EXTERNAL SCIENTIFIC REPORT

Echinococcus multilocularis infection in animals GP/EFSA/AHAW/2012/01[1]

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ABSTRACT

Alveolar echinococcosis (AE) is a parasitic disease caused by infection with the larvae of *Echinococcus multilocularis* (EM), a tapeworm found in definitive hosts such as foxes, jackals and dogs. Small rodents are intermediate hosts for EM. Although cases of AE in animals in endemic areas are relatively common, human cases are rare. In recent years, the presence of the parasite EM has been reported in areas of Europe in which it had previously not been recognised. At the same time, increases in the prevalence of EM in foxes have been observed in several European countries. In addition, urban fox populations have become established in many central European cities, reaching high population densities and sometimes with a high prevalence of EM infections, increasing the risk of transmission to humans. At present, documentation supporting the absence of the parasite has been submitted by four EU Member States. Regulation (EU) No 1152/2011 stipulates that a pre-movement anti-parasite treatment must be applied to dogs entering these countries and that a pathogen-specific surveillance programme, adhering to certain requirements regarding sampling and detection techniques, must be operated by these countries. The Commission must review this regulation no later than December 2016 in the light of scientific developments regarding EM infection in animals. EFSA will be asked to provide a scientific opinion on EM infections in animals by November 2015. To assist with this review, EFSA funded the project "*Echinococcus multilocularis* infection in animals". In order to be able to provide a comprehensive and quantitative assessment of EM infections in animals, the current knowledge and data on the epidemiology and risk factors related to this disease were collected in the EU and adjacent countries; the information and data, on the aspects listed above, were gathered by means of eight systematic reviews of literature and data.

KEY WORDS

Echinococcus multilocularis, systematic review, risk factors, deworming drugs, epidemiology, diagnosis, control.

DISCLAIMER

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INTRODUCTION AND OBJECTIVES

The tapeworm *Echinococcus multilocularis* (EM) is the causative agent of alveolar echinococcosis (AE), one of the most health-threatening helminthic zoonoses in the northern hemisphere. The parasite requires two mammalian hosts to achieve its life cycle: a carnivore definitive host (DH), such as the red fox (*Vulpes vulpes*), the Arctic fox (*Vulpes lagopus*), the raccoon dog (*Nyctereutes procyonoides*) or the dog (*Canis lupus familiaris*), and a rodent intermediate host (IH), with regard to which many species appear susceptible. In the past, the risk of humans becoming infected with this parasite was considered to be negligible and restricted to certain geographical areas, depending on the adaptations of the parasite to specific definitive/intermediate hosts and particular environmental conditions. These ecological barriers are slowly being breached by the direct consequences of recent globalisation: international trade, animal introductions (and new potential DHs, such as the raccoon dog) and human travel. Climate change may also affect both definitive and, especially, IH ecology. Moreover, the introduction of definitive/intermediate hosts has enabled this zoonotic parasite to spread. In fact, the presence of infected foxes in Sweden and the discovery of a European genotype in North America may have been caused by the accidental translocation of dogs. In addition, the introduction of wildlife, either accidentally or intentionally, has apparently occurred in Great Britain (where, for example, infected beavers have been imported from Germany), in the Japanese islands (i.e. as a result of translocated foxes) and in the Svalbard Archipelago, Norway (where Arctic foxes resulted infected by this parasite). During the past 30 years, the presence of this parasite has been reported in several areas of Europe in which it had previously not been identified. At the same time, a putative increase in the prevalence of this tapeworm in foxes has been observed in several European countries. Moreover, urban fox populations have become established in many central European cities, such as Copenhagen, Geneva, Stuttgart and Zurich, which may increase the risk of transmission to humans. In addition, the increased distribution of neozootic species, such as the raccoon dog (*Nyctereutes procyonoides*), the feral nutria (*Myocastor coypus*) and the muskrat (*Ondatra zibethicus*), could increase the likelihood of these species playing roles as definitive or IHs for EM.

Within the European Union, the Schengen Agreements along with the directive on the right to move freely (EU, 2004) mean that the travel of people between the majority of European countries occurs with very little formal control. For this reason, the transport of companion animals across borders provides a real threat in Europe for the spread and introduction of zoonotic pathogens, such as *Echinococcus* spp. The lifting of border restrictions in Europe has meant that pet owners can mostly travel freely with their animals. However, historically, non-endemic countries for EM, such as the UK, Finland, Malta, Ireland, Norway and, until recently, Sweden, had *ad hoc* regulations regarding the treatment of dogs and cats for tapeworm before entry (EU Directive 998/2003[3]). The treatment requirements were harmonised between these different countries in 2012 (EU Directive 1152/2011[4]). In fact, from 1 January 2012, import controls relating to tapeworm were implemented by the European Commission; these lay down the tapeworm control import conditions that pet animals must comply with when being moved into EM-free Member States (MSs) from other MSs or adjacent countries (ACs). The conditions are directly applicable in four EM-free MSs (Finland, Ireland, Malta and the UK) and have the objective of protecting public and animal health from the risk of the tapeworm EM (EFSA, 2012). The epidemiological role of dogs in endemic settings is of limited importance for the life cycle of the parasite. However, the risk of the transmission cycle of the EM parasite being established in suitable wild intermediate and definitive hosts in previously parasite-free areas is greater than negligible, if the parasite is introduced through the movement of infected dogs shedding eggs of the tapeworm.

[3] Regulation (EC) No 998/2003 of the European Parliament and of the Council of 26 May 2003 on the animal health requirements applicable to the non-commercial movement of pet animals and amending Council Directive 92/65/EEC.

[4] Commission delegated Regulation (EU) No 1152/2011 of 14 July 2011 supplementing Regulation (EC) No 998/2003 of the European Parliament and of the Council as regards preventive health measures for the control of *Echinococcus multilocularis* infection in dogs.

For this reason, Regulation (EU) No 1152/2011 stipulates that a pre-movement anti-parasite treatment must be applied to dogs entering these countries and that a pathogen-specific surveillance programme, adhering to certain requirements regarding sampling and detection techniques, must be operated by these countries.

The aim of this project is to provide a comprehensive review of the available data and literature on EM infections in animals. Data on the epidemiology, risk factors, diagnosis and control of this disease were identified and collected. This was approached by incorporating a network of European disease experts and European networks, such as the National Reference Laboratories for Parasites (NRLs) coordinated by the European Union Reference Laboratory for Parasites (EURLP), and summarising information on current surveillance activities, sampling plans and additional information gathered during the project. The outcome, together with scientific data collected during the project, will form the basis of developing the required objectives.

The specific objectives are as follows:

- to establish a network of experts, identify data requirements and review literature (Work Package (WP) 1)
  - The Consortium members and external experts that were temporarily recruited are from throughout Europe to ensure that all geographical and thematic areas are represented and that sufficient links to countries not directly participating could be established. The EURLP helped in the recruitment of this expertise. There are already good links and reports available for appraisal, so the establishment of a network of excellence with associated literature reviews ensured that all nine objectives related to EM infection in animals were covered.
- to identify and collect the current knowledge and data on the nine objectives of the present call
  - Databases, community summary reports and scientific publications were accessed and information was shared through the network via brief summary reports. Epidemiological data on intermediate, definitive and human hosts were collected from each European MS or AC.
  - Information and data were gathered by means of systematic reviews of literature and data (databases, community summary reports, scientific publications and EU-funded research projects) and network information (NRLs, EURLP). Tables reporting the epidemiological presence distribution and prevalence of this pathogen were generated. The nine objectives of the present call were split into four thematic areas (WPs), comprising eight systematic reviews, as summarised in the following sections.

Work Package 2: epidemiology

For WP2, the following systematic review was carried out:

- a systematic review on the geographical distribution and the prevalence of EM infection in animals and the importance of the different host species in the life cycle of this parasite in the EU and ACs (European Food Safety Authority (EFSA) requests 2 and 4).

Work Package 3: risk factors

For WP3, the following systematic reviews were performed:

- a systematic review on the risk factors for the introduction and establishment of EM in EM-free areas as a result of movements of domestic and wildlife species involved in the EM life cycle (EFSA request 1);

- a systematic review on the risk factors associated with human AE (EFSA request 6);

- a systematic review on the impact of EM infection in animals on public health in the EU and ACs (EFSA request 7).

Work Package 4: diagnosis and treatment

For WP4, the following systematic review were performed:

- a systematic review on the laboratory techniques for the detection of EM in live or dead animals (EFSA request 8);

- a systematic review on the effectiveness of available EM deworming drugs, resulting in treatment protocols for dog, cats and ferrets (EFSA request 9).

Work Package 5: monitoring, surveillance and control

For WP5, the following systematic review were carried out:

- a systematic review on the monitoring and surveillance programmes for EM infection in definitive and intermediate hosts (EFSA request 3);

- a systematic review on the programmes for the eradication of EM in wildlife host species (EFSA request 5).

Work Package 6: attend meetings to discuss key decisions with EFSA and generate the final report (WP6)

Meetings were arranged at convenient times and frequencies to ensure that all parties were kept informed of the progress. These meetings were used for training on the systematic review approach. Any matters arising from either the network or EFSA were addressed at the appropriate stage of the project.

MATERIALS AND METHODS

1. Consortium composition

The project is coordinated by Istituto Superiore di Sanità (ISS; project coordinator: Adriano Casulli), with defined roles for project management advice provided by Alessia Possenti and Luca Busani (WP1 and WP6). Literature searching and management was carried out by Alessia Possenti, who managed the databases of retrieved information (from scientific publication databases (e.g. CDC (Center for Disease Control and Prevention), ECDC (European Center for Disease Control and Prevention), EFSA and OIE (World Organisation for Animal Health)), network information from NRLs/EURLP, personal communications and EU-funded research projects). Each of the partners and consultants coordinated different aspects of the project for their particular organisation; therefore, there is one point of contact for the EFSA network. Four members of the consortium were WP leaders in order to (i) communicate with the database manager; (ii) create lists of available datasets for the WPs; (iii) avoid duplication of data; and (iv) facilitate consortium–applicant–EFSA communication. The WP leaders are as follows: Antti Oksanen, EVIRA (Finnish Food Safety Authority), Finland, for WP2; Franz Conraths, FLI (Federal Research Institute for Animal Health), Germany, for WP3; Joke

van der Giessen, RIVM (National Institute for Public Health and the Environment), the Netherlands, for WP4; and Franck Boue, ANSES (French Agency for Food, Environmental and Occupational Health and Safety), France, for WP5. The other members supported their own partner leader, with the exception of Partner 5 (NVRI (National Veterinary Research Institute), Poland) and Partner 6 (CSIC (Agencia Estatal Consejo Superior de Investigaciones Cientificas), Spain) who supported the leader of WP2.

The project finances and milestones were monitored, and brief summary reports of progress were provided during the project. These data were circulated for comment by all members of the network to ensure that any conclusions or recommendations were agreed by all parties. Feedback from each of the interim meetings was provided to the network. These meetings were attended by a representative of ISS.

The members of the Consortium are ISS (Italy), ANSES (France), RIVM (the Netherlands), FLI (Germany), EVIRA (Finland), NVRI (Poland) and CSIC (Spain). These institutes are all internationally recognised in the area of zoonotic diseases. The other participants (temporarily recruited external experts) in the project were scientists from the Institute of Parasitology of Zurich (IPZ) (Switzerland), the Institute of Parasitology of Bern (IPB) (Switzerland), Hohenheim University (Germany), University Hospital of Ulm (UUlm) (Germany) and the Norwegian School of Veterinary Science (NVH) (Norway) (see Table 1 WP1 and Figure 1 WP1). External experts were recruited based on their expertise with regard to the topics of the present call. These external experts should provide a valuable contribution to the project because of their areas of expertise from these additional European countries; they have not been included as partners because they are not included on the EFSA list of eligible partners. EU experts were temporarily recruited and invited to participate in workshops and their contributions were sought when drafting the project report. They, therefore, contributed to the project as external experts and details of their work are included below.

Peter Deplazes, IPZ (Switzerland)

Peter Deplazes provided the technical support needed for establishing the geographical distribution and prevalence of EM infection in animals in the EU and ACs, including wildlife and domestic species that can act as definitive and intermediate hosts. This expertise on data collection and analysis is considered very beneficial to project (WP2 support).

Bruno Gottstein, IPB (Switzerland)

Bruno Gottstein provided the technical support needed for establishing the effectiveness of available EM deworming drugs and the treatment protocols for dogs, cats and ferrets. This expertise on data collection and analysis is considered very beneficial to project (WP4 support).

Thomas Romig, HU (Germany)

Thomas Romig provided the technical support needed for the monitoring and surveillance programmes of EM infection in definitive and intermediate hosts. This expertise on data collection and analysis is considered very beneficial to project (WP2 and WP5 support).

Peter Kern, UUlm (Germany)

Peter Kern provided the technical support needed for the assessment of the risk factors associated with human EM infections/human AE in the EU and ACs. This expertise on data collection and analysis is considered very beneficial to project (WP3 support).

Lucy Robertson, NVH (Norway)

Lucy Robertson provided the technical support needed for the assessment of the risk factors and the steps of the risk pathway for the introduction and establishment of EM in EM-free areas as a result of movements of domestic and wildlife species involved in the EM life cycle in the EU and ACs. This expertise on data collection and analysis is considered very beneficial to project (WP3 support).

Table 1 WP1: Consortium composition

Name	Affiliation	Consortium	Role
Adriano Casulli	ISS, Italy	Applicant	Project coordinator
Luca Busani	ISS, Italy	Applicant	Project management
Alessia Possenti	ISS, Italy	Applicant	Literature support, administrative issue, project management
Fenicia Vescio	ISS, Italy	Applicant	meta-analysis
Franck Boue	ANSES, France	Partner 1	WP5 leader
Gerald Umhang	ANSES, France	Partner 1	WP5 support
Joke van der Giessen	RIVM, Netherlands	Partner 2	WP4 leader
Miriam Maas	RIVM, Netherlands	Partner 2	WP4 support
Sanne van den End	RIVM, Netherlands	Partner 2	WP4 support
Franz J Conraths	FLI, Germany	Partner 3	WP3 leader
Carolina Probst	FLI, Germany	Partner 3	WP3 support
Antti Oksanen	EVIRA, Finland	Partner 4	WP2 leader
Jacek Karamon	NVRI, Poland	Partner 5	WP2 support
Mar Siles-Lucas	CSIC, Spain	Partner 6	WP2 support
Maria De Giusti	Sapienza University, Italy	SR advisor	SR advisor for WP3
Paolo Villari	Sapienza University, Italy	SR advisor	SR advisor for WP4
Giuseppe La Torre	Sapienza University, Italy	SR advisor	SR advisor for WP2 and WP5
Corrado De Vito	Sapienza University, Italy	SR advisor	SR expert for WP4
Alice Mannocci	Sapienza University, Italy	SR advisor	SR expert for WP2
Emanuele Maffongelli	Sapienza University, Italy	SR advisor	SR support for WP2
Daniele Mipatrini	Sapienza University, Italy	SR advisor	SR support for WP2
Rosella Saulle	Sapienza University, Italy	SR advisor	SR expert for WP3
Vittoria Colamesta	Sapienza University, Italy	SR advisor	SR expert for WP5
Silvia D'Aguanno	Sapienza University, Italy	SR advisor	SR support for WP5
Thomas Romig	Hohenheim University, Germany	External expert	Support for WP2
Peter Kern	UUlm, Germany	External expert	Support for WP3 (human related)
Bruno Gottstein	IPB, Switzerland	External expert	Support for WP4
Peter Deplazes	IPZ, Switzerland	External expert	Support for WP5
Lucy Robertson	NVH, Norway	External expert	Support for WP3 (animal related)

SR, systematic review.

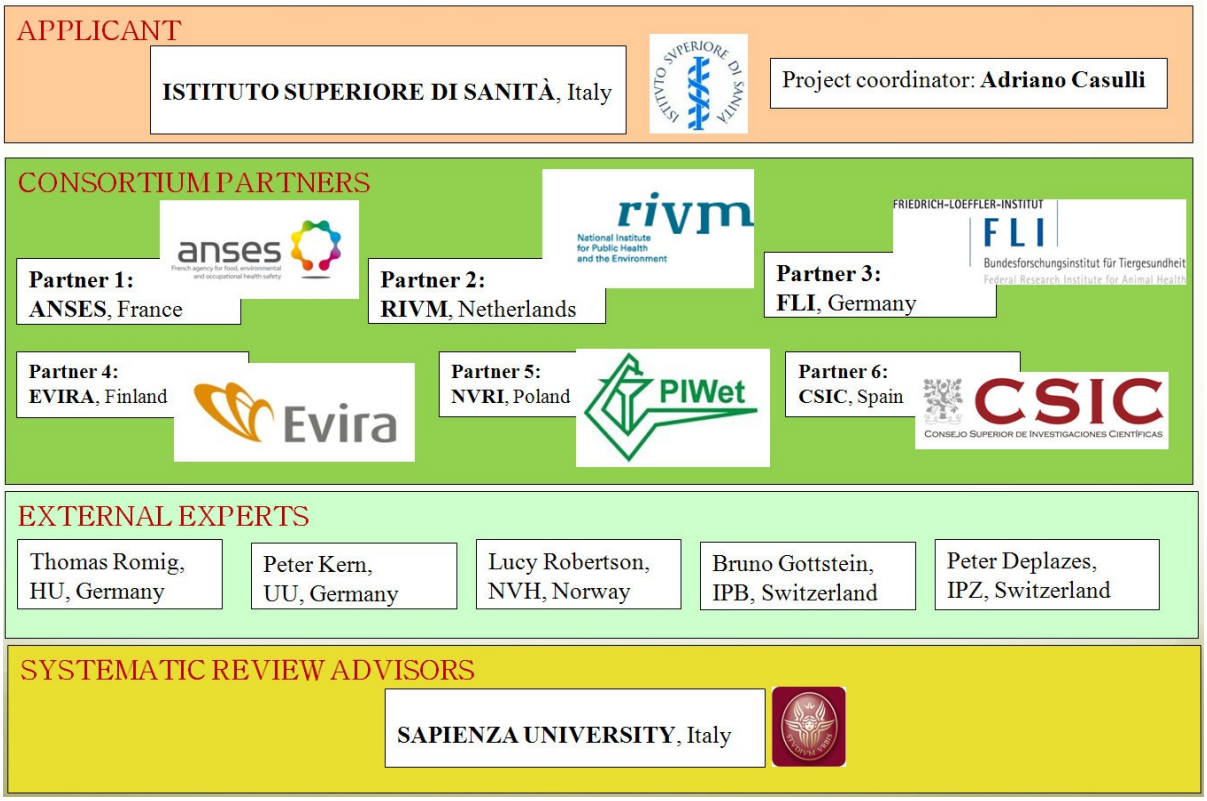


Figure 1 WP1: Project management organogram

2. Project description

In order to achieve the objectives of this call, the project has been divided into six WPs (see Figure 2 WP1). Each of these is divided into a number of milestones to facilitate project management and to ensure that the objectives are fully completed. In addition to WP1 (project network management) and WP6 (project communication), there are four separate scientific WPs (WP2, WP3, WP4 and WP5) which group the eight objectives of the present call (see Table 2 WP1); however, there are many areas of the project, which overlap and are complementary in nature. In these cases, discussions between consortium members and experts ensured that areas of potential harmonisation were identified. This allowed time and cost savings, both within the project, as objectives were achieved concurrently, and in the long term by streamlining EFSA reporting and monitoring schemes for this pathogen (EFSA, 2011). The framework of the project covers three main work areas: current information gathering, epidemiological quantitative evaluation of the pathogen and the appraisal and reporting of recommendations produced at the end of the project.

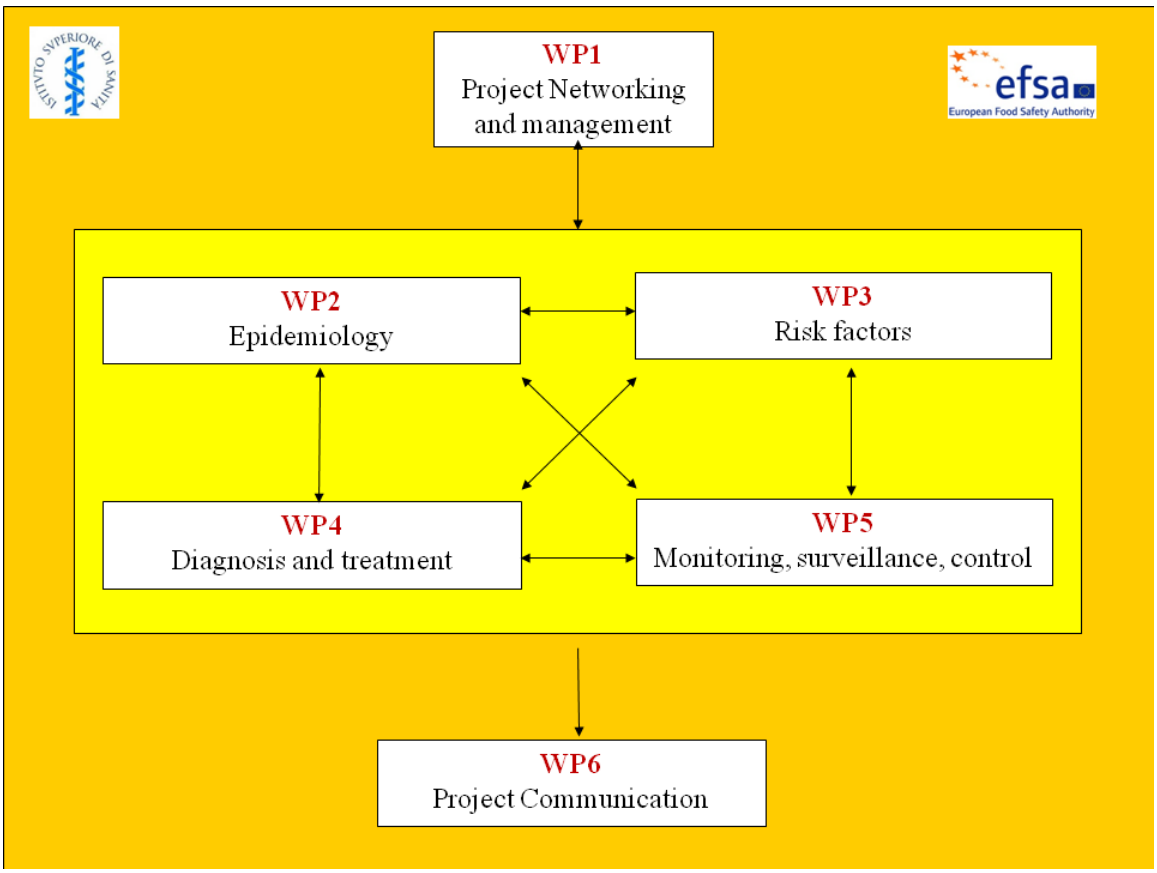


Figure 2 WP1: Project structure based on WPs

Table 2 WP1: EFSA requests, related WPs and outcomes

EFSA requests and related systematic reviews	WP	Outcomes
1. The risk factors and steps of the risk pathway for the introduction and establishment of EM in EM-free areas as a result of movements of domestic and wildlife species involved in the EM life cycle.	WP3	List of risk factors and risk pathways. Opinion on the relevant risk factors and risk pathways.
2. The geographical distribution and the prevalence of EM infection in animals, including wildlife and domestic species, that can act as definitive and intermediate hosts.	WP2	Database with data on the distribution and prevalence of EM infection in animals. Maps of the geographical distribution and the prevalence of EM infection in animals.
3. Monitoring and surveillance programmes of EM infection in definitive and intermediate hosts.	WP5	List of monitoring and surveillance programmes. Description of programmes.
4. The importance of the different definitive and intermediate hosts species in the life cycle of EM.	WP2	List of the main definitive and intermediate hosts species in the life cycle of EM. Maps of the distribution of the most important species.
5. Programmes for the eradication of EM in wildlife host species.	WP5	List of programmes, methods and evaluation for EM eradication in wildlife host species.
6. The risk factors associated with human EM infections/human AE.	WP3	List of risk factors and risk pathways. Opinion on the relevant risk factors and risk pathways with score.
7. The impact of EM infection in animals on public health.	WP3	Main related epidemiological data by country. Opinion on the impact of EM infection in humans.

EFSA requests and related systematic reviews	WP	Outcomes
8. Laboratory techniques for the detection of EM in live or dead animals.	WP4	List of the routinely applied laboratory methods for the diagnosis of EM. Comparability analysis of the methods used.
9. The effectiveness of available EM deworming drugs and the treatment protocols for dogs, cats and ferrets.	WP4	List of available treatments by animal species. Qualitative/semi-quantitative evaluation of the effectiveness.

3. Systematic review approach

This section specifies the approaches and the necessary methodological considerations for different kinds of data sources that were applied in four WPs (WP2, WP3, WP4 and WP5). Taking into account the kind of data that we collected in the framework of the project, the Data Collection Framework (DCF) of the EFSA zoonoses report is the most suitable for the harmonisation and integration of data collected on EM. In this regard, we defined the structure of data extraction tables, as far as possible, in accordance with this DCF. The resulting tables could be analysed, to some extent, in the framework of the EU zoonoses report.

The eight systematic reviews on EM were conducted in accordance with the seven steps outlined in the following sections.

3.1. Step 1: preparing the systematic review and a priori protocols

The methods to be used in all steps of the systematic review process were detailed a priori in review protocols, which define the specification of the review questions, the objectives, the inclusion/exclusion criteria, the search strategy, the data collection and extraction process, the risk of bias and the approach to statistical analysis and the synthesis of results.

3.2. Step 2: methods for searching research studies

The information sources which were likely to yield relevant studies (published and unpublished) were identified to minimise the effects of publication bias. Publication searches were performed for journals, books and "grey literature" (i.e. research findings in reports, working papers, dissertations and conference proceedings).

The search strategy (search terms, their logical combination and language restrictions) was developed to capture the review question and identify relevant studies. Any ongoing modifications to the search strategy were tracked and justified.

References and the documents retrieved were managed using the bibliographic software Review Manager (RevMan, Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). This software was used to manage (store and classify) the references downloaded from bibliographic databases. The searches were documented and reported by a flow chart and narrative description, in order to make the search process as transparent as possible and to enable it to be evaluated and reproduced.

Bibliographic searches, within the eight protocols, were carried out using the following databases:

- MEDLINE (Medical Literature Analysis and Retrieval System Online)
- EMBASE (*Excerpta Medica* Database)
- SciSearch (Science Citation Index)

- BIOSIS (Biological Abstracts)
- CABI (Centre for Agricultural Bioscience International)
- Google Scholar.

The systematic search of the abstracts/manuscripts was carried out in a centralised way for all the WPs by the Documentation Service of the ISS. The platform used for this systematic review was STN International (Scientific & Technical Information Network International, Fiz Karlsruhe (Fachinformationszentrum Karlsruhe; available online: http://www.fiz-karlsruhe.de/stn.html?&L=1). The search was carried out on 5 November 2013. An additional search was performed on 11 February 2015 to identify any papers that had been published since the initial search. The results of these two searches were combined.

The search was restricted to eight languages (English, Italian, Polish, Dutch, German, Spanish, French and Finnish) and electronic databases.

The databases were searched using keywords associated with the Boolean operators "AND" and "OR". The question mark ("?") was used to expand searches by looking for words with similar prefixes using more than one letter (i.e. "echinococc?" was used to search for "echinococcus", "echinococci", "echinococcosis" and "echinococcoses"). The hash mark ("#") was used to expand searches by looking for words with similar prefixes using one letter (i.e. dog# was used to search for "dog" or "dogs").

Different combinations were tailored for each electronic database in order to narrow the amount of results retrieved but, at the same time, to maximise the number of relevant studies.

First, the titles and abstracts were screened for relevance to the study question; if the title or abstract did not give a clear indication of relevance, the full text was screened. After this initial selection, full-text articles were evaluated for eligibility, in accordance with the inclusion/exclusion criteria. Data extraction was performed independently by two researchers; any disagreements were resolved either by consensus among researchers or by arbitration by an additional independent researcher. Data were extracted from the selected studies by completing data extraction tables.

3.2.1. Grey literature searching

EU reports and conference proceedings were searched using the keywords "EU report", "European Union report", "conference proceedings", "*Echinococcus multilocularis*", "*E. multilocularis*" and "alveolar echinococcosis".

Questionnaires were sent to the NRL (National Reference Laboratory) for Parasites in Europe.

Bachelor, Masters and PhD theses searches were carried out using the keywords "*Echinococcus multilocularis*" and "alveolar echinococcosis" and the following databases (available online):

- http://ethos.bl.uk/Home.do
- http://www.dart-europe.eu/basic-search.php
- https://www.daad.de/deutschland/promotion/phd/en/13306-phdgermany-database/
- https://catalogue.lse.ac.uk/Record/1149203

- http://www.theses.fr/
- http://biblioteca.ucm.es/
- http://digital.csic.es/
- https//www.tesisenred.net/
- http://www.proquest.com/en-US/catalogues/databases/detail/abi_inform.shtml
- https://portal.dnb.de/opac.htm
- http://www.sudoc.abes.fr/
- http://www.collectionscanada.gc.ca/thesescanada/
- http://library.stanford.edu/guides/find-dissertations-and-theses
- http://www.oclc.org/support/services/firstsearch/documentation/dbdetails/details/WorldCatDissertations.en.html
- https://qspace.library.queensu.ca/handle/1974/290.

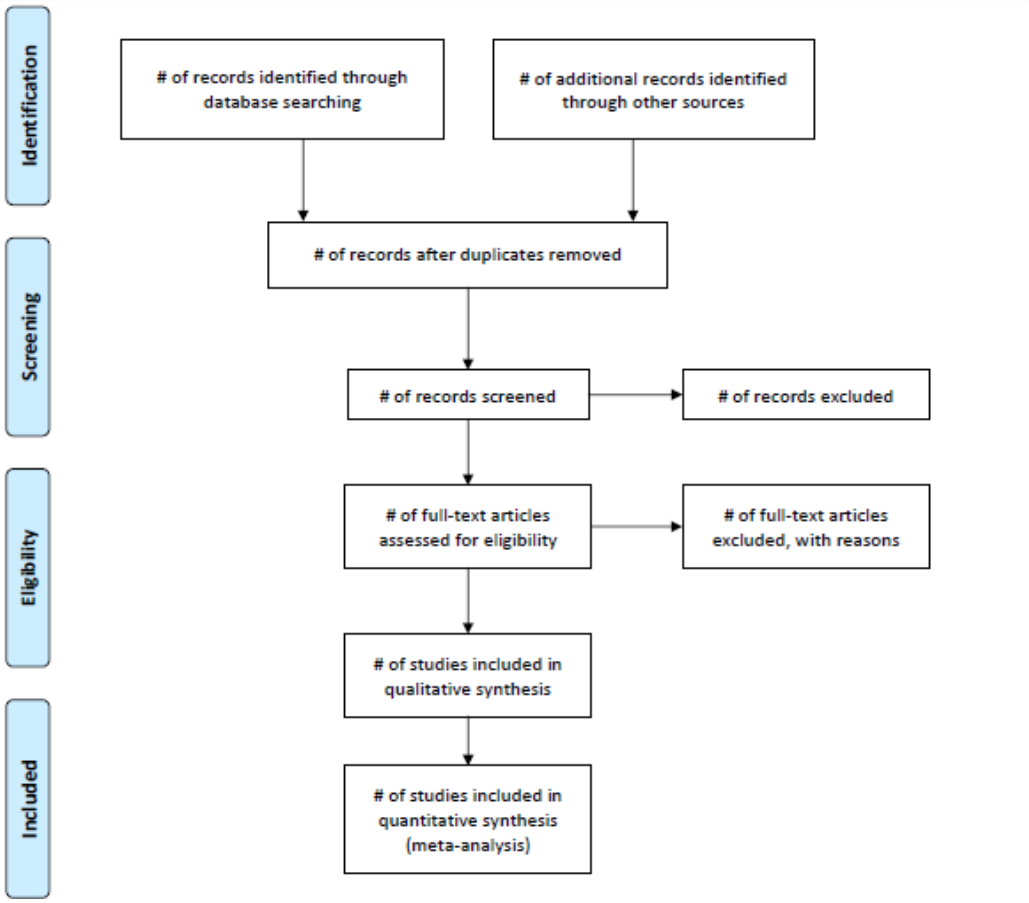


Figure 3 WP1: Methods and results based on PRISMA flow diagram

3.3. Step 3: selecting studies for inclusion or exclusion

Once searching was complete, relevant studies were efficiently assessed for inclusion against criteria that were defined a priori in the protocol (see Step 1, Section 3.1). For studies retrieved from electronic databases, the selection process was conducted in two stages:

1. screening of titles and abstracts for relevance to the study question;
2. examining full-text reports for the eligibility of studies.

The independent assessment by two reviewers (at all stages of the selection process) reduced the introduction of errors and personal biases. The study selection process was reported using a flow chart (see Figure 3 WP1, according to Liberati *et al.*, 2009 and Moher *et al.*, 2009). A list of studies excluded from the review, based on screening the full text, was reported and the reasons for exclusion were given. Each stage of the study selection process was documented, in order to make it assessable and reproducible. The following information was reported:

- the number of removed duplicates;
- the number of studies screened by titles and abstracts;
- a list of excluded studies, screened by titles and abstracts;
- the number of full-text screened studies;
- the number of full-text studies included;
- the number of full-text studies excluded;
- a list of excluded studies screened by full text (including the reason for exclusion for each study).

3.4. Step 4: collecting data from the included studies and creating evidence tables

The guiding principle for data collection was to determine study findings and to report study characteristics that influence the external applicability, internal validity and relevance of the findings. Details of any tools for recording the data (e.g. data forms and software) and the procedure for data collection, including the number of reviewers, were reported. The systematic collection of data from each primary research study had a key role in ensuring the reproducibility of the *E. multilocularis* systematic reviews. The data collection requirements were tailored to the review questions and the planned analyses were specified a priori in the review protocol (Step 1). The data collection step in the systematic review forms the basis of the research synthesis methods.

3.5. Step 5: assessing the methodological quality of included studies

The methodological quality assessment of each included study was critically appraised (La Torre *et al.*, 2006). In these systematic reviews, each study underwent a standardised assessment, checking whether or not it met a pre-defined list of methodological characteristics, in order to assess the degree to which it is susceptible to bias. The common types of bias (selection, performance, detection, attrition and reporting) that can occur in many different study designs was evaluated. The assessment of methodological quality involved using tools (i.e. checklists) to identify those aspects of study design, execution or analysis that induce a possible risk of bias. Quality assessment was performed using the following different methodological approaches, depending on study design:

- Jadad Score and Cochrane Collaboration's tool for assessing risk of bias was applied for randomised clinical trials (Jadad *et al.,* 1996; Higgins *et al.,* 2011).

- The Newcastle–Ottawa Scale (NOS) was adopted for observational studies: cohort, case–control and cross-sectional studies (Wells *et al.,* 2014.).

- The QUADAS-2 tool was applied for diagnostic studies (Whiting *et al.*, 2011). It consists of four key domains: patient selection, index test, reference standard and flow and timing, each of which is assessed in terms of risk of bias and the first three in terms of concerns regarding applicability.

The assessments of quality were performed by two researchers independently. After the assessment of the first studies, these scales could be refined.

3.6. Step 6: presenting the data and results

Three main types of information were presented in the results section of these systematic reviews:

1. the characteristics of the primary studies that are included in the systematic review, which vary according to the protocol being considered;

2. the data that the consortium collected from the primary studies to analyse;

3. the results of analyses carried out on those data by the consortium.

This information was considered important for assisting with interpretation and ensuring the transparency of the process. The information was presented in tabular form. The results section of this systematic review provides a narrative statement of the results.

3.7. Step 7: interpreting the results and drawing conclusions

The following issues were addressed in the conclusions section of these systematic reviews:

1. the quantity of evidence related to the total number of papers screened and included, and the quantity of evidence related to the sample size of these studies;

2. the quality of the evidence, which includes an assessment of the quality of the body of evidence for each individual outcome, involving considerations of study methodological quality, heterogeneity, precision of parameter or effect estimates, and risks of bias;

3. the interpretation of the results, which includes the interpretation of both the statistical significance and the biological significance of the finding;;

4. any potential limitations to the review process;

5. agreements or disagreements with other studies or reviews.

The conclusions are clearly worded, based on the evidence reviewed, and provide a focused answer to the questions asked for these systematic reviews. Specific gaps in the evidence were highlighted and recommendations for further research were included. Where possible, research recommendations were listed in order of priority, with an explanation. The reports of EM systematic reviews were structured in accordance with the PRISMA statement (see Figure 3 WP1).

RESULTS

Bibliographic searches carried out using six databases (MEDLINE, EMBASE, SciSearch, BIOSIS, CABI and Google Scholar) through the platform STN International identified 10 737 scientific papers, of which 5 316 were deleted because they were duplicates. At the end of the search, 5 421 papers were identified within the eight protocols, of which 4 569 were excluded as result of only title and abstract screening. A total of 813 full-text papers were assessed for eligibility, data were extracted from 443 studies and it was possible to perform meta-analyses on 362 studies. Studies deemed to be relevant to more than one question were independently analysed in each systematic review. For each protocol, paper identifications are as follow:

4. Work Package 2: epidemiology

4.1. EFSA requests 2 and 4: a systematic review on the geographical distribution and prevalence of *Echinococcus multilocularis* infection in animals and the importance of the different host species in the life cycle of this parasite in the EU and adjacent countries

Studies on the distribution of EM have shown the presence of the parasite in defined areas of the EU and ACs. Nevertheless, a full assessment of the current epidemiological situation of EM in the EU and ACs has not been performed to date. This systematic review gives an overview of scientific and grey literature on the distribution and prevalence (if available) of EM in the EU and ACs. With this information, tables showing the presence/absence, or the lack of reliable reports, were compiled.

4.1.1. Aim

The objectives of this systematic review were to determine the known wild and domestic definitive and intermediate hosts of EM, and the geographical distribution of this parasite. When available, data on presence/absence, prevalence and worm burden of EM in the EU and ACs are given. The importance of the different definitive and intermediate host species in the life cycle of EM in different parts of the EU and ACs was assessed.

