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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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

**Beat Müllhaupt**, MD. Gastroenterology and Hepatology, University Hospital Zürich, Rämistrasse 100, 8091 Zürich, Switzerland.
**Valerio Manno,** Dstat. Statistical Service, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy.
**Azzurra Santoro**, 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.
**Federica Santolamazza**, 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.

* These authors contributed equally to this work

**Correspondence to:**
Adriano Casulli, PhD
WHO Collaborating Centre for the Epidemiology, Detection and Control of Cystic and Alveolar Echinococcosis;
European Union Reference Laboratory for Parasites (EURLP);
ISTITUTO SUPERIORE di SANITÀ (ITALIAN INSTITUTE of HEALTH). Viale Regina Elena, 299, 00161 Rome, ITALY
adriano.casulli@iss.it

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## Summary

The neglected zoonosis, cystic echinococcosis (CE) affects poor pastoral and rural communities in both low and medium-high income countries. In Europe, it should be regarded as an orphan and rare disease. Although human CE 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, data on the number, incidence and trend of human cases in Europe was extracted by means of systematic review approach from both the scientific and grey literature, accounting for the period of publication 1997–2021. The highest number of human cases at country level was calculated from various data sources to generate a descriptive model of human CE in Europe. This study identified 64 376 human CE cases from 40 European countries. Mean annual incidence in Europe was 0·64/100 000 during 1997–2020 and 0·50/100 000 during 2017–19.

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

## Key messages

- This study is aiming to shed light on the unrecognized incidence of CE in Europe unveiling its epidemiological impact by providing a quantitative measure of number, incidence and trends of human cases documented within the period 1997–2021.
- Since human CE cases are generally under-reported and data suffer from uncertainty also due to misdiagnosis, data provided by this study should be considered as a conservative estimate of the real impact of this zoonotic infection historically occurring in Europe.
- This study identified for the years 2017–19 a mean number of CE cases at least four-fold higher compared to the European Surveillance system data.
- Decreasing trends have been recorded in most Southern Mediterranean and some Eastern European countries where CE has traditionally been highly prevalent.
- Increasing trends have been identified in some Eastern and South-eastern European countries but unexpectedly also in most non-endemic countries of Northern and Western Europe.
- Based on recent incidence rates and trends, the current epicentre of CE in Europe is represented by the Balkan Peninsula.
- CE 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 (NTDs).

## Background

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

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

*multilocularis* involves primarily small rodents as intermediate hosts and canids as definitive hosts (mainly red foxes).[6,8] In both CE and AE, humans act as dead-end hosts with hand-to-mouth and foodborne/waterborne transmission of infective parasite eggs. CE and AE are both chronic diseases in humans. CE is a disabling disease with a low fatality rate, while AE is mostly a life-threatening disease since it causes a tumor-like progression. Within the "echinococcosis" disease group, CE is the most prevalent in Europe, as well as globally, causing severe morbidity and relative low mortality among human populations.[5] CE mainly affects the liver and the lungs, although the parasite can be localized in any organ or tissue.[9] CE is characterized 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 (e.g. abdominal pain); more severe clinical manifestations may also derive from complications such as cyst rupture or super-infections.

CE occurs in poor pastoral and rural communities, but it is also prevalent in those of medium-high income countries, including European ones, where it should be considered as an orphan and a rare disease.[10] Although human CE, 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 under-diagnosis, mis-diagnosis and consequently mis-reporting and under-reporting of CE cases.[11]

Some biological characteristics of the parasite, such as the time lag 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 in order to attribute the source of infection.[12,13] Moreover, due to this long latency period, it is not clear what are the main sources of infection, the pathways of transmission and the potential risk factors associated with odds of infection. In addition, outbreaks, as occurrence of CE 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 CE cases, in absence of data on source of infection during the anamnesis, may be mis-diagnosed. Moreover, CE can be asymptomatic or paucisymptomatic for years with absence of signs of acute infection for easy case retrieval which may contribute to under-diagnosis of cases. Unlike other parasitic infections, CE 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 parasitic cysts.[15,16] Therefore, serology alone is not a reliable diagnostic tool, and even in combination with imaging requires experienced personnel for its interpretation, consequently leading to mis-diagnosis. Due to the barrier provided by the cyst wall, biomarkers 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 can be present in the fecal samples to support the diagnosis, contrary to what generally adequate for the diagnosis of other helminths, which reside in the human intestine. An exception for the direct detection of the parasite is the *vomica* event for lung CE, a rare occurrence when part of ruptured cysts is expelled and directly detected in the expectorate. Finally, CE can be silent for years and when symptoms are present, they are unspecific, with no pathognomonic clinical signs related to the presence of CE cysts. These parasitic characteristics may result in mis-diagnosis of cases by less experienced physicians.

