 359, 366, 367	353, 357, 366, 368	353, 357, 366, 368	353, 357, 368	343	343	343	343	343	343	343	343	343	343	343	343	343	
Serbia	377	377	369	369	369	369	369	369	369	369	369	369	369	378	378	379	380	381	382	383	384	385	386		
Slovak Republic	388	389	390	391	392	393	394	395	396	397	398	399	400, 508	401, 508	402, 508	403, 508	507	506, 507	506	504, 505	504, 505	504, 505	504, 505	504, 505	
Slovenia	414, 415	414, 415	414, 415	414	414, 415	404, 414	404, 412, 414	404, 407, 408, 414	404, 415	404, 415	415	415	415	415	415	405, 411, 415	405, 415	405, 413, 415, 416	415	405, 415	405	405	405	405, 417	417
Spain	426, 427	426, 428	426, 429	426, 430	426, 431	426, 432	426, 433	426, 434	426, 435	426, 436	426, 437	426, 438	426, 439	426, 440	426, 441	426, 442	426, 443	426, 444	426, 445	426, 446	426, 447	426, 448	426, 449	426, 450	

Sweden	457	457	457	457	457	457	457	457	452	452	452	452	452	452,453	452,453	452,454	452,454	452,454	452,454	452,455	452,455	452,455	452,455	452,455	452,455		
Switzerland	459,461	459,461	459,461	459,461	458,459,461	458,459,461	458,459,461	458,459,461	458,459,461	458,459,461	458,459,461	458,459,461	458,459,461	458,459,461	458,459,461	458,459,461	458,459,461	458,459,461	458,459,461	458,459,461	458,459,461	458,459,461	458,459,461	458,459,461	458,459,461	458,459,461	458,459,461
United Kingdom	488	486,490,491	492	493	470	470	470	470	470	470	471	472	473	474	475	508	507	506,507	506	480	504,505	482	504,505	486			
Ukraine				498	498	498	498	498	498	498	498	498	498	498	498	498	498										