4.1.2. Search

Databases were searched using keywords associated with the Boolean operators "AND" and "OR". The question mark ("?") was used to expand searches by looking for words with similar prefixes using more than one letter (i.e. "echinococc?" was used to search for "echinococcus", "echinococci", "echinococcosis" and "echinococcoses"). The hash mark ("#") was used to expand searches by looking for words with similar prefixes using one letter (i.e. dog# was used to search for "dog" or "dogs").

Different combinations were tailored for each electronic database in order to narrow the amount of results retrieved but, at the same time, to maximise the number of relevant studies.

The full electronic search strategy, including any limits used, was:

[ECHINOCOCCUS MULTILOCULARIS OR (ECHINOCOCOCCUS AND MULTILOCULARIS) OR E# MULTILOCULARIS OR ALVEOLAR ECHINOCOCCOSIS OR A# ECHINOCOCCOSIS] AND (DOG OR DOGS OR CAT OR CATS OR CANIS OR FELIS OR CANID? OR FELID? OR WOLF OR WOLVES OR ANIMAL OR ANIMALS OR FOX OR FOXES OR VULPES OR FERRET OR FERRETS OR RODENTI OR RODENTS OR RODENTIA OR NUTRIA# OR MUSKRAT# OR JACKAL# OR ARVICOLID? OR ARVICOLINAE OR WORM BURDEN OR HOST OR HOSTS OR HOSTED) AND (OCCURRENCE# OR GEOGRAPHIC? DISTRIBUT? OR

GEOGRAPHIC? DIFFUS? OR INCIDENCE# OR FREQUENCY OR EPIDEMIC OUTBREAK# OR ENDEMIC OUTBREAK# OR PREVALENCE# OR EPIDEMIOLOGY).

A search using the STN International platform was carried out on 5 November 2013. An additional search was performed on 11 February 2015 to identify any papers that had been published since the initial search. The results of these two searches were combined. If database outcomes overlapped, all duplicated articles were removed. Review Manager (RevMan) software was used to prepare and maintain this systematic review.

4.1.3. Study selection

The inclusion criteria were as follows:

- studies published from 1900 to present;
- studies published in English, German, French, Polish, Finnish, Dutch, Spanish or Italian;
- studies based on cross-sectional design or cohort studies;
- primary research studies published or in press;
- reports on wild or domestic EM hosts.

The list of included articles are available in Appendix I WP2-R2,4: *List of included studies*.

The exclusion criteria were as follows:

- studies providing data from outside Europe (EU and AC);
- case reports;
- reports on EM in humans;
- studies on agents other than EM (e.g. *E. granulosus*);
- reviews, letters or editorials without original data;
- duplicated data;
- articles with full texts written in languages other than those that at least one member of the team can read and understand (i.e. English, German, French, Polish, Finnish, Dutch, Spanish and Italian).

The list of excluded articles are available in Appendix II WP2-R2,4: *List of exncluded studies*.

Studies included in the meta-analyses met the following criteria:

- studies with the presence of prevalence data (total number of studied animals and number of positive animals);
- studies with a definition of a geographical area (whenever possible using NUTS 1, 2 and 3 codes);

- studies including different geographical areas were divided into sub-studies and each sub-study was evaluated independently;

- if the same samples were analysed with different diagnostic methods, data coming from the sedimentation and counting technique (SCT), intestinal scraping technique (IST) or similar were taken into account;

- if the same study was conducted in the same geographical area but in different periods (e.g. in different years or months), the study was divided into sub-studies and each sub-study was evaluated independently.

Studies excluded from the meta-analyses were as follows:

- studies in which it was not possible to disaggregate data per nation.

The study selection process concerning the WP2 is reported using the flow chart showed in Fig 1 WP2.

4.1.4. Data extraction

Data were extracted by completing the fields of a data extraction form).

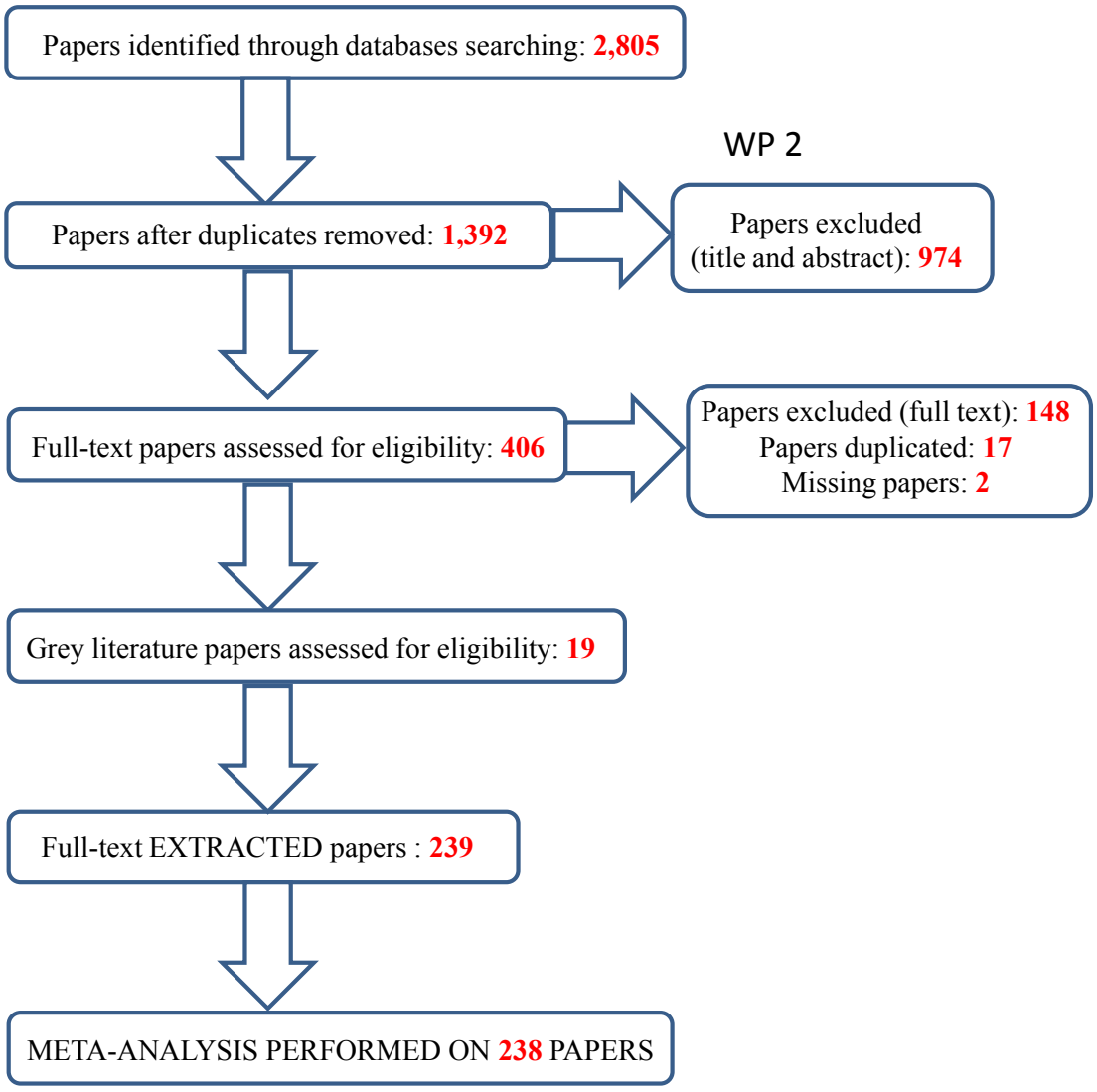


Figure 1 WP2: Flow chart of selection of the studies

4.1.5. Statistical approach and meta-analysis

Statistical analyses were conducted using the statistical software Stats Direct 2.8.0 (StatsDirect Ltd., Altrincham, UK).

The animal species were divided into two main groups: DHs and IHs.

The DHs were:

- red fox (*Vulpes vulpes*)
- Arctic fox (*Vulpes lagopus*)
- dog (*Canis lupus f. familiaris*)
- raccoon dog (*Nyctereutes procyonoides*)

- wild canids (wolf (*Canis lupus*) and golden jackal (*Canis aureus*))
- cat (*Felis silvestris f. catus*).

The IHs were:

- arvicolid rodents (including *Arvicola* spp., *Clethrionomys*[=*Myodes*] *glareolus* and *Microtus* spp.)
- murid rodents (including *Apodemus* spp., *Micromys minutus*, *Mus musculus* and *Rattus* spp.)
- mustelids (including *Mustela* spp., *Neovison vison*, *Lutra lutra*, *Meles meles* and *Martes* spp.)
- insectivores (including *Sorex* spp., *Talpa europea*, *Neomys fodiens* and *Erinaceus europaeus*)
- muskrat (*Ondatra zibethicus*), which is an arvicolid rodent but is treated separately
- nutria or coypu (*Myocastor coypus*)
- swine (domestic and wild pigs (*Sus scrofa f. domesticus* and *Sus scrofa*)).

The meta-analyses were performed both on definitive and intermediate hosts according to the classification described above.

Each meta-analysis group included studies conducted in the same geographical area: Europe, countries and three NUTS levels.

With regard to the DHs, studies containing prevalence data obtained exclusively by enzyme-linked immunosorbent assays (ELISAs) designed to detect pathogen-specific copro-antigens (copro-antigen ELISAs) were subsequently excluded from meta-analysis because of the low specificity of this test. All included studies were cross-sectional; therefore, meta-analyses on proportions were performed.

The pooled prevalence of EM infection among species was calculated considering all studies included in the review and after stratifying by different countries and NUTS levels.

The Cochran's Q test was performed to assess the degree of heterogeneity between studies, and the I^2 statistic was used to describe the percentage of total variation across studies as a result of heterogeneity. If the p-value from this Q test was < 0.05 and I^2 was > 50 %, heterogeneity was found and a random-effect model is shown. However, if heterogeneity was not found, a fixed-effect model is reported.

A forest plot was produced to describe the pooled analysis; this shows the single proportions of the studies and the pooled proportion with relative 95 % confidence intervals (CIs).

Publication bias was quantified by inspection of funnel plots and computation of Egger and Begg test probability values. When the meta-analysis included a low number of studies, it was not possible to assess publication bias by inspection of funnel plots.

4.1.6. Limits of the analysis

The meta-analyses were not stratified for the years/months in which the studies were conducted. The reason for this was that, because of other stratifications, little data were left to be stratified.

4.1.7. Quality assessment

The quality of all the included studies was assessed by two researchers using the NOS (Wells *et al.*, 2014). It should be noted that the quality assessment could not be performed on "grey literature".

4.1.8. Synthesis of results and discussion

4.1.8.1. EFSA request 2: the geographical distribution and the prevalence of EM infection in animals, including wildlife and domestic species, that can act as definitive and intermediate hosts

Gaps were found in the literature regarding the following aspects directly related to this request: (i) NUTS level specifications beyond the national level were absent in many reports, making it difficult to localise infection foci within specific areas of each country; (ii) many EU countries and ACs (n = 18) had no data on EM prevalence in definitive or intermediate hosts, even in cases where EM infection was probable because the parasite had been found in surrounding countries; (iii) data on the prevalence of the parasite in DHs, apart from red foxes, and in some IHs were scarce and often reported in only one study; (iv) the number of screened animals was considered insufficient in reports in which the prevalence rates found were low; and (v) publication bias (there may be unpublished studies about the absence of EM within the EU and/or ACs).

In the following sections, the pooled prevalence rates of EM for each country, found in different DHs and IHs, are shown.

Prevalence in definitive hosts

For a better interpretation of the results, the geographical distribution and prevalence values in red foxes from each country are synthesised in Table 1 WP2 (which includes data obtained before 2000) and Table 2 WP2 (which includes data obtained after 2000). Any studies beginning before 2000 and finishing in 2000 were included in Table 1 WP2, and studies beginning before 2000 and finishing after 2000 were included in Table 2 WP2. Geographical distribution and prevalence values for other screened DHs are shown in a dedicated table (Table 4 WP2).

Table 1 WP2: Pooled EM prevalence rates of EM in red foxes before 2000

Country	No of studies included	Pooled prevalence (%)	95 % CI (%)	Time range of studies (years)	NUTS	No of studies without NUTS (only country in general)
Austria	6	8.0	2–17	1989–2000	AT22, AT34	3 (AT)
Belgium	7	13.5	3.6–28.4	1993–2000	BE2, BE3, BE34	0
Czech Republic	7	12.7	6.1–21.2	1994–1999	CZ010, CZ031, CZ032	3 (CZ)
France	18	23	16.0–30.0	1968–2000	FR411–414, FR42, FR421, FR43, FR718, FR722, FR72	1 (FR)
Germany	253	13.8	12.3–15.3	1973–2000	DE1, DE11, DE111–119,	4 (DE)

Country	No of studies included	Pooled prevalence (%)	95 % CI (%)	Time range of studies (years)	NUTS	No of studies without NUTS (only country in general)
					DE11A–11D, DE12, DE121–129, DE12A–12C, DE131–139, DE13A, DE14, DE141–149, DE2, DE21D, DE21L, DE300, DE4, DE41, DE6, DE7, DE72, DE9, DE91, DE911, DE913–919, DE91A, DE922–923, DE925–929, DE931–939, DE93A–93B, DE941–949, DE94A–94H, DEA, DEB, DEB12–B19, DEB1A–1B, DEB22–25, DEB34–35, DEB37, DEB3B–DEB3F, DEB3H, DEB3J, DEC, DEC0, DEE, DEF0, DEG, DEG0, DEG04, DEG0B, DEG0E–G0F, DEG0H, DEG0P	
Italy	1	0.55 [(a)]	NA	1997–2000	ITD	0

Country	No of studies included	Pooled prevalence (%)	95 % CI (%)	Time range of studies (years)	NUTS	No of studies without NUTS (only country in general)
Netherlands	3	4.0	2.0–6.0	1995–2000	NL11, NL42	1 (NL)
Poland	33	2.0	1.3–3.0	1994–2000	PL11–12, PL21–22, PL31–32, PL323–324, PL34, PL41, PL411, PL418, PL42, PL421–422, PL425, PL43, PL431–432, PL5, PL51, PL516, PL52, PL61–63	1 (PL)
Romania	2	0	0	1981–1992	RO123	0
Slovakia	3	23.3	3.9–52.2	1998–2000	SK0	0
Lichtenstein	1	34.9 [a]	NA	1990–1992	LI000	0
Norway	2	0	NA	1988–1989	–	2 (NO)
Switzerland	45	26.8	23.0–30.7	1988–2000	CH011–012, CH02, CH021–025, CH031–033, CH040, CH051–057, CH063, CH070,	0
Bulgaria	No data	No data	No data	No data	No data	No data
Croatia	No data	No data	No data	No data	No data	No data
Cyprus	No data	No data	No data	No data	No data	No data
Denmark	No data	No data	No data	No data	No data	No data
Finland	No data	No data	No data	No data	No data	No data
Greece	No data	No data	No data	No data	No data	No data
Hungary	No data	No data	No data	No data	No data	No data
Ireland	No data	No data	No data	No data	No data	No data
Latvia	No data	No data	No data	No data	No data	No data
Lithuania	No data	No data	No data	No data	No data	No data
Luxembourg	No data	No data	No data	No data	No data	No data
Malta	No data	No data	No data	No data	No data	No data
Portugal	No data	No data	No data	No data	No data	No data
Slovenia	No data	No data	No data	No data	No data	No data
Spain	No data	No data	No data	No data	No data	No data
Sweden	No data	No data	No data	No data	No data	No data
United Kingdom	No data	No data	No data	No data	No data	No data

Country	No of studies included	Pooled prevalence (%)	95 % CI (%)	Time range of studies (years)	NUTS	No of studies without NUTS (only country in general)
Albania	No data	No data	No data	No data	No data	No data
Belarus	No data	No data	No data	No data	No data	No data
Bosnia and Herzegovina	No data	No data	No data	No data	No data	No data
Iceland	No data	No data	No data	No data	No data	No data
Kosovo	No data	No data	No data	No data	No data	No data
Moldova	No data	No data	No data	No data	No data	No data
Montenegro	No data	No data	No data	No data	No data	No data
Former Yugoslav Republic of Macedonia	No data	No data	No data	No data	No data	No data
Russia	No data	No data	No data	No data	No data	No data
Serbia	No data	No data	No data	No data	No data	No data
Turkey	No data	No data	No data	No data	No data	No data
Ukraine	No data	No data	No data	No data	No data	No data

(a): Prevalence reported in a single study (not pooled).
NA, not applicable.

Table 2 WP2: Pooled EM prevalence rates of EM in red foxes after 2000

Country	No of studies included	Pooled prevalence (%)	95 % CI (%)	Time range of studies (years)	NUTS	No of studies without NUTS (only country in general)
Austria	6	6.5	4.3–9.1	2000–2005	AT12, AT130	4 (AT)
Belgium	10	8.0	3.0–16.0	2000–2012	BE10, BE3, BE34	3 (BE)
Croatia	1	0 [(a)]	NA	2013	–	1
Czech Republic	3	16.0	4.0–35.0	2005–2010	–	3 (CZ)
Denmark	6	0.5	0.2–0.8	2000–2013	DK0, DK01	3 (DK)
Estonia	4	24.5	13.0–38.2	2003–2014	EE00	0
Finland	8	0	0	2000–2013	–	8 (FI)
France	54	13.9	9.8–18.6	2000–2010	FR102, FR104, FR106, FR108, FR211–214, FR221–223, FR231, FR241–243, FR245–246, FR251–253, FR261–264, FR301–302, FR411–414, FR431–434, FR6, FR711, FR714–718, FR722	7 (FR)

Country	No of studies included	Pooled prevalence (%)	95 % CI (%)	Time range of studies (years)	NUTS	No of studies without NUTS (only country in general)
Germany	41	29.2	26.0–32.4	2000–2012	DE111, DE134, DE21, DE212, DE21D–21E, DE21L, DE27E, DE7, DE9, DEA2, DEE, DEE0, DEG	9 (DE)
Hungary	42	8.0	5.6–10.7	2008–2013	HU10, HU211–213, HU221–223, HU231–233, HU31, HU311–313, HU321–323, HU331–333	3 (HU)
Ireland	7	0	0	2003–2013	IE0	0
Italy	25	1.5	0.5–2.9	2000–2012	ITC20, ITC31–32, ITC4, ITC46, ITD, ITD10, ITD20, ITD33, ITE, ITE1	1 (IT)
Latvia	14	36.8	22.2–52.9	2002–2008	LV003, LV005, LV007, LV008, LV009	0
Lithuania	2	58.0	54.0–62.0	2001–2006	LT00	0
Luxembourg	9	16.7	9.4–25.6	2005–2012	–	9 (LU)
Netherlands	11	4.7	1.9–9.0	2000–2013	NL11, NL42	7 (NL)

Country	No of studies included	Pooled prevalence (%)	95 % CI (%)	Time range of studies (years)	NUTS	No of studies without NUTS (only country in general)
Poland	36	14.8	9.6–20.8	2000–2014	PL1, PL11–12, PL21–22, PL3, PL31–34, PL323–324, PL42–43, PL51–52, PL61–63	4 (PL)
Romania	30	4.5	2.9–6.4	2000–2010	RO111–116, RO121–126, RO421, RO423–424	0
Slovakia	61	27.3	24.4–30.3	2000–2013	SK0, SK010, SK021–023, SK031–032, SK041–042	0
Slovenia	2	0.9	0.2–5.3	2002–2005	SI0	0
Spain	1	0 [(a)]	NA	2012	–	1
Sweden	10	0.2	0.1–0.3	2000–2012	–	10 (SE)
United Kingdom	8	0	0	2000–2014	UKC, UKN	6 (UK) (without North Ireland)
Norway	29	0	0	2000–2014	NO0, NO011–012, NO021–022, NO031–034, NO041–043, NO051–053, NO061–062, NO071–073	10 (NO)
Switzerland	13	17.0	6.1–31.9	2000–2003	CH013, CH040, CH056	9 (CH)
Ukraine	4	2.8	6.0–12.0	2000–2010	–	4 (UA)
Bulgaria	No data	No data	No data	No data	No data	No data

Country	No of studies included	Pooled prevalence (%)	95 % CI (%)	Time range of studies (years)	NUTS	No of studies without NUTS (only country in general)
Cyprus	No data	No data	No data	No data	No data	No data
Greece	No data	No data	No data	No data	No data	No data
Malta	No data	No data	No data	No data	No data	No data
Portugal	No data	No data	No data	No data	No data	No data
Albania	No data	No data	No data	No data	No data	No data
Belarus	No data	No data	No data	No data	No data	No data
Bosnia and Herzegovina	No data	No data	No data	No data	No data	No data
Iceland	No data	No data	No data	No data	No data	No data
Kosovo	No data	No data	No data	No data	No data	No data
Moldova	No data	No data	No data	No data	No data	No data
Montenegro	No data	No data	No data	No data	No data	No data
Macedonia	No data	No data	No data	No data	No data	No data
Russia	No data	No data	No data	No data	No data	No data
Serbia	No data	No data	No data	No data	No data	No data
Turkey	No data	No data	No data	No data	No data	No data

(a): Prevalence reported in a single study (not pooled).
NA, not applicable.

Four countries reported the absence of EM in red foxes: Finland, Ireland, the UK and Norway. For Norway, screening in Arctic foxes showed the presence of EM in only the Arctic archipelago of Svalbard.

Twenty countries reported the presence of EM in red foxes. A preliminary rank of those countries groups the different countries as follows:

- low prevalence (pooled prevalence of ≤ 1 %) in Denmark, Slovenia and Sweden;
- medium prevalence (pooled prevalence of > 1 % but ≤ 10 %) in Austria, Belgium, Hungary, Italy, the Netherlands, Romania and Ukraine;
- high prevalence (pooled prevalence of > 10 %) in the Czech Republic, Estonia, France, Germany, Latvia, Lithuania, Poland, Slovakia, Lichtenstein and Switzerland.

Specific gaps in the assessment of the prevalence rates of EM in red foxes are that (i) the vast majority of studies are concentrated in six countries (Germany, France, Slovakia, Switzerland, Poland and Hungary (> 40 studies per country)), while for the other countries the pooled prevalence is based on few studies or, in three cases (Lichtenstein, Croatia and Spain), on single studies; (ii) sampling in some countries has been done in only specific areas in which it was known that prevalence rates would be high and thus extrapolation of data at national level could be biased; (iii) the presence of the parasite in red foxes cannot be excluded in countries where no data are available (n = 18) but this host is present; and (iv) bias may arise as a result of the sampling strategy used (sampling strategy data are summarised in the Table 3 WP2).

Table 3 WP2: Sampling strategy for red foxes and Arctic foxes (Svalbard Islands, Norway)

Country	Code	Sampling strategy			
		No papers rabies program	No papers hunted or shot	No papers convenience sampling or control programmes	No papers with data not reported
Austria	AT	0	5	1	10
Belgium	BE	0	9	1	1
Switzerland	CH	1	13	6	4
Czech Republic	CZ	2	3	1	4
Germany	DE	2	24	20	20
Denmark	DK	0	4	2	0
Estonia	EE	0	4	0	0
Spain	ES	0	0	1	0
Finland	FI	0	5	3	1
France	FR	0	15	4	8
Croatia	HR	0	0	1	0
Hungary	HU	3	2	2	1
Ireland	IE	1	2	1	2
Italy	IT	0	8	1	2
Lithuania	LI	0	3	0	0
Luxemburg	LU	0	0	3	6
Latvia	LV	1	0	0	0
Netherlands	NL	0	8	1	4
Norway	NO	0	6	5	1
Norway (Arctic fox)	NO	0	0	3	0
Poland	PL	1	16	3	1
Romania	RO	0	3	0	1
Sweden	SE	0	3	4	2
Slovenia	SI	1	2	0	0
Slovakia	SK	2	9	5	4
United Kingdom	UK	2	4	0	3
Ukraine	UA	0	1	0	1
Total (309)	TOT	16	149	68	76

Approximately half of the analysed papers (149/309) describe studies in which foxes were hunted or shot, revealing bias related to the sampling strategy. In 16 additional papers, foxes were obtained as a result of rabies programmes, probably mainly by shooting. It should be taken into account that this kind of sampling strategy can cause bias with regard to restrictions in the places of sampling, since hunting is, generally, conducted in areas distant from human living nuclei. Therefore, in more than half of the prevalence studies, synanthropic fox populations living in villages, towns or cities are not included in the sampled animals.

A map (Figure 2 WP2) of the presence and pooled prevalence of EM in foxes in the EU and ACs is shown below. As shown, the highest prevalence rates of EM in red foxes seem to be concentrated in central and north-eastern Europe.

A more detailed map (Figure 3 WP2) shows the geographical distribution and pooled prevalence of EM in red foxes at NUTS 1 level.

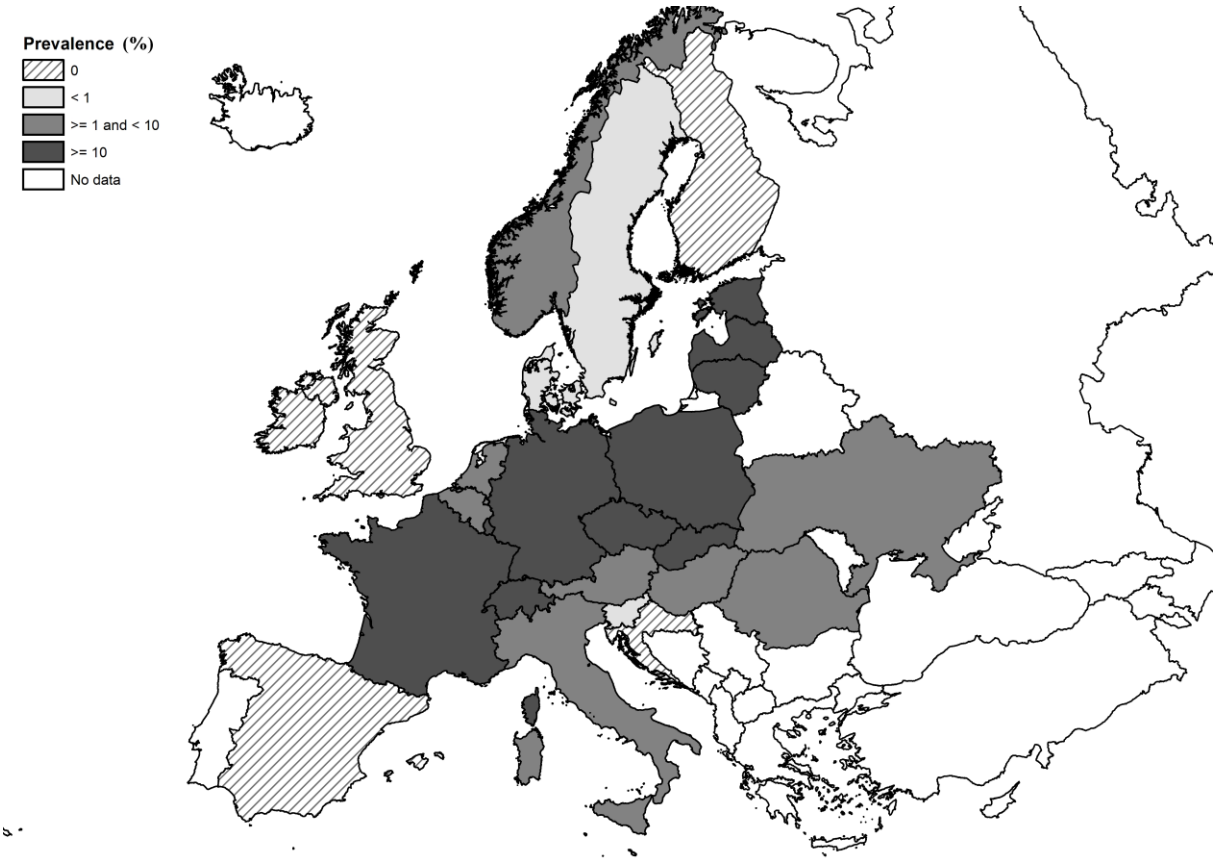


Figure 2 WP2: Pooled prevalence of EM in red and Arctic foxes in the EU and ACs at national level (data obtained from studies after 2000). Note: the pooled prevalence data for Norway originated from only Arctic foxes on the Svalbard islands; prevalence data from Spain and Croatia originated from single studies

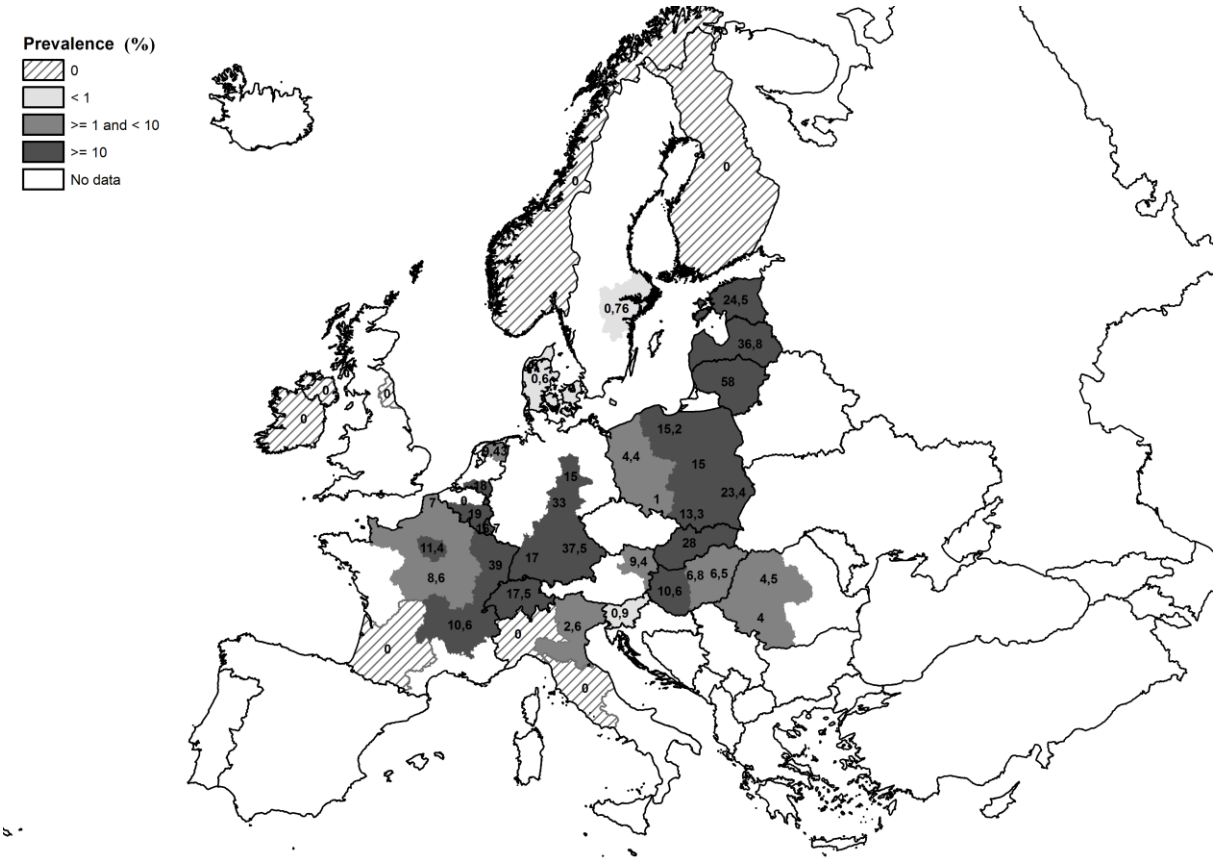


Figure 3 WP2: Pooled prevalence of EM in red foxes in the EU and ACs at NUTS 1 level (data obtained from studies after 2000). Note: prevalence data from NL1 (Netherlands) and SE1 (Sweden) originated from single studies; only studies reporting NUTS information were taken into account

In the following sections, detailed information about the geographical distribution and the prevalence of EM in DHs other than red foxes are reported for each country (see Table 4 WP2).

Table 4 WP2: Pooled prevalence rates of EM in raccoon dogs, other wild canids (golden jackal and wolf), cats and dogs

Country	Host	No of studies included	Pooled prevalence (%)	95 % CI (%)	Time range of studies (years)	NUTS	No of studies without NUTS (only country)
Austria	Cat	1	0 [(a)]	NA	2004–2005	–	1
	Dog	1	0 [(a)]	NA	2004–2005	–	1
Cyprus	Dog	1	0 [(a)]	NA	2012	–	1
Czech Republic	Cat	2	50	8.0–92.0	1997–2004	CZ032	0
	Dog	1	1.8 [(a))]	NA	1998	CZ032	0

Country	Host	No of studies included	Pooled prevalence (%)	95 % CI (%)	Time range of studies (years)	NUTS	No of studies without NUTS (only country)
Denmark	Raccoon dog	4	0	0	2011–2013	DK032, DK0	0
	Cat	1	0.6 [(a)]	NA	2004–2005	DK0	0
	Dog	1	0 [(a)]	NA	2004–2005	DK0	0
	Wild canids	1	0 [(a)]	NA	2012	–	1
Estonia	Raccoon dog	1	1.6 [(a)]	NA	2012	–	1
Finland	Raccoon dog	4	0	0	2012	FI1	3
	Dog	1	0 [(a)]	NA	2012	–	1
	Wild canids	2	0	0	2013	–	2
France	Cat	3	1.5	0.2–7.9	1989–2012	FR71	1
	Dog	8	0.4	0.1–0.9	1988–2013	FR7, FR433, FR722	1
Germany	Raccoon dog	4	2.5	0.1–7.9	1998–2008	DE41, DE4	0
	Cat	14	0.6	0.3–1.0	1973–2005	DE13, DE14, DE144, DE41, DEG0, DE1, DE4, DEB	3
	Dog	6	0.3	0.2–0.3	1973–2012	DE1, DE4, DE40	1
Hungary	Wild canids	2	4.7	0.1–15.3	2007–2013	–	2
Italy	Cat	1	0 [(a)]	NA	2004–2005	–	1
	Dog	2	0	0	2004–2012	–	2
Latvia	Raccoon dog	1	21 [(a)]	NA	2002–2008	LV0	0
	Wild canids	1	5.9 [(a)]	NA	2003–2008	LV00	0
Lithuania	Raccoon dog	1	8.2 [(a)]	3.4–16.2	2001–2006	LT00	0
	Dog	1	0.8 [(a)]	NA	2005–2006	LT0	0
Luxembourg	Cat	1	0 [(a)]	NA	2004–2005	–	1
	Dog	1	0 [(a)]	NA	2004–2005	–	1
Malta	Dog	2	0	0	2012–2013	–	2

Country	Host	No of studies included	Pooled prevalence (%)	95 % CI (%)	Time range of studies (years)	NUTS	No of studies without NUTS (only country)
Netherlands	Raccoon dog	1	0 [(a)]	NA	2012	–	1
	Dog	2	0	0	2004–2013	–	1
	Cat	1	0.3 [(a)]	NA	2004–2005	–	1
Poland	Raccoon dog	3	10.4	4.1–19.3	NR	–	1
	Cat	2	0	0	NR	–	1
	Dog	2	0	0	NR	–	1
Slovakia	Raccoon dog	3	28.0	4.0–64.0	2002–2007	SK0	0
	Cat	3	0	0	2002–2012	SK0	0
	Dog	5	0.4	0.1–1.3	2002–2012	SK0, SK04	0
	Wild canids	1	0 [(a)]	NA	2013	–	1
Sweden	Raccoon dog	1	0 [(a)]	NA	2000–2009	–	1
	Dog	2	0	0	2012–2013	–	2
	Wild canids	2	0	0	2012–2013	–	2
United Kingdom	Cat	1	0 [(a)]	NA	2004–2005	–	1
	Dog	1	0 [(a)]	NA	2004–2005	–	1
Norway	Arctic fox	2	5.8	3.9–8.2	1996–2004	NO0	0
Switzerland	Cat	2	4.6	0.3–13.6	1999–2012	CH022	0
	Dog	7	1.2	0.1–3.4	1996–2013	CH02, CH022, CH040	0
Ukraine	Raccoon dog	1	0 [(a)]	NA	1998–2010	–	1
	Wild canids	1	0 [(a)]	NA	1998–2010	–	1
Belgium		0	No data	No data	No data	No data	No data
Bulgaria		0	No data	No data	No data	No data	No data
Croatia		0	No data	No data	No data	No data	No data
Greece		0	No data	No data	No data	No data	No data
Ireland		0	No data	No data	No data	No data	No data
Portugal		0	No data	No data	No data	No data	No data
Romania		0	No data	No data	No data	No data	No data
Slovenia		0	No data	No data	No data	No data	No data
Spain		0	No data	No data	No data	No data	No data
Albania		0	No data	No data	No data	No data	No data
Belarus		0	No data	No data	No data	No data	No data
Bosnia and Herzegovina		0	No data	No data	No data	No data	No data

Country	Host	No of studies included	Pooled prevalence (%)	95 % CI (%)	Time range of studies (years)	NUTS	No of studies without NUTS (only country)
Macedonia		0	No data	No data	No data	No data	No data
Iceland		0	No data	No data	No data	No data	No data
Kosovo		0	No data	No data	No data	No data	No data
Moldova		0	No data	No data	No data	No data	No data
Montenegro		0	No data	No data	No data	No data	No data
Russia		0	No data	No data	No data	No data	No data
Serbia		0	No data	No data	No data	No data	No data
Turkey		0	No data	No data	No data	No data	No data

(a): Prevalence coming from only one study, not pooled prevalence.
NA, not applicable.
NR, not reported.

Five different potential DHs for EM, other than red foxes, have been screened in the studied literature: three wild animal species (raccoon dogs and the wild canids golden jackal and wolf) and two domestic animal species (cats and dogs).