For all these reasons, imaging techniques, in particular ultrasound, are the main diagnostic tools for human CE, while 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 cyst stage classification has been developed by the WHO Informal Working Group for Echinococcosis (WHO-IWGE).[18] In this context, CE clinical management is currently based on cyst stage specific approach. Cyst-stage specific approaches currently available for the clinical management of CE 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 European Union (EU) case-definition mainly accounts for under-reporting of CE, since it is "echinococcosis" and therefore does not provide a distinction between CE and AE, which have 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 ECDC via the European Surveillance System (TESSy).[20] Moreover, multicystic stages of CE can be wrongly recorded as AE, therefore leading to mis-diagnosis and consequently mis-reporting and under-reporting. Finally, even if correct CE diagnosis was made and cases attended as outpatients, they are not always captured by hospital discharge records at national level, therefore contributing to under-reporting. The above mentioned regulatory, biological, clinical and diagnostic factors lead to the lack and inadequacy of reporting and consequently to neglect of CE as a public health issue in Europe and worldwide. For this reason, this study conducted within the MEME project (https://onehealthejp.eu/jrp-meme/) aims at unveiling the historical and current numbers of human CE in Europe by providing quantitative measure from different data-sources of CE human cases reported during last 25 years (1997–2021) at country level in Europe.

## Methods

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

### Search strategy and selection criteria

This SR is presented, in accordance with the PRISMA guidelines (Appendix, p. 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.[23] 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 strategy was: (“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 until Apr 30, 2022 without any language restriction for the identification of papers, reports, datasets, conference abstracts, systematic reviews (where 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. Countries (n=40) included in the search were Albania, Austria, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Montenegro, the Netherlands, Norway, Poland, Portugal, Republic of Cyprus, Republic of Moldova, Republic of North Macedonia, “Republic of Kosovo”, Romania, Serbia, Slovak Republic, Slovenia, Sweden, Switzerland, Spain, United Kingdom and Ukraine. Duplicates between databases were removed and the inclusion or exclusion of data source was carried out by independent researchers.

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

**Data curation**

The highest number of human cases at country level per year was calculated by summing cases from the different data sources with no overlapping to generate a descriptive model of human CE in Europe during the period 1997–2021. Primary data from different data sources (e.g. case series) were considered not duplicated at the same time period when they were reported from different clinical centres, or recorded by different CE cohorts (e.g. liver CE, lung CE, unusual locations) or different clinical management (e.g. surgical interventions, percutaneous interventions). In case of 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 little data on this disease was retrieved for all or part of the period under consideration (i.e. Belgium, Czech Republic, Denmark, France, Ireland, Luxembourg, Poland, Republic of Cyprus, Slovenia, Switzerland and United Kingdom). Unpublished single centre cohorts were obtained from Bosnia-Herzegovina (n=1), the Republic of Cyprus (n=2) and Switzerland (n=4) where 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 CE cases were calculated from the number of national hospitalizations since records of CE cases were not present or were scarce, compared to their hospitalizations. To avoid cases duplication in Romania and Spain from multiple hospitalizations of the same person over time, a decrease correction factor was applied to national hospitalizations. In fact, we identified two reference single centre large cohorts in Bucharest and Salamanca which recorded both number of cases and hospitalizations. Then we used the ratio of cases/hospitalizations from reference cohorts to calculate the number of cases at national level from national hospitalizations. Unspecified “echinococcosis” cases were included in the study as CE cases, only for those countries that are non-endemic for human AE (i.e. Albania, Bosnia-Herzegovina, Bulgaria, Republic of Cyprus, Finland, Greece, Ireland, Italy, Montenegro, Portugal, Republic of Cyprus, Republic of Kosovo, Republic of North Macedonia, Serbia, Spain, United Kingdom and Ukraine).[24] For co-endemic countries for CE and AE (i.e. Austria, Belarus, Belgium, Croatia, Czech Republic, Denmark, Estonia, France, Germany, Hungary, Latvia, Lithuania, Luxembourg, the Netherlands, Norway, Poland, Republic of Moldova, Slovak Republic, Slovenia, Sweden and Switzerland)[24] unspecified “echinococcosis” cases were excluded and only data reporting CE were included with the exception of France where unspecified cases were attributed to CE since they had hospital records characteristics similar to CE cases.[25] The annual data coverage of this study was calculated as the total number of years in which data where extracted compared to the total number 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 SR was used as a proxy for the identification of locally acquired and imported cases at country level.[26]