The specific gaps found in these data are that (i) the number of studies is very low for the five DHs; (ii) some of the DHs are geographically restricted (e.g. Arctic fox are restricted to northern latitudes and golden jackal are found in only a few countries); (iii) some of the DHs are not found on islands (e.g. raccoon dogs); and (iv) some of the DHs are protected species (e.g. wolf) and are thus not suitable for large screenings.

The pooled results show that sylvatic animals, not including red foxes, are more frequently infected than domestic animals (e.g. dogs and cats). This should be taken into account when doing epidemiological studies in areas where no prevalence or low to medium prevalence is expected; in these areas, if red foxes cannot be screened, sylvatic animals should, preferably, be screened if the aim of the epidemiological study is to demonstrate the absence or presence of EM.

Two species showing high prevalence rates are "alien" introductions in the EU and ACs: raccoon dog and golden jackal, although the latter is native to the south-eastern part of the EU and ACs. Importantly, raccoon dog is currently not established in some areas that are free of EM (e.g. the UK, Ireland and Malta), but it is present in high numbers in Finland. A third species with high prevalence rates, the Arctic fox, is present in only a few northern countries, namely northern Russia, Iceland, and the Norwegian Arctic archipelago of Svalbard, and there is also a small population on the Scandinavian peninsula.

In general, high prevalence rates of EM in the two alien species mentioned above correlate with high rates of infection in foxes.

Cats and dogs do not seem to be important in terms of prevalence and are found to be infected in only some areas with high pooled prevalence rates of EM in red foxes; however, dogs can be regarded as potentially relevant hosts with regard to EM introduction into areas that are free of the parasite by travelling from endemic to distant (non-endemic) areas with their owners, and also with regard to transmission to humans in endemic areas because of their closer contact with humans than sylvatic DHs.

In the following section, the detailed information about the geographical distribution and the prevalence of EM in different IHs are reported for each country (see Table 5 WP2).

Table 5 WP2: Pooled prevalence rates of EM in arvicolids, muskrat, nutria, swine (domestic and wild), Insectivora, Muridae rodents and Mustelidae

Country	Host	No of studies included	Pooled prevalence (%)	95 % CI (%)	Time range of studies (years)	NUTS	No of studies without NUTS (only country)
Belgium	Arvicolids	4	0.2	0.0–0.6	2003–2004	BE22	0
	Muskrat	2	16.0	7.0–28.0	2003–2006	BE3	0
	Insectivores	1	0 [(a)]	0	2003–2004	BE22	0
	Murids	1	0 [(a)]	0	2003–2004	BE22	0
Czech Republic	Arvicolids	5	1.3	0.1–3.7	1997	CZ032	0
	Insectivores	4	0	0	1997	CZ032	0
	Murids	3	0	0	1997	CZ032	0
	Mustelids	3	0	0	1997–1999	CZ032	0
Denmark	Mustelids	2	0	0	2012–2013	–	2
Finland	Arvicolids	3	0	0	2000–2012	–	1
	Swine	2	0	0	2000–2009	–	2
France	Arvicolids	37	4.8	1.6–9.7	1975–1995	FR7, FR41, FR43, FR72, FR431, FR432, FR631, FR722, FR724	2
	Muskrat	2	1.1	0.2–2.8	1985–2010	FR434	1
	Nutria	1	5.8 [(a)]	NA	2002–2003	–	1
	Insectivores	1	0 [(a)]	0	1999–2000	FR722	0
	Swine	2	0	0	2012–2013	–	1
Germany	Arvicolids	6	0.6	0.4–1.0	1979–1995	DE1, DE11A, DE141, DE143	0
	Muskrat	51	3.8	2.8–4.9	1974–2003	DE1, DE115, DE119,	0

Country	Host	No of studies included	Pooled prevalence (%)	95 % CI (%)	Time range of studies (years)	NUTS	No of studies without NUTS (only country)
						DE131–139, DE141–142, DE145–149, DE11A–11D DE12C, DE13A, DE9, DE915, DE916, DE918, DE919, DE926, DE932, DE935, DE942, DE947, DE949, DE93B, DE94C, DE94G, DE4A2, DE4A5, DEF	
	Nutria	1	0.4 [(a)]	NA	2010	DEA2	0
	Murids	3	0	0	1979–1986	DE11A	0
	Mustelids	14	0	0	1973–2012	DE1, DE4, DEB, DEF	3
Lithuania	Swine	1	0.4 [(a)]	NA	2005–2006	–	1
Luxembourg	Muskrat	1	1.8 [(a)]	NA	NR	–	1
Netherlands	Muskrat	1	0.06 [(a)]	NA	1998–1999	–	1
Poland	Arvicolids	7	0	0	2004–2006	PL12, PL21, PL32, PL34, PL62	0
	Insectivores	4	0	0	2004–2006	PL12, PL21, PL32, PL34, PL62	0
	Murids	8	0	0	NR	PL12,	1

Country	Host	No of studies included	Pooled prevalence (%)	95 % CI (%)	Time range of studies (years)	NUTS	No of studies without NUTS (only country)
	Mustelids	10	0	0	2004–2006	PL21, PL32, PL34, PL62 PL12, PL21, PL32, PL34, PL62	–
Romania	Arvicolids	2	1.4 [(a)]	0.2–3.8	1989–2010	RO123	1
	Swine	1	0 [(a)]	NA	1989	RO123	0
Sweden	Arvicolids	1	0 [(a)]	0	2011	SE23	0
Norway	Arvicolids	5	27.0	18.0–37.0	1999–2009	NO0	2
	Swine	1	0 [(a)]	0	2000–2013	NO0	1
Switzerland	Arvicolids	26	13.3	10.8–16.1	1993–2008	CH013, CH022, CH040	0
	Murids	3	0	0	1999–2002	CH031	0
	Swine	1	0 [(a)]	NA	2012	–	1
Bulgaria		No data	No data	No data	No data	No data	No data
Croatia		No data	No data	No data	No data	No data	No data
Cyprus		No data	No data	No data	No data	No data	No data
Ireland		No data	No data	No data	No data	No data	No data
Malta		No data	No data	No data	No data	No data	No data
Portugal		No data	No data	No data	No data	No data	No data
United Kingdom		No data	No data	No data	No data	No data	No data
Albania		No data	No data	No data	No data	No data	No data
Belarus		No data	No data	No data	No data	No data	No data
Bosnia and Herzegovina		No data	No data	No data	No data	No data	No data
Iceland		No data	No data	No data	No data	No data	No data
Kosovo		No data	No data	No data	No data	No data	No data
Moldova		No data	No data	No data	No data	No data	No data
Montenegro		No data	No data	No data	No data	No data	No data
Macedonia		No data	No data	No data	No data	No data	No data
Russia		No data	No data	No data	No data	No data	No data
Serbia		No data	No data	No data	No data	No data	No data
Turkey		No data	No data	No data	No data	No data	No data

(a): Prevalence coming from only one study, not pooled prevalence.
NA, not applicable.
NR, not reported.

The following potential IHs for EM have been screened in different countries: muskrat (*Ondatra zibethicus*), arvicolids (*Arvicola* spp., *Clethrionomys[=Myodes] glareolus* and *Microtus* spp.), nutria

(*Myocastor coypus*), murids (*Mus musculus*, *Rattus rattus*, *Rattus norvegicus* and *Apodemus* spp.), swine (domestic pig (*Sus scrofa f. domesticus*) and wild boar (*Sus scrofa*)), insectivores (*Sorex* spp., *Talpa europea* and *Neomys fodiens*) and mustelids (*Mustela* spp., *Martes* spp., *Lutra lutra* and *Meles meles*).

The specific gaps in these data are that (i) the number of studies is very low for all the IHs, excluding arvicolids and muskrat; and (ii) some of the IHs are geographically restricted.

The distribution of the prevalence rates of EM of defined IHs (muskrats and arvicolids) matches (although the prevalence is lower) the distribution of the prevalence rates of EM in red foxes for the majority of countries. These IHs show similar pooled prevalence rates for EM as sylvatic DHs, other than foxes, and are thus potentially good sentinels to check for the presence of the parasite in specific settings. Swine, insectivores and, especially, mustelids seem to play no role in the life cycle of the parasite. EM-positive swine were found in some regions (Germany and Lithuania); therefore, swine could be regarded as domestic IH sentinels. It should be mentioned that some data regarding the presence of EM in swine from EFSA reports (EFSA, 2015; ID 413 Appendix I WP2) were not added to this table, because the data were based on case reports.

More specifically, prevalence rates in muskrats and arvicolids seem to parallel those found in red foxes. Nevertheless, if foxes cannot be screened, a larger number of muskrats and arvicolids than foxes would have to be screened to confirm the absence of EM,. This is because fox to *Arvicola* spp. prevalence rates seem to correlate at a ratio of around 3:1. Within arvicolids, *Myodes glareolus* and *Microtus* spp. prevalence correlates with fox prevalence at a ratio of 1:4–6 where both hosts are found.

An exceptional case seems to be Svalbard in Norway, where *Microtus* spp. showed around 27 % EM prevalence and the DH (Arctic fox) showed around only 9 % prevalence. This could be attributed to ecological variables specific for this DH–IH interaction, since the IH (*Microtus levis*) has a very limited spatial distribution consisting mainly of one hillside, while Arctic fox are not even limited to the Spitsbergen island, as they can stroll on ice. The only additional potential DH in this area is the dog, but this DH has not been screened in this area.

Within murids, *Apodemus* spp. is the host with the highest prevalence rates, with similar prevalence, in France, to that of the arvicolid *Myodes glareolus* (Delattre *et al.*, 1988; ID 140 Appendix I WP2).

Only one study reported *Mus musculus* infected with EM (Petavy *et al.*, 1991; ID 252 Appendix I WP2).

In general, murids are not frequently positive for EM, at least those that have been screened so far. The number of murid individuals in a population may be high and therefore they might play a role in the life cycle of EM. However, the number of studies, and rodents examined, is very small, so they are to be regarded as neglected hosts.

No mustelids screened to date showed EM infection, and thus seem to be unsuitable hosts for EM.

The following table summarises data reporting the presence (“yes”) or absence (“no”) of EM infection, and any lack of data (grey cells) regarding EM, in definitive and intermediate hosts in EU countries and ACs (Table 6 WP2). In this table, data on swine from EFSA reports (EFSA, 2013; ID 412 Appendix I WP2) were reported, even if they are case reports.

Table 6 WP2: Data on presence/absence and lack of data of EM infection in DH and IH

Country	DH				IH		
	Red fox	**Raccoon dog**	**Others (sylvatic)**	**Others (domestic)**	**Arvicolids**	**Muskrat**	**Others**
Austria	Yes	NA	NA	No (cat, dog)	NA	NA	No (murids, insectivores, swine)
Belgium	Yes	NA	NA	NA	Yes	Yes	No (murids; insectivores)
Bulgaria	NA	NA	NA	NA	NA	NA	NA
Croatia	No	NA	NA	NA	NA	NA	NA
Cyprus	NA	NA	NA	No (dog)	NA	NA	NA
Czech Republic	Yes	NA	NA	Yes (cat, dog)	Yes	NA	No (murids; mustelids; insectivores)
Denmark	Yes	No	No (wild canids)	Yes (cat), no (dog)	NA	NA	No (mustelids, swine)
Estonia	Yes	Yes	NA	NA	NA	NA	No (swine)
Finland	No	No	No (wild canids)	No (dog)	No	NA	No (arvicolids, swine)
France	Yes	NA	NA	Yes (cat, dog)	Yes	Yes	Yes (nutria, murids), No (insectivores, swine)
Germany	Yes	Yes	NA	Yes (cat, dog)	Yes	Yes	Yes (nutria, swine), No (murids, mustelids)
Greece	NA	NA	NA	NA	NA	NA	No (swine)
Hungary	Yes	NA	Yes (golden jackal)	NA	NA	NA	No (swine)
Ireland	No		NA	NA	NA	NA	NA
Italy	Yes	NA	NA	No (cat, dog)	NA	NA	No (swine)
Latvia	Yes	Yes	Yes (wild canid)	NA	NA	NA	No (swine)
Lithuania	Yes	Yes	NA	Yes (dog)	NA	NA	Yes (swine)
Luxembourg	Yes	NA	NA	No (cat, dog)	NA	Yes	NA
Malta	NA	NA	NA	No (dog)	NA	NA	NA
Netherlands	Yes	No	NA	Yes (cat), No (dog)	NA	Yes	NA
Poland	Yes	Yes	NA	No (cat, dog)	No	NA	No (murids; mustelids; insectivores), Yes (swine)
Portugal	NA	NA	NA	NA	NA	NA	NA
Romania	Yes	NA	NA	NA	Yes	NA	No (swine)
Slovakia	Yes	Yes	NA	Yes (dog), no (cat)	NA	NA	No (swine)
Slovenia	Yes	NA	NA	NA	NA	NA	No (swine)
Spain	No	NA	NA	NA	NA	NA	No (swine)

Country	DH				IH		
	Red fox	Raccoon dog	Others (sylvatic)	Others (domestic)	Arvicolids	Muskrat	Others
Sweden	Yes	No	No (wild canids)	No	No		No (swine)
United Kingdom	No	NA	NA	No (cat, dog)	NA	NA	NA
Albania	NA	NA	NA	NA	NA	NA	NA
Belarus	NA	NA	NA	NA	NA	NA	NA
Bosnia and Herzegovina	NA	NA	NA	NA	NA	NA	NA
Macedonia	NA	NA	NA	NA	NA	NA	NA
Iceland	NA	NA	NA	NA	NA	NA	NA
Kosovo	NA	NA	NA	NA	NA	NA	NA
Lichtenstein	Yes	NA	NA	NA	NA	NA	NA
Moldova	NA	NA	NA	NA	NA	NA	NA
Montenegro	NA	NA	NA	NA	NA	NA	NA
Norway	No	NA	Yes (Arctic fox)	NA	Yes	NA	No (swine)
Russia	NA	NA	NA	NA	NA	NA	NA
Serbia	NA	NA	NA	NA	NA	NA	NA
Switzerland	Yes	NA	NA	Yes (cat, dog)	Yes	NA	No (murids, swine)
Turkey	NA	NA	NA	NA	NA	NA	NA
Ukraine	Yes	No	No (wolf)	NA	NA	NA	NA

Countries in **green** are those potentially free from EM. Countries in grey have no data on any of the suitable EM DHs or IHs. In **yellow** those countries that have detected the presence of the parasite are shown, but data on the main DH and/or IH are lacking (see WP2, EFSA request 4). Cells marked in **red** indicate that those animal species should be screened, if present, either to ascertain the absence of the parasite or the presence of specific hosts important for maintaining the parasite life cycle (see WP2, EFSA request 4). When the main DH and IH are not present, alternative and suitable hosts to be screened should be found (e.g. in Malta and Cyprus).
NA, not assessed.

4.1.8.2. EFSA request 4: the importance of the different definitive and intermediate host species in the life cycle of EM

Gaps were found in the literature regarding the following aspects: (i) the number of studies for the different hosts and the number of screened animals is very low, excluding red foxes, muskrat and arvicolids; (ii) data on worm burden and worm maturity for the different DHs or cyst fertility in different IHs are mostly not available in the literature, precluding the assessment of the real role of each host in the maintenance of the life cycle of the parasite.

Definitive hosts

If present, the red fox is the most important DH in the life cycle of EM. Alternatively, secondary DHs could be screened in areas were the red fox is absent (see below).

In order to clarify the importance of the other screened DHs reported in the literature in the life cycle of EM, a table showing pooled prevalence rates for each DH, other than red foxes, has been generated (see Table 7 WP2).

Table 7 WP2: Pooled prevalence rates of EM in DHs other than red foxes

Species (or group of species)	No of studies included	Pooled prevalence (%)	95 % CI (%)	Time range of studies (years)	NUTS	Studies without NUTS (only country)
Dog (*Canis lupus f. familiaris*)	48	0.3	0.2–0.5	1973–2013	SK0, SK04, DE1, DE40, DK0, FR7, FR722, FR433, CH02, CH022, CH040, CZ032, ITE43	8 (AT, DE, LU, NL, IT, PL, LT)
Cat (*Felis silvestris f. catus*)	32	0.5	0.3–0.8	1973–2013	DE1, DE4, DEB, DEG0, DE41, DE13, DE144, CH022, SK0, DK0, FR71, CZ032	8 (AT, DE, LU, NL, IT, PL, UK)
Arctic fox (*Vulpes lagopus*)	2	9.0	6.0–12.0	1996–2013	NO0	1 (Svalbard only)
Raccoon dog (*Nyctereutes procyonoides*)	24	2.2	0.8–4.1	1998–2013	LT00, LV0, SK0, DK0, DK032, DE4, DE41,	3 (UA, SE, PL)
Wolf (*Canis lupus*)	8	1.4	0.3–3.4	1998–2013	LV00	1 (UA)
Golden jackal (*Canis aureus*)	2	4.7	0.1–15.3	2007–2013	–	1 (HU)

The ranking of prevalence rates in DHs could be used to hypothesise the importance of these different DHs in the life cycle of EM. The data presented show the following ranking, from the most to the least important DH (with pooled prevalence of > 3 %) in the life cycle of EM: red fox, golden jackal, Arctic fox, raccoon dog then wolf. Although data on golden jackal and Arctic fox are scarce (one and two studies, respectively), these are the only data available for these two animal species, and cannot be disregarded. Despite the uncertainties due to the low number of studies in those two species, data have been included in this report for the following reasons: (i) these are the only data available for the two above-mentioned species and (ii) parasite burden and prevalence in the studied individuals is quite high, which is indicative of the important role that these species could play in the maintenance and transmission of the parasite. In this regard, if prevalence rates in those species had been very low or zero, uncertainties about these studies would be higher. It is worth mentioning that Arctic fox are restricted to the northern area of the EU and ACs because of their habitat needs, but the golden jackal population seems to have an increasing trend from eastern EU and adjacent countries towards the west, which should be taken into account when considering the potential future spread of EM.

This ranking could also be useful with regard to providing recommendations for the screening of DHs to better ascertain the presence or absence of the parasite; the hosts should be screened as follows: in the absence of the most important DH, the second most important DH should be screened, etc.

Nevertheless, both the presence of hosts and the protected status of some species (e.g. wolves) are a matter to be taken into account when a recommendation for screening is given. Presence of defined hosts in specific countries can be checked at:

- www.european-mammals.org/php/mapmaker.php

- http://www.europe-aliens.org/speciesSearch.do

When not only presence but also transmission or maintenance of the cycle has to be assessed, the suitability of each host, to allow full maturation of the parasite (worms producing infective eggs) and the worm burden, should be taken into account. This aspect could not be analysed here, because of the lack of information, and thus the relative importance of each DH in the life cycle of the parasite could not be fully assessed. As stated by other authors, cats appear to have only a minor role in the maintenance of EM in endemic areas, and infections in cats may be of minimal public health significance (Thompson *et al.*, 2006).

Intermediate hosts

In order to clarify the importance of the screened IHs reported in the literature in the life cycle of EM, a table showing the pooled prevalence rates for each IH group has been generated (Table 8 WP2).

Table 8 WP2: Pooled prevalence rates of EM in IHs

Species (or group of species)	No of studies included	Pooled prevalence (%)	95 % CI (%)	Time range of studies (years)	NUTS	Studies without NUTS (only country)
Muskrat (*Ondatra zibethicus*)	57	4.2	3.0–5.6	1974–2010	BE3, DE1, DE115, DE119, DE131–139, DE141–142, DE145–149, DE11A–11D, DE12C, DE13A, DE915, DE916, DE918, DE919, DE926, E932, DE935, DE942, E947, DE949, DE93B, DE94C, DE94G, DE4A2, DE4A5, DEF DE9, DEA5, FR251, FR434, NL11	LU
Nutria (*Myocastor coypus*)	2	1.04	0.41–1.96	2002–2010	DEA2	FR
Arvicolids (*Arvicola* spp., *Myodes glareolus*, *Microtus* spp.)	115	6.0	4.0–8.2	1979–2013	BE22, DE1, DE11A, DE143, DE141, CH013, CH040, CH031, CH032, FR7, FR41, FR43, FR72, FR722, FR724, FR432, FR631, FR431, CZ032, PL12, PL21, PL32, PL34, PL62, RO123, SE23	FI, NO
Murids (*Mus musculus, Rattus rattus, Rattus norvegicus, Apodemus* spp.)	24	1.1	0.2–2.8	1979–2009	DE11A, CH031, FR722, FR431, CH013, CH040, CZ032, PL12, PL21, PL32, PL34, PL62	–

Species (or group of species)	No of studies included	Pooled prevalence (%)	95 % CI (%)	Time range of studies (years)	NUTS	Studies without NUTS (only country)
Pig (*Sus scrofa f. domesticus*) and wild boar (*Sus scrofa*)	10	0.001	0–0.006	1989–2009	RO123, DEG0P	LT, SE, FI, NO, CH
Insectivores (*Sorex* spp., *Talpa europea, Neomys fodiens*)	10	0	0	1997–2006	BE22, CZ032, FR722, PL12, PL21, PL32, PL34, PL62	–
Mustelids	40	0	0	1974–2013	DE1, DE4, DEB, DEF0, SK0, CZ032	DK, PL, UA

Pooled prevalence rates in the screened IH groups show that muskrats and arvicolids (and more specifically *Arvicola* spp.) are important in the life cycle of the parasite. For nutria and murids, the number of screened animals is too low to draw conclusions, although it seems that they could play a role in the life cycle of EM in areas with medium to high prevalence rates in red foxes. Swine, insectivores and, especially, mustelids seem to play no role in the life cycle of the parasite.

When not only presence, but also transmission or maintenance of the cycle have to be assessed, the suitability of each host to allow full maturation of the parasite (protoscolex production in cysts) should be taken into account. This aspect could not be analysed here, because of the lack of information, and thus the relative importance of each IH in the life cycle of the parasite could not be fully assessed.

To further address this request, a table was generated including pooled prevalence data for the different DHs and IHs in each EU and adjacent country in which EM infections have been reported. The data were stratified according to the pooled prevalence of EM in red foxes (or Arctic foxes in Svalbard, Norway) (Table 9 WP2).

Countries were subdivided into 0-, low-, medium- or high-prevalence or no-data groups according to the pooled prevalence of EM in red foxes (or Arctic foxes in Norway).

For each country, the pooled prevalence of EM infection in DHs and IHs are reported according to data from the literature. Luxembourg was included at the end of the table, because it has no available data on the prevalence of the parasite in foxes.

Table 9 WP2: Grouping of countries according to EM level of prevalence in red foxes in relationship with DH and IH investigated

Level of prevalence in red foxes (%)	Name of countries	DHs (investigated in the country)	Pooled prevalence (%)	IHs (investigated in the country)	Pooled prevalence (%)
0 (0)	Finland	Raccoon dog	0	Arvicolids	0
		Dog	0	Swine	0
		Wild canids (Wolf)	0		
	Ireland	No data	No data	No data	No data

Level of prevalence in red foxes (%)	Name of countries	DHs (investigated in the country)	Pooled prevalence (%)	IHs (investigated in the country)	Pooled prevalence (%)
	United Kingdom	Dog	0 [(a)]	No data	No data
		Cat	0 [(a)]		
0.00001–1 (low)	Denmark	Cat	0.6 [(a)]	Mustelids	0
		Dog	0 [(a)]	No data	No data
		Raccoon dog	0		
		Wild canids	0		
	Sweden	Raccoon dog	0 [(a)]	Arvicolids	0
		Dog	0 [(a)]		
		Wild canids	0 [(a)]		
	Slovenia	No data	No data	No data	No data
1.00001–10 (medium)	Austria	Dog	0 [(a)]	No data	No data
		Cat	0 [(a)]		
	Belgium	No data	No data	Muskrat	16.00
				Insectivores	0
				Arvicolids	0.2
				Murids	0
	Hungary	Wild canids (Golden jackal)	4.7 [(a)]	Swine	0
	Italy	Dog	0 [(a)]	No data	No data
		Cat	0 [(a)]		
	Netherlands	Cat	0.3 [(a)]	Muskrat	0.06
		Dog	0 [(a)]		
		Raccoon dog	0 [(a)]		
	Norway (5.82 %) (only Svalbard archipelago)	No data	No data	*Microtus* spp.	27.51
				Swine	0
	Romania	No data	No data	Arvicolids	1.4
				Swine	0
	Ukraine	Wolf	0 [(a)]	Mustelids	0
		Raccoon dog	0 [(a)]		
> 10 (high)	Poland	Raccoon dog	10.4	Mustelids	0
				Insectivores	0
		Dog	0 [(a)]	Arvicolids	0
	Switzerland	Dog	1.2	Arvicolids	13.3
				Murids	0.01
				Swine	0
	Czech Republic	Dog	1.8 [(a)]	Mustelids	0
				Insectivores	0
		Cat	50	Arvicolids	1.3
				Muridae	0
	Germany	Dog	0.3	Muskrat	3.8
		Cat	0.6	Nutria	0.4
		Raccoon dog	2.5	Mustelids	0
				Arvicolids	0.7
				Muridae	0
	Estonia	Raccoon dog	1.6	No data	No data
	France	Dog	0.4	Muskrat	1.01
		Cat	1.5	Nutria	0.04
				Insectivores	0
				Arvicolids	4.8

Level of prevalence in red foxes (%)	Name of countries	DHs (investigated in the country)	Pooled prevalence (%)	IHs (investigated in the country)	Pooled prevalence (%)
				Muridae	1
	Lichtenstein	No data	No data	No data	No data
	Lithuania	Dog	0.8 (a)	Swine	0.4
		Raccoon dog	8.2 (a)		
	Latvia	Raccoon dog	21 (a)	No data	No data
		Wolf	5.9 (a)		
	Slovakia	Dog	0.4	No data	No data
		Cat	0 (a)		
		Raccoon dog	28.0		
		Wild canids	0		
No data	Luxembourg	Dog	0 (a)	No data	No data
		Cat	0 (a)		

(a): Prevalence coming from only one study, not pooled prevalence.
Underlined data from nations where arctic foxes were sampled.

It should be stressed that the data presented in this table were frequently derived from a single study, and occasionally the number of animals sampled was low or very low, hampering the drawing of sound conclusions.

Taking into account that the number of studies and number of animals screened in many cases are too low to draw conclusions, the comments made in the following sections should be regarded as tentative.

The importance of the different definitive hosts in low-, medium- and high-prevalence rated countries

As mentioned above, the red fox is the most important DH host for EM, and thus it was used to stratify the prevalence rates in other DHs. In the following paragraphs, the importance of each screened DH, according to country, is discussed, stratified by the pooled prevalence of EM in red foxes (or Arctic foxes in Norway) and resulting in the classification, with regard to EM infection, of countries into 0-, low-, medium- or high-prevalence or no-data groups (see Table 9 WP2).

The other DHs reported in different countries include raccoon dog, golden jackal, Arctic fox, wolf, dog and cat. Of these, raccoon dog, dog and cat have been screened in countries with prevalence rates in foxes of 0 or low. None of these DHs, at this level of prevalence, seem to play a role in the life cycle of the parasite, although issues related to the representativeness of the sample number should be taken into account, since, occasionally, the number of screened animals is low. The Arctic fox is an exception: on Spitsbergen, Svalbard, there are no red foxes and the life cycle of EM is dependent on the Arctic fox.

For countries stratified in the medium-prevalence group, both raccoon dogs and golden jackals, if present, seem to participate in the life cycle of the parasite, with prevalence rates roughly similar to those found for red foxes in the same countries (pooled prevalence of 8 % in Hungary). By contrast, wolves, dogs and cats seem to play no role in countries with medium prevalence levels.

For countries with high prevalence levels, raccoon dogs also seem to be important in the life cycle of the parasite, with prevalence rates of between one-seventh and two-thirds of the pooled prevalence rates in foxes. A special case is Slovakia, in which the pooled prevalence rate in foxes is similar (≈ 27 %) to the prevalence found in raccoon dogs. Importantly, in high-prevalence rated countries, an additional DH (i.e. wolf) seems to start playing a role in the life cycle of the parasite, although with lower prevalence rates (one-sixth) than in foxes and raccoon dogs.

In summary, if prevalence rates are 0 or low for foxes, no other DH seems to play important role in the life cycle of EM. In contrast, when a defined prevalence rate in red fox is achieved (> 3 %), both raccoon dogs and golden jackals, if present, seem to play a similar role to foxes in the life cycle of the parasite. This is also the case for countries in which fox prevalence rates are high, and in this epidemiological situation an additional DH (i.e. wolf) shows up as a potentially important host in the life cycle of the parasite. With regard to domestic hosts (dogs and cats), only a very low prevalence of the parasite could be found and only in the high endemic situations (see Table 10 WP2), and thus these hosts seem to be irrelevant to the life cycle of the parasite, especially when 0-, low- and medium-prevalence rates are found in foxes. In addition, it should be stressed that cats have been shown to be a "bad" host for EM, because full maturity of the parasite is limited in the cat intestine. Nevertheless, as mentioned before, the dog, a domestic DH, could potentially reach any EM-free area from endemic areas, thus its importance is limited for parasite life cycle maintenance but is relevant for parasite introduction in non-endemic areas.

Table 10 WP2: Pooled EM prevalence rates in red foxes compared with pooled EM prevalence rates in dogs

Country	Red foxes			Dogs		
	No of studies included	Pooled prevalence (%)	95 % CI (%)	No of studies included	Pooled prevalence (%)	95 % CI (%)
Austria	6	6.5	4.3–9.1	1	0 [(a)]	0
Belgium	10	8.0	3.0–16.0	No data	No data	No data
Croatia	1	0	0	No data	No data	No data
Czech Republic	3	16.0	4.0–35.0	1	1.8 [(a)]	NA
Denmark	6	0.5	0.2–0.8	1	0 [(a)]	0
Estonia	4	24.5	13.0–38.2	No data	No data	No data
Finland	8	0	0	No data	No data	No data
France	54	13.9	9.8–18.6	8	0.4	0.1–0.9
Germany	41	29.2	26.0–32.4	6	0.3	0.2–0.3
Hungary	42	8.0	5.6–10.7	No data	No data	No data
Ireland	7	0	0	No data	No data	No data
Italy	25	1.5	0.5–2.9	1	0	0
Latvia	14	36.8	22.2–52.9	No data	No data	No data
Lithuania	2	58.0	54.0–62.0	1	0.8 [(a)]	NA
Netherlands	11	4.7	1.9–9.0	2	0	0
Poland	36	14.8	9.6–20.8	2	0	0
Romania	30	4.5	2.9–6.4	No data	No data	No data
Slovakia	61	27.3	24.4–30.3	5	0.4	0.1–1.3
Slovenia	2	0.9	0.2–5.3	No data	No data	No data
Spain	1	0	NA	No data	No data	No data
Sweden	10	0.2	0.1–0.3	2	0	0
United Kingdom	8	0	0	1	0 [(a)]	NA
Lichtenstein	No data	No data	No data	No data	No data	No data
Norway	29	0	0	No data	No data	No data
Switzerland	53	27.4	23.8–31.2	3	1.6	0.2–8.8
Ukraine	4	2.8	0.1–9.0	No data	No data	No data
Bulgaria	No data	No data	No data	No data	No data	No data
Croatia	No data	No data	No data	No data	No data	No data
Cyprus	No data	No data	No data	No data	No data	No data
Greece	No data	No data	No data	No data	No data	No data
Luxembourg	9	16.7	9.4–25.6	1	0 [(a)]	0

Country	Red foxes			Dogs		
	No of studies included	Pooled prevalence (%)	95 % CI (%)	No of studies included	Pooled prevalence (%)	95 % CI (%)
Malta	No data	No data	No data	No data	No data	No data
Portugal	No data	No data	No data	No data	No data	No data
Albania	No data	No data	No data	No data	No data	No data
Belarus	No data	No data	No data	No data	No data	No data
Bosnia and Herzegovina	No data	No data	No data	No data	No data	No data
Macedonia	No data	No data	No data	No data	No data	No data
Iceland	No data	No data	No data	No data	No data	No data
Kosovo	No data	No data	No data	No data	No data	No data
Moldova	No data	No data	No data	No data	No data	No data
Montenegro	No data	No data	No data	No data	No data	No data
Russia	No data	No data	No data	No data	No data	No data
Serbia	No data	No data	No data	No data	No data	No data
Turkey	No data	No data	No data	No data	No data	No data

(a): Prevalence reported in a single study (not pooled).
NA: not applicable

Importance of the different intermediate hosts in low-, medium- and high-prevalence rated countries

As mentioned above, a broad range of potential IHs, including *Ondatra zibethicus, Myocastor coypus*, arvicolids (including *Arvicola* spp., *Myodes glareolus* and *Microtus* spp.), murids (including *Mus musculus, Rattus rattus, Rattus norvegicus, Apodemus* spp. and *Micromys minutus*), swine (*Sus scrofa f. domesticus* and *Sus scrofa*), insectivores (including *Sorex* spp., *Talpa europea and Neomys fodiens*) and mustelids (including *Mustela* spp., *Martes* spp., *Lutra lutra* and *Meles meles*), have been screened in different countries

With regard to the interpretation of the results, it should be stressed that countries with 0- or low-prevalence rates in foxes have screened only two types of IH, namely *Arvicola* spp. (in Finland and Sweden) and swine (in Finland), or, in some cases, no IHs have been screened (Ireland, Denmark, Slovenia and the UK). Therefore, to interpret these results, the potential importance of those IHs in medium- and high-prevalence situations should first be assessed.

In medium-prevalence rated countries, the muskrat, with a 0.06 % prevalence rate in the Netherlands (fox pooled prevalence rate of 4.7 %), and arvicolids (1.4 % prevalence rate in Romania), seem to be the only IHs for the parasite. Other IHs (mustelids, insectivores and murids) seem to play no role in the life cycle of the parasite in this setting.

In highly endemic countries, prevalence rates are high for the muskrat, followed by *Arvicola* spp. and *Microtus* spp., in areas with prevalence rates for foxes of > 16 % (France and Switzerland), but prevalence decrease in areas with < 16 % of infected red foxes. More consistently, prevalence in *Clethrionomys glareolus* is found in areas with fox prevalence rates of both > 16 % and < 16 %. The other IHs screened in these countries seem to have no importance in the life cycle of the parasite.

Therefore, muskrat and *Clethrionomys glareolus*, if present, seem to be important IHs in the life cycle of the parasite. Under specific conditions, *Arvicola* spp. and *Microtus* spp. could be important in the life cycle of the parasite. Swine, mustelids, insectivores, murids and coypu (*Myocastor coypus*) seem to play small or no roles in the life cycle of the parasite, although it should be stressed that the number of IHs for specific groups is too low to draw definitive conclusions, especially regarding murids.

5. Work Package 3: risk factors

5.1. EFSA request 1: **a systematic review on the risk factors for introduction and establishment of *Echinococcus multilocularis* (EM) in EM-free areas through movements of domestic and wildlife species involved in the EM life cycle**

It is known that domestic animals, in particular dogs and cats, are involved in the life cycle of EM. Details of the life cycle are reported elsewhere in this report, in particular for WP2. If infected animals are introduced into areas free of EM, this may lead to the establishment of the parasite. The same holds true for infected wildlife species, which can serve as DHs (i.e. carnivores such as the red fox and the raccoon dog) or IHs (in particular, rodents). The risk factors must be known in order to assess the risk of the introduction of EM into EM-free areas and the establishment of the parasite in such regions. We consider "introduction" to be when EM enters a new area, while we consider "establishment" to be when EM enters a new area and the life cycle of the parasite is established.

5.1.1. Aim

The objectives of this systematic review were to determine the possible risk factors for the introduction and establishment of EM into EM-free areas as a result of the movement of animals through definitive and intermediate hosts.

5.1.2. Search

Databases were searched using keywords associated with the Boolean operators "AND" and "OR". The question mark ("?") was used to expand searches by looking for words with similar prefixes using more than one letter (i.e. "echinococc?" was used to search for "echinococcus", "echinococci", "echinococcosis" and "echinococcoses"). The hash mark ("#") was used to expand searches by looking for words with similar prefixes using one letter (i.e. dog# was used to search for "dog" or "dogs"). Different combinations were tailored for each electronic database in order to narrow the amount of results retrieved but, at the same time, to maximise the number of relevant studies. The full electronic search strategy, including any limits used, was:

[ECHINOCOCCUS MULTILOCULARIS OR (ECHINOCOCOCCUS AND MULTILOCULARIS) OR E# MULTILOCULARIS OR ALVEOLAR ECHINOCOCCOSIS OR A# ECHINOCOCCOSIS] AND (DOG OR DOGS OR CAT OR CATS OR CANIS OR FELIS OR CANID? OR FELID? OR WOLF OR WOLVES OR ANIMAL OR ANIMALS OR FOX OR FOXES OR VULPES OR FERRET OR FERRETS OR RODENT OR RODENTS OR RODENTIA OR NUTRIA# OR MUSKRAT# OR MUSK RAT# OR JACKAL# OR ARVICOLID? OR ARVICOLINAE OR HOST OR HOSTS OR HOSTED OR WILDLIFE) AND (RISK FACTOR# OR RISK#) AND (INTRODUCT? OR ESTABLISHMENT? OR ADDITION OR INGRESS OR PRESENCE).

A search using the STN International platform was carried out on 5 November 2013. An additional search was performed on 11 February 2015 to identify any papers that had been published since the initial search. The results of these two searches were combined. If database outcomes overlapped, all duplicated articles were removed. Review Manager (RevMan) software was used to prepare and maintain this systematic review.

5.1.3. Study selection

The inclusion criteria were:

- studies published from 1900 to present;
- studies published in English, German, French, Polish, Finnish, Dutch, Spanish or Italian;

- Reports on wild or domestic EM hosts.
- studies based on cross-sectional, case–control or cohort design;
- primary research studies published or in press;
- reports on wild or domestic EM hosts.

The list of included articles are available in Appendix I WP3-R1: *List of included studies.*

The exclusion criteria were as follows:

- descriptive studies or case report studies missing data-driven assessments of potential risk factors and protective factors and steps of the risk pathway for introduction and establishment of EM;
- studies on agents other than EM (e.g. *E. granulosus*);
- reviews, letters or editorials without original data;
- duplicated data;
- articles with full texts written in languages other than those that at least one member of the team can read and understand (i.e. English, German, French, Polish, Finnish, Dutch, Spanish and Italian).

The list of excluded articles are available in Appendix II WP3-R1: *List of excluded studies.*

The study selection process concerning the WP3 request 1 is reported using the flow chart showed in Fig 1 WP3.

5.1.4. Data extraction

Data were extracted by completing the fields of a data extraction form.

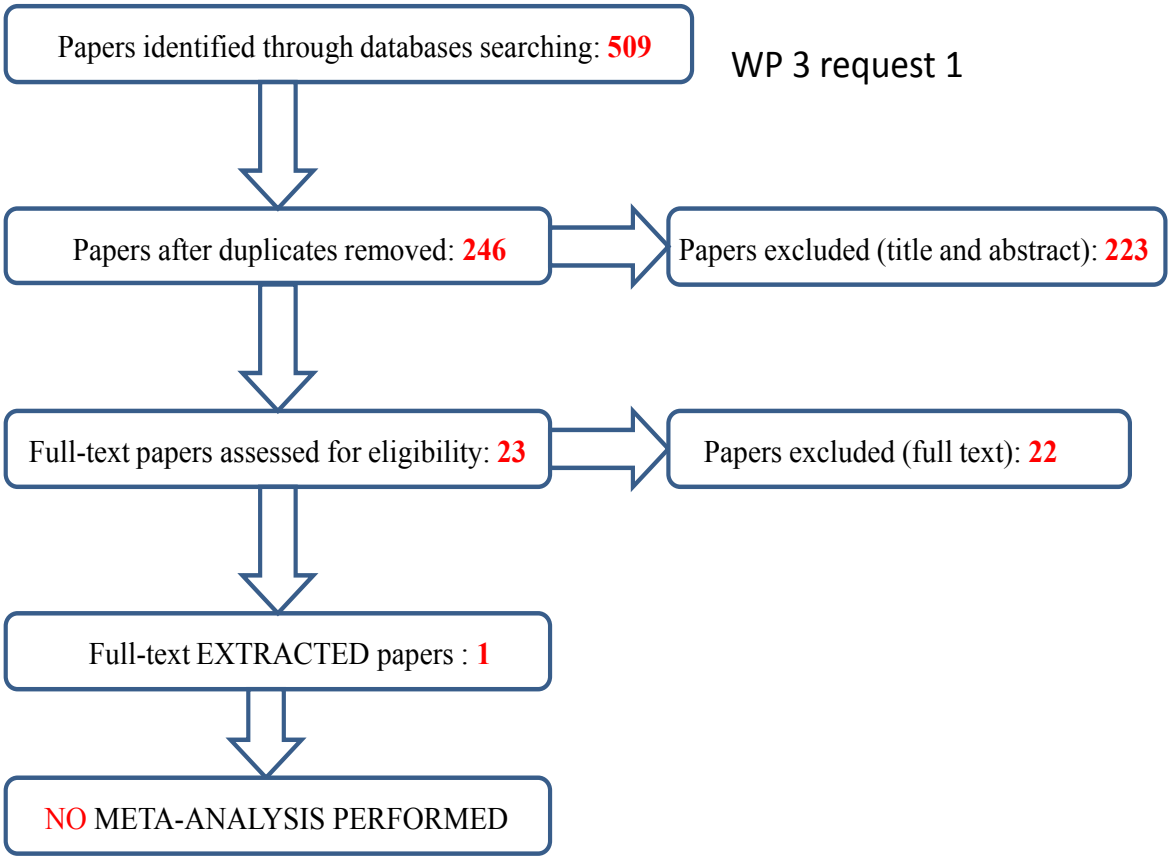


Figure 1 WP3: Flow chart of selection of the studies

5.1.5. Statistical analysis

No statistical analysis was performed because only one study was included.

5.1.6. Quality assessment

The quality assessment was performed using the available tools, and considering study design, for observational studies, in accordance with the NOS (Wells *et al.*, 2014).

5.1.7. Synthesis of results and discussion

For this systematic review, a total of 509 publications were identified using the agreed a priori protocol. After removal of duplicates, the titles and abstracts of 246 papers were screened and 223 papers were excluded. The full text of the remaining 23 publications was read and 22 papers were excluded because they failed to meet the inclusion criteria of the a priori protocol. The remaining publication is summarised in the following sections. Meta-analysis was not possible with only one publication.

In the only eligible study, Stieger and colleagues (2002; ID 8 Appendix I WP3 Request 1) analysed the high reported prevalences of EM in foxes in the city of Zurich, Switzerland. From a total of 604 tested putative fox faecal samples, 156 (25.8 %) were positive in a copro-antigen ELISA with a distinct increase in the proportion of positive samples from the urban to the periurban zone. Furthermore, samples collected in the border zone had significantly more copro-antigen-positive results during winter. The prevalence of EM in rodent IHs was 9.1 % (81/889) in *Arvicola terrestris* (with 3.5 % of

the animals harbouring between 14 and 24 4400 protoscoleces) and 2.4 % (2/83) in *Clethrionomys glareolus*. EM-infected *A. terrestris* were found in 9 of 10 trapping sites in the border zone. The high infection pressure in the periphery of urban areas might pose a risk of infection with EM for both domestic carnivores and inhabitants. This work shows that differences in the prevalence, habitats and ecology in definitive and intermediate hosts may represent risk factors in urban and periurban areas for the introduction and establishment of EM. It should be noted, however, that this work was conducted in an area with a high prevalence of EM infection in foxes in the surrounding area. It is difficult to assess whether or not this is comparable to the situation in EM-free countries.

As only a single study met the inclusion criteria of the a priori protocol for EFSA request 1, we also evaluated publications that considered possible risk factors for the infection of intermediate and definitive hosts with EM (Table 1 WP3), and for potential pathways of introduction and establishment of the life cycle (Table 2 WP3). These issues were addressed in greater detail in a systematic review of echinococcosis in domestic and wild animals (Otero-Abad *et al.*, 2013; ID 57 Appendix II WP2). This review article lists studies that assessed potential associations between EM infection in foxes and environmental factors, such as seasonal and spatial variations of the prevalence, altitude, average annual maximum temperature, precipitation, geographical areas and land use. The authors also extracted studies that identified statistically significant determinants of infection of foxes with this parasite. These variables included the age of the foxes (juveniles were more frequently infected than adults, at least under high endemic conditions) and the intensity of infection (which, again, was higher in juvenile foxes).

Table 1 WP3: Possible risk factors for intermediate and definitive hosts

Host	Factors contributing to the infection rates
Foxes (DH)	Host population dynamics, interactions with prey animals, spatial distribution, seasonal changes and age. As such factors are interrelated, it can be challenging to resolve independent risk factors for infection Epidemiological studies have reported a higher prevalence and/or abundance in juvenile foxes (one-year old) than adults. There is less scientific evidence to support that being a male increases the infection status of an animal (perhaps these are confounding factors) (Leiby and Kritsky, 1974; Trackmann *et al.*, 1998, ID 255 Appendix I WP2; Losson *et al.*, ID31 Appendix I WP5 Request 3) Climatic conditions (with marked spatial distribution): regional meteorological conditions, such as low temperatures or high annual precipitation (related to eggs survival), have been reported as being associated with the infection rates in foxes (Denzin *et al.*, 2005, ID 193 Appendix I WP2; Miterpakova *et al.*, ID 130 Appendix I WP2; Hegglin *et al.*, 2007, ID 51 Appendix I WP2) Geographical location (with marked spatial distribution): highest parasite burden in foxes from regions with a high quota of agricultural land and permanent grassland (related to the presence of microrodents) (Trackmann *et al.*, 1998, ID 255 Appendix I WP2; Raoul *et al.*, 2001, ID 118 Appendix I WP2; Konig *et al.*, 2005, ID 29 Appendix I WP2; Immelt *et al.*, 2009; ID 11 Appendix II WP3) Host population dynamics and interactions with IHs, frequently influenced by urbanisation level: transmission dynamics depend directly on the densities and predator–prey relationship between definitive and intermediate hosts. These two factors differ greatly among the level of urbanisation in different areas. Despite a higher prevalence in foxes from rural areas than from urban areas, a high infection pressure is frequently reported in the periphery of cities (Saitoh and Takahashi, 1998; Hofer *et al.*, 2000, ID 14 Appendix I WP2; Stieger *et al.*, 2002 ID 8 Appendix I WP3 Request 1; Deplazes *et al.*, 2004, ID 232 Appendix I WP2; Fischer *et al.*, 2005, ID 165 Appendix I WP2; Hegglin *et al.*, 2007, ID 51 Appendix I WP2) Living in an endemic area where a cycle between intermediate and definitive

Host	Factors contributing to the infection rates
	hosts could maintain the transmission. Endemic areas with high density of rodents (Miterpakova *et al.*, 2006; ID 130 Appendix I WP2) The infection level is also dependant on fox population density (Raoul *et al.*, 2003; ID 357 Appendix II WP2) Presence of good IHs (microrodents): stability of the southern European border in the Alps seems to be related to the presence/absence of *Microtus arvalis*. Positive faeces from infected Arctic fox were confined within the habitat of the only IH available in the Svalbard islands, *Microtus levis* (Guerra *et al.*, 2014; ID 388 Appendix I WP2)
Dogs (DHs)	Being a farm, hunting or stray dog that is free to roam and consequently has access to rodents as prey. (Stehr-Green *et al.*, 1988, ID 35 Appendix I WP3 Request 6; Budke *et al.*, 2005; Ziadinov, 2008, ID 33 Appendix I WP4 Request 8) Dog owner's lack of deworming treatment in dogs (linked with poor health education) Living in an endemic area where a cycle between intermediate and definitive hosts could maintain the transmission. Endemic areas with high density of rodents. (Wang *et al.*, 2007; ID 10 Appendix II WP3 Request 6) Presence of good definitive and intermediate hosts (foxes and microrodents) to maintain the cycle
Rodents (IHs)	The risk of infection is influenced by ecological and environmental factors that ultimately shape their numbers and age-structure A significant factor is increasing age, but also habitat, season, yearly fluctuation or a combination of those. Low average day temperatures significantly increased the infection risk in *A. terrestris* (related to egg survival). Annual fluctuations in vole populations had a significant effect on the yearly prevalence recorded in *A. terrestris* (Gottstein *et al.*, 2001, ID 58 Appendix I WP2; Stieger *et al.*, 2002, ID Appendix I WP3 Request 1; Stien *et al.*, 2010, ID 146 Appendix I WP2; Burlet *et al.*, 2011; ID 21 Appendix II WP3 Request 6) Living in an endemic area where a cycle between intermediate and definitive hosts could maintain the transmission

Table 2 WP3: Possible pathways of introduction of EM

Possible pathways	Hosts	Comments
Free movement of wildlife	Rodents as IHs (at local scale)	Local scale dispersion, not relevant
	Foxes as DHs (at medium scale)	Dispersal and migratory routes of foxes (< 10 km/year). Relevant for maintaining the cycle and the biomass of the parasite. May influence the geographical dispersion of the parasite
	Wolves as DHs (at wide scale)	Dispersal and migratory routes of wolves (equal or more than 1 000 km/year). High biotic potential for colonising new areas and spreading diseases (Schurer *et al.*, 2014)
Direct human input	Dog movements with owners over long distances	No direct evidence. Alaskan dogs with EM belonging to the European genotypes due to sledge dog introduction? (Jenkins *et al.*, 2012)
	Intermediate and definitive hosts with wildlife introductions/re-introductions	Positive Bavarian beaver introduced into the UK in 2006. Six months' quarantine with no other control measures. This beaver found dead in enclosure in 2010. No cycle established (Barlow *et al.*, 2011; ID 313 Appendix II WP2)
	IHs (rodents) with contaminated produce	Between 1920 and 1960, a sibling vole (*Microtus levis*) was accidentally introduced in Svalbard with the transport

Possible pathways	Hosts	Comments
		of fodder. Cycle established with positive Arctic foxes migrating over sea ice. 100 % of voles are now positive.(Henttonen *et al.*, 2001, ID 146 Appendix I WP2)
	International trade of food contaminated with eggs	Outdoor-grown vegetables and berries contaminated with fox faeces were long suspected to be a source of infection. Nevertheless, seems to be anecdotal and does not emerge as an important risk factor. May be possible at local scale with high parasitic pressure

5.2. EFSA request 6: a systematic review on the risk factors associated with human alveolar echinococcosis

Humans can be aberrant IH of EM and may develop the clinical condition AE, which can be lethal if left untreated. Carnivores, in particular the red fox in Europe, but also the raccoon dog, dogs and cats, represent DHs for the parasite, while mainly rodents serve as natural IHs. Humans contract infection with EM by the ingestion of eggs of the parasite. AE is a rare disease in humans in Europe with a long incubation period; therefore, the identification of risk factors for infection is difficult.

5.2.1. Aim

The objectives of this systematic review were to determine the possible risk factors and known risk factors associated with human infections with EM in the EU and ACs.

5.2.2. Search

Databases were searched using keywords associated with the Boolean operators "AND" and "OR". The question mark ("?") was used to expand searches by looking for words with similar prefixes using more than one letter (i.e. "echinococc?" was used to search for "echinococcus", "echinococci", "echinococcosis" and "echinococcoses"). The hash mark ("#") was used to expand searches by looking for words with similar prefixes using one letter (i.e. dog# was used to search for "dog" or "dogs"). Different combinations were tailored for each electronic database in order to narrow the amount of results retrieved but, at the same time, to maximise the number of relevant studies. The full electronic search strategy, including any limits used, was:

[ECHINOCOCCUS MULTILOCULARIS OR (ECHINOCOCOCCUS AND MULTILOCULARIS) OR E# MULTILOCULARIS OR ALVEOLAR ECHINOCOCCOSIS OR A# ECHINOCOCCOSIS] AND (RISK FACTOR# OR RISK#) AND (HUMAN# OR PEOPLE OR PERSON OR MAN OR MEN OR WOMEN OR WOMAN OR PATIENT#).

A search using the STN International platform was carried out on 5 November 2013. An additional search was performed on 11 February 2015 to identify any papers that had been published since the initial search. The results of these two searches were combined. If database outcomes overlapped, all duplicated articles were removed. Review Manager (RevMan) software was used to prepare and maintaining this systematic review.

5.2.3. Study selection

The inclusion criteria were:

- studies published from 1900 to present;

- studies published in English, German, French, Polish, Finnish, Dutch, Spanish or Italian;
- studies based on cross-sectional or case–control design, cohort studies or studies with experimental infection;
- primary research studies published or in press.

The list of included articles are available in Appendix I WP3-R6: *List of included studies.*

The exclusion criteria were as follows:

- descriptive studies or case report studies missing data-driven assessments of potential risk factors and protective factors for human infection with EM;
- studies on agents other than EM (e.g. *E. granulosus*);
- reviews, letters or editorials without original data;
- duplicated data;
- articles with full texts written in languages other than those that at least one member of the team can read and understand (i.e. English, German, French, Polish, Finnish, Dutch, Spanish and Italian).

The list of excluded articles are available in Appendix II WP3-R6: *List of excluded studies.*

The study selection process concerning the WP3 request 6 is reported using the flow chart showed in Fig 2 WP3.

5.2.4. Data extraction

Data were extracted by completing the fields of a data extraction form.

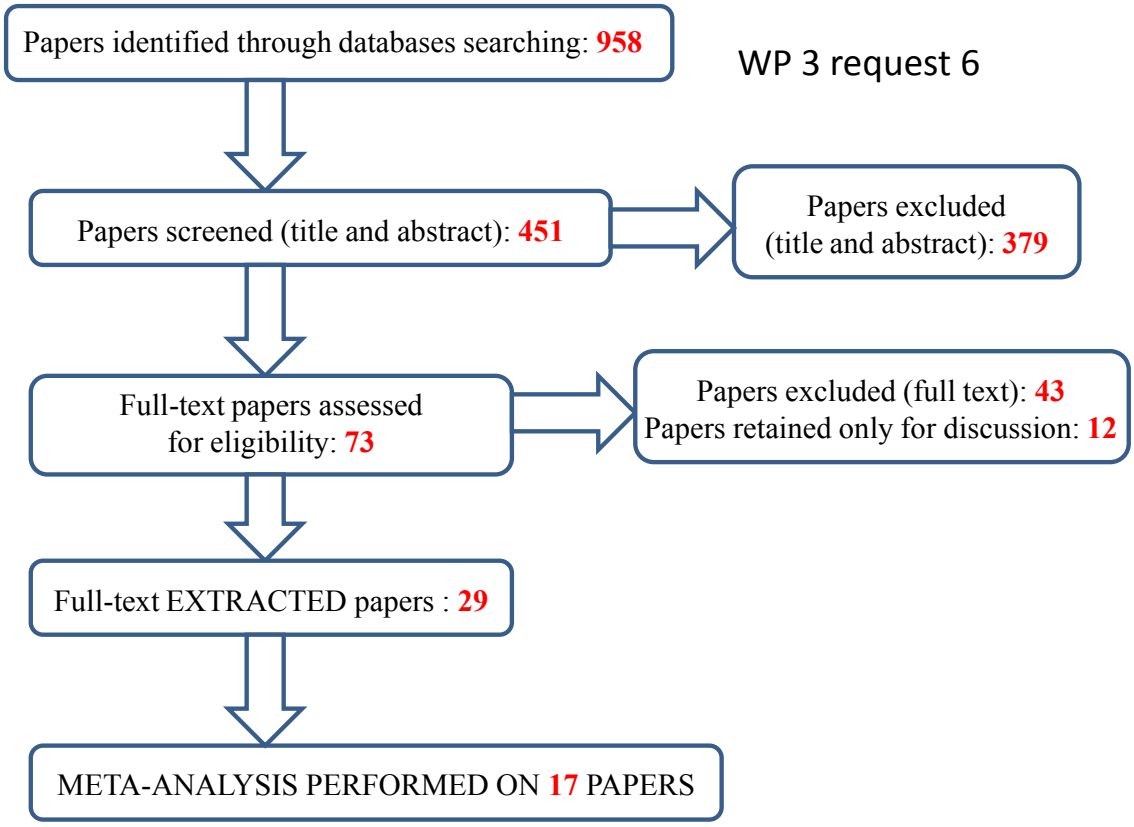


Figure 2 WP3: Flow chart of selection of the studies

5.2.5. Statistical approach and meta-analysis

The statistical analysis was performed using the software Review Manager 5.2.

Statistical analysis was performed separately for each study, and depended on the study designs (cross-sectional and case–control studies), and then it was stratified in relation to the different risk factors reported in the included studies.

The pooled odds ratio, with relative 95 % CI, was calculated and plotted in a forest plot. A Cochran's Q test was performed to assess the degree of heterogeneity between studies, and the I^2 statistic was used to describe the percentage of total variation across studies as a result of heterogeneity. If the p-value from this Q test was < 0.05 and I^2 was > 50 %, heterogeneity was found and the random-effect model is shown. However, if heterogeneity was not found, a fixed-effect model is reported. A forest plot was produced to describe the pooled analysis. Publication bias was quantified by inspection of funnel plots and computation of Egger and Begg test probability values. When the meta-analysis included a low number of studies, it was not possible to assess publication bias by inspection of funnel plots.

Meta-analyses data are summarised in Table 3 WP3, Table 4 WP3 and Table 5 WP3 (below).

5.2.6. Quality assessment

The quality assessment was performed using the available tools, and considering study design, for observational studies, in accordance with the NOS (Wells *et al.*, 2014).

5.2.7. Synthesis of results and discussion

For this systematic review, a total of 958 publications were identified using the agreed a priori protocol. After removal of duplicates, the titles and abstracts of 451 papers were screened and 379 papers were excluded. The full text of the remaining 73 publications was read and 43 papers were excluded because they failed to meet the inclusion criteria of the a priori protocol. Another 12 publications were retained for discussion or narrative systematic review, as the reported data weren't suitable for meta-analysis (nor or only partial raw data reported). The remaining 17 publications were subjected to meta-analysis. To this end, data were separately extracted from case–control studies (n = 6) and cross-sectional studies (n = 11) using Review Manager 5.2 software.

While the question related to risk factors referred to only the EU and ACs, it was decided that all globally relevant risk factors should be included. Therefore, studies conducted outside the EU and ACs (i.e. in China, Japan and North America) were included; however, it is necessary to separate globally relevant risk factors from influence variables that reflect the socio-cultural determinants of infection in areas outside the EU and ACs.

Ten of the eleven cross-sectional studies included in the meta-analysis were conducted in China. The following risk factors with regard to human infection with EM, of potential global relevance, were identified: dog ownership, playing with dogs, female gender, age of > 20 years and occupation (herding) (Table 3 WP3). It must be emphasised that these factors could be influenced by the socio-cultural situation in the affected areas of China.

Five of the seven case–control studies were conducted in the EU, one in China and one in North America. Dog ownership, cat ownership, having a kitchen garden, occupation (farming), haymaking in meadows not adjacent to water, going to forests for vocational reasons, chewing grass and handling foxes were identified as potential risk factors, whereas particular human leucocyte antigen (HLA) types turned out to be protective against AE (Table 4 WP3).

When the analysis was restricted to case–control studies performed in Europe, dog ownership, cat ownership, living in a rural area, having a kitchen garden, occupation (farming), haymaking in meadows not adjacent to water, going to forests for vocational reasons, chewing grass and handling foxes were identified as potential risk factors, whereas particular HLA types turned out to be protective against AE (Table 5 WP3).

It should be emphasised that some of these potential risk factors may represent confounders (e.g. age, gender and even dog ownership). In principle, a deeper analysis of the European data may be possible if the raw data from the relevant studies are made available, by the owners of the information, for a joint analysis; such an analysis could also aim to separate true risk factors from potential confounders (e.g. by stratification or appropriate multivariate analysis in a separate project).

Table 3 WP3: Cross-sectional studies, with odds ratios and 95 % CIs, reporting possible risk factors associated with human AE. Data were obtained from Asian and European studies

Potential risk factor	No of studies	No of participants	Statistical method	Effect estimate
1.1 Dog ownership	5	13 883	Odds ratio (M–H, fixed, 95 % CI)	2.88 (2.30, 3.62)
1.2 Playing with dogs	3	5 916	Odds ratio (M–H, fixed, 95 % CI)	3.48 (2.20, 5.52)
1.3 Hand washing before eating	3	5 348	Odds ratio (M–H, fixed, 95 % CI)	6.94 (4.99, 9.66)

1.4 Gender: female	10	42 812	Odds ratio (M–H, fixed, 95 % CI)	1.50 (1.35, 1.67)
1.5 Age > 20 years	8	24 988	Odds ratio (M–H, fixed, 95 % CI)	2.96 (2.39, 3.68)
1.6 Ethnic group: Tibetan	4	25 952	Odds ratio (M–H, fixed, 95 % CI)	2.03 (1.56, 2.63)
1.7 Low income	2	4 124	Odds ratio (M–H, fixed, 95 % CI)	3.92 (2.42, 6.36)
1.8 Source of drinking water other than well or tap	5	23 714	Odds ratio (M–H, fixed, 95 % CI)	1.81 (1.52, 2.17)
1.9 Occupation: farming	5	17 878	Odds ratio (M–H, fixed, 95 % CI)	1.29 (0.97, 1.72)
1.10 Occupation: herding	5	21 045	Odds ratio (M–H, fixed, 95 % CI)	2.22 (1.76, 2.81)
1.11 Drinking unboiled water	2	7 096	Odds ratio (M–H, fixed, 95 % CI)	0.63 (0.48, 0.84)
1.12 Hunting/handling foxes	3	9 442	Odds ratio (M–H, fixed, 95 % CI)	1.29 (0.97, 1.71)
1.13 Low level of education	2	5 297	Odds ratio (M–H, fixed, 95 % CI)	4.81 (2.73, 8.48)

M–H, Mantel–Haenszel method.

Table 4 WP3: Case–control studies, with odds ratios and 95 % CIs, reporting possible risk factors associated with human AE. Data were obtained from Asian and European studies

Potential risk factor	No of studies	No of participants	Statistical method	Effect estimate
2.1 Dog ownership	5	1 068	Odds ratio (M–H, fixed, 95 % CI)	2.50 (1.73, 3.62)
2.2 Allowed dog into the house	2	216	Odds ratio (M–H, fixed, 95 % CI)	1.80 (0.90, 3.62)
2.3 Playing with dogs	2	216	Odds ratio (M–H, fixed, 95 % CI)	1.42 (0.75, 2.66)
2.4 Cat ownership	2	265	Odds ratio (M–H, fixed, 95 % CI)	2.63 (1.42, 4.85)
2.5 Living in rural area	3	803	Odds ratio (M–H, fixed, 95 % CI)	3.44 (2.19, 5.41)
2.6 Have a kitchen garden	2	746	Odds ratio (M–H, fixed, 95 % CI)	5.21 (2.65, 10.22)
2.7 Occupation: farming	4	1 011	Odds ratio (M–H, fixed, 95 % CI)	4.50 (2.74, 7.39)
2.8 Did haymaking in meadows not adjacent to water	2	238	Odds ratio (M–H, fixed, 95 % CI)	3.50 (1.63, 7.55)
2.9 Went to forests for vocational reasons	2	266	Odds ratio (M–H, fixed, 95 % CI)	2.61 (1.13, 6.05)
2.10 Ate unwashed strawberries	4	1 006	Odds ratio (M–H, fixed, 95 % CI)	1.39 (0.87, 2.23)
2.11 Chewed grass	2	252	Odds ratio (M–H, fixed, 95 % CI)	3.20 (1.65, 6.20)
2.12 Hunting	5	1 064	Odds ratio (M–H, fixed, 95 % CI)	1.13 (0.69, 1.83)
2.13 Handling foxes	4	959	Odds ratio (M–H, fixed, 95 % CI)	2.27 (1.35, 3.81)
2.14 Eating mushrooms	2	255	Odds ratio (M–H, fixed, 95 % CI)	0.72 (0.38, 1.39)

Potential risk factor	No of studies	No of participants	Statistical method	Effect estimate
2.15 Consumption of wild vegetables and fruit	5	1 046	Odds ratio (M–H, fixed, 95 % CI)	1.38 (0.90, 2.10)
2.16 Protective factors (HLA)	2	743	Odds ratio (M–H, fixed, 95 % CI)	0.50 (0.32, 0.80)

M–H, Mantel–Haenszel method.

Table 5 WP3: Case–control studies, with odds ratios and 95 % CIs, reporting possible risk factors associated with human AE. Data used focus only on European studies

Potential risk factor	No of studies	No of participants	Statistical method	Effect estimate
2.1 Dog ownership	4	1 011	Odds ratio (M–H, fixed, 95 % CI)	2.30 (1.56, 3.40)
2.2 Allowed dog into the house	2	216	Odds ratio (M–H, fixed, 95 % CI)	1.80 (0.90, 3.62)
2.3 Playing with dogs	1	159	Odds ratio (M–H, fixed, 95 % CI)	2.07 (0.97, 4.42)
2.4 Cat ownership	2	265	Odds ratio (M–H, fixed, 95 % CI)	2.63 (1.42, 4.85)
2.5 Living in rural area	2	746	Odds ratio (M–H, fixed, 95 % CI)	3.12 (1.95, 5.01)
2.6 Have a kitchen garden	2	746	Odds ratio (M–H, fixed, 95 % CI)	5.21 (2.65, 10.22)
2.7 Occupation: farming	4	1 011	Odds ratio (M–H, fixed, 95 % CI)	4.50 (2.74, 7.39)
2.8 Did haymaking in meadows not adjacent to water	2	238	Odds ratio (M–H, fixed, 95 % CI)	3.50 (1.63, 7.55)
2.9 Went to forests for vocational reasons	2	266	Odds ratio (M–H, fixed, 95 % CI)	2.61 (1.13, 6.05)
2.10 Ate unwashed strawberries	4	1 006	Odds ratio (M–H, fixed, 95 % CI)	1.39 (0.87, 2.23)
2.11 Chewed grass	2	252	Odds ratio (M–H, fixed, 95 % CI)	3.20 (1.65, 6.20)
2.12 Hunting	4	1 007	Odds ratio (M–H, fixed, 95 % CI)	1.25 (0.73, 2.15)
2.13 Handling foxes	3	902	Odds ratio (M–H, fixed, 95 % CI)	2.84 (1.57, 5.15)
2.14 Eating mushrooms	2	255	Odds ratio (M–H, fixed, 95 % CI)	0.72 (0.38, 1.39)
2.15 Consumption of wild vegetables and fruit	4	990	Odds ratio (M–H, fixed, 95 % CI)	1.50 (0.98, 2.31)
2.16 Protective factors (HLA)	1	604	Odds ratio (M–H, fixed, 95 % CI)	0.55 (0.34, 0.88)

M–H, Mantel–Haenszel method.

5.3. EFSA request 7: a systematic review on the impact of *Echinococcus multilocularis* infection in animals on public health in the EU and adjacent countries

Humans can be aberrant IHs of EM and may develop the clinical condition AE, which can be lethal if left untreated. Carnivores, in particular the red fox in Europe, but also the raccoon dog, dogs and cats, represent DHs of the parasite, while mainly rodents serve as natural IHs. Humans contract infection with EM by the ingestion of eggs of the parasite. AE is a rare disease in humans in Europe with a long incubation period; therefore, the identification of risk factors for infection is difficult. However, infection of animals with EM may have a measurable impact on public health. Knowledge on the impact of infection of animals with EM on public health in the EU and ACs will inform potential interventions in wildlife populations (e.g. the treatment of foxes with praziquantel-containing bates to eliminate the EM burden) and prepare the ground for decisions regarding restrictions or control measures if animals are to be moved from EM-affected areas into EM-free regions.

5.3.1. Aim

The objective of this systematic review was to determine the impact of EM infection in animals on public health in the EU and AC.

5.3.2. Search

Databases were searched using keywords associated with the Boolean operators "AND" and "OR". The question mark ("?") was used to expand searches by looking for words with similar prefixes using more than one letter (i.e. "echinococc?" was used to search for "echinococcus", "echinococci", "echinococcosis" and "echinococcoses"). The hash mark ("#") was used to expand searches by looking for words with similar prefixes using one letter (i.e. dog# was used to search for "dog" or "dogs"). Different combinations were tailored for each electronic database in order to narrow the amount of results retrieved but, at the same time, to maximise the number of relevant studies. The full electronic search strategy, including any limits used, was:

[ECHINOCOCCUS MULTILOCULARIS OR (ECHINOCOCOCCUS AND MULTILOCULARIS) OR E# MULTILOCULARIS OR ALVEOLAR ECHINOCOCCOSIS OR A# ECHINOCOCCOSIS] AND (OCCURRENCE# OR INCIDENCE# OR PREVALENCE# OR FREQUENCY OR EPIDEMIC OUTBREAK# ORF ENDEMIC OUTBREAK# OR DALYS OR COST# OR BURDEN OR IMPACT OR EPIDEMIOLOGY OR GEOGRAHIC? DISTRIBUT? OR GEOGRAPHIC? DIFFUS?) AND (HUMAN# OR MAN OR MEN OR WOMAN OR WOMEN OR PATIENT# OR PEOPLE OR PERSON) AND (PUBLIC AND HEALTH).

A search using the STN International platform was carried out on 5 November 2013. An additional search was performed on 11 February 2015 to identify any papers that had been published since the initial search. The results of these two searches were combined. When database outcomes overlapped, all duplicated articles were removed. Review Manager (RevMan) software was used to prepare and maintain this systematic review.

5.3.3. Study selection

The inclusion criteria were:

- studies published from 1950 to present;
- studies published in English, German, French, Polish, Finnish, Dutch, Spanish or Italian;
- primary research studies published or in press.

The list of included articles are available in Appendix I WP3-R7: *List of included studies.*

The exclusion criteria were as follows:

- descriptive studies or case report studies missing data-driven assessments of potential risk factors and protective factors and steps of the risk pathway for introduction and establishment of EM;
- studies on agents other than EM (for example *E. granulosus*).
- reviews, letters or editorials without original data;
- duplicated data;
- studies providing data from outside Europe (EU countries or ACs);
- articles with full texts written in languages other than those that at least one member of the team can read and understand (i.e. English, German, French, Polish, Finnish, Dutch, Spanish and Italian).

The list of excluded articles are available in Appendix II WP3-R7: *List of excluded studies.*

The study selection process concerning the WP3 request 7 is reported using the flow chart showed in Fig 3 WP3.

5.3.4. Data extraction

Data were extracted by completing the fields of a data extraction form.

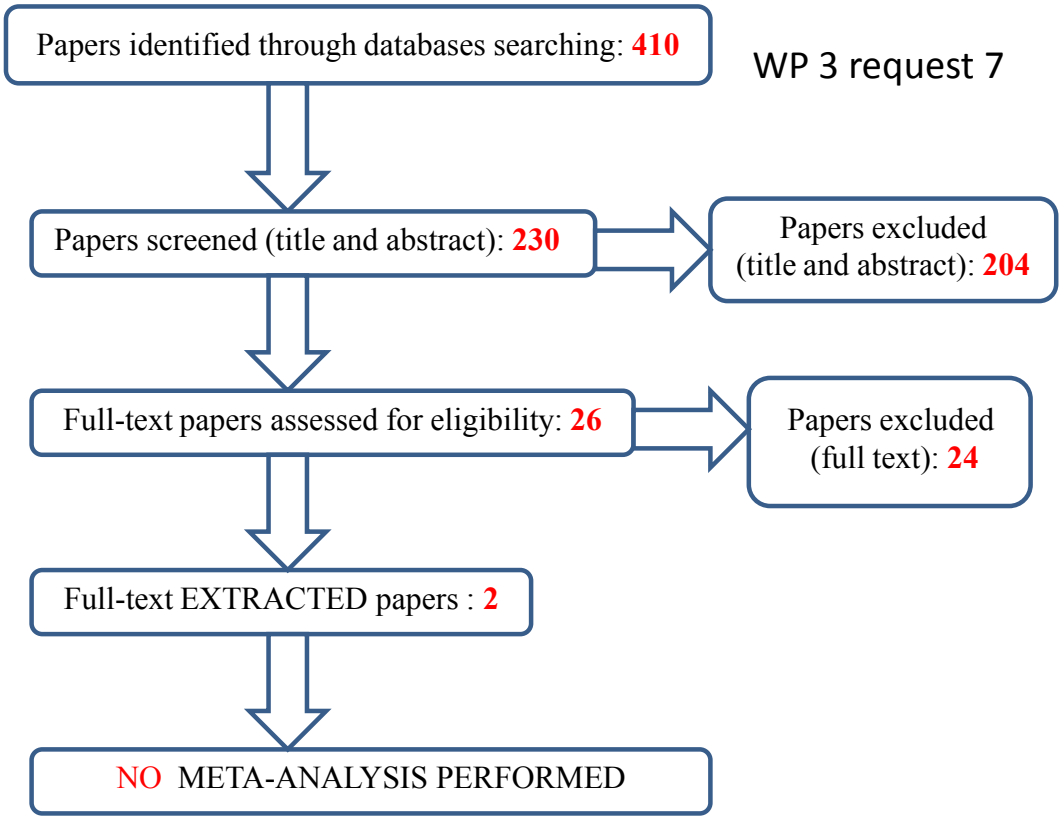


Figure 3 WP3: Flow chart of selection of the studies

5.3.5. Statistical analysis

No statistical analysis was performed because the only two included studies have different study designs (cross-sectional vs. case–control design).

5.3.6. Quality assessment

The quality assessment was performed using the available tools, and considering study design, for observational studies, in accordance with the NOS (Wells *et al.*, 2014).

5.3.7. Synthesis of results and discussion

For this systematic review, a total of 410 publications were identified using the agreed a priori protocol. After removal of duplicates, the titles and abstracts of 230 papers were screened and 204 papers were excluded. The full text of the remaining 26 publications was read and 24 papers were excluded because they failed to meet the inclusion criteria of the a priori protocol. The remaining two publications, both conducted in Germany (one case–control and one cross-sectional study), are summarised in the following sections. Meta-analysis was not possible with only two publications from which data could be extracted.

Kimmig and Mühling (1985; ID 2 Appendix I WP3 Request 7) tested approximately 2 200 people in the district of Reutlingen, Baden-Württemberg, Germany, by serology. They found nine positive or suspect sera, among which one person was identified as an AE patient by computer tomography and the infection was confirmed in this patient after surgery. The authors concluded that the prevalence of

AE infections in the human population in the studied endemic area was in the range of at least 0.1 % and that the contact frequency was approximately 1 %.

Nothdurft and colleagues (1995; ID 8 Appendix I WP3 Request 7) conducted a retrospective cross-sectional study to investigate the epidemiology of echinococcosis in Bavaria, southern Germany. A standardised questionnaire was sent to all hospitals in Bavaria requesting information about patients seen from 1985 to 1989. In a second step, a team of reviewers was sent to all relevant hospitals for active case finding using hospital statistics and medical records. A total of 216 patients with echinococcosis were detected, of whom 58 had AE. According to these data, the prevalence in Bavaria was calculated to be 0.5 per 100 000 inhabitants, with peak prevalence values in the counties of Swabia (2.4/100 000) and Upper Bavaria (0.6/100 000). The annual mean incidence of newly diagnosed cases amounted to 0.03 per 100 000. The distribution of the prevalence in humans was closely correlated with the prevalence of EM in foxes throughout Bavaria ($p < 0.05$). Farmers are the occupational group with the highest risk of acquiring echinococcosis, with a prevalence/odds ratio of 14.6 for Swabia and 8.8 for Upper Bavaria, when compared with the general rural population.

In a review article, which had to be excluded from the systematic review of this project because of the agreed exclusion criteria with regard to review articles, Torgerson and colleagues (2010; ID 21 Appendix II WP3 Request 7) assessed the global burden of AE in humans. They estimated that there are 18 234 (95 % CI 11 900–28 200) new cases of AE per annum globally, with 16 629 (92 %) of these occurring in China and just 1 606 cases occurring outside China. They concluded that AE results in a median of 666 434 disability-adjusted life years (DALYs) (a measure of the overall disease burden, expressed as the number of years lost as a result of ill health, disability or early death) per annum (95 % CI 331 000–1 300 000). The age at onset was younger in China than in Europe. The estimated median annual number of cases from EU countries was 130, with the highest count for Germany (61), followed by France (21), and the Baltic states Estonia, Latvia and Lithuania with nine cases each. The estimated annual number of cases from Switzerland was 20.