## 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),

in which 83 033 hospitalizations were recorded, with an annual data coverage of 12·3% within the considered period (Table 1).[25,29,30] Only three published cross-sectional studies by ultrasound population-based surveys were identified in Europe.[31,32,33] One of these cross-sectional studies, at large scale, estimated around 8000 and 37 000 CE infections in rural endemic areas of Bulgaria and Romania, respectively, during the period 2014–15.[32] Data from these surveys, as from ERCE clinical register, were extracted but not useful for any final calculation on numbers, incidence rates or trends of CE.[11,31,32,33]

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

CE deaths were recorded in 16 countries (40%) in a total of 895 cases during the considered period, corresponding to a hospitalized case fatality rate (CFR) of 1·39% (Table 1). In addition, 192 deaths were reported as “echinococcosis” from 4 countries (e.g. Germany, Latvia, Lithuania and Poland), where it was not possible to differentiate CE from AE deaths (Table 1).

Mean annual incidence at European countries and EU level in the period 1997–2020 were 0·64/100 000 and 0·50/100 000, respectively. As indicated by WHO, high endemicity areas for CE (1–5/100 000)[32] in the period 1997–2020 were identified in eight European countries: Albania (2·25/100 000), Bosnia-Herzegovina (1·00/100 000), Bulgaria (5·32/100 000), Italy (1·21/100 000), Republic of Moldova (4·65/100 000), Republic of North Macedonia (1·08/100 000), Romania (2·16/100 000) and Spain (1·00/100 000) (Table 2; Figure 2). Mean annual incidences at European countries and EU level during the recent period 2017–19 were 0·46/100 000 and 0·35/100 000, respectively. During the recent period (2017–19), high endemicity areas for CE[34] were identified in five European countries: Albania (2·94/100 000), Bulgaria (2·93/100 000), Republic of Moldova (1·70/100 000), Republic of North Macedonia (1·41/100 000) and Romania (1·63/100 000) (Table 2; Figure 3).

The annual data coverage for analysis of trends was 74·8% within the considered period (1997–2019), with an average of 17·2 years (95% CI 16·5-17·8) data coverage per country (Appendix, p. 31-33 and 34-36). Considering the observed annual incidences and those predicted by the model, a general decrease in the number of human CE cases has been identified in Europe from 1997 to 2020 (Figure 4). In particular, the statistically significant decreasing trends were detected in most Southern and some Eastern European countries where the disease has traditionally been highly prevalent, such as Bosnia-Herzegovina, Bulgaria, France, Greece, Italy, Republic of Moldova, Romania, Spain and Ukraine, but also in Croatia, the Czech Republic and Poland (Figure 4; Table 2). Mostly statistically significant increasing trends were detected in Eastern and South-eastern European countries (Balkans and Southern Baltics) such as Belarus, Montenegro, the Republic of North Macedonia, Serbia, Slovenia and Lithuania (Figure 4; Table 2). Mostly statistically significant increasing trends were also detected 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 CE cases in the last 25 years. A synthesis of CE endemicity and whether these CE cases at country level should be considered as locally acquired, imported or both, was reported in Table 2, where low incidences in non-endemic countries were commonly associated only with imported cases.

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

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

## Discussion

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

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

### Potential bias which may lead to over-estimation

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

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

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

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

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

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

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

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

Bulgaria and Romania.[32] This active search of CE carriers aiming at the detection of asymptomatic cases in rural areas identified a prevalence of 0·41% in both countries. This resulted in an estimated total of 45 000 people that may be infected with *E. granulosus s.l.* Extrapolating this estimated prevalence to the top five countries with the highest incidence rates (Albania, Bulgaria, Republic of Moldova, Republic of North Macedonia and Romania), the current number of cases 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 (CFR), the data sources from two out of 16 recording countries such as France and Spain are mainly based on national hospital records which, unlike the case series or the national institute of statistics data, cannot ascertain whether CE was the cause of death or resulted from other comorbidities (Appendix, p. 4-30).[25,29] Nevertheless, the CFR at European level identified in this study is consistent both with national data not derived from hospitalizations (Table 1) and with other cohorts from the literature.[3,47-49] As for locally acquired versus imported cases, it should also be noted that documented human CE cases in non-endemic countries with no travel history abroad (e.g. Germany) suggest that some infections may be locally acquired through food traded from endemic countries or by direct contact with dogs that had travelled abroad.[50] Finally, imported cases may present an important contribution to CE health burden at country level, even in endemic countries such as Italy, which recorded 13·6% all documented cases during the period 2001–14 were in foreign patients.[30]