6. Work Package 4: diagnosis and treatment

6.1. EFSA request 8: **a systematic review on the laboratory techniques for the detection of *Echinococcus multilocularis* in live or dead animals**

Various laboratory techniques have been described for the detection of EM, for example the SCT and the IST for dead animals, and the copro-antigen ELISA and DNA-based tests for live animals. However, the sensitivity and specificity of these tests vary with the worm burden and stage of the infection, which complicates interpretation and comparison.

6.1.1. Aim

The objectives of this systematic review were to compare the current laboratory techniques available for the detection of EM in live or dead animals and their sensitivity, specificity and predictive values, to assist in the development of (standardised) test protocols.

6.1.2. Search

Databases were searched using keywords associated with the Boolean operators “AND” and “OR”. The question mark (“?”) was used to expand searches by looking for words with similar prefixes using more than one letter (i.e. “echinococc?” was used to search for “echinococcus”, “echinococci”, “echinococcosis” and “echinococcoses”). The hash mark (“#”) was used to expand searches by looking for words with similar prefixes using one letter (i.e. dog# was used to search for “dog” or “dogs”).

Different combinations were tailored for each electronic database in order to narrow the amount of results retrieved but, at the same time, to maximise the number of relevant studies.

The full electronic search strategy, including any limits used, was:

[ECHINOCOCCUS MULTILOCULARIS OR (ECHINOCOCOCCUS AND MULTILOCULARIS) OR E# MULTILOCULARIS OR ALVEOLAR ECHINOCOCCOSIS OR A# ECHINOCOCCOSIS] AND (DOG OR DOGS OR CAT OR CATS OR CANIS OR FELIS OR CANID? OR FELID? OR WOLF OR WOLVES OR ANIMAL OR ANIMALS OR FOX OR FOXES OR VULPES OR FERRET OR FERRETS OR RODENT OR RODENTS OR RODENTIA OR NUTRIA# OR MUSKRAT# OR MUSK RAT# OR JACKAL# OR ARVICOLID? OR ARVICOLINAE OR HOST OR HOSTS OR HOSTED) AND (IDENTIFICATION OR DETERMINATION OR DETECTION OR ELISA OR ENZYME LINKED IMMUNOSORBENT ASSAY# OR PCR OR POLYMERASE CHAIN REACTION OR DIAGNOSTIC METHOD# OR COPRO ANTIGEN OR COPRODNA OR COPRO DNA OR SEDIMENTATION COUNTING TECHNIQUE OR INTESTINAL SCRAPING OR EGG# ISOLATION OR SEROLOGY OR NECROPSY OR SCT OR IST OR ASSAY# OR DIAGNOSIS OR ANALYSIS OR DIAGNOSIS).

A search using the STN International platform was carried out on 5 November 2013. An additional search was performed on 11 February 2015 to identify any papers that had been published since the initial search. The results of these two searches were combined. If database outcomes overlapped, all duplicates articles were removed. Review Manager (RevMan) software was used to prepare and maintain this systematic review.

6.1.3. Study selection

The inclusion criteria were:

- studies published from 1900 to present;
- studies published in English, German, French, Polish, Finnish, Dutch, Spanish or Italian;
- studies based on cross-sectional, case–control or cohort design;
- primary research studies published or in press;
- methods used to detect active or latent infection in live or dead animals;
- studies based on the evaluation of a diagnostic test in terms of sensitivity, specificity, likelihood ratios (LRs), diagnostic odds ratios and area under the receiver operating characteristic (ROC) curve, through a comparison with another test.

The list of included articles are available in Appendix I WP4-R8: *List of included studies*.

The exclusion criteria were as follows:

- studies of human diagnostics;
- descriptive studies of test development, without testing in experimentally or naturally infected animals;
- studies on agents other than (e.g. *E. granulosus*);

- reviews, letters or editorials without original data;
- duplicated data;
- articles with full texts written in languages other than those that at least one member of the team can read and understand (i.e. English, German, French, Polish, Finnish, Dutch, Spanish and Italian).

The list of excluded articles are available in Appendix II WP4-R8: *List of excluded studies.*

The study selection process concerning the WP4 request 8 is reported using the flow chart showed in Fig 1 WP4.

6.1.4. Data extraction

Data were extracted by completing the fields of a data extraction form.

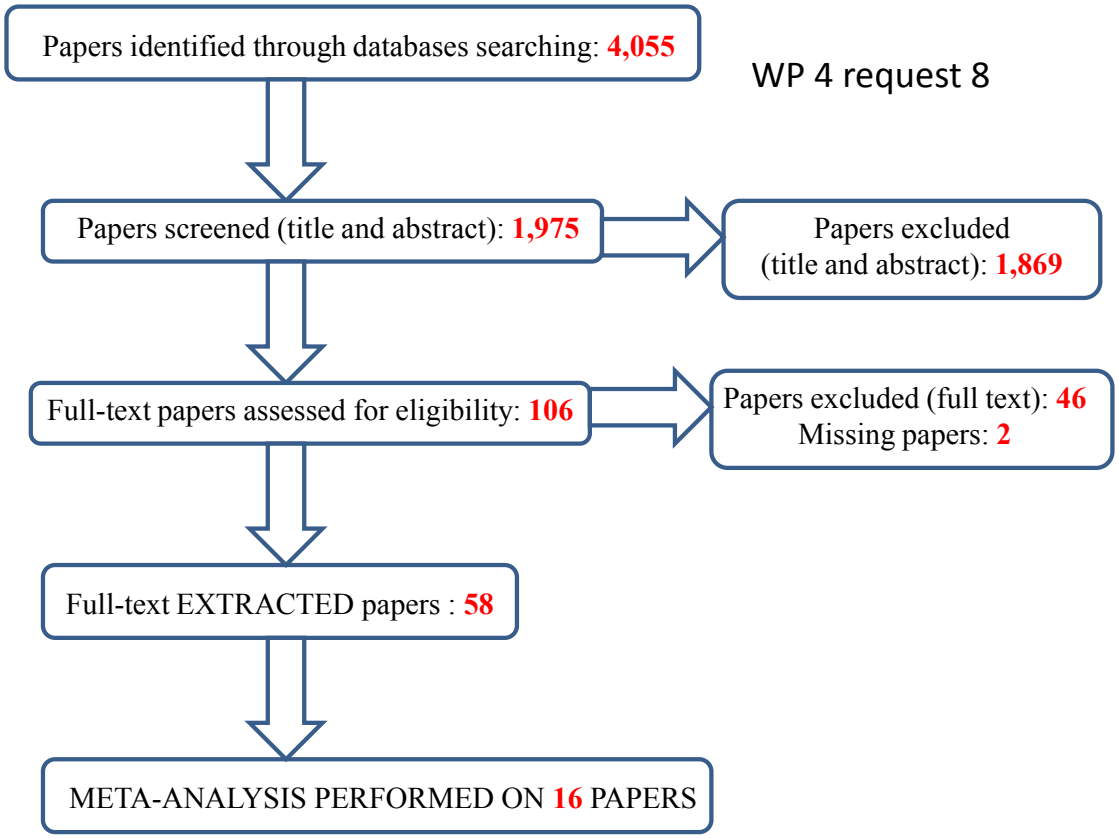


Figure 1 WP4: Flow chart of selection of the studies

6.1.5. Statistical approach and meta-analysis

For a study to be eligible for data extraction, it had to describe at least two diagnostic tests, of which one was often a gold standard assay (reference test), performed on the same species. In addition, articles on studies in which the assay was tested on animals with a known status, because either they were experimentally infected or they originated from an area free of EM, were included,. Each study also had to include data on true positives, false positives, true negatives and false negatives. If the IST

was compared with another test, the IST was considered the reference test; however, in the quality assessment, it was not regarded as the gold standard. In all the other studies, for which the above does not apply, the test with the highest sensitivity was the reference test.

To perform a meta-analysis with multiple studies, both the index test and the reference standard should be the same and the study designs should be comparable. A meta-analysis was performed if at least four studies could be pooled. Summary estimates of the following measures, representing an average operating point across studies, were calculated with the bivariate model:

- sensitivity (proportion of actual positives which are correctly identified as such);
- specificity (proportion of negatives which are correctly identified as such);
- positive likelihood ratio (LR+; the probability of an animal that has the disease testing positive divided by the probability of an animal that does not have the disease testing positive);
- negative likelihood ratio (LR–; the probability of an animal that has the disease testing negative divided by the probability of an animal that does not have the disease testing negative);
- diagnostic odds ratio (ratio of the odds of the test being positive if the subject has a disease relative to the odds of the test being positive if the subject does not have the disease).

Similarly, estimated summary ROC curves, assuming that the true underlying ROC curve in each study has the same shape, were calculated using the Rutter and Gatsonis HSROC (hierarchical summary receiver operating characteristic) model (Rutter and Gatsonis, 2001)All statistical calculations were performed using Review Manager 5.2 and Stata 12.0 (StataCorp LP, College Station, TX, USA) software packages.

6.1.6. Limits of the meta-analysis

Many studies were not included in the meta-analyses, because of their high heterogeneity in the index tests and reference tests used, or because necessary data were missing.

6.1.7. Quality assessment

To assess the methodological quality of diagnostic accuracy studies, we evaluated the risk of bias and applicability concerns with the QUADAS-2 tool (Whiting *et al.*, 2011). The results of the quality assessment are shown in Figure 2 WP4 and Figure 3 WP4.

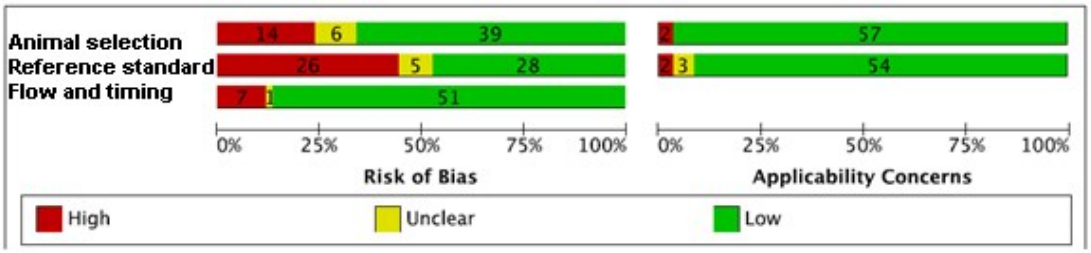


Figure 2 WP4: Summary of the risk of bias and applicability concerns of all studies combined, showing the summary of the authors' scores on each domain, presented as percentages across included studies

Figure 3 WP4: Risk of bias and applicability concerns with scores given per study. A summary of the authors' scores for each domain is given for each included study

The results of the quality assessment show that the methodological quality of the included studies ranged from studies with no risk of bias or applicability, to studies with three negatively scored points, which may thus have a risk of bias or applicability concerns. The most common risk of bias was related to the reference standard. For as concern the quality assessment in this SR, the only diagnostic assay that was regarded as a reference standard was the SCT. Also, if animals had a known infection status due to an experimental infection or because they originated from a known non-endemic area, in this SR was regarded as a reference standard to which a diagnostic method could be compared. The most common risk of bias was related to the reference standard. Therefore, studies that had the IST as the reference test were

negatively scored here, although the IST is also often considered a gold standard. However, because in many articles the index test in these comparisons performed (much) better, we decided it would be better to rate only the SCT as a gold standard test.

6.1.8. Synthesis of results and discussion

6.1.8.1. Available diagnostic tests

Most of the commonly used laboratory techniques described for the detection of EM are described in the 2010 scientific EFSA report (EFSA, 2010). In this EFSA report, the sensitivity and specificity of the different assays are also reported. The values of these test characteristics are not similar to our findings, as different studies were used to compile both reports. In contrast to the EFSA-reported tests, the use of microscopy on faecal samples was also included in this systematic review, but histology was excluded, because this systematic review focuses on laboratory techniques.

6.1.8.2. Test characteristics

Articles were very heterogenic with regard to the study designs. Therefore, meta-analysis could only be performed for two combinations: for the copro-antigen ELISA as an index test and the SCT as a reference test, and for the copro-polymerase chain reaction (PCR), for the 12S ribosomal RNA (rRNA) gene target, and the IST. Meta-analysis could be carried out for only natural infection of the animal species *Vulpes vulpes* (red fox). For the other animal species, no pooled analyses were performed, because of the lack of data.

For the other laboratory techniques for the detection of EM, a brief description is given below, together with a descriptive analysis of the literature found as part of this systematic review. Various modifications of the standard techniques have also been described.

6.1.8.3. Sedimentation and counting technique (SCT) for dead animals

For the SCT,, the intestine is removed at necroscopy, opened and incubated in physiological saline. The intestinal mucosa is squeezed between two fingers, followed by multiple sedimentation steps. After sedimentation, the worms can be counted from the sediment with a binocular microscope. Freezing of the carcass or the unopened intestine at –80 °C for one week or three days, respectively, minimises the risk of infection.

The SCT is considered the gold standard, with a high sensitivity and high specificity, based on the morphologic features of EM. The SCT has the disadvantage that it is a time consuming; in addition, stringent safety precautions should be implemented and the use of SCT is restricted to the examination of necropsy material. The SCT has the advantage that it allows the quantification of the worm burden. It is considered the gold standard and was often used as the reference test in the studies considered. However, it is clear that the sensitivity of the SCT may be less than 100 %, and that this is influenced by the worm burden, as shown by Karamon and colleagues (2010). They estimated the limit of detection of the SCT by testing samples of small intestines, experimentally enriched with known numbers of EM tapeworms. Forty samples containing 2, 5, 10 and 30 tapeworms were examined and EM was detected in 30 % using two spiked adult worms, increasing to 40 % (5 worms), 60 % (10 worms) and 100 % (30 worms) (Table 1 WP4). These results show that the sensitivity of the SCT depends on the worm burden. The worms that were used for spiking the samples, however, had been stored in 70 % ethanol, which could potentially influence the SCT (Karamon, 2010). The detection limit of the SCT needs to be further investigated. It may be that new molecular techniques may prove to be more sensitive than the SCT, although it is still regarded as the gold standard.

Table 1 WP4: Results from the examination of intestinal samples containing different numbers of EM worms using the SCT. From Karamon and collagues (2010; ID 5 Appendix I WP4 Request 8)

No. of *E. multilocularis* worms in sample	No. of examined samples	% Of positive results	Mean no. of detected worms (range)	SD (CV%)
2	10	30	0.3 (0–1)	0.48 (161.02)
5	10	40	0.6 (0–2)	0.84 (140.55)
10	10	60	1.3 (0–5)	1.64 (125.88)
30	10	100	8.4 (2–14)	4.84 (57.56)

SD, standard deviation; CV%, coefficient of variation.

6.1.8.4. Modifications of the sedimentation and counting technique: segmented SCT (SSCT)

Umhang and colleagues (2011; ID 80 Appendix I WP2) reported a modification of the SCT, the segmented SCT (SSCT). The SSCT is performed by cutting the intestine into five equally sized segments, and using only segments 1 and 4 for the SCT. The SCCT was 98.3 % as sensitive as the SCT, but was less time consuming.

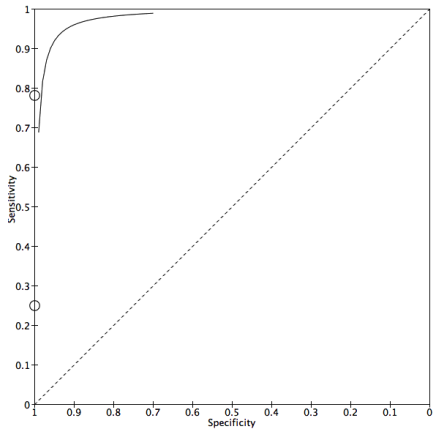
6.1.8.5. Shaking in a vessel technique (SVT)

Duscher and colleagues (2005; ID 30 Appendix I WP4 Request 8) described a modified sedimentation technique for examining the intestines of smaller helminths, such as EM, namely the shaking in a vessel technique (SVT). The SVT makes use of a vessel with a steel mesh lid, and involves several shaking steps in the vessel. No sedimentation is necessary which saves time, and the method reduces the risk of loosing worms during decantation. The sensitivity was deemed to be better than for the IST (see below), with which it was compared in the study, and the specificity of the SVT is very high, as with the SCT, because diagnosis is based on the morphologic features of EM.

6.1.8.6. Intestinal scraping technique (IST) for dead animals

For the IST, 15 deep mucosal scrapings are made from the intestines after necropsy. These scrapings can be performed with microscope slides. At microscopic examination, the adult worms can be counted. As with the SCT, the IST has a high specificity, because the diagnosis is based on the morphologic features of EM. However, in contrast to SCT, only small parts of the mucosa are investigated and therefore parasites present in low numbers may be missed, resulting in a lower sensitivity. For this reason, the IST was not considered a gold standard when it was compared with other tests, as often other assays, such as PCR, detected infections that the IST did not. These could have been false positives, but are more likely to be true positives that were missed in the IST.

IST is a time-consuming technique (but not as labour intensive as SCT); furthermore, stringent safety precautions should be implemented. Freezing of the carcass or the unopened intestine at –80 °C for one week or three days, respectively, minimises the risk of infection. The use of the IST is restricted to the examination of necropsy material. Figure 4 WP4 shows the ROC curve and forest plot of the comparison of the IST with the SCT, as described in two articles (Hofer *et al.*, 2000, ID 82 Appendix I WP4 Request 8; Karamon *et al.*, 2012, ID 9 Appendix I WP4 Request 8). Both showed a high specificity, but a variable sensitivity.



Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Karamon 2012.5	2	0	6	119	0.25 [0.03, 0.65]	1.00 [0.97, 1.00]		
Hofer S 2000	68	0	19	83	0.78 [0.68, 0.86]	1.00 [0.96, 1.00]		

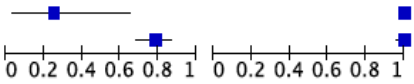


Figure 4 WP4: ROC curve and forest plot of the comparison of studies using the IST as an index test and the SCT as a reference test

6.1.8.7. Microscopy of faecal samples from live animals

Faecal samples can be examined for taeniid eggs by flotation enrichment and sieving, followed by microscopy. The sensitivity of this technique is not that high, because intermittent shedding of eggs may result in false negative results. It is difficult to differentiate different types of taeniid eggs, because they appear identical under the microscope, resulting in a lower specificity. Furthermore, it is not possible to estimate the infection intensity (worm burden) by microscopic detection of taeniid eggs. However, an advantage of this method is that it is simple and no expensive equipment is necessary.

6.1.8.8. Copro-antigen enzyme-linked immunosorbent assay (ELISA) using samples from live animals

Faecal samples can be examined by ELISA to detect pathogen-specific antigens in the faeces (copro-antigens). The excretion of copro-antigens is closely correlated with the presence of intestinal worms. The copro-antigen ELISA can detect antigens even during the prepatent period. The detection rate rises with increasing worm burden. Deplazes and colleagues (1999) defined the overall diagnostic sensitivity of the copro-antigen ELISA in foxes with a known worm burden, as determined using the SCT. The sensitivity of the copro-antigen ELISA ranged from 40 % to 100 % in faecal samples of animals with worm burdens ranging from 4 to 20 to 520 to 60 000, respectively. The overall sensitivity was 84 % (Table 2 WP4), with a higher sensitivity of the copro-antigen ELISA in faecal samples with a moderate to high worm burden.

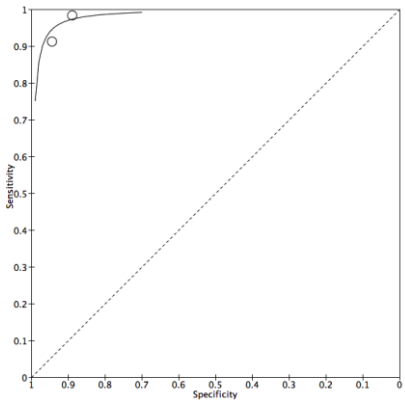
Table 2 WP4: Sensitivity of copro-antigen ELISA for detecting EM. From Deplazes (1999; ID 1 Appendix I WP4 Request 8)

E.m. worm burden of foxes[1]	Number of foxes	CA-ELISA positive	CA-ELISA negative	Sensitivity (%)
4–20	10	4	6	40
21–350	19	16	3	84
520–60,000	26	26	0	100
Average/animal: 3,787	total: 55	total: 46	total: 9	average: 84

[1]Worm numbers determined by the sedimentation and counting technique (see text and Table I).

The specificity reported in the studies for *Echinococcus* spp. antigens is high (Deplazes *et al.*, 1999, ID 1 Appendix I WP4 Request 8; Morishima *et al.*, 2005, ID 35 Appendix I WP4 Request 8; Alther *et al.*, 1996, ID 85 Appendix I WP4 Request 8); however, in the field, cross-reactivity can occur with antigens from *Taenia* spp. or other helminths. The copro-antigen ELISA can be performed on both live and dead animals and, because of its ease of use and relative inexpensiveness, it is useful for large population studies in known-infected areas. However, because of its lower sensitivity, especially when worm burdens are low, the copro-antigen ELISA is less useful for testing animals in regions with a sporadic or unknown endemicity.

Figure 5 WP4 shows the ROC curve and the forest plot of the comparison of the copro-antigen ELISA with the IST as a reference test, based on the studies from Nonaka and colleagues (2008; ID 41 Appendix I WP4 Request 8) and Machnicka and colleagues (2003; ID 21 Appendix I WP4 Request 8). Both studies show a high specificity, 94 % and 89 %, respectively, and also a high sensitivity, 91 % and 98 %, respectively.



Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Nonaka 2008.3	42	2	4	34	0.91 [0.79, 0.98]	0.94 [0.81, 0.99]
Machnicka 2003.1	62	16	1	129	0.98 [0.91, 1.00]	0.89 [0.83, 0.94]

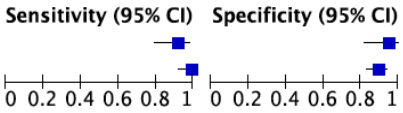


Figure 5 WP4: ROC curve and forest plot of the comparison of the copro-antigen ELISA and the IST

A meta-analysis was performed on four studies comparing the copro-antigen ELISA with (a modified) SCT (Reiterova *et al.*, 2005, ID 37 Appendix I WP4 Request 8; Deplazes *et al.*, 1999, ID 1 Appendix I WP4 Request 8; Sakai *et al.*, 1998, ID 16 Appendix I WP4 Request 8; Yimam *et al.*, 2002, ID 14 Appendix I WP4 Request 8) (see Figure 6 WP4 and Table 3 WP4). The combined sensitivity of the studies of the copro-antigen ELISA is 82 % (95 % CI 74–88 %) and the specificity is 89 % (95 % CI 75–96 %). This means that the copro-antigen ELISA is quite good at correctly identifying cases (82 % sensitivity), but is better for correctly excluding the presence of EM (89 % specificity). The accuracy of the test is also explained by the LR values, both of which are different from 1 (LR+ = 7.9 and LR– = 0.2), which account for the findings of moderately in favour and against diagnosis, respectively. Finally, the odds ratio of much higher than 1 indicates a good performance of the copro-antigen ELISA. However, the selection of field studies and the prevalence in the study area (high endemic) will influence the outcomes of the test characteristics. Limited information is present from low endemic areas.

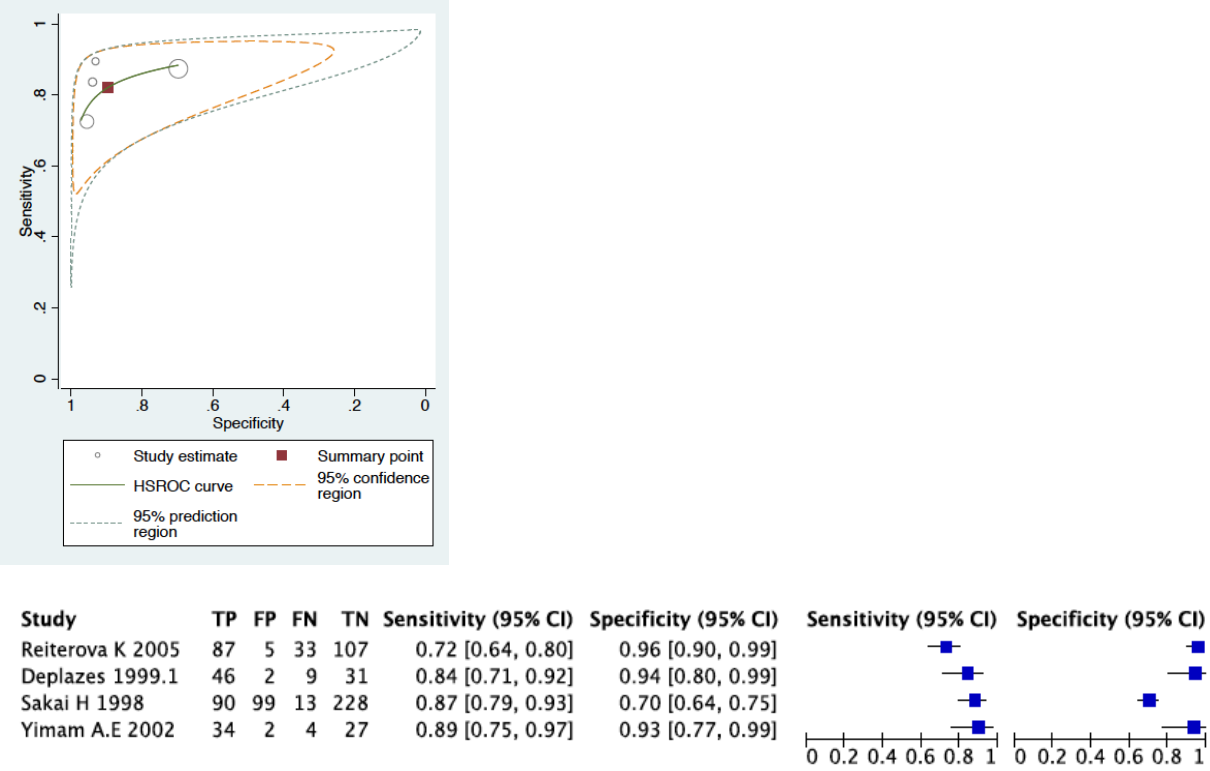


Figure 6 WP4: ROC curve with 95 % confidence region and forest plot, pooling studies that compare the copro-antigen ELISA with the SCT

Table 3 WP4: Results of the meta-analysis of four studies comparing the copro-antigen ELISA with the SCT as the reference assay

Summary point	Coefficient	95 % CI
Sensitivity	0.82	0.74–0.88
Specificity	0.89	0.75–0.96
DOR	39.35	17.99–86.11
LR+	7.87	3.33–18.58
LR–	0.20	0.15–0.27

DOR, diagnostic odds ratio.

6.1.8.9. DNA-based tests for faecal samples from live animals

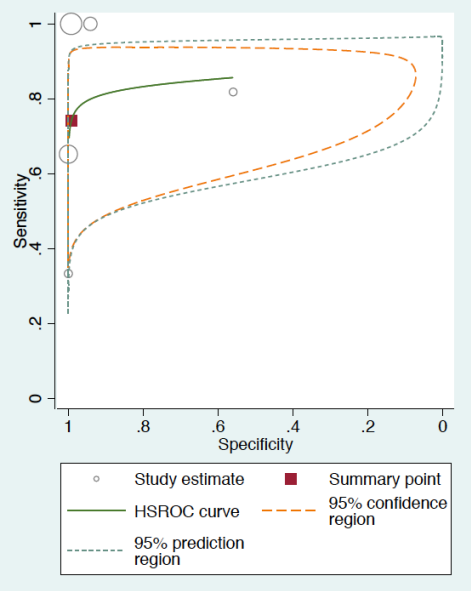
PCR tests are used to detect EM DNA in faecal samples. Three steps are included in the diagnostic procedure: (i) DNA needs to be isolated (DNA extraction step), followed by (ii) the specific amplification of EM DNA and subsequently (iii) the visualisation or measurement of the PCR products. Various methods exist for the different steps. For DNA extraction, the methods described consist of phenol–chloroform DNA extraction (e.g. Bretagne *et al.*, 1993, ID 27 Appendix I WP4 Request 8; Van der Giessen *et al.*, 1999, ID 36 Appendix I WP4 Request 8; Monnier *et al.*, 1996, ID 15 Appendix I WP4 Request 8; Maas *et al.*, 2014, ID 94 Appendix I WP4 Request 8), commercial DNA isolation kits (Al-Sabi *et al.*, 2007, ID 12 Appendix I WP4 Request 8; Jiang *et al.*, 2012, ID 4 Appendix I WP4 Request 8; Ni *et al.*, 2014, ID 92 Appendix I WP4 Request 8) or the DNA fishing /magnetic capture method (Isaksson, *et al.* 2014, ID 101 Appendix I WP4 Request 8; Oines *et al.*, 2014, ID 93 Appendix I WP4 Request 8). The DNA amplification step can differ between studies if DNA from different target genes (e.g. 12S rRNA, U1 small nuclear RNA (snRNA), internal

transcribed spacer (ITS) 1 or cyclooxygenase (COX) 1) is amplified. Furthermore, DNA amplification can be performed by PCR-amplification and detection of a single target or, in a multiplex PCR, multiple DNA sequences can be amplified and detected. Multiplex PCR can be used to, for example, detect multiple parasites in one PCR. Also, DNA amplification can be performed by nested PCR or real-time PCR.

Because of the large variability in both the DNA extraction and the DNA amplification methods, it is difficult to compare studies using exactly the same PCR methods.

In general, when targeting a specific gene fragment of EM, PCR can be highly specific. To increase the sensitivity, larger volumes of faeces are required, but this is often hampered by the DNA extraction method. Inhibition of the PCR may result in false negative results, lowering the sensitivity of the PCR. A solution to this problem is to extract DNA from purified taeniid eggs or to use an internal control. PCR gives no information about the worm burden, although a quantitative-PCR (Q-PCR) can give information on the (relative) amount of DNA in a sample. New techniques like the DNA fishing/magnetic capture method followed by real-time PCR show high sensitivity and high specificity, especially with worm burdens of > 100 worms. This technique can be partially automated, making it well suited to nationwide EM surveillance programmes (Isaksson, 2014, ID 101 Appendix I WP4 Request 8; Oines, 2014, ID 93 Appendix I WP4 Request 8).

Figure 7 WP4 and Table 4 WP4 show the meta-analysis that was performed on the comparison of the copro-PCR for the 12S rRNA target (index test) and the IST (reference test). The results of the pooled analysis show quite a good performance of the copro-PCR test. However, since all studies are performed in a low endemic areas, the results also show a low number of positives and a high number of true negatives. This produces an overestimation of the diagnostic odds ratio and of the LR+ with a CI range that is too wide. The most recent study (Maas *et al.*, 2014, ID 94 Appendix I WP4 Request 8) indicates that the copro-PCR has a lower specificity, but this was because of the better sensitivity of the copro-PCR assay compared with the IST, which led to positives being incorrectly defined as false positives. This explains the lower specificity. The better sensitivity of the PCR compared with the IST is suggested by other studies; however, the results of these studies were not as clear and, therefore, it was decided that the IST would not be classified as a reference standard in the quality assessment.



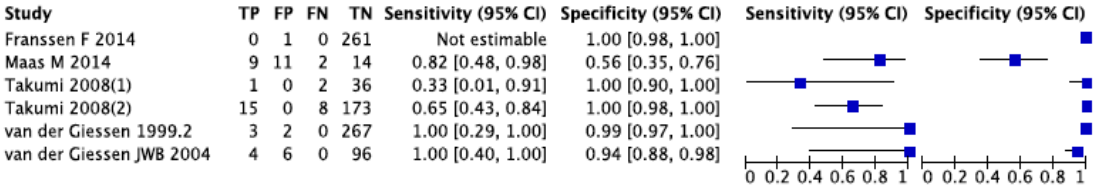


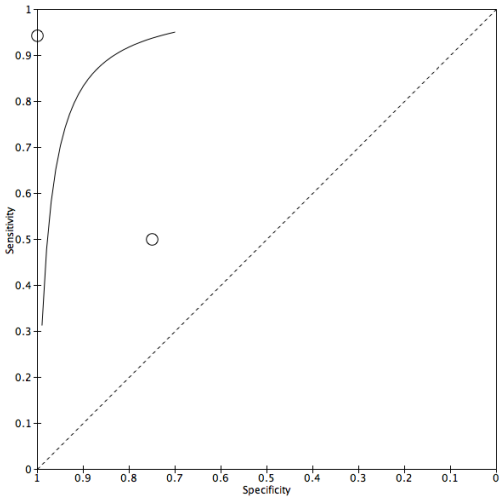
Figure 7 WP4: ROC curve with 95 % CI and forest plot, pooling studies that compare the copro-PCR (12S rRNA) with the IST

Table 4 WP4: Results of the meta-analysis of six studies comparing the copro-PCR (12S rRNA) with the IST as the reference assay

Summary point	Coefficient	95 % CI
Sensitivity	0.74	0.54–0.87
Specificity	0.99	0.72–1.00
DOR	359.06	10.23–12 607.12
LR+	93.85	2.20–4 006.82
LR–	0.26	0.14–0.49

DOR, diagnostic odds ratio.

Figure 8 WP4 shows the ROC curve and the forest plot of the comparison of the copro-PCR in which the target was the U1 snRNA gene, compared with the results from the SCT.



Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Bretagne S 1992	3	1	3	3	0.50 [0.12, 0.88]	0.75 [0.19, 0.99]		
Mathis A 1996	33	0	2	20	0.94 [0.81, 0.99]	1.00 [0.83, 1.00]		

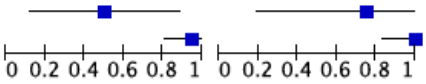


Figure 8 WP4: ROC curve and forest plot of the comparison of the copro-PCR (U1 snRNA) and the SCT

In conclusion, many copro-PCR assays were included in this review; however, it was almost impossible to select studies for comparison that used exactly the same methods for the assays because of the various DNA extraction methods used, the different gene targets used and the different gold standard assays used. The study population (i.e. high endemic or low endemic areas) in which the assay is tested may also influence the results. In many studies, copro-PCR assays were more sensitive than IST or SCT, and found more animals positive. It is likely that this is because of a higher sensitivity than the reference test, rather than because of a low specificity of the index test.

6.1.9. Conclusion

In conclusion, the studies on the test efficiency of the diagnostic tests for detection of EM in live or dead animals are very heterogenic, which complicates drawing any conclusions from them. To perform a meta-analysis, studies which have used the same methods are needed. Because there are many study designs possible, on different animals species, in both experimental and natural settings, it is difficult to exactly compare the same methods, as there are large or small differences between studies. Although many diagnostic papers are available, a meta-analysis was possible for only two combinations.

The diagnostic methods used for the post-mortem examination of foxes have a high sensitivity and are highly specific, but can only be used for dead animals. In addition, these tests are very labour intensive. The diagnosis of EM in living foxes and living DHs in general is dependent on the stage of infection (i.e. prepatent or patent infections) and may be hampered by intermittent shedding. Using microscopy on faecal samples is difficult because the eggs cannot be differentiated from other taenidd eggs. The copro-antigen ELISA gives good sensitivity in high endemic areas, but is not highly sensitive in animals with low worm burdens. The use of PCR to detect EM in faecal samples is a sensitive and specific test for EM infection, but provides no information on worm burden.

The predictive values of the different tests are also very dependent on the prevalence of EM in the particular study area and the worm burdens of the animals. The SCT is considered the gold standard, but even this test has limitations in terms of sensitivity, which was shown from the study by Karamon and colleagues (2010). From this systematic review, there is not enough evidence for recommending a diagnostic technique.

6.2. EFSA request 9: a systematic review on the efficacy of available *Echinococcus multilocularis* deworming drugs, resulting in treatment protocols for dog, cats and ferrets

Deworming drugs are widely used in veterinary practice. Praziquantel is currently the most-used anthelmintic for the treatment of EM infections. Praziquantel is an anisochinoline derivative that kills both the immature and the mature stages of EM in the intestine (WHO/OIE, 2001). This cestocide interacts with the integument of the immature and/or mature worm stages and increases their calcium permeability, leading to muscle contraction and deregulation of the metabolism (Doenhoff *et al.,* 2008). The drug can be orally, parenterally or topically administered. After oral administration, Praziquantel is rapidly and well absorbed in the duodenum and peak blood levels are reached after 30 minutes to two hours (in dog). After parenteral administration, blood levels are higher. The half-life of praziquantel is three hours in the dog. The drug penetrates very well in tissues, including the central nervous system. Hydroxylation takes place in the liver. Of the administered dose, 60–80 % is excreted in the urine, bile and faeces. Praziquantel is a highly effective anthelmintic, and its use is recommended by the European Scientific Counsel Companion Animal Parasites (ESCAPP, 2010). The recommended dose for treatment of echinococcosis is 5–10 mg/kg body weight for parenteral administration (intramuscular (IM) or subcutaneous (SC)). For the dog, it is advised that praziquantel is given as a single oral dose of 5 mg/kg body weight (Riviere and Papich, 2009 and FIDIN).

Epsiprantel is another anthelmintic that is recommended by the ESCAPP for the treatment of EM infections in dogs and cats. Epsiprantel is a more recently developed isochinoline derivative with the same characteristics as praziquantel. The recommended dose for the dog is 2.25 mg/kg body weight.

The available deworming drugs for the treatment of EM were reviewed in this systematic review, using both scientific and grey literature. The efficacy is defined as the measure of how well treatment works in clinical trials or laboratory studies.

6.2.1. Aim

The objectives of this systematic review were to give an overview of scientific and grey literature on the deworming drugs available for the treatment of EM and to establish a treatment protocol for dogs, cats and ferrets, if possible.

6.2.2. Search

Databases were searched using keywords associated with the Boolean operators “AND” and “OR”. The question mark (“?”) was used to expand searches by looking for words with similar prefixes using more than one letter (i.e. “echinococc?” was used to search for “echinococcus”, “echinococci”, “echinococcosis” and “echinococcoses”). The hash mark (“#”) was used to expand searches by looking for words with similar prefixes using one letter (i.e. dog# was used to search for “dog” or “dogs”).

Different combinations were tailored for each electronic database in order to narrow the amount of results retrieved but, at the same time, to maximise the number of relevant studies.

The full electronic search strategy, including any limits used, was:

[ECHINOCOCCUS MULTILOCULARIS OR (ECHINOCOCCUS AND MULTILOCULARIS) OR E# MULTILOCULARIS OR ALVEOLAR ECHINOCOCCOSIS OR A# ECHINOCOCCOSIS] AND [ANTHELMINTIC# OR ANTIHELMINTIC# OR PRAZIQUANTEL OR DEWORM? OR DE WORM? OR ANTINEMATOD? OR VERMIFUGE# OR DRUG# TREATMENT OR (PHARMACOLOGICAL AND TREATMENT)] AND (DOG# OR CAT# OR FERRET# OR CANIS OR FELIS OR CANID? OR FELID?).

A search using the STN International platform was carried out on 5 November 2013. An additional search was performed on 11 February 2015 to identify any papers that had been published since the initial search. The results of these two searches were combined. If database outcomes overlapped, all duplicates articles were removed. Review Manager (RevMan) software was used to prepare and maintain this systematic review.

6.2.3. Study selection

The inclusion criteria were:

- studies published from 1900 to present;
- studies of dogs, cats or ferrets;
- observational or experimental studies (with or without a control group);
- studies published in English, German, French, Polish, Finnish, Dutch, Spanish or Italian;
- primary research studies published or in press.

The list of included articles are available in Appendix I WP4-R9: *List of included studies*.

The exclusion criteria were as follows:

- studies on deworming drugs for humans and animals other than dogs, cats or ferrets;
- descriptive studies of drug development, without testing in experimentally or naturally infected animals;
- studies on agents other than EM (e.g. *E. granulosus*);
- reviews, letters or editorials without original data;
- duplicated data;
- articles with full texts written in languages other than those that at least one member of the team can read and understand (i.e. English, German, French, Polish, Finnish, Dutch, Spanish and Italian).

The list of excluded articles are available in Appendix II WP4-R9: *List of excluded studies*.

The study selection process concerning the WP4 request 9 is reported using the flow chart showed in Fig 9 WP4.

6.2.4. Data extraction

Data were extracted by completing the fields of a data extraction form.

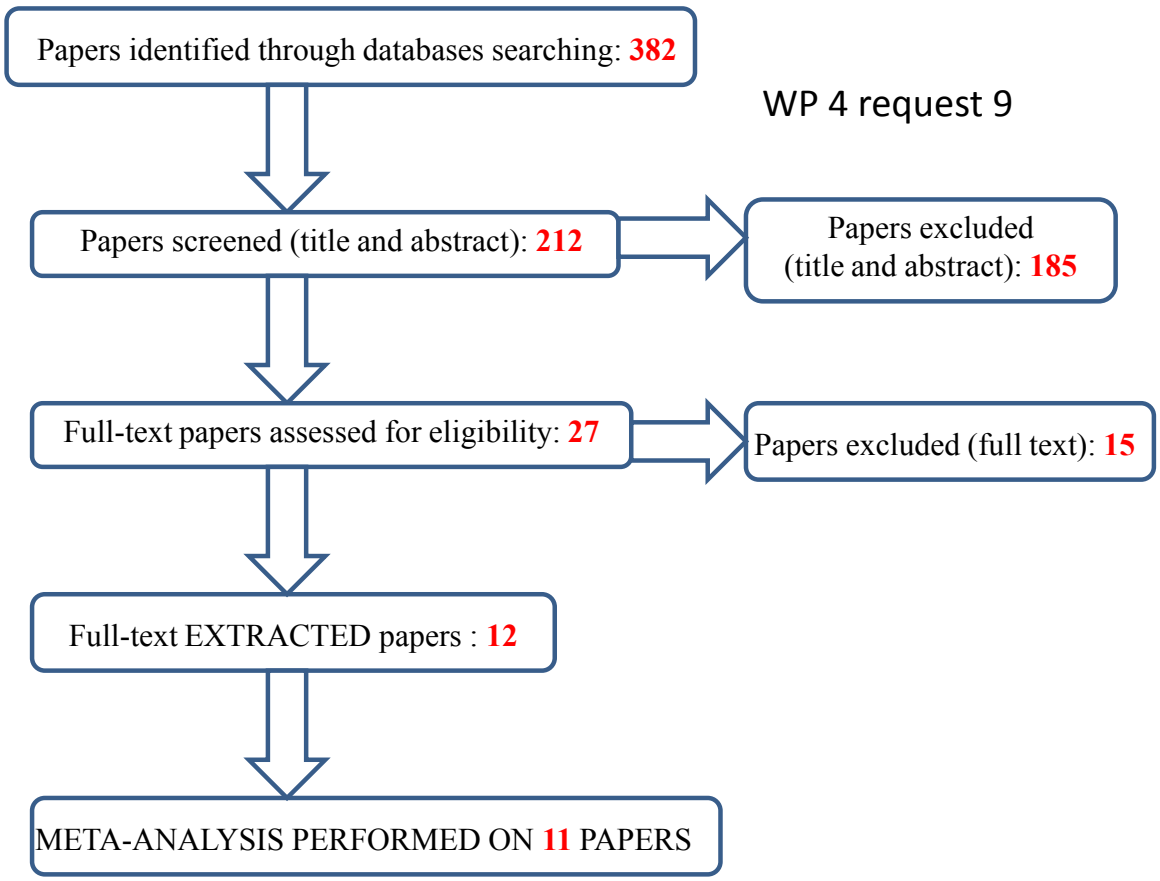


Figure 9 WP4: Flow chart of selection of the studies

6.2.5. Statistical approach and meta-analysis

Different meta-analyses were performed taking into account the different deworming drugs analysed.

Pooling and analysis of data were carried out using Review Manager 5.2. Separate analyses were planned for each intervention and compared with placebo. Intervention effects were calculated as odds ratios with 95 % CIs. If a study included more than one intervention group with a single comparator arm, both intervention groups were included and the number of animals in the common comparator arm were split across the separate intervention arms. Heterogeneity was quantified using the I^2 statistic and using the χ^2-test of heterogeneity. Pooled data were reported only if heterogeneity was not statistically significant ($p > 0.05$). Funnel plots were used to assess publication bias.

6.2.6. Limits of the meta-analysis

There were few available data; therefore, only some studies are included in the meta-analysis.

Some comparisons were carried out irrespective of dosages, formulations and days post inoculum (dpi).

6.2.7. Quality assessment

The quality assessment was performed using the Cochrane tool for quality assessment of methodology of randomised controlled trials (Higgins and Altman , 2008).

6.2.8. Synthesis of results and discussion

Limited data were available in the studies, and only 12 studies could be used for data extraction. Data regarding dosages (ranging from 0.1 to 10 mg/kg body weight), administration (oral, IM or SC injection, or topical), drug duration and time between intervention (treatment) and sampling, and assessment of drug efficacy were extracted from the studies. In addition, information about the form of the drug administered (i.e. tablet or gelatin capsules/liquid for injection or topical application), the number of protoscoleces administered at experimental infection, the worm burden found at necropsy, and the time between experimental infection, intervention (immature and mature stages) and testing (necropsy) was collected.

The 12 studies were highly heterogeneous in their treatment protocols, and therefore no meta-analysis was possible. From the 12 selected studies, only one study examined the anthelmintic drug epsiprantel. All of the other studies examined the anthelmintic praziquantel, either as a monodrug, or in combination with other anthelmintic drugs, tested in various dosing regimens and formulations. A description of the various studies is given below. All studies used necropsy to determine the effect of the intervention.

6.2.8.1. Dogs: praziquantel versus placebo against immature worms by dosage and time after deworming

Six studies described the use of praziquantel against immature EM in dogs (Rommel *et al.*, 1976, ID 8 Appendix I WP4 Request 9; Thomas *et al.*, 1978, ID 12 Appendix I WP4 Request 9; Andersen *et al.*,1981, ID 1 Appendix I WP4 Request 9; Andersen *et al.*, 1985, ID 7 Appendix I WP4 Request 9; Sakashita *et al.*, 1995, ID 10 Appendix I WP4 Request 9; Schroeder *et al.*, 2009, ID 3 Appendix I WP4 Request 9). All of these studies show that praziquantel is effective against immature EM in dogs. The efficacy of the drug seems to decrease with decreasing dose. Dosages of below 1 mg/kg body weight were not tested. Andersen and colleagues (1985) reported that a dose of 1 mg/kg body weight was 100 % effective; however, Rommel and colleagues (1976) reported that, at a dose of 1 mg/kg body weight, an efficacy of only 82 % was achieved, and at a dose of 2.5 mg/kg body weight the efficacy increased to 97 %. With concentrations of 5 or 10 mg/kg body weight, 100 % efficacy was achieved. These results are confirmed by Thomas and colleagues (1978), who reported reaching an efficacy of 95 % at a dose of 1 mg/kg body weight, 96 % efficacy for 2.5 mg/kg body weight and 100 % efficacy for both 5 and 10 mg/kg body weight. The remaining studies used doses of only 5 mg/kg body weight or higher and all reported 100 % efficacies, although these studies varied in, for example, the formulations used, whether a monodrug or a combination was used, and the timing of the intervention. The time between the day of intervention and the assessment of the effect of intervention varied from two to three days (Thomas *et al.*, 1978) to 16 days (Rommel *et al.*, 1976). If a dose of > 5 mg/kg body weight was administered, 100 % efficacy was reached after two to three days.

In conclusion, a dose of 5–10 mg/kg of praziquantel seems to be effective at completely deworming dogs in three days.

6.2.8.2. Dogs: praziquantel versus placebo against mature worms by dosage and time after deworming

Three articles described the use of praziquantel against mature EM, showing that praziquantel is effective against mature EM in dogs (Rommel *et al.*, 1976, ID 8 Appendix I WP4 Request 9; Sakamoto *et al.*, 1976, ID 13 Appendix I WP4 Request 9; Thomas *et al.*, 1978, ID 12 Appendix I WP4

Request 9). However, the efficacy of the drug decreases with decreasing dose. Doses of less than 1 mg/kg body weight did not result in a satisfactory level of efficacy: one dog was treated with a single, oral dose of 0.5 mg/kg body weight with the pure form of praziquantel in gelatin capsules, resulting in 67 % efficacy and two dogs were treated similarly, but with a dose of 0.1 mg/kg body weight resulting in 0 % efficacy (Thomas *et al.*, 1978; ID 12 Appendix I WP4 Request 9). This ineffectiveness of concentrations of less than 1 mg/kg body weight was confirmed by Sakamoto and colleagues (1997; ID 13 Appendix I WP4 Request 9). Although both Thomas and colleagues (1978) and Sakamoto and colleagues (1976) showed 100 % efficacy and 99.95 % efficacy, respectively, at a concentration of 1 mg/kg body weight, the efficacy found at a concentration of 2.5 mg/kg body weight, was only 96 % (Rommel *et al.*, 1976; ID 8 Appendix I WP4 Request 9). Sakamoto and colleagues (1977; ID 13 Appendix I WP4 Request 9) reported a 99.99 % efficacy at a dose of 5 mg/kg body weight. However, the differences among these studies must be emphasised, regarding, for example, the formulations used, the timing of the interventions and the infective doses. The time between the day of intervention and the assessment of the effect of intervention was two or three days. If a dose of > 5 mg/kg body weight was administered, 100 % efficacy was reached after two to three days.

In conclusion, the available literature suggest that a dose of 5–10 mg/kg body weight of praziquantel has an efficacy of 99.99 % or higher with regard to deworming dogs in three days.

6.2.8.3. Cats: praziquantel versus placebo against immature worms

Five studies examined cats and treatment with praziquantel against immature EM (Andersen *et al.*, 1981, ID 1 Appendix I WP4 Request 9; Charles *et al.*, 2005, ID 9 Appendix I WP4 Request 9; Jenkins *et al.*, 2000, ID 4 Appendix I WP4 Request 9; Jenkins *et al.*, 2003, ID 2 Appendix I WP4 Request 9; Tielemans *et al.*, 2014, ID 23 Appendix I WP4 Request 9). No studies were performed on cats and the use of praziquantel against mature EM. One study reported the use of a topical formulation, containing emodepside (3 mg/kg) and praziquantel (12 mg/kg), and showed that depending on the initial infective dose, efficacy was 98.5 % (with an infective dose of 39 600 protoscolices) or 100 % (with an infective dose of 10 000 or 20 000 protoscolices) (Charles *et al.*, 2005; ID 9 Appendix I WP4 Request 9). Tielemans and colleagues (2014, ID 23 Appendix I WP4 Request 9) also reported on topical administration. In this study, they infected with 30 000 protoscolices and reported an efficacy of 100 % using a combination drug including a 10 mg/kg body weight dose of praziquantel (Tielemans *et al.*, 2014; ID 23 Appendix I WP4 Request 9). Another study examined the topical use of praziquantel, at a dose of 8 mg/kg body weight, and also reported 100 % efficacy using an infective dose of 10 000 (Jenkins *et al.*, 2000; ID 4 Appendix I WP4 Request 9). All other studies reported 100 % efficacy and used dosages, in oral or injectable form, of 5 mg/kg body weight or higher. The time between the day of intervention and the assessment of the effect of intervention varied from two days (Jenkins *et al.*, 2000 ID 4 Appendix I WP4 Request 9; Charles *et al.*, 2005; ID 9 Appendix I WP4 Request 9) to 13 days (Jenkins *et al.*, 2000; ID 4 Appendix I WP4 Request 9). As described above, Charles and colleagues (2005; ID 9 Appendix I WP4 Request 9) reported only a 98.5 % efficacy in one of the three experiments. In the study by Jenkins and colleagues (2003; ID 2 Appendix I WP4 Request 9), 100 % efficacy was reached after five days. It remains to be determined whether the insufficient efficacy reported by Charles and colleagues (2005; ID 9 Appendix I WP4 Request 9) was because of the high infective dose used or the time between intervention and testing. Until further studies become available, the time from intervention to 100 % efficacy should be considered to be five days.

In conclusion, the available studies suggest that praziquantel is effective at deworming cats at an oral or injectable dose of 5 mg/kg body weight or higher in five days. Topical application seems to work well for doses of > 8 mg/kg body weight, unless the cat is infected with a very high number of EM.

6.2.8.4. Cats and dogs: epsiprantel versus placebo

Only one study examined the use of epsiprantel. This anthelmintic was 100 % effective for deworming only cats, at a dose of 2.7 mg/kg body weight, infected with 22 600 protoscolices. However, the dogs that were used in the study were infected with 200 000 or 80 000 protoscolices and reached, respectively, 99.6 % and 99.9 % efficacy using dosages of between 4.9 and 5.8 mg/kg body weight. These infective doses are very high compared with the other studies, and this may influence the result.

Also, the two experiments that evaluated the efficacy of the drugs in dogs were based on a shorter time between deworming and necropsy (four days in dogs vs. six days in cats). The time from intervention to the assessment of efficacy was four days for all groups.

These findings confirm the recommendation from the ESCCAP to treat dogs in endemic areas at four weekly intervals (i.e. within the prepatent period) with an effective anthelmintic containing praziquantel. However, the ESCCAP also recommends the use of epsiprantel. According to our analysis, epsiprantel is 100 % effective in only cats. In dogs, epsiprantel reached an efficacy of 99.6 % in dogs infected with 200 000 protoscolices. In high-risk situations (e.g. prior to entry into non-endemic countries), the ESCCAP also recommends the treatment of cats, because although cats are considered poor hosts for EM, they are sporadically infected and can also shed eggs. Praziquantel is commonly available in tablet or injectable (Droncit®) form. Praziquantel is available in combination preparations (Drontal®, Profender®, Excil®, Cestem®, Mansonil® and Milbemax®) and also in a topical formulation (Droncit® Spot On) specifically for cats.

6.2.9. Conclusion

In conclusion, the studies demonstrated efficacy of a single dose of praziquantel against mature and immature EM at concentrations > 5 mg/kg body weight. Most studies showed that the efficacy of praziquantel was increased with a higher dose. The efficacy of praziquantel in combination with other anthelmintic drugs is good. The efficacy of the topical administration of praziquantel in cats was 98.5 % in one study, although two other studies reported 100 % efficacy. These differences may relate to the high infective dose used in the first study. Topical administration is a useful advance for controlling EM infection in cats. The results on the efficacy of epsiprantel may also have been influenced by the high infective doses used: epsiprantel reached 100 % efficacy in cats, whereas in dogs, infected with 200 000 protoscolices, it was 99.6 %.

No serious side effects were seen after treatment with praziquantel at necropsy. In one study (Jenkins et al., 2000), one-fifth of the cats showed transient scratching as a result of the topical administration of praziquantel. In the epsiprantel study (Eckert *et al.*, 2001; ID 5 Appendix I WP4 Request 9), several dogs in one treatment group (dosage: 5.4 mg/kg body weight) showed bloody diarrhoea.

No information was found about the time of egg/parasite dispersal after treatment, so no recommendation can be given regarding how long after treatment faeces need to be discarded. Studies in ferrets were not available.

7. Work Package 5: monitoring, surveillance and control

7.1. EFSA request 3: a systematic review on the monitoring and surveillance programmes for *Echinococcus multilocularis* infection in definitive and intermediate hosts

EM is a cestode, responsible for a rare zoonosis, AE. The life cycle of the parasite is mostly sylvatic and is based on the predator–prey relationship between DHs (mainly foxes) and IHs (small rodents) and on the survival of the free stage of the parasite (oncospheres) in the environment. Domestic dogs or cats can also be sporadically infected but the parasitic biomass of EM occurs in wildlife. EM is present in the northern hemisphere and is endemic in Europe, where its geographical distribution has been reported to be increasing over the last two decades, in theory as a consequence of increasing fox populations. Moreover, the prevalence recorded in historically endemic areas has also increased over the same time.

Because of the absence of a proper monitoring network, the studies used in this report have been designed to describe programmes at a given prevalence of the parasite. Different epidemiological studies in Europe have been published, giving information about the prevalence of EM in wildlife, principally in foxes, but only few data are available on IHs. Sampling was also different from one study to another: sampling was extensive in some areas and used a comprehensive sampling strategy, whereas in other studies the samples analysed were collected without any surveillance programme.

"Surveillance" is considered as the continuous scrutiny of the factors that determine the occurrence and distribution of a disease. It implies only the observation and reporting of findings, without intervention.

"Monitoring" is often used interchangeably with "surveillance". It usually refers to the ongoing measurement of health services or health programmes in order to evaluate the particular programme/service or intervention, with the constant adjustment of performance in relation to the results. "Monitoring" is the observation of changes after some intervention(s).

Since there are no official monitoring systems in most of the EU MSs, the only source of information was the scientific literature.

7.1.1. Aim

The objectives of this systematic review were to identify and describe the monitoring and surveillance programmes on EM in the intermediate and definitive hosts, and to determine the scale of monitoring and surveillance in the EU and AC.

7.1.2. Search

Databases were searched using keywords associated with the Boolean operators "AND" and "OR". The question mark ("?") was used to expand searches by looking for words with similar prefixes using more than one letter (i.e. "echinococc?" was used to search for "echinococcus", "echinococci", "echinococcosis" and "echinococcoses"). The hash mark ("#") was used to expand searches by looking for words with similar prefixes using one letter (i.e. dog# was used to search for "dog" or "dogs").

Different combinations were tailored for each electronic database in order to narrow the amount of results retrieved but, at the same time, to maximise the number of relevant studies.

The full electronic search strategy, including any limits used, was:

[ECHINOCOCCUS MULTILOCULARIS OR (ECHINOCOCOCCUS AND MULTILOCULARIS) OR E# MULTILOCULARIS OR ALVEOLAR ECHINOCOCCOSIS OR A# ECHINOCOCCOSIS] AND (DOG# OR CAT# OR FOX OR FOXES OR RODENT# OR RODENTIA OR CANIS OR CANID? OR FELIS OR FELID? OR VULPES OR DOMESTIC OR SYLVATIC? OR WILD?) AND (MONITORING OR SURVEILLANCE? OR CONTROL?)

A search using the STN International platform was carried out on 5 November 2013. An additional search was performed on 11 February 2015 to identify any papers that had been published since the initial search. The results of these two searches were combined. If database outcomes overlapped, all duplicates articles were removed. Review Manager (RevMan) software was used to prepare and maintain this systematic review.

7.1.3. Study selection

The inclusion criteria were:

- Studies published from 1900 to present;
- studies published in English, German, French, Polish, Finnish, Dutch, Spanish or Italian;
- studies based on cross-sectional, case–control or cohort design;
- primary research studies published or in press;
- reports on wild or domestic EM monitoring or surveillance.

The list of included articles are available in Appendix I WP5-R3: *List of included studies.*

The exclusion criteria were as follows:

- studies providing data from outside Europe (EU countries and ACs);
- studies on humans;
- studies on agents other than EM (e.g. *E. granulosus*);
- reviews, letters or editorials without original data or case reports;
- duplicated data;
- articles with full texts written in languages other than those that at least one member of the team can read and understand (i.e. English, German, French, Polish, Finnish, Dutch, Spanish and Italian).

The list of excluded articles are available in Appendix II WP5-R3: *List of excluded studies.*

The study selection process concerning the WP5 request 3 is reported using the flow chart showed in Fig 1 WP5.

7.1.4. Data extraction

Data were extracted by completing the fields of a data extraction form.

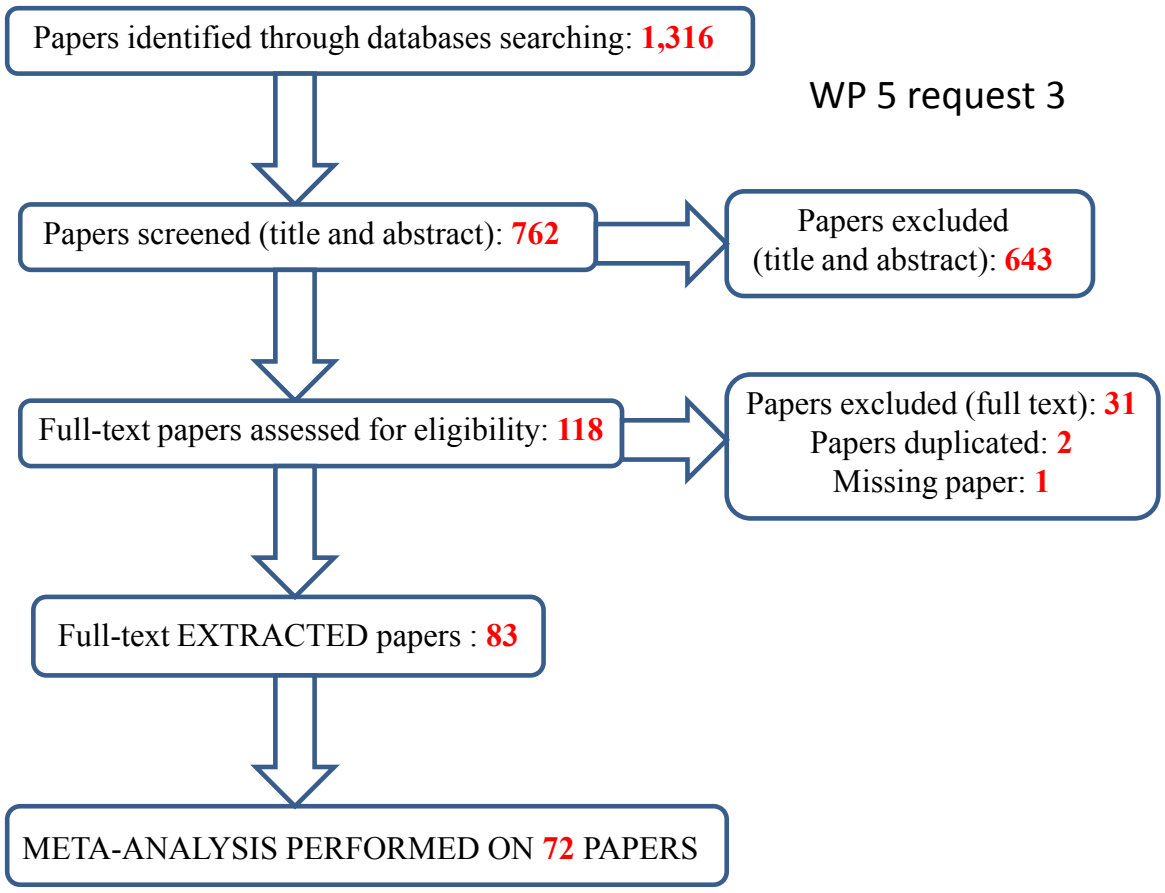


Figure 1 WP5: Flow chart of selection of the studies

7.1.5. Statistical approach and meta-analysis

Meta-analyses were performed by considering the study design and two main groups: DH and IH groups.

The DHs were divided into red fox (*Vulpes vulpes*), dog (*Canis lupus f. familiaris*), cat (*Felis silvestris f. catus*) and wild canidae, such as golden jackal (*Canis aureus*) and raccoon dog (*Nyctereutes procyonoides*).

The IHs were grouped into macrogroups: microrodents (*Apodemus* spp., *Arvicola* spp., *Clethrionomys*[=*Myodes*]*glareolus*, *Microtus minutus* and *Mus musculus*), aquatic rodents (*Ondatra zibethicus* and *Myocastor coypus*) and pig (*Sus scrofa f. domesticus*).

Each meta-analysis included studies conducted in the same geographical area: Europe, the same MS/AC and, if possible, the same NUTS 2 level.

Furthermore, within the microrodent macrogroup, the meta-analyses were performed at European scale targeting *Apodemus* spp., *Arvicola* spp., *Clethrionomys[=Myodes]glareolus* and *Microtus minutus*. In the aquatic rodent macrogroup, the meta-analyses were performed without distinction between *Ondatra zibethicus* and *Myocastor coypus*.

With regard to the DHs, different meta-analyses were performed taking according to the diagnostic method used.

The pooled prevalence proportion (%) was calculated using the meta-analytic approach, according to the sample size of the target species tested in relation to the population of that species in the country. A forest plot was produced to describe the pooled analysis. To perform meta-analysis, the heterogeneity was considered. The Cochran's Q test was performed to assess the degree of heterogeneity between studies, and the I^2 statistic was used to describe the percentage of total variation across studies as a result of heterogeneity. If the p-value from the Q test was < 0.05 and I^2 was > 50 %, heterogeneity was found and a random-effect model is shown. However, if heterogeneity was not found, a fixed-effect model is reported.

Publication bias was quantified by inspection of funnel plots and computation of Egger and Begg test probability values, if possible. If the meta-analysis included a low number of studies, it was not possible to assess publication bias by inspection of funnel plots.

7.1.6. Limits of the meta-analysis

This meta-analysis was not stratified for the years/months in which the studies were performed.

It was not possible to perform a meta-analysis that divided the studies into surveillance and monitoring types.

7.1.7. Quality assessment

The quality assessment was performed using the available tools, considering study design, for observational studies, in accordance with the NOS (Wells *et al.*, 2014.).

7.1.8. Synthesis of results

For this systematic review, 72 papers were selected for the meta-analysis. Because of the absence of surveillance and/or monitoring terms within many of these papers (even if those papers can be considered as surveillance/monitoring studies), this review is not totally exhaustive. Since there are no official monitoring systems in most of the EU and ACs, the only source of information is the scientific literature.

Nevertheless, studies from 18 out of 28 EU countries and from two ACs were selected. The countries that are not represented in this review are from the eastern and southern parts of the EU. The countries that have historically been associated with EM (France, Switzerland, Germany and Austria) are the focus of most of the studies (28 papers). Countries considered to be free from the parasite (e.g. the UK, Ireland, Norway and Finland) or as newly endemic (e.g. Sweden and Denmark) were also represented (by 13 papers). The distribution of EM-infected foxes is often heterogeneous at population and spatial level; therefore, the studies selected were not generally performed at the national level, except for countries considered to be EM free or newly endemic and where large surveillance programmes have been conducted. Moreover, EM prevalence may vary across a country and thus the use of NUTS 2 levels is a more suitable geographical scale for the analyses. Furthermore, the NUTS 2 level is a more adapt unit for managing the home range of foxes.

According to the definition used for monitoring, as ongoing survey, only 3 out of 72 papers belong to this category (Berke *et al.*, 2008, ID 43 Appendix I WP5 Request 3; Takumi *et al.*, 2008, ID 98 Appendix I WP5 Request 3; Miterpakova *et al.*, 2011, ID 482 Appendix I WP5 Request 3). In the surveillance papers, the control period ranged from a few months to a few years, but without any adjustment of performances in relation to the results.

7.1.8.1. Fox results

Foxes were the main target for the surveillance/monitoring programmes, and they are considered as the main DH for EM. With regard to EM surveillance/monitoring, the fox population is the only population of wild animal that could be randomly sampled to avoid bias, even if hunting and night shooting do not represent a real random selection process. The other wild carnivore species, such as raccoon dogs and jackals, were rarely targeted in these programmes, principally because of their low presence in Europe. The main diagnostic method used (60 %) in wild DHs is the analysis of the intestinal content after necropsy by IST or SCT methods (direct detection of the parasite) and, in some studies (13 %), faeces were analysed by copro-antigen ELISA (indirect detection). Diagnostic methods were not taken into account in the meta-analyses because of the heterogeneity of the tests used during the monitoring/surveillance programmes. All positives results were considered as equivalent, regardless of the analytical method used.

Because of the high heterogeneity of prevalence values reported in the studies, data from foxes were divided into three prevalence categories. These three categories were completed by adding a geographical scale at NUTS 2 level, since it generally corresponds to the scale used in the different studies. Depending on the level of prevalence recorded at NUTS 2 level, the categories were reported as follows:

- < 1 % (not considered as EM free according to EU legislation) (Table 2 WP5);
- from 1 to 10 % (low endemicity) (Table 3 WP5);
- >10 % (medium to high endemicity) (Table 4 WP5).

Studies conducted at country level have been differently analysed with only two prevalence categories, as follows:

- <1 % (for countries considered as EM free) (Table 5 WP5);
- <1 % (for countries not considered as EM free) (Table 6 WP5);
- >1 % (for countries with medium to high levels of EM prevalence) (Table 7 WP5).

The table of the minimum sample sizes for given prevalence thresholds and populations sizes (95 % CI) was used to determine the cut-off (Table 1 WP5). The tabulated sample size represents the minimal number of animals that need to be examined to find at least one positive animal, if the proportion of infected animals is above the chosen threshold at the given population size (Cannon and Roe, 1982).

In the absence of an estimation of the fox population size, it was considered as infinite in the determination of the sample size required. The sampling size retained was 299 animals for a 1 % prevalence in an unknown population size, and 29 animals for a 10 % prevalence.

Table 1 WP5: Tabulation of minimum sample sizes for given prevalence thresholds (horizontal) and populations sizes (vertical) at the 95 % confidence level. This is represents part of the table from Cannon and Roe (1982)

Population size (N)	Prevalence thresholds											
	50 %	40 %	30 %	25 %	20 %	15 %	10 % [(a)]	5 %	2 %	1 % [(a)]	0.5 %	0.1 %
10	4	5	6	7	8	9	10	10	10	10	10	10
20	5	6	7	9	10	13	16	19	20	20	20	20
30	5	6	8	9	11	14	19	26	30	30	30	30
40	5	6	8	10	12	15	21	31	40	40	40	40
50	5	6	8	10	12	16	22	35	48	50	50	50
60	5	6	8	10	13	16	23	38	55	60	60	60
4 000	5	6	9	11	14	19	29	58	146	288	556	2 108
5 000	5	6	9	11	14	19	29	59	147	290	564	2 253
6 000	5	6	9	11	14	19	29	59	147	291	569	2 358
7 000	5	6	9	11	14	19	29	59	147	292	573	2 437
8 000	5	6	9	11	14	19	29	59	147	293	576	2 498
9 000	5	6	9	11	14	19	29	59	148	294	579	2 548
10 000	5	6	9	11	14	19	29	59	148	294	581	2 588
∞	5	6	9	11	14	19	29 [(a)]	59	149	299 [(a)]	598	2 995

(a): Prevalence thresholds and population size selected for the analysis

7.1.8.2. Definitive hosts

Fox

NUTS 2 level

Table 2 WP5: Meta-analysis for foxes with prevalence of ≤ 1 % (not considered as EM free)

No of papers	No of studies included in the meta-analysis	No of studies with sample size (N ≥ 299)	Effect model	Cochran Q (p-value)	I^2 (%)	Pooled prevalence (%) NUTS2 level	95 % CI (%)
8	13	4	Fixed	0.86	0.00	0.29	0.10–0.57

NUTS2: BE10, BE22, BE25, DEF0, FR51, ITC2, ITC31, ITC32, ITC46, ITD 33, PL22–PL52 and PL51.

Table 3 WP5: Meta-analysis for foxes with prevalence of between 1 % and 10 %

No of papers	No of studies included in the meta-analysis	No of studies with sample size (29 < N < 299)	Effect model	Cochran Q (p-value)	I^2 (%)	Pooled prevalence (%) NUTS2 level	95 %CI (%)
14	20	19	Random	< 0.0001	87.90	5.23	3.87–6.79

NUTS2: AT13, AT22, BE21, BE23, BE24, DE40, DE93, DEE0, HU10, HU23, HU32, HU33, ITD20, NL11, NL42, PL33, PL41, PL42, PL43 and PL51.

Table 4 WP5: Meta-analysis for foxes with prevalence of ≥ 10 %

No of papers	No of studies included in the meta-analysis	No of studies with sample size (N ≥ 29)	Effect model	Cochran Q (p-value)	I^2 (%)	Pooled prevalence (%) NUTS2 level	95 % CI (%)
25	34	33	Random	< 0.0001	96.8	23.39	20.78–26.10

NUTS2: BE34, CH01, CH02, CH03, DE12, DE21, DE91, DE92, DE94, DEE0, DEG0, FR26, FR43, HU21, HU22, HU31, ITD 10, PL12, PL21, PL31, PL32, RO11, SK01, SK02, SK03 and SK04.

Country level

Studies conducted at the country level were analysed separately and only two prevalence categories were retained: those with a prevalence of ≤ 1 % (for EM-free or extremely low endemic areas) or > 1 % (for medium to highly endemic areas). Furthermore, it appears to be relevant to make a distinction between countries considered as EM free and endemic countries.

Table 5 WP5: Meta-analysis for foxes with prevalence of ≤ 1 % in MSs considered as EM free (FI, IR, NO and UK)

No of papers	No of studies included in the meta-analysis	No of studies with sample size (N ≥ 299)	Effect model	Cochran Q (p-value)	I^2 (%)	Pooled prevalence (%) NUTS2 level	95 % CI (%)
6	8	8	Fixed	1.00	0	0	0–0.07

Table 6 WP5: Meta-analysis for foxes with prevalence ≤ 1 % in MS not considered as EM free (DK, SE)

No of papers	No of studies included in the meta-analysis	No of studies with sample size (N ≥ 299)	Effect model	Cochran Q (p-value)	I^2 (%)	Pooled prevalence (%) NUTS2 level	95 % CI (%)
6	6	6	Random	0.003	72	0.18	0.05–0.40

Table 7 WP5: Country level for foxes with prevalence of > 1 % (AT, BE, CH, DE, HU and SK)

No of papers	No of studies included in the meta-analysis	No of studies with sample size N ≥ 29	Effect model	Cochran Q (p-value)	I^2 (%)	Pooled prevalence (%) NUTS2 level	95 % CI (%)
12	12	12	Random	< 0.0001	99.4	18.87	11.37–27.74

With regard to foxes at NUTS 2 level, in areas with an expected prevalence of ≤ 1 %, the sample size was satisfactory in only 4 out of 13 studies. In areas with an expected prevalence of > 1 %, the sample size was acceptable in 52 out of 54 studies. At the country level, the required sample size is in accordance with the prevalence in all of the 26 studies. Studies on foxes examining monitoring/surveillance programmes were consistent when the prevalence in foxes is > 1 %. Particular attention should be paid to EM-free or low endemic areas. Even in countries endemic for EM, the sample size should be adjusted to the expected prevalence of the studied area. On the other hand, sample size was correctly considered for performing surveillance at the country level, even for countries that are EM free or at low endemicity level.

Other species of definitive host

For the other species of DHs (dog, cat and raccoon dog) and IHs (small rodent, aquatic rodent and pig), the studies were stratified according to EM prevalence in red foxes in the involved country

because foxes are considered as the species with the highest prevalence. Based on this, studies were assigned to one of the two prevalence categories: ≤ 1 % (for EM-free or extremely low endemic areas) or >1 % (for medium to highly endemic areas). Meta-analyses of these two categories were performed on cats (Table 8 WP5, Table 9 WP5), dogs (Table 10 WP5, Table 11 WP5), raccoon dogs (Table 12 WP5, Table 13 WP5), small rodents (Table 14 WP5, Table 15 WP5) and aquatic rodents (Table 16 WP5).

Regardless of foxes, other DH species may be targeted for EM diagnosis among domestic carnivores, but also wild species if such populations are present in the areas. Only raccoon dogs (six papers) and jackals (one paper) were investigated within the framework of monitoring/surveillance programmes and generally by using SCT; even copro-antigen ELISA and/or PCR were used in Finland and Norway (Wahlström *et al.*, 2011; ID 352 Appendix II WP2). Dogs and, to a lesser extent, cats were also investigated as domestic DHs in 13 papers (13/73 = 19.4 %), notably in countries with very low prevalence or considered as EM free (four papers). A coprological approach, involving copro-antigen ELISA or copro-PCR, was used in all of the studies except one. In fact, other invasive methods for EM diagnosis are generally not applicable to dogs and cats.