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

## Conclusion

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

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

## Contributors

AC conceived the study, extracted the data, performed statistical analysis, 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 analysis. BAR, DP, MF, BB, DC, BŠ, EZ, MJG, GK, CC, IR, SS, VL, BD, ZH, JK, MP, AO, LM, MS, RS, VG, IA, US, PT, DA, VŠ, DM, HB, FC, MBG, FC, SG, MS, BM and MV extracted and interpreted the data in the second round. All authors reviewed the article, and approved submission. AC received funding for this study.

## Declaration of interests

All authors declare no competing interests.

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## Figures & Tables

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

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

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

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

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

**Figure 4.** Time trend analysis of the number of human cystic echinococcosis cases at country level (observed cases and predicted cases for the years 2020–2024). * Statistically significant time trend ($p<0{\cdot}05$).

**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

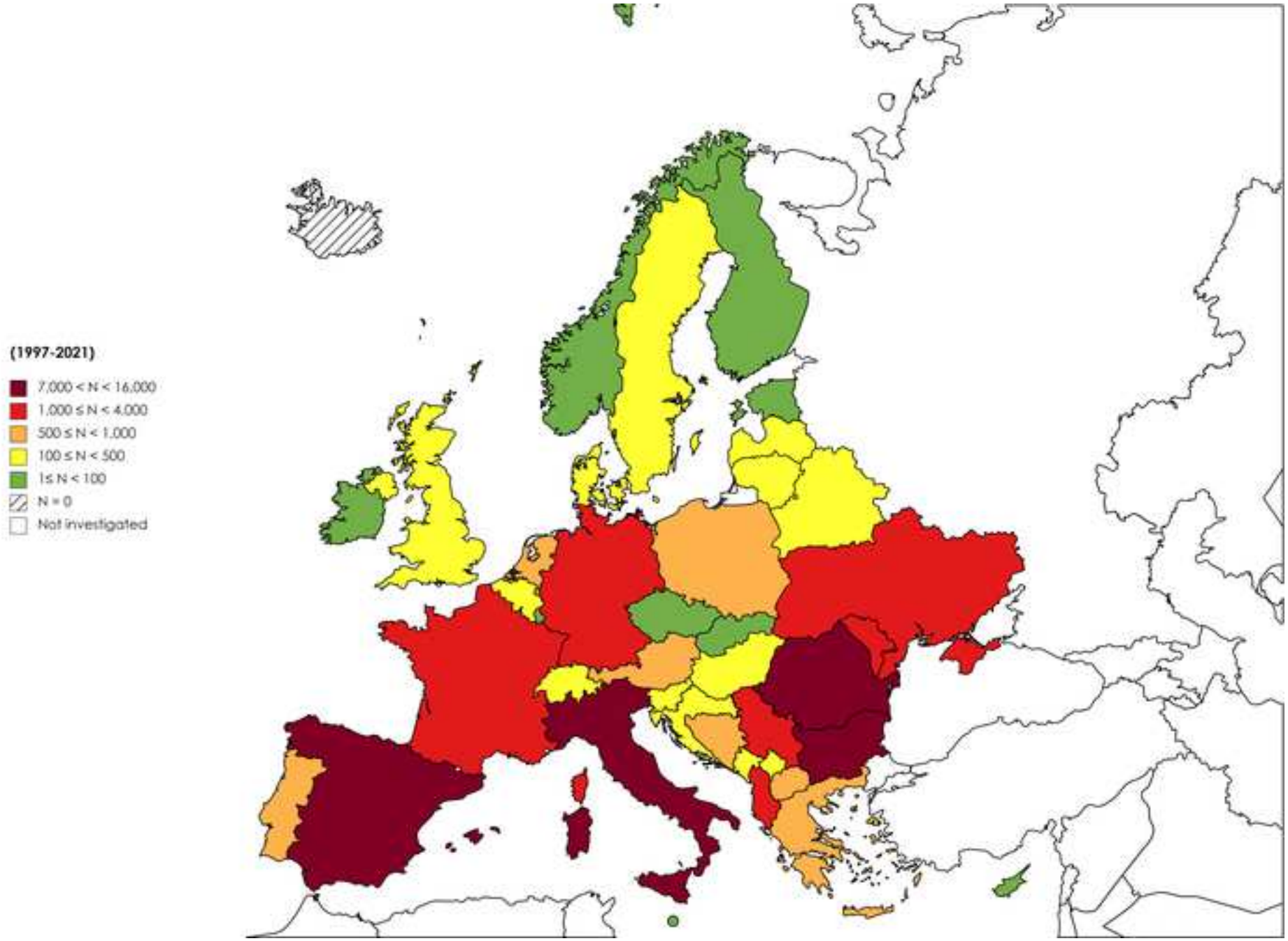


Figure 2. Incidence 1997-2020

Click here to access/download;Figure;Fig 2 Incidence_1997_2020.tif

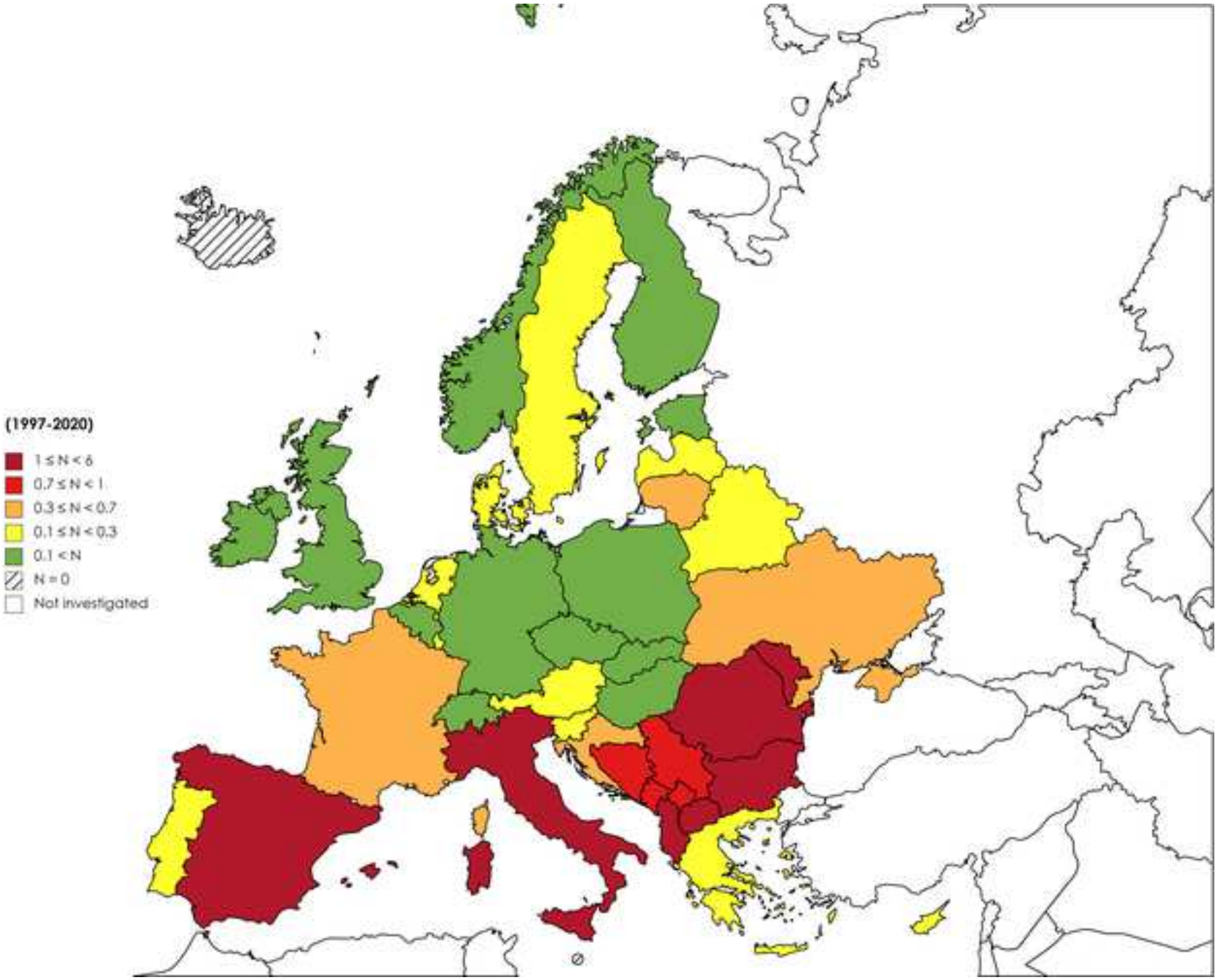


Figure 3. Incidence 2017-19

Click here to access/download;Figure;Fig 3 Incidence_2017_2019.tif

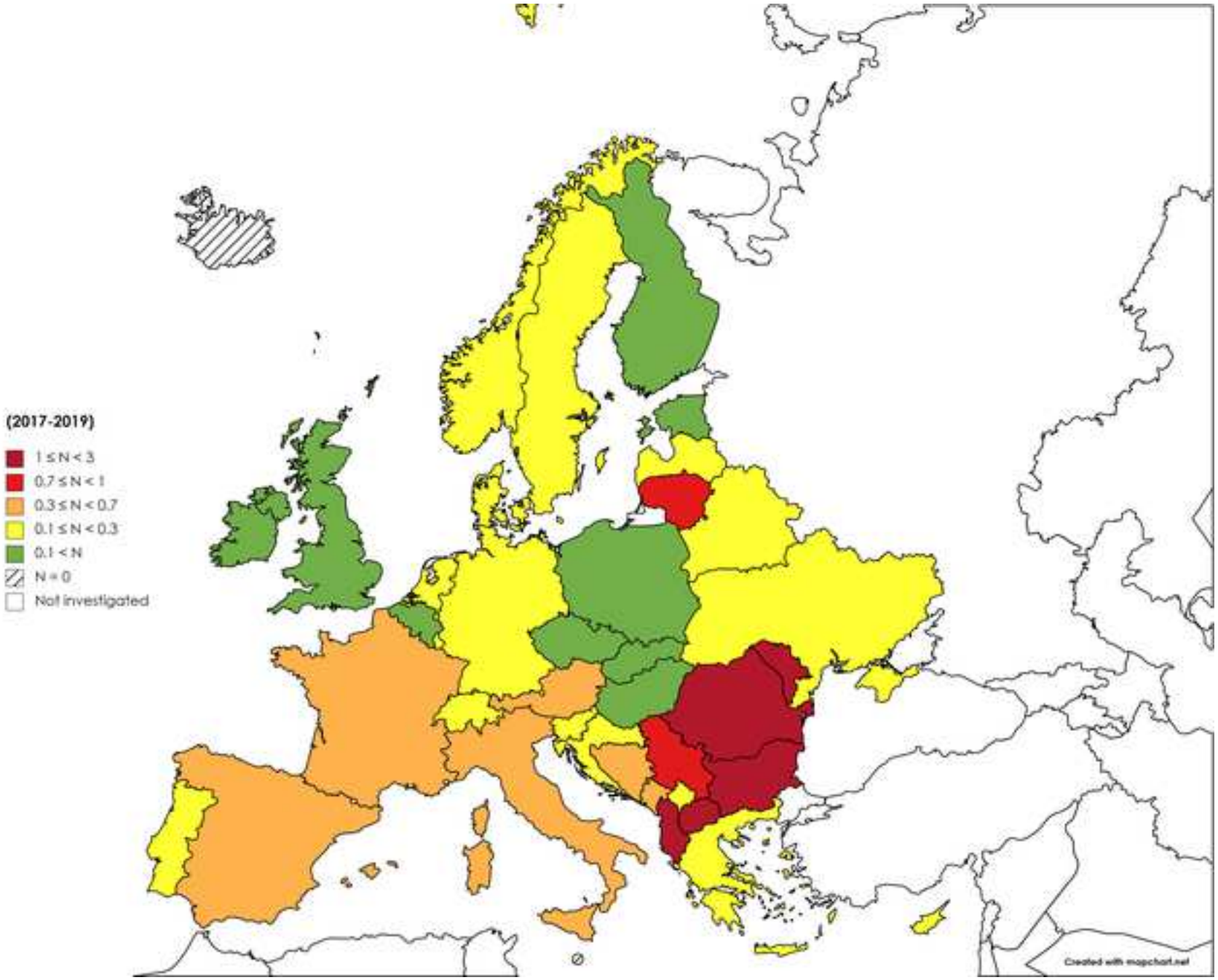
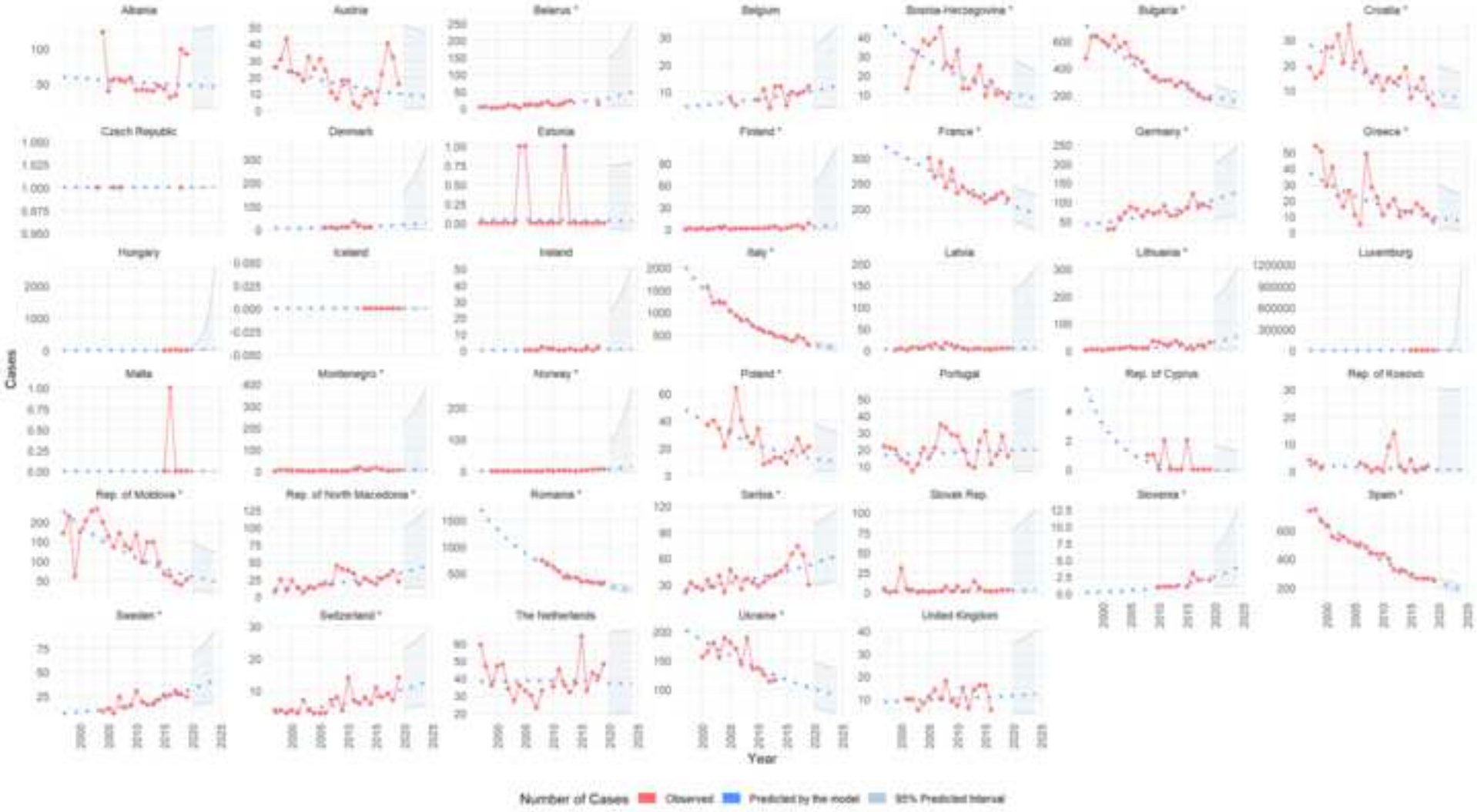