Cat

Table 8 WP5: Meta-analysis for cats in medium to high endemic areas (prevalence in foxes > 1 %)

No of papers	No of studies included in the meta-analysis	No of studies with sampling size adapted to detect an expected prevalence of 1 % (N ≥ 299)	Effect model	Cochran Q (p-value)	I^2 (%)	Pooled prevalence (%) NUTS2 level	95 % CI (%)
5	9	5	Fixed	0.06	46.0	0.46	0.35–0.60

Table 9 WP5: Meta-analysis for cats in low-level endemic areas (prevalence in foxes ≤ 1 %)

No of papers	No of studies included in the meta-analysis	No of studies with sampling size adapted to detect an expected prevalence of 1 % (N ≥ 299)	Effect model	Cochran Q (p-value)	I^2 (%)	Pooled prevalence (%) NUTS2 level	95 % CI (%)
1	3	0	Fixed	0.96	0.00	0.75	0.07–2.18

Dog

Table 10 WP5: Meta-analysis for dogs in medium to high endemic areas (prevalence in foxes > 1 %)

No of papers	No of studies included in the meta-analysis	No of studies with sampling size adapted to detect an expected prevalence of 1 % (N ≥ 299)	Effect model	Cochran Q (p-value)	I^2 (%)	Pooled prevalence (%) NUTS2 level	95 % CI (%)
5	9	6	Random	0.001	69.4	0.24	0.070–0.51

Table 11 WP5: Meta-analysis for dogs in low-level endemic areas (prevalence in foxes ≤ 1 %)

No of papers	No of studies included in the meta-analysis	No of studies with sampling size adapted to detect an expected prevalence of 1 % (N ≥ 299)	Effect model	Cochran Q (p-value)	I^2 (%)	Pooled prevalence (%) NUTS2 level	95 % CI (%)
4	7	3	Fixed	0.99	0	0	0–0.24

Raccoon dog

Table 12 WP5: Meta-analysis for raccoon dogs in medium to high endemic areas (prevalence in foxes > 1 %)

No of papers	No of studies included in the meta-analysis	No of studies with sampling size adapted to detect an expected prevalence of 1 % (N ≥ 299)	Effect model	Cochran Q (p-value)	I^2 (%)	Pooled prevalence (%) NUTS2 level	95 % CI (%)
3	3	1	Random	0.04	68.5	0.002	0.003–0.021

Table 13 WP5: Meta-analysis for raccoon dogs in low-level endemic areas (prevalence in foxes ≤ 1 %)

No of papers	No of studies included in the meta-analysis	No of studies with sampling size adapted to detect an expected prevalence of 1 % (N ≥ 299)	Effect model	Cochran Q (p-value)	I^2 (%)	Pooled prevalence (%) NUTS2 level	95 % CI (%)
2	2	1	Fixed	0.65	0	0	0–0.52

The sample size was not adapted to the expected prevalence in approximately half of the studies. Because of the very low prevalence generally observed in domestic carnivores, it appears to be essential to adapt the sample size, especially in low-level endemic areas (with a prevalence in foxes of ≤ 1 %). The meta-analysis revealed that there is no significant difference in prevalence between low- and medium to high endemic areas for any of the three DH species in question. Because of the presence of only one paper on jackals, no meta-analysis was performed for this species. Interestingly, the prevalence value of 9 % obtained by analysis of 11 jackals is similar to the prevalence of 12.6 % in foxes (n = 150) obtained previously by a study performed in Hungary (Sreter *et al.*, 2004; ID 87 Appendix I WP5 Request 3). Furthermore, regardless of the endemic status of the sampled areas, the pooled prevalence in dogs, cats or raccoon dogs is < 1 %. This is considered to reflect a generally low prevalence level in these DHs, even if much higher prevalence values are reported by some studies examining high-level endemic areas in eastern European countries.

7.1.8.3. Intermediate hosts

With regard to IHs, rodent species, such as *Microtus* spp. and *Arvicola* spp., are the main targets for monitoring/surveillance programmes (nine papers) because they are the main IH species in Europe (Giraudoux *et al.*, 2007;, ID 346 AppendixII WP2). Other species considered as accidental or aberrant hosts, such as aquatic rodents (five papers on nutria and muskrat) and swine (two papers on pig and wild boar), were also represented. Systematically, the larval stage of the parasite was diagnosed by macroscopic observation during necropsy, followed by PCR confirmation in half of the studies.

Diagnosis was more frequently performed in small rodents than the other IHs probably because of the frequent presence of small non-fertile or calcified lesions.

Microrodents

Table 14 WP5: Meta-analysis for microrodents in medium to high endemic areas (prevalence in foxes of > 1 %)

No of papers	No of studies included in the meta-analysis	No of studies with sampling size adapted to detect an expected prevalence of 1 % (N ≥ 299)	Effect model	Cochran Q (p-value)	I^2 (%)	Pooled prevalence (%) NUTS2 level	95 % CI (%)
5	5	3	Random	< 0.0001	96.5	3.08	0.27–8.78

Table 15 WP5: Meta-analysis for microrodents in low-level endemic areas (prevalence in foxes of ≤ 1 %)

No of papers	No of studies included in the meta-analysis	No of studies with sampling size adapted to detect an expected prevalence of 1 % (N ≥ 299)	Effect model	Cochran Q (p-value)	I^2 (%)	Pooled prevalence (%) NUTS2 level	95 % CI (%)
4	4	1	Random	< 0.0001	98.8	2.36	0.58–14.08

*Aquatic rodents: muskrat (*Ondatra zibethicus*) and nutria (*Myocastor coypus*)*

Table 16 WP5: Meta-analysis for aquatic rodents in medium to high endemic areas (prevalence in foxes > 1 %)

No of papers	No of studies included in the meta-analysis	No of studies with sampling size adapted to detect an expected prevalence of 1 % (N ≥ 299)	Effect model	Cochran Q (p-value)	I^2 (%)	Pooled prevalence (%) NUTS2 level	95 % CI (%)
5	5	5	Random	< 0.0001	99.3	5.10	0.45–14.33

Surprisingly, for small rodents, the pooled prevalence (2.4 %) obtained in low-level endemic areas is higher than that in foxes (≤ 1 %). This is because of the exceptional situation the Svalbard islands (Norway), where an extremely high prevalence of 26.3 % is recorded (Henttonen *et al.*, 2001; ID 62 Appendix I WP5 Request 3), while mainland Norway is considered free from EM. If Svalbard is excluded, no EM infection of small rodents was observed, despite the analysis of more than 23 000 samples in low-level endemic areas. In high-level endemic areas (> 1 % in foxes), the pooled prevalence (3.1 %) is considered relatively high, but it is mainly influenced by local studies in very high-level endemic areas, such as areas in Switzerland (Gottstein *et al.*, 1996, ID 56 Appendix I WP5 Request 3; Reperant *et al.*, 2009, ID 83 Appendix I WP5 Request 3).

With regard to aquatic rodents, the pooled prevalence of 5.1 % is relatively high when considering that data from studies of areas that have become endemic relatively recently, such as in the west of France (Umhang *et al.*, 2013, ID 24 Appendix I WP5 Request 3) and the Netherlands (Borgsteede *et al.*, 2003, ID 79 Appendix I WP5 Request 3), were added to data from studies of high-level endemic areas in Germany and Belgium (Baumeister *et al.*, 1996, ID 89 Appendix I WP5 Request 3; Hanosset *et al.*, 2008, ID 57 Appendix I WP5 Request 3; Mathy *et al.*, 2009, ID 20 Appendix I WP5 Request 3).

7.1.9. Discussion

The meta-analyses were performed according to the target species studied in scientific research programmes, but independently from the matrix analysed and the diagnostic method used. The analysis, performed at national level, also focussed on the sample size of the target species (IH or DH), according to the EM prevalence in foxes, in order to identify the best strategy for monitoring or surveillance programmes. For wildlife monitoring or surveillance programmes, in the absence of information regarding the population size, the threshold retained for the sampling size, according to Cannon and Roe (1982), was 299 and 29 for expected prevalences of <1 % and 10 %, respectively. The aim was to allocate all studies to different categories according to the prevalence of EM.

For all studies carried out in the EU, the fox was the main target DH because this species has a predominant role in the maintenance of the sylvatic EM life cycle through large contamination of the environment with infected faeces. The studies on foxes, related to monitoring/surveillance programmes, were consistent. For the other DHs investigated for EM, the results suggest a low prevalence level, even if studies were conducted in high-level endemic areas. With regard to raccoon dogs and jackals, the other wild DH species, sampling areas were restricted to some EU countries and the recorded EM prevalence was generally lower than that detected in foxes from the same area. For domestic DHs (cats and dogs), necropsy for direct diagnosis is not conceivable. An indirect diagnosis on faeces could be considered on domestic DHs with new Q-PCR analysis approaches, but such surveillance studies would have relatively high costs because of the high number of animals that would have to be screened because of the very low prevalence in dogs. Finally, other DHs (e.g. cat, dog, raccoon dog and jackal) are not interesting target species for monitoring/surveillance programmes in countries or areas where the expected prevalence in foxes is ≤ 1 %.

Another possibility is to monitor EM in small rodent IHs. A direct diagnosis by macroscopic cyst detection at necropsy, which could be confirmed by PCR analysis, is easily conceivable. Nevertheless, the meta-analysis results indicate that small rodents are not good indicators for EM infection on a large scale: despite the analysis of more than 23 000 samples in low-level endemic areas (prevalence in foxes ≤ 1 %), no positive rodents were observed.

The surveillance of aquatic rodents could be used to give an indication of the presence of EM, even in newly endemic areas where the prevalence of foxes is around 5 % (Umhang *et al.*, 2013; ID 24 Appendix I WP5 Request 3). Muskrats and nutrias have been involved in large trapping campaigns, since they were listed as pests, and so they could easily be used as bioindicators of EM in areas considered free of this parasite through a morphological examination for liver parasite lesions with or without molecular confirmation. With regard to the other IHs investigated, pigs do not appear to be relevant because of the general indoor intensive breeding conditions used in Europe.

With regard to the sample size, this systematic review highlighted that, in low-level endemic areas (prevalence in foxes ≤ 1 %), the minimum sample size recommended for parasite detection is rarely reached, except for studies performed at the national level. In this context of low prevalence (observed for the other IHs and DHs), foxes are the main, and often the only, species targeted by surveillance/monitoring programmes, and are potentially supported by aquatic rodents in areas where they are culled. As regards the possibility of status modification from free to introduction/establishment, the monitoring/surveillance of EM-infected foxes should be repeated every year to confirm the free status of the country.

7.2. EFSA request 5: a systematic review on the programmes for the eradication of *Echinococcus multilocularis* in wildlife host species

The life cycle of EM is mostly sylvatic and is based on the predator–prey relationship between DHs (mainly foxes) and IHs (rodents) and on the survival of the free stage of the parasite (oncospheres) in the environment. Domestic dogs and cats can also be sporadically infected but the parasitic biomass of EM occurs in wildlife. In Europe, different studies have shown that fox populations have increased since the end of the 1990s (Chautan *et al.*, 2000; Gloor *et al.*, 2001), with more observations of foxes living in urban areas (Romig *et al.*, 1999, ID 17 Appendix II WP3 Request 1; Hofer *et al.*, 2000, ID 14 Appendix I WP2; Fischer *et al.*, 2005 ID 165 Appendix I WP2; Robardet *et al.*, 2008, ID 34 Appendix I WP2). These factors give rise to the question of whether or not prophylaxis could be used to reduce the presence of free eggs in the environment in order to manage the risk of human AE. Therefore, different research programmes have focused on fox treatment by anthelmintic baits containing praziquantel to manage EM infection in wildlife.

7.2.1. Aim

The objectives of this systematic review were to identify the programmes for the control and eradication of EM and to report these different strategies with their results in the EU and ACs from 1950 to present.

7.2.2. Search

Databases were searched using keywords associated with the Boolean operators "AND" and "OR". The question mark ("?") was used to expand searches by looking for words with similar prefixes using more than one letter (i.e. "echinococc?" was used to search for "echinococcus", "echinococci", "echinococcosis" and "echinococcoses"). The hash mark ("#") was used to expand searches by looking for words with similar prefixes using one letter (i.e. dog# was used to search for "dog" or "dogs"). Different combinations were tailored for each electronic database in order to narrow the amount of results retrieved but, at the same time, to maximise the number of relevant studies. The full electronic search strategy, including any limits used, was:

[ECHINOCOCCUS MULTILOCULARIS OR (ECHINOCOCOCCUS AND MULTILOCULARIS) OR E# MULTILOCULARIS OR ALVEOLAR ECHINOCOCCOSIS OR A# ECHINOCOCCOSIS] AND (DOG# OR FOX OR FOXES OR CANIS OR CANID? OR VULPES OR DOMESTIC OR SYLVATIC? OR WILD?) AND [ANTHELMINTIC# OR ANTIHELMINTIC# OR PRAZIQUANTEL OR DEWORM? OR DE WORM? OR ANTINEMATOD? OR VERMIFUGE# OR BAIT? OR ANTI HELMINTIC# OR ANTIHELMINT?) AND (PROGRAM? OR ERADICAT? OR CONTROL? OR ELIMINAT?)

A search using the STN International platform was carried out on 5 November 2013. An additional search was performed on 11 February 2015 to identify any papers that had been published since the initial search. The results of these two searches were combined. If database outcomes overlapped, all duplicates articles were removed. Review Manager (RevMan) software was used to prepare and maintain this systematic review.

7.2.3. Study selection

The inclusion criteria were:

- studies published from 1950 to present;
- studies published in English, German, French, Polish, Finnish, Dutch, Spanish or Italian;

- reports on eradication (or surveillance) programmes of EM in wildlife host species;
- studies based on cross-sectional, cohort and case–control design;
- experimental studies (trials);
- primary research studies published or in press.

The list of included articles are available in Appendix I WP5-R5: *List of included studies.*

The exclusion criteria were as follows:

- studies on agents other than (e.g. *E. granulosus*);
- studies providing data from outside Europe (EU countries and ACs);
- reviews, case reports, letters or editorials without original data;
- duplicated data;
- studies on humans;
- articles with full texts written in languages other than those that at least one member of the team can read and understand (i.e. English, German, French, Polish, Finnish, Dutch, Spanish and Italian).

The list of excluded articles are available in Appendix II WP5-R5: *List of excluded studies.*

The study selection process concerning the WP5 request 5 is reported using the flow chart showed in Fig 2 WP5.

7.2.4. Data extraction

Data were extracted by completing the fields of a data extraction form.

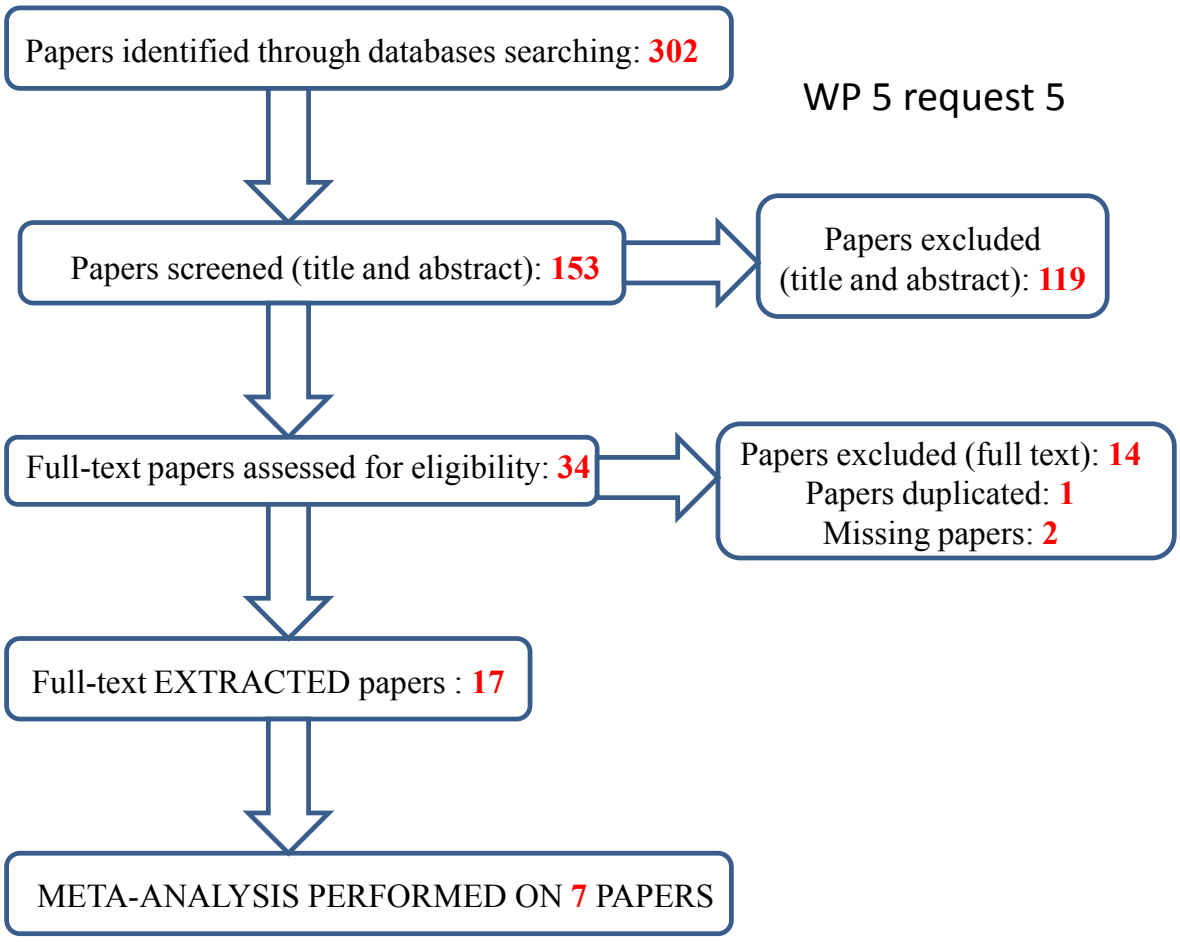


Figure 2 WP5: Flow chart of selection of the studies

7.2.5. Statistical approach and meta-analysis

The meta-analyses were performed considering the study design (all included studies were trial), two main groups of hosts (DHs and IHs) and the reference areas (bait area vs. control area).

In performing meta-analyses, two approaches were used. The first meta-analysis was performed across studies with available data on sample size and the number of positive samples at the start and at the end of the study. In this approach, we calculated the pooled risk difference (RD) for both bait and control areas by analysing the difference between the event rate (EM positive) at the start of the study and the event rate (EM positive) at the end of the study. Then, the 95 % CIs of the RD obtained from bait and control areas were compared. If there was an overlap between the 95 % CIs for the two areas, the difference was not considered statistically significant.

The second meta-analytic approach consisted of combining studies with the following available data: a value for sample size and a value for positive samples (in the studies used for this approach, values were not referred to with regard to any start or end time point) for both bait and control areas. We supposed that these data were obtained at the end of the studies; therefore, we combined them with data from the end of the studies. The pooled prevalence proportion (%) for bait and control areas was then calculated and the two 95 % CIs for pooled prevalence were compared to analyse if there was any overlap.

A forest plot was used to describe the pooled analysis. To perform meta-analysis, the heterogeneity was considered. The Cochran's Q test was performed to assess the degree of heterogeneity between studies, and the ^{2} statistic was used to describe the percentage of total variation across studies as a result of heterogeneity. If the p-value from the Q test was < 0.05 and I^2 was > 50 %, heterogeneity was found and a random-effect model is shown. However, if heterogeneity was not found, the fixed-effect model is reported.

Publication bias was quantified by inspection of funnel plots and computation of Egger and Begg test probability values, if possible. If the meta-analysis included a low number of studies, it was not possible to assess publication bias by inspection of funnel plots.

7.2.6. Limits of the meta-analysis

There were few available data; therefore, only some studies are included in the meta-analysis.

Meta-analyses were not stratified by country or for the years in which the studies were performed.

7.2.7. Quality assessment

The quality assessment was performed using the available tools, considering study design. For trials, we used the Cochrane Collaboration's tool for assessing the risk of bias (Higgins *et al.,* 2011).

7.2.8. Synthesis of results and discussion

Because of the low number of studies examining the control of EM in wildlife in Europe, non-European countries were also included in order to obtain a more complete overview of the different programmes implemented. A full-text extraction was performed on 17 papers, mainly from Germany (n = 6) and Switzerland (n = 3), but also one from France and the Slovak republic. The other papers correspond to two non-European countries: Japan (n = 5) and the USA (Alaska; n = 1).

All the studies targeted the main DH, namely the red fox, except for a study in the village of the Saint-Laurent Island in Alaska, where the target species was dog (Rausch *et al.*, 1990, ID 32 Appendix I WP5 Request 5). With the exception of this Alaskan study, the method of control used in all studies was the distribution, in the environment, of baits containing praziquantel (generally 50 mg). The bait density was between 15 and 50 baits/km², but in the majority of studies (n = 8) 15–20 baits/km² were used. Some trials also targeted fox dens (Tsukada *et al.*, 2002; ID 30 Appendix I WP5 Request 5) or examined the direct treatment of dogs with anthelmintic drugs (Rausch *et al.*, 199; ID 32 Appendix I WP5 Request 5).

The surface areas of bait distribution were extremely varied, generally ranging from a few to several hundred km², and distribution was carried out on foot and/or by car, or, when the surface area of bait distribution was several thousand kilometres, as in two of the German studies, the distribution of baits was accomplished by plane (Tackmann *et al.*, 2001, ID 3 Appendix I WP5 Request 5; Romig *et al.*, 2007, ID 17 Appendix I WP5 Request 5).

The treatment period ranged from 7 months to 5.5 years, with only 8 out of 17 studies covering a period exceeding one year. With regard to the dog study in Alaska, treatment was maintained for 10 years; this was probably facilitated by the low number of animals treated (70–90) and the direct interaction with dog owners rather than a distribution of baits in the environment. The frequency of treatment mainly ranged from one to three months, with a lower frequency in only three studies performed over three years (Tackmann *et al.*, 2001, ID 3 Appendix I WP5 Request 5; König *et al.*, 2005, ID 29 Appendix I WP2; Hegglin *et al.*, 2008, ID 18 Appendix I WP5 Request 5).

The monitoring of EM during the control studies was essentially accomplished by the analysis of fox intestines (by IST or SCT in nine papers) after shooting or trapping, or by copro-antigen ELISA performed on faeces (eight papers). In two studies, rodents and foxes were trapped in parallel (Hegglin *et al.*, 2003; ID 19 Appendix I WP5 Request 3), or alone when the target species was the domestic dog (Rausch *et al.,* 1990; ID 32 Appendix I WP5 Request 5) in order to perform monitoring by diagnostic testing of cysts in the liver.

Depending on the studies, control areas were defined as areas similar to the treated areas and were monitored simultaneously or, if simultaneous monitoring was not possible, the control areas corresponded to the treated areas before the distribution of the praziquantel baits.

By considering the prevalence data from the beginning and the end of the studies, if available, in the treated areas, it was found that the deworming treatment resulted in a slight to a high decrease in the prevalence of EM in 23 out of 26 treated areas. In one of the treated areas that did not show a decrease in prevalence, the prevalence remained stable, at 50 %, but, in this case, the prevalence in the control area increased from 33 % to 49 %, suggesting a positive effect of treatment (Antolova *et al.*, 2006; ID 9 Appendix I WP5 Request 5). In the two other areas that did not show any decrease in prevalence, the diminution of baiting frequency from 8.7 times per year to 4 times per year, then 2 times per year, explains the increase of EM prevalence, especially as the prevalence also increased in the control area (from 59 to 69 %) during the same period (Romig *et al.*, 2007; ID 17 Appendix I WP5 Request 5). An absence of EM at final monitoring was observed only once and corresponded to a treated area (156 km²) surrounded by another treated area (410 km²), which probably restricted the intrusion of infected foxes into this central area (Schelling *et al.*, 1997; ID 1 Appendix I WP5 Request 5). This study confirms that the control of fox infection could be effective in a restricted area, while complete eradication is not possible, because this would necessitate a continuous long-term strategy of action, with a considerable cost for an uncertain result.

With regard to the possibility of meta-analysis, raw data on the prevalence of the parasite were available for only five studies examining a total of five different areas. The study in Alaska from Rausch and colleagues (1990; ID 32 Appendix I WP5 Request 5) did not focus on foxes, but focussed on dogs, and the monitoring of EM was conducted on rodents, so it was discarded from the meta-analysis despite the presence of raw data. When taking into account the difference in final prevalence of the five selected studies in control and treated areas, a significant difference was recorded in favour of diminution of the prevalence in baited areas(Table 17 WP5).

Table 17 WP5: Pooled risk difference (RD) of treated and control areas

Area	Pooled RD [(a)]
Control	0.035 (95 % CI –0.04 to 0.11)
Treated	–0.24 (95 % CI –0.40 to –0.09)

(a): Calculated by analysing the difference between the number of EM positive samples at the start of a study and the number of EM positive samples at the end of a study.

Despite a high heterogeneity in the size of the treated and control surface areas, the use of praziquantel at a suitable bait density generally leads to a decrease in the prevalence of EM in foxes, demonstrating the efficacy of the treatment.

Nevertheless, since the deworming treatment did not prevent further infection by predation on infected IHs, the treatment should be maintained for at least several years in order to have a prolonged and significant effect on decreasing EM prevalence.

The fox is the target species not only because it is the principal DH but also because treatment of rodents or eggs in the environment is not conceivable. In general, eradication seems impossible, except in exceptional cases, such as island-based programmes. Furthermore, with regard to the cost, it would be impossible to perform praziquantel baiting on a large scale and for a long time (more than several years). It is most relevant and cost-effective to control EM by baiting in restricted, high endemic areas where the risk of contamination of humans is high, and pursuing this for several decades considering the long latency of AE (Hegglin and Deplazes, 2013; ID 64 Appendix II WP2).

As regards this systematic review, even if programmes for EM eradication in wildlife are theoretically feasible, it appears unlikely because of the long-lasting effort needed to distribute drugs over time and space. The associated costs of these interventions should be evaluated with regard to the costs gained in terms of prevented human cases.

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APPENDICES

APPENDIX I WP2 Request 2 and 4: *List of included articles*

1. Distribution of the tapeworm *Echinococcus multilocularis* in the fox (*Vulpes vulpes*) and muskrat (*Ondatra-zibethicus*) in the Freiburg administrative district. Ewald, D. Mitteilungen des Badischen Landesvereins fuer Naturkunde und Naturschutz E V Freiburg im Breisgau, (1990) Vol. 15(1), pp. 81–100.
2. Serological (Em2-ELISA) and parasitological examinations of fox populations for *Echinococcus multilocularis* infections. Gottstein, B.; Deplazes, P.; Eckert, J.; Muller, B.; Schott, E.; Helle, O.; Boujon, P.; Wolff, K.; Wandeler, A.; Schwiete, U.; et al. Journal of veterinary medicine. Series B, (May 1991) Vol. 38(3), pp. 161–8.
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APPENDIX I WP3 Request 1: *List of included articles*

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APPENDIX I WP3 Request 7: *List of included articles*

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97. Detection of *Echinococcus multilocularis* in faeces by nested PCR with the use of diluted DNA samples. Karamon, J. Polish journal of veterinary sciences, (2014) Vol. 17, No. 1, pp. 79–83.
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APPENDIX I WP4 Request 9: *List of included articles*

1. Efficacy of praziquantel against immature *Echinococcus multilocularis* in dogs and cats. Andersen, F.L.; Crellin, J.R.; Cox, D.D. American journal of veterinary research, (1981 Nov) Vol. 42, No. 11, pp. 1978–9.
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3. Efficacy of emodepside plus praziquantel tablets (Profender tablets for dogs) against mature and immature cestode infections in dogs. Schroeder, I.; Altreuther, G.; Schimmel, A.; Deplazes, P.; Kok, D.J.; Schnyder, M.; Krieger, K.J. Parasitology research, (2009 Aug) Vol. 105 Suppl 1, pp. S31–8.
4. Efficacy of Droncit Spot-on (praziquantel) 4 % w/v against immature and mature *Echinococcus multilocularis* in cats. Jenkins, D.J.; Romig, T. International journal for parasitology, (2000 Jul) Vol. 30, No. 8, pp. 959–62.
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10. Detection of *Echinococcus multilocularis* coproantigens in experimentally infected dogs using murine monoclonal antibody against adult worms. Sakashita, M.; Sakai, H.; Kohno, H.; Ooi, H.K.; Oku, Y.; Yagi, K.; Ito, M.; Kamiya, M. Japanese Journal of Parasitology (1995), Volume 44, Number 5, pp. 413–420.
12. The efficacy of praziquantel against cestodes in cats, dogs and sheep. Thomas, H.; Gonnert, R. Research in veterinary science, (1978 Jan) Vol. 24, No. 1, pp. 20–5.
13. The anthelmintic effect of Droncit on adult tapeworms of *Hydatigera taeniaeformis*, *Mesocestoides corti*, *Echinococcus multilocularis*, *Diphyllobothrium erinacei* and *D. latum*. Sakamoto, T. Veterinary Medical Review (1977), Number 1, pp. 64–74.
23. Efficacy in cats of a novel topical combination of fipronil, (S)-methoprene, eprinomectin, praziquantel, against induced infestations of *Echinococcus multilocularis*. Tielemans, E.; Manavella, C.; Visser, M..; Theodore, C.S; Rosentel. Veterinary parasitology, (2014 Apr 28) Vol. 202, No. 1–2, pp. 26–9.

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1. Combining information from surveys of several species to estimate the probability of freedom from *Echinococcus multilocularis* in Sweden, Finland and mainland Norway. Wahlstroem, H.; Isomursu, M.; Hallgren, G.; Christensson, D.; Cedersmyg, M.; Wallensten, A.; Hjertqvist, M.; Davidson, R.K.; Uhlhorn, H.; Hopp, P. Acta Veterinaria Scandinavica (Febr. 2011), Volume 53, Number 9.
2. *Echinococcus multilocularis* infections in domestic dogs and cats from Germany and other European countries. Dyachenko, V.; Gawlowska, S.; Pantchev, N.; Vrhovec, M.G.; Bauer, C. Veterinary Parasitology, (7 Nov 2008) Vol. 157, No. 3–4, pp. 244–253.
3. A diagnostic study of *Echinococcus multilocularis* in red foxes (*Vulpes vulpes*) from Great Britain. Learmount, J.; Zimmer, I.A.; Conyers, C.; Boughtflower, V.D.; Morgan, C.P.; Smith, G.C. Veterinary parasitology, (2012 Dec 21) Vol. 190, No. 3–4, pp. 447–53.
5. *Echinococcus multilocularis* and *Toxocara canis* in urban red foxes (*Vulpes vulpes*) in Brussels, Belgium. Brochier, B.; Blander, H. de; Hanosset, R.; Berkvens, D.; Losson, B.; Saegerman, C.; de Blander, H. Preventative Veterinary Medicine (2007), Volume 80, Number 1, pp. 65–73.
6. Prevalence of *Echinococcus multilocularis* in out door cats in West Bohemia (Czech Republic). Svobodova, V.; Lenska, B. Helminthologia (Bratislava), (December 2004) Vol. 41, No. 4, pp. 221–222.
7. Occurence of *Echinococcus multilocularis* in red foxes (*Vulpes vulpes*) in southern Poland. Borecka, A.; Gawor, J.; Malczewska, M.; Malczewski, A. Helminthologia (Bratislava), (MAR 2008) Vol. 45, No. 1, pp. 24–27.
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APPENDIX I WP5 Request 5: *List of included articles*

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32. A programme to reduce the risk of infection by *Echinococcus multilocularis*: the use of praziquantel to control the cestode in a village in the hyperendemic region of Alaska. Rausch, R.L.; Wilson, J.F.; Schantz, P.M. Annals of Tropical Medicine and Parasitology (1990), Volume 84,

Number 3, pp. 239–250.
34. Efficacy of anthelmintic baiting of foxes against *Echinococcus multilocularis* in northern Japan. Takahashi, K.; Uraguchi, K.; Hatakeyama, H.; Giraudoux, P.; Romig, T. Veterinary parasitology, (Nov 2013) Vol. 198, No. 1–2, pp. 122–6.

APPENDIX II WP2 Request 2 and 4: *List of excluded articles*

ID	REFERENCE	REASON for EXCLUSION
5	Comparison of the geographic distribution and prevalence of *Echinococcus multilocularis* and rabies infection. Fesseler, M.; Muller, B.; Eckert, J. Tierarztliche Umschau, (May 1991) Vol. 46(5), pp. 287–292.	Human
32	*Echinococcus multilocularis* : the prevalence of the fox tapeworm with possible serious consequences for humans. Van der Giessen, J.W.B.; Borgsteede, F.H.M. Tijdschrift voor diergeneeskunde, (May 2002) Vol. 127(10), pp. 318–21.	Not a primary research
43	Epidemiology of *Echinococcus multilocularis* and *E. granulosus* in central Europe. Eckert, J. Parassitologia, (Dec 1997) Vol. 39(4), pp. 337–44.	Not a primary research
45	Ecology and epidemiology of *Echinococcus multilocularis* in Europe. Deplazes P. Parassitologia, (Jun 2006) Vol. 48(1–2), pp. 37–9.	Not a primary research
48	Echinococcosis due to *Echinococcus multilocularis* in France: life cycle. L' echinococcose a *Echinococcus multilocularis* en France: reflexions a propos de son cycle. Colas, F.; Deiller, M. Epidemiologie et Sante Animale (1987), No 12, pp. 107–123.	Not a primary research
50	Modelling the spatial distribution of *Echinococcus multilocularis* infection in foxes . Pleydell, D.R.J.; Raoul, F.; Tourneux, F.; Danson, F.M.; Graham, A.J.; Craig, P.S.; Giraudoux, P. Acta tropica, (Aug 2004) Vol. 91 (3), pp. 253–65.	Lack of epidemiological data
57	A Systematic Review of the Epidemiology of Echinococcosis in Domestic and Wild Animals. Otero-Abad, B.; Torgerson, P.R. PloS Neglected Tropical Diseases, (Jun 2013) Vol. 7(6), pp. 1–16.	Not a primary research
65	The present situation of echinococcosis in Europe. Romig, T.; Dinkel, A.; Mackenstedt, U. Parasitology international, (2006) Vol. 55 Suppl, pp. S187–91.	Not a primary research
68	A fifteen-year-investigation on the prevalence of *Echinococcus multilocularis* in the red fox population of Lower Saxony - An overview. von Keyserlingk-Eberius, M. Journal Fur Verbraucherschutz Und Lebensmittelsicherheit-Journal Of Consumer Protection And Food Safety, (Nov 2008) Vol. 3(4), pp. 421–428.	Lack of epidemiological data
72	Choropleth mapping of regional count data of *Echinococcus multilocularis* among red foxes in Lower Saxony, Germany. Berke, O. Preventative veterinary medicine, (Dec 2001) Vol. 52(2), pp. 119–31.	Not a primary research
78	Actual aspects in the epidemiology of echinococcosis in Europe. ISS/WHO/FAO-CC/IZSTe/98.29 Modern methods for the diagnosis and control of echinococcosis in dogs. Eckert, J.; Deplazes, P. Veterinary public health reports (1999), pp. 81–95.	Not a primary research
83	Hepatic alveolar echinococcosis (*Echinococcus multilocularis*) in a dog. Pezelet, C. Pratique Medicale et Chirurgicale de l'Animal de Compagnie (2013), Vol. 48(1), pp. 21–26.	Case report

ID	REFERENCE	REASON for EXCLUSION
85	Prevalence of the dangerous for humans tapeworm *Echinococcus multilocularis* in red foxes in Poland. Gawor, J.; Malczewski, A.; Rocki, B.; Malczewska, M.; Borecka, A. Medycyna Weterynaryjna, (May 2004) Vol. 60(5), pp. 489–491.	Not a primary research
88	Radiographic, ultrasonographic, and computed tomographic appearance of alveolar echinococcosis in dogs. Scharf, G.; Deplazes, P.; Kaser-Hotz, B.; Borer, L.; Hasler, A.; Haller, M.; Fluckiger, M. Veterinary radiology & ultrasound: the official journal of the American College of Veterinary Radiology and the International Veterinary Radiology Association, (Sep-Oct 2004) Vol. 45(5), pp. 411–8.	Case report
97	Natural occurrence of *Echinococcus multilocularis* Leuckart, 1863, in the domestic cat: first report from a peri-urban area in France. Petavy, A.F.; Prost, C.; Gevrey, J.; Gilot, B.; Deblock, S. Comptes Rendus de l'Academie des Sciences, III (Sciences de la Vie) (1988), Vol. 307(9), pp. 553–556.	Case report
99	*Echinococcus multilocularis* in animal hosts : New data from western Europe. Romig, T.; Bilger, B.; Dinkel, A.; Merli, M.; Mackenstedt, U. Helminthologia (Bratislava), (Sept 1999) Vol. 36(3), pp. 185–191.	Not a primary research
115	Recent data on a current zoonosis: alveolar echinococcus due to *Echinococcus multilocularis*. Hanosset, R.; Mignon, B.; Losson, B. Annales de Medecine Veterinaire, (2004) Vol. 148(4), pp. 153–167.	Not a primary research
117	*Echinococcus multilocularis* infection of a ring-tailed lemur (*Lemur catta*) and a nutria (*Myocastor coypus*) in a French zoo. Umhang, G; Lahore, J.; Nicolier, A.; Boue, F. Parasitology international, (Dec 2013) Vol. 62(6), pp. 561–3	Case report
126	The fox as a definitive host of *Echinococcus* and its role in the spread of hydatid disease. Gemmell, M.A. Bulletin of the World Health Organisation, (1959) Vol. 20(1), pp. 87–99.	*E. granulosus*
127 366	*Echinococcus multilocularis*: new epidemiological insights in Central and Eastern Europe. Kolarova, L. Helminthologia (1999), Vol. 36(3), pp. 193–200	Not a primary research
136	Canine alveolar echinococcosis-a case report. Wohlsein, P.; Algermissen, D.; Wohlsein, P.; Grimm, F.; Grammell, T. Kleintierpraxis, (Oct 2009) Vol. 54(10), pp. 558.	Case report
137	Echinococcosis surveillance: bayesian time-space analysis of *Echinococcus multilocularis* -infections in foxes in Thuringia, Germany. Staubach, C.; Hoffmann, L.; Schmid, V.; Ziller, M.; Tackmann, K.; Conraths, F.J. Epidemiologie et Sante Animale (2011), No 59-60, pp. 23–25.	Same result as ID 141, combined results
138	*Echinococcus multilocularis* in Austrian foxes from 1991 until 2004. Duscher, G.; Pleydell, D.; Prosl, H.; Joachim, A. Journal of veterinary medicine. B, Infectious diseases and veterinary public health, (Apr 2006) Vol. 53(3), pp. 138–44.	Not a primary research