Figure 4. Time trend analysis 1997-2019

Click here to access/download;Figure;Fig 4 trends.png

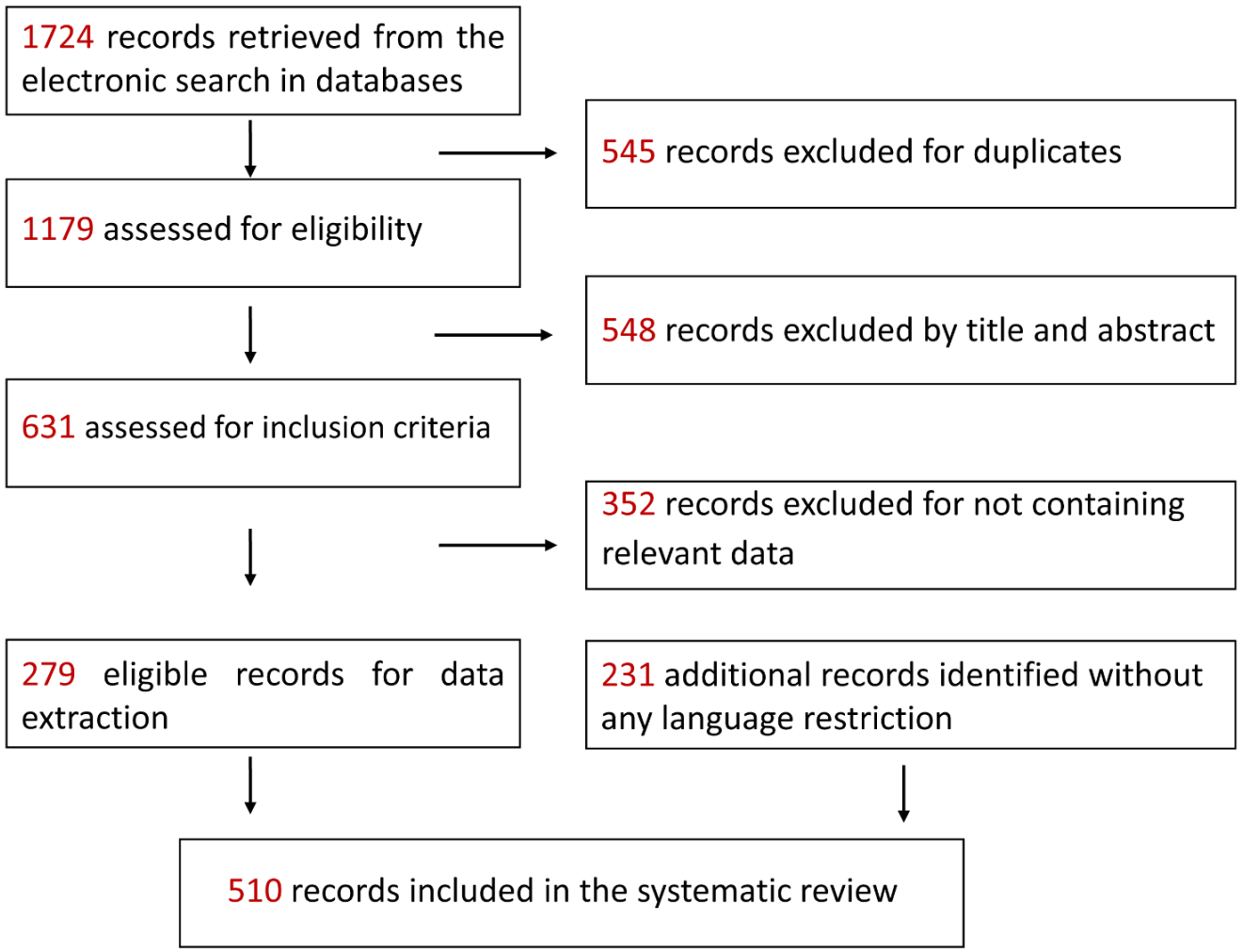


**SUPPLEMENTARY file 1.** PRISMA 2020 checklist.

| 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 |
| **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 | 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 |
| **Czech Republic** | | | | | | | 114 | | 112, 113 | 112, 113, 115 | 112, 113, 116 | 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 | 140, 141, 142, 143, 144, 145 | | 139 | 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 |
| **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 | |
| **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 | |
| **Iceland** | | | | | | | | | | | | | | | | | 507 | 506, 507 | 506 | 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 | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **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 | | |
| **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 | 308 | |
| **Republic of Cyprus** | 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 | 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 | 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 | 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, 406, 407, 408, 414 | 404, 415 | 404, 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 | | |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Sweden** | 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, 454 | 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, 460, 461 | 458, 459, 460, 461 | 458, 459, 460, 461 | 458, 459, 460, 461 | 458, 459, 460, 461 | 458, 459, 460, 461 | 458, 459, 460, 461 | 458, 459, 460, 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 | | | | | | | | |