ID	REFERENCE	REASON for EXCLUSION
139	On the occurrence of *Echinococcus multilocularis* and other helminths of the red fox (*Vulpes vulpes* L.) in south Saxony-Anhalt. Pfeifer, F. Tieraerztliche Hochschule Hannover, Hannover DT Dissertation (1996) 151 pp.	Not a primary research
144	*Echinococcus multilocularis* in south-eastern Europe (Romania). Siko Sandor, B.; Deplazes, P.; Ceica, C.; Tivadar, C.S.; Bogolin, I.; Popescu, S.; Cozma, V. Parasitology research, (May 2011) Vol. 108(5), pp. 1093–7.	Not a primary research
152	Aspects of the cycle of *Echinococcus multilocularis* and of the epidemiology of alveolar echinococcosis in the Jura mountains of Switzerland. Brossard, M. Revue medicale de la Suisse romande, (Feb 1989) Vol. 109(2), pp. 85–7.	Not a primary research
153	Lethal alveolar echinococcosis in a dog: clinical symptoms and pathology. Meyer, A.; Conraths, F.J.; Schneemann, C.; Wienrich, V.; Kershaw, O.; Gruber, A.D. Berliner Munchener Tierarztliche Wochenschrift, (Sep-Oct 2013) Vol. 126(9–10), pp. 408–414.	Case report
158	Importance and current status of larval echinococcosis in France. II. *Echinococcus multilocularis*. Chermette, R. Point Veterinaire (1983), Vol. 15(74), pp. 29–35.	Not a primary research and lack of epidemiological data
160	First description of natural *Echinococcus multilocularis* infections in chinchilla (*Chinchilla laniger*) and Prevost's squirrel (*Callosciurus prevostii borneoensis*). Staebler, S.; Steinmetz, H.r; Keller, S.; Deplazes, P. Parasitology research, (Nov 2007) Vol. 101(6), pp. 1725–7.	Case report
164	Demonstration of the prevalence of *Echinococcus multilocularis* in foxes in Lower Saxony. Keyserlingk, M.; Thoms, B.; Koerfer, K.H. Tieraerztliche Umsch (1994), Vol. 49(6), 374.	Lack of epidemiological data
166	WHO/OIE manual on echinococcosis in humans and animals: a public health problem of global concern. Eckert, J.; Gemmell, M.A.; Meslin, F.X.; Pawowski, Z.S. WHO/OIE manual on echinococcosis in humans and animals: a public health problem of global concern (2001), pp. i-xvii + 265 pp	Not a primary research
169	The domestic cat and dog as natural definitive hosts of *Echinococcus (alveococcus) multilocularis* in southern federal republic of Germany. Eckert, J.; Muller, B.; Partridge, A.J. Tropenmedizin und Parasitologie, (Sep 1974) Vol. 25(3), pp. 334–337.	Case report
173	Recent data on the epidemiology of alveolar hydatid disease in France. Deblock, S.; Petavy, A.F. Bulletin de la Societe de Pathologie Exotique et de ses Filiales (1990), Vol. 83(2), pp. 242–248,	Not a primary research
175	*Echinococcus multilocularis* in a swamp beaver (*Myocaster coypus*). Worbes, H.; Schacht, K.H.; Eckert, J. Angewandte Parasitologie, (Aug 1989) Vol. 30(3), pp. 161–5.	Case report

ID	REFERENCE	REASON for EXCLUSION
179	The house mouse: a potential intermediate host for *Echinococcus multilocularis* in France. Petavy, A.F.; Deblock, S.; Walbaum, S. Transactions of the Royal Society of Tropical Medicine and Hygiene (1990), Vol. 84(4), pp. 571–572	Case report
180	Dogs as carriers (intermediate host) of larvae of *Echinococcus multilocularis*. Geisel, O.; Barutzki, D.; Minkus, G.; Hermanns, W.; Loescher, T. Kleintierpraxis (1990), Vol. 35(6), p. 275–280.	Case report
182	The infection of red foxes with *Echinococcus multilocularis* as potential risk for humans in Poland. Gawor, J.; Borecka, J.; Malczewski, A. Zycie Weterynaryjne (2008), Vol. 83(1), pp. 24–27.	Not a primary research
190	Current spread and epidemiology of *Echinococcus multilocularis*. Romig, T.; Bilger, B.; Mackenstedt, U. Deutsche tierarztliche Wochenschrift, (Aug 1999) Vol. 106(8), pp. 352–7.	Not a primary research
192	*Echinococcus multilocularis* in the Iberian Peninsula. Carvalho-Varela, M. Anais da Escola Superior de Medicina Veterinaria, Lisboa (1986), Vol. 23–24, pp. 102–117.	Lack of epidemiological data
194	Distribution of *Echinococcus multilocularis* in south-western Germany. Zeyhle, E. Probleme der Echinokokkose unter Berucksichtigung parasitologischer und klinischer Aspekte. (Aktuelle Probleme in Chirurgie und Orthopadie, Band 23). (1982), pp. 26–32.	Human
197	Diagnostics and epidemiology of alveolar echinococcosis in slaughtered pigs from large-scale husbandries in Germany. Bottcher, D.; Bangoura, B.; Schmaschke, R.; Muller, K.; Fischer, S.; Vobis, V.; Meiler, H.; Wolf, G.; Koller, A.; Kramer, S.; Overhoff, M.; Gawlowska, S.; Schoon, H.-A. Parasitology research, (Feb 2013) Vol. 112(2), pp. 629–36.	Case report
198	The first detection of *Echinococcus multilocularis* in slaughtered pigs in Poland. Karamon, J.; Sroka, J.; Cencek, T. Veterinary parasitology, (Apr 2012) Vol. 185(2–4), pp. 327–9.	Case report
199	Detection of *Echinococcus multilocularis* in wild boars in France using PCR techniques against larval form. Boucher, J.M.; Hanosset, R.; Augot, D.; Bart, J.M.; Morand, M.; Piarroux, R.; Pozet-Bouhier, F.; Losson, B.; Cliquet, F. Veterinary Parasitology, (May 2005) Vol. 129(3–4), pp. 259–266.	Case report
203	Fauna of gastro-intestinal parasites in red foxes in Western Poland. Balicka-Ramisz, A.; Ramisz, A.; Pilarczyk, B.; Bienko, R. Medycyna Weterynaryjna, (2003) Vol. 59(10), pp. 922–925.	Not a primary research
209	The intestinal helminths of the red fox and some other carnivores in southwest Germany. Loos-Frank, B.; Zeyhle, E. Zeitschrift fur Parasitenkunde, (1982) Vol. 67(1), pp. 99–113.	Not concerning EM
210	Helminthozoonoses the current situation in Slovakia. Letkova, V. Folia Veterinaria (2006), Vol. 50(4), pp. 201–204.	Not a primary research
212	First case of *Echinococcus multilocularis* in foxes in north-west Brandenburg. Tackmann, K.; Beier, D. Tieraerztliche Umsch (1992), Vol. 47(4), 276 p.	Case report

ID	REFERENCE	REASON for EXCLUSION
214 370	CE and AE in Eastern Europe. Malczewski, A. NATO Science Series: Life and Behavioural Sciences, Volume 341. Proceedings of the NATO Advanced Research Workshop on cestode zoonoses: echinococcosis and cysticercosis: an emergent and global problem, Poznan, Poland, 10–13 September 2000 (2002), pp. 81–89	Not a primary research
216	Cystic echinococcosis in Sardinia: farmers' knowledge and dog infection in sheep farms. Varcasia, A.; Tanda, B.; Giobbe, M.; Solinas, C.; Pipia, A.P.; Malgor, R.; Carmona, C.; Garippa, G.; Scala, A. Veterinary parasitology, (Sep 2011) Vol. 181(2–4), pp. 335–40.	*E. granulosus*
217	The genomic *Echinococcus* microsatellite EmsB sequences: from a molecular marker to the epidemiological tool. Knapp, J.; Bart, J.M.; Maillard, S.; Gottstein, B.; Piarroux, R. Parasitology, (Mar 2010) Vol. 137(3), pp. 439–49.	Lack of epidemiological data
219	Hosts of E.m. in Lorraine and their consequences on human contamination. II. Analytical study: Fox - rodents relationship and occurence of the parasite. Artois, M.; Stahl, P.; Bonnin, J.L.; et. al. Bulletin de la Societe Francaise de Parasitologie, (1986) Vol. 4(1), pp. 65–72	Not a primary research
223	A dog with alveolar echinococcosis: the larval stage of the fox tapeworm. van Riel, A.; Sjollema, B.; Klarenbeek, S.; van der Giessen, J. Tijdschrift voor diergeneeskunde, (Nov 2007) Vol. 132(21), pp. 828–31.	Case report
224	Detection of the larva of *Taenia multilocularis* in 2 voles (*Microtus arvalis* and *Clethrionomys glareolus*) in a focus of alveolar echinococcosis in the Massif Central (France). Petavy, A.F.; Deblock, S.; Gilot, B. Comptes rendus de l'Academie des sciences. Serie III, Sciences de la vie, (1984) Vol. 299(18), pp. 735–7.	Case report
225	Fox defecation behaviour in relation to spatial distribution of voles in an urbanised area: An increasing risk of transmission of *Echinococcus multilocularis*?. Robardet, E.; Caillot, C.; Augot, D.; Boue, F.; Barrat, J.; Giraudoux, P. International Journal for Parasitology, (Febr 2011) Vol. 41(2), pp. 145–154.	Lack of epidemiological data
228	Serological studies on *Echinococcus multilocularis* in the definitive host. Pfister, T.; Schad, V.; Frank, W. Mitteilungen der Oesterreichischen Gesellschaft fuer Tropenmedizin und Parasitologie (1991), Volume 13, pp. 31–39, Vortraege anlaesslich der XXIV. Tagung vom 22. bis 24. November 1990.	Lack of epidemiological data
234	Helminth parasites of mammals in zoological gardens. Perec-Matysiak, A.; Okulewicz, A.; Hildebrand, J.; Zalesny, G. Wiadomosci Parazytologiczne (2007), Vol. 53(1), pp. 15–20.	Not a primary research
244	Comparison of endemic districts for *Echinococcus multilocularis* and for rabies in Central Europe. Fessler, M. Schweizer Archiv fuer Tierheilkunde (1991), Vol. 133(4), 187 p., Abstract of dissertation, Vet. Med. Fac., Zuerich, 1990.	Not a primary research

ID	REFERENCE	REASON for EXCLUSION
246	Hepatic alveolar echinococcosis in cynomolgus monkeys (*Macaca fascicularis*). Bacciarini, L.N.; Gottstein, B.; Pagan, O.; Rehmann, P.; Grone, A. Veterinary pathology, (May 2004) Vol. 41(3), pp. 229–34.	Case report
248	Current findings on the epidemiology of alveolar echinococcosis in France. Deblock, P.S.; Petavy, A.F. Bulletin de la Societe de pathologie exotique, (1990) Vol. 83(2), pp. 242–8.	Not a primary research
249	The area of Auvergne, France, a new focus of alveolar echinococcosis. Petavy, A.F.; Rey, M.; Deblock, S.; Cambon, M. Lyon Medical, (1981) Vol. 245(Suppl.10), pp. 111–115.	Not a primary research
257	Spread of *Echinococcus multilocularis* in Europe? NATO Science Series: Life and Behavioural Sciences, Volume 341. Romig, T. Proceedings of the NATO Advanced Research Workshop on cestode zoonoses: echinococcosis and cysticercosis: an emergent and global problem, (2002), pp. 65–80.	Not a primary research
258	*Echinococcus multilocularis* in Europe--state of the art. Romig, T. Veterinary research communications, (Sep 2009) Vol. 33 Suppl 1, pp. 31–4.	Not a primary research
261	Control strategy for *Echinococcus multilocularis*. Hegglin, D.; Deplazes, P. Emerging Infectious Diseases, (Oct 2008) Vol. 14(10), pp. 1626–1628.	Lack of epidemiological data
262	*Echinococcus multilocularis* in Germany: increased awareness or spreading of a parasite? Lucius, R.; Bilger, B. Parasitology today (Personal ed.), (Nov 1995) Vol. 11(11), pp. 430–4.	Not a primary research
266	Alveolar echinococcosis in a dog. Matz-Rensing K.; Zoller M.; Habermalz, G.; Dinkel, A.; Kaup, F.J. Kleintierpraxis, (Nov 2002) Vol. 47(11), pp. 683.	Case report
270	Alveolar echinococcosis in a captive red-necked wallaby (*Macropus rufogriseus*). Peters, M.; Kilwinski, J.; Wohlsein, P.; Conraths, F.J. Berliner Und Munchener Tierarztliche Wochenschrift, (Jan-Feb 2010) Vol. 123(1–2), pp. 63–69.	Case report
271	Geography of alveolar echinococcosis. Giraudoux, P.; Raoul, F.; Boue, F.; Combes, B.; Piarroux, R.; Bresson-Hadni, S.; Vuitton, D.-A. Bulletin de l'Academie nationale de medecine, (Jun-Jul 2008) Vol. 192(6), pp. 1119–25.	Not a primary research
272	Taeniasis, cystocercosis, echinococcosis and hydatidosis in Yugoslavia at the present time. Petrovic, Z. Parasitologia Hungarica, (1979) Vol. 12, pp. 37–39.	Slavic text (short text summarising different studies)
273	Is the neozoan raccoon dog epidemiologically relevant as a definitive host of *Echinococcus multilocularis*?. Tackmann, K.; Goretzki, J.; Sutor, A.; Schwarz, S.; Poetzsch, C.; Conraths, F.J. IJMM International Journal of Medical Microbiology, (Mar 2004) Vol. 293(Suppl. 38), pp. 58–59. Meeting Info.: 21st Congress of the German-Society-of-Parasitology. Wurzburg, Germany. March 17 –20, 2004. German Soc Parasitol.	Lack of epidemiological data

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274	*Echinococcus multilocularis* an endemic cestode of foxes in south Germany, biology, epidemiology , and public-health importance. Frank, W. Wiener Tierarztliche Monatsschrift, (1984) Vol. 71(1), pp. 19–22.	Not a primary research
276	Distribution of echinococcosis/hydatidosis in Italy. Lorenzini, R.; Ruggieri, A. Journal of Helminthology (1987), Vol. 61(3), pp. 261–267.	*E. granulosus*
277	*Echinococcus multilocularis*: A rare cestode of the domestic cat in France. Deblock, S.; Prost, C.; Walbaum, S.; Petavy, A.F. International Journal for Parasitology, (1989) Vol. 19(6), pp. 687–688.	Case report
278	The muskrat as a new natural intermediate host for *E. multilocularis* in France. Boussinesq, M.; Bresson, S.; Liance, M.; Houin, R. Bulletin de la Societe Francaise de Parasitologie, (1985) Vol. 2, pp. 41.	Case report
280	Risk of alveococcosis for humans in Poland. Gawor, J.; Malczewski, A.; Stefaniak, J.; Nahorski, W.; Paul, M.; Kacprzak, E.; Myjak, P. Przeglad epidemiologiczny, (2004) Vol. 58(3), pp. 459–65.	Not a primary research
281	Alveolar echinococcosis in a cynomolgus monkey. Rietschel, W.; Kimmig, P. Tierarztliche Praxis, (Feb 1994) Vol. 22(1), pp. 85–8.	Case report
282	*Echinococcus* and *Taenia* spp. from captive mammals in the United Kingdom. Boufana, B.; Craig, P.S.; Stidworthy, M.F.; Masters, N.; Greenwood, A.G.; Bell, S.; Wood, R.; Chantrey, J.; Unwin, S.; Lawrence, R.P.; Potter, A.; McGarry, J.; Redrobe, S.; Killick, R.; Wyatt, K.; Foster, A.P.; Mitchell, S.; Sako, Y.; Nakao, M.; Ito, A.; Lord, B. Veterinary Parasitology, (Nov 2012) Vol. 190(1–2), pp. 95–103.	Case report
285	First observations of the alveolar echinococcosis in the Auvergne. Roy, M.; Morin, B.; Petavy, A. G.; Cambon, M.; Baril, A. Nouvelle Presse Medicale. (1977), Vol. 6(43), pp. 4070–4071.	Human
286	Overview of the epidemiological situation on echinococcosis in the Mediterranean region. Seimenis, A. Acta tropica, (Feb 2003) Vol. 85(2), pp. 191–5.	*E. granulosus*
298	The raccoon dog (*Nyctereutes procyonoides*) in Germany - an established Neozoon as host and vector for parasites and other pathogenes. Sutor, A.; Schwarz, S.; Conraths, F.J. Berliner Munchener Tierarztliche Wochenschrift, (Nov-Dec 2011) Vol. 124(11–12), pp. 457–464.	Not a primary research
300	Epidemiological study of two foci of alveolar hydatidosis in France. Contat, F.; Petavy, A.F.; Deblock, S.; Euzeby, J. Sciences Veterinaires Medecine Comparee (1983), Vol. 85(2), pp. 79–82.	Not a primary research
303	Spatiotemporal distribution of four species of cestodes in a landscape of mid-altitude mountains (Jura, France). Le Pesteur, M.H.; Giraudoux, P.; Delattre, P.; Damange, J.P.; Quere, J.P. Annales de Parasitologie Humaine et Comparee, (1992) Vol. 67, (5), pp. 155–160.	Not a primary research

ID	REFERENCE	REASON for EXCLUSION
304	The natural occurrence of *Alveococcus multilocularis* in the *Microtus nivalis* in Bulgaria. Genov, T.P.; Svilenov, D.K.; Polyakova-Krusteva, O.T. Doklady Bolgarskoi Akademii Nauk (Comptes Rendus de l'Academie Bulgare des Sciences) (1980), Vol. 33(7), pp. 981–984.	Case report
305 318	*Echinococcus multilocularis* introduction and establishment in wildlife via imported beavers. Kosmider, R.; Paterson, A.; Voas, A.; Roberts, H. The Veterinary record, (Jun 2013) Vol. 172(23), pp. 606.	Not a primary research
308	Alveolar hydatidosis (*Echinococcus multilocularis*) in a captive rhesus monkey (*Macaca mulatta*) in Germany. Brack, M.; Tackmann, K.; Conraths, F.J.; Rensing, S. Tropical Medicine & International Health, (Aug 1997) Vol. 2(8), pp. 754–759.	Case report
312	*Echinococcus multilocularis* in the European beaver (*Castor fibre* L.) from Serbia: first report. Cirovi,c D.; Pavlovic, I.; Kulisic, Z.; Ivetic, V.; Penezic, A.; Cosic, N. The Veterinary record, (Jul 2012) Vol. 171(4), pp. 100.	Case report
313	*Echinococcus multilocularis* in an imported captive European beaver (*Castor fibre*) in Great Britain. Barlow, A.M.; Gottstein, B.; Mueller, N. The Veterinary record, (Sep 2011) Vol. 169(13), pp. 339.	Case report
314	*Arvicola terrestris* reservoir and focalizing element of alveolar echinococcosis in France. Houin, R.; Liance, M.; Dumas, J.M.; Puel, F. Molecular and Biochemical Parasitology, (1982) No. Suppl, pp. 258–259.	Lack of epidemiological data
317	Incomplete development of larval *Echinococcus multilocularis* (Cestoda: Taeniidae) in spontaneously infected wild boars. Pfister, T.; Schad, V.; Schelling, U.; Lucius, R.; Frank, W. Parasitology research, (1993) Vol. 79(7), pp. 617–8.	Case report
320	Spontaneous Echinococcosis in a colony of lion-tailed macaques (*Macaca silenus*). Blankenburg, A.; Sauermann, U.; Kaup, F.-J. Folia Primatologica, (Sept 2001) Vol. 72(3), pp. 156.	Case report
321	A historical view of alveolar echinococcosis , 160 years after the discovery of the first case in humans: part 1. What have we learnt on the distribution of the disease and on its parasitic agent? Vuitton, D.A.; Wang, Q.; Zhou, H.-X.; Raou,l F.; Knapp, J.; Bresson-Hadni, S.; Wen, H.; Giraudoux, P. Chinese medical journal, (Sep 2011) Vol. 124(18), pp. 2943–53.	Not a primary research
322	Alveolar echinococcosis: from an incurable rural disease to a controlled urban infection. Vuitton, D.A.; Bresson-Hadni, S.; Giraudoux, P.; Bartholomot, B.; Laplante, J.-J.; Delabrousse, E.; Blagosklonov, O.; Mantion, G. Presse medicale (Paris, France: 1983), (Feb 2010) Vol. 39(2), pp. 216–30.	Not a primary research

ID	REFERENCE	REASON for EXCLUSION
323 337	Genetic diversity of the cestode *Echinococcus multilocularis* in red foxes at a continental scale in Europe. Knapp, J.; Bart, J.-M.; Giraudoux, P.; Glowatzki, M.-L.; Breyer, I.; Raoul, F.; Deplazes, P.; Duscher, G.; Martinek, K.; Dubinsky, P.; Guislain, M.-H.; Cliquet, F.; Romig, T.; Malczewski, A.; Gottstein, B.; Piarroux, R. PLoS neglected tropical diseases, (2009) Vol. 3(6), pp. e452.	Lack of epidemiological data
324	Biological, epidemiological, and clinical aspects of echinococcosis, a zoonosis of increasing concern. Ecker, J.; Deplazes, P. Clinical microbiology reviews, (Jan 2004) Vol. 17(1), pp. 107–35.	Not a primary research
325	*Echinococcus multilocularis*. Craig, P. Current opinion in infectious diseases, (Oct 2003) Vol. 16(5), pp. 437–44.	Not a primary research
326	Epidemiology of echinococcosis. Romig, T. Langenbeck's archives of surgery /Deutsche Gesellschaft fur Chirurgie, (Sep 2003) Vol. 388(4), pp. 209–17.	Not a primary research
327	Echinococcosis --an international public health challenge. Torgerson, P.R.; Budke, C.M. Research in veterinary science, (Jun 2003) Vol. 74(3), pp. 191–202.	Not a primary research
328	Epidemiology of alveolar echinococcosis with particular reference to China and Europe. Vuitton, D.A.; Zhou, H.; Bresson-Hadni, S.; Wang, Q.; Piarroux, M.; Raoul, F.; Giraudoux, P. Parasitology, (2003) Vol. 127 Suppl, pp. S87–107.	Not a primary research
329	Veterinary aspects of alveolar echinococcosis - a zoonosis of public health significance. Deplazes, P.; Eckert, J. Veterinary parasitology, (Jul 2001) Vol. 98(1–3), pp. 65–87.	Not a primary research
330	Echinococcosis : an emerging or re-emerging zoonosis? Eckert, J.; Conraths, F.J.; Tackmann, K. International journal for parasitology, (Nov 2000) Vol. 30(12–13), pp. 1283–94.	Not a primary research
332	Detection, screening and community epidemiology of taeniid cestode zoonoses: cystic echinococcosis, alveolar echinococcosis and neurocysticercosis. Craig, P.S.; Rogan, M.T.; Allan, J.C. Advances in parasitology, (1996) Vol. 38, pp. 169–250.	Human and not a primary research
333	Alveolar echinococcosis. Anonymous Releve epidemiologique hebdomadaire /Section d'hygiene du Secretariat de la Societe des Nations = Weekly epidemiological record /Health Section of the Secretariat of the League of Nations, (Feb 1990) Vol. 65(6), pp. 37–8.	Human
334	*Echinococcus multilocularis* in Svalbard, Norway: microsatellite genotyping to investigate the origin of a highly focal contamination. Knapp, J.; Staebler, S.; Bart, J.M.; Stien, A.; Yoccoz, N.G.; Drogemuller, C.; Gottstein, B.; Deplazes, P. Infection, genetics and evolution: journal of molecular epidemiology and evolutionary genetics in infectious diseases, (Aug 2012) Vol. 12(6), pp. 1270–4.	Lack of epidemiological data

ID	REFERENCE	REASON for EXCLUSION
335	Assessment of use of microsatellite polymorphism analysis for improving spatial distribution tracking of *echinococcus multilocularis* . Knapp, J.; Bart, J.M.; Glowatzki, M.L.; Ito, A.; Gerard, S.; Maillard, S.; Piarroux, R.; Gottstein, B. Journal of clinical microbiology, (Sep 2007) Vol. 45(9), pp. 2943–50.	Lack of epidemiological data
336	Hydatidosis: a global problem of increasing importance. Matossian R.M.; Rickard M.D.; Smyth J.D. Bulletin of the World Health Organisation, (1977) Vol. 55(4), pp. 499–507.	*E. granulosus*
338	*Echinococcus multilocularis* - A zoonosis of anthropogenic environments?. Romig, T.; Thoma, D.; Weible, A.-K. Journal of Helminthology, (Jun 2006) Vol. 80(2), pp. 207–212.	Lack of epidemiological data
340	Editorial: The burden of echinococcosis .Schantz, P.M. American Journal of Tropical Medicine and Hygiene, (Jul 2005) Vol. 73(1), pp. 1.	Lack of epidemiological data
342	Ecological epidemiology : the role of landscape structure in the transmission risk of the fox tapeworm *Echinococcus multilocularis* (Leukart 1863) (Cestoda: Cyclophyllidea: Taeniidae). Graham, A.J.; Danson, F.M.; Craig, P.S. Progress in Physical Geography (2005), Vol. 29(1), pp. 77–91.	Lack of epidemiological data and not a primary research
343	Genetic diversity of *Echinococcus* spp. in Russia. Special Issue: Control of cestode zoonoses in Asia: role of basic and applied science. Konyaev, S.V.; Yanagida, T.; Nakao, M.; Ingovatova, G.M.; Shoykhet, Y.N.; Bondarev, A.Y.; Odnokurtsev, V.A.; Loskutova, K. S.; Lukmanova, G.I.; Dokuchaev, N.E.; Spiridonov, S.; Alshinecky, M.V.; Sivkova, T.N.; Andreyanov, O.N.; Abramov, S.A.; Krivopalov, A.V.; Karpenko, S. V.; Lopatina, N.V.; Dupal, T.A.; Sako, Y.; Ito, A. Parasitology (2013), Vol. 140(13), pp. 1637–1647.	Lack of epidemiological data
344	Alveolar echinococcosis in an American bulldog in Saxony-Anhalt: A case report. Behrens, S.; Heckers, K.O.; Aupperle, H. Tieraerztliche Umschau (2012), Vol. 67(4), pp. 124–128,	Case report
346	*Echinococcus multilocularis*: why are multidisciplinary and multiscale approaches essential in infectious disease ecology? Giraudoux, P.; Pleydell, D.; Raoul, F.; Vaniscotte, A.; Ito, A.; Craig, P.S. Tropical Medicine and Health (2007), Vol. 35(4), pp. 293–299,	Lack of epidemiological data
347	Helminths transmissible from domestic carnivores to man: risk assessment and prevention strategies. Guillot, J.; Bouree, P. Bulletin de l'Academie Nationale de Medecine (2007), Vol. 191(1), pp. 67–81.	Case reports and not a primary research
349	Current research in echinococcosis. Craig, P.S. Parasitology Today (1994), Vol. 10(6), pp. 209–211	Human and not a primary research
350	Problems of epidemiology and prophylaxis of alveococosis (multilocular echinococcosis): a general review-with particular reference to the U.S.S.R. Lukashenko, N. P. International Journal for Parasitology (1971), Volume 1, Number 2, pp. 125–134.	Not a primary research

ID	REFERENCE	REASON for EXCLUSION
351	A real-time multiplex-nested PCR system for coprological diagnosis of *Echinococcus multilocularis* and host species. Dinkel, A.; Kern, S.; Brinker, A.; Oehme, R.; Vaniscotte, A.; Giraudoux, P.; Mackenstedt, U.; Romig, T. Parasitology Research, (Aug 2011) Vol. 109(2), pp. 493–498.	Lack of epidemiological data
352	Combining information from surveys of several species to estimate the probability of freedom from *Echinococcus multilocularis* in Sweden, Finland and mainland Norway. Wahlstrom, H.; Hallgren, G.; Christensson, D.; Uhlhorn, H.; Isomursu, M.; Cedersmyg, M.; Wallensten, A.; Hjertqvist, M.; Davidson, R.K.; Hopp, P. Acta Veterinaria Scandinavica, (Feb 2011) Vol. 53, pp. 1 –13.	Not a primary research
357	*Echinococcus multilocularis*: secondary poisoning of fox population during a vole outbreak reduces environmental contamination in a high endemicity area. Raoul, F.; Michela,t D.; Ordinaire, M.; Decote, Y.; Aubert, M.; Delattre, P.; Deplazes, P.; Giraudoux, P. International Journal For Parasitology, (Aug 2003) Vol. 33(9), pp. 945–954.	Lack of epidemiological data
358	Alveolar echinococcosis: characteristics of a possible emergence and new perspectives in epidemiosurveillance. Giraudoux, P.; Raoul, F.; Bardonnet, K.; Vuillaume, P.; Tourneux, F.; Cliquet, F.; Delattre, P.; Vuitton, D.A. Medecine et Maladies Infectieuses, (Mar 2001); Vol. 31(Supp. 2), pp. 247S-256S.	Not a primary research
359	The "dangerous fox tapeworm" (*Echinococcus multilocularis*) and alveolar echinococcosis of humans in central Europe. Eckert, J. Berliner und Munchener tierarztliche Wochenschrift, (Jun-Jul 1996); Vol. 109(6–7), pp. 202–10.	Not a primary research
360	Controlling *Echinococcus multilocularis* -ecological implications of field trials. Hansen, F.; Tackmann, K.; Jeltsch, F.; Wissel, C.; Thulke, H.-H. Prev Vet Med. (Jul 2003); 30;60(1), pp. 91–105.	Lack of epidemiological data
361	*Echinococcus multilocularis* - tapeworm in red foxes (*Vulpes vulpes*) and their danger for humans. Gawor, J.; Malczewski, A.; Rocki, B. Medycyna Weterynaryjna (2004); 60(4),pp. 349–351	Not a primary research
362	Canine echinococcosis: Global epidemiology and genotypic diversity. Carmena D.; Cardona G. A. Acta Trop. (Dec 2013); 128(3), pp. 441–60.	Not a primary research
363	The impact of globalisation on the distribution of *Echinococcus multilocularis*. Davidson R. K.; Romig T.; Jenkins E.; Tryland M.; Robertson L.J. Trends Parasitol. (Jun 2012); 28(6), pp. 239–47.	Not a primary research
365	Red fox (*Vulpes vulpes*) as reservoir of parasites and source of zoonosis. Okulewicz A.; Hildebrand J.; Okulewicz J.; Perec A. Wiad Parazytol. (2005); 51(2), pp. 125–32.	Not a primary research
368	Epidemiology and prevention of echinococcosis in France. Petavy A.F.; Deblock S.; Walbaum S. La Revue du praticien. (1990); Vol. 40.	Not a primary research
ID	REFERENCE	REASON for EXCLUSION

369	Role of pet dogs and cats in the transmission of helminthic zoonoses in Europe, with a focus on echinococcosis and toxocarosis. Deplazes, P.; Schweiger, A.; van Knapen, F.; Overgaauw, P.A.M. Vet Parasitol. (Nov 2011); 182(1), pp. 41–53.	Not a primary research
371	Spatial and temporal epidemiology of *Echinococcus multilocularis*: Results of the European project echinorisk. Kern, P.; Giraudoux, P.; Romig, T. American Journal of Tropical Medicine and Hygiene, (Dec 2005) Vol. 73(6), Suppl. S, pp. 28.	Lack of epidemiological data
372	Alveolar hydatidosis: epidemiological review. Gilot, B.; Petavy, A.F.; Contat, F. Epidemiologie et Sante Animale (1983). Vol 4, pp. 17–28	Not a primary research
373	The hydatid tapeworm - pig echinococossis. Lis, H.; Gorski, K. Zycie Weterynaryjne (2012), Vol 87(3), pp. 241–242.	E. granulosus
374	Echinococcoses of animals and humans in the Russian Federation. Bessonov, A. S. NATO Science Series: Life and Behavioural Sciences, (2002), Vol 341, pp. 91–98.	Not a primary research
375	The aetiology of alveolar echinococcosis in the central districts of the barabinsk forest-steppe (novosibirsk region). Lukashenko, N.P.; Zorikhina, V.I. Med. Parazit. I Parazit. Bol., (1961) Vol. 30(2), pp. 159–168.	Russian text
376	*Echinococcus multilocularis* infection in Russia and neighbouring countries. Bessonov, A. S. Helminthologia (Bratislava), (June, 1998) Vol 35(2), pp. 73–78.	Not a primary research
377	Revelation of *Echinococcus multilocularis* (Leuckart, 1856) in the muskrat (*Ondatra zibethicus*) of the delta of the Selenga River (Russia). Masur, O.E.; Fomina, A.S. Russian Journal of Biological Invasions (2012), Vol 3(4), pp. 251–254, Translated from Rossiiskii Zhurnal Biologicheskikh Invasii (2012) No 3, 38–43.	No EU or AC (epidemiological data in Russia)
378	Nosogeography of the alveolar form of echinococcosis in Siberia. Bregadze, I.L.; Semenov, V.S. Med. Parazit. I Parazit. Bol., (1961) Vol. 30(2), pp. 168–172.	Russian text
379	Zoonoses in countries of the former Soviet Union. Mitro, S. Osteuropastudien der Hochschulen des Landes Hessen. Reihe 1, Giessener Abhandlungen zur Agrar- und Wirtschaftsforschung des Europaeischen Ostens (1994), No 204, 134 p.	Not a primary research
380	Dynamics of the force of infection: insights from *Echinococcus multilocularis* infection in foxes. Lewis Fraser, I.; Otero-Abad, B.; Torgerson, P.R; Hegglin, D.; Deplazes, P. PLoS neglected tropical diseases (Mar 2014) Vol. 8(3), pp. e2731.	Not a primary research
387	UK meets *E multilocularis* surveillance requirements, says EFSA. Anonymous. The Veterinary record (Nov 2013) Vol. 173(20), pp. 486.	No epidemiological data
389	Using the genetics of *Echinococcus multilocularis* to trace the history of expansion from an endemic area. Umhang, G.; Hormaz, V.; Boue, F.; Knapp, J.; Raoul, F. Infection, Genetics and Evolution, (Mar 2014) Vol. 22, pp. 142–149.	Not a primary research

ID	REFERENCE	REASON for EXCLUSION
390	Northern Slovakia-highly endemic area ofalveolar echinococcosis. Antolova, D.; Miterpakova, M. Tropical Medicine and International Health, (Sept 2013) Vol. 18, Supp. 1, pp. 223.	Lack of epidemiological data
393	Updates on the surveillance program on parasites of raccoon dogs and foxes in Denmark 2011–2012. Al-Sabi, M.N.S.; Enemark, H.L.; Chriel, M.; Jensen, T.H. Tropical Medicine and International Health, (Sept 2013) Vol. 18, Supp. 1, pp. 96.	Same data reported in another paper (ID386)
394	The biological potential of the raccoon dog (*Nyctereutes procyonoides*, Grey 1834) as an invasive species in Europe - new risks for disease spread? Sutor, A.; Schwarz, S.; Conraths, F.J. Acta Theriologica (2014) , Vol 59(1), pp. 49–59.	Not a primary research
395	Multi criteria-based ranking for risk management of food-born parasites. Report of a Joint FAO/WHO Expert Meeting. Microbiological Risk Assessment Series (2014) , No 23, xvii + 302 p.	Not a primary research
397	Update on *Echinococcus multilocularis* with particular emphasis on its impact on humans. Fisher, M. The Veterinary Nurse (2014), Vol 5(4), pp. 202–206.	No epidemiological data
398	Enteric pathogens ofdogsandcatswith public health implications. Kantere, M.; Athanasiou, L.V.; Chatzopoulos, D.C.; Spyrou, V.; Valiakos, G.; Kontos, V.; Billinis, C. American Journal of Animal and Veterinary Sciences (2014), Vol 9(2), pp. 84–94.	Not a primary research
401	The raccoon dog (*Nyctereutes procyonoides*) in the Netherlands-its present status and a risk assessment. Mulder, J.L. Lutra, (Jun 2013) Vol. 56, No. 1, pp. 23–43.	Not a primary research

APPENDIX II WP3 Request 1: *List of excluded articles*

ID	REFERENCE	REASON for EXCLUSION
1	Evaluation of fox-chasing enclosures as sites of potential introduction and establishment of *Echinococcus multilocularis*. Lee, G.W.; Lee, K.A.; Davidson, W.R. Journal of wildlife diseases, (Jul 1993) Vol. 29(3), pp. 498–501.	No risk factor
2	*Echinococcus multilocularis* and Toxocara canis in urban redfoxes (Vulpes vulpes) in Brussels, Belgium. Brochier, B.; De Blander, H.; Hanosset, R.; Berkvens, D.; Losson, B.; Saegerman, C. Preventative veterinary medicine, (Jun 2007) Vol. 80(1), pp. 65–73.	No risk factor
3	Risk of *Echinococcus multilocularis* introduction and establishment in British wildlife via imported beavers. Kosmider, R.; Paterson, A.; Voas, A.; Roberts, H. Veterinary Record (2013), Vol 172(23), 606 p.	No quantitative data on risk factors described
4	*Echinococcus multilocularis* in foxes in Vienna and surrounding territories. *Echinococcus multilocularis* bei Fuechsen in Wien und Umgebung. Duscher, G.; Steineck, T.; Guenter, P.; Prosl, H.; Joachim, A. Wiener Tieraerztliche Monatsschrift (2005), Vol 92(1), pp. 16–20.	No risk factor
5	Echinococcus risk from imported beavers. Pizzi, R.; Cracknell, J.; Carter, P. Veterinary Record (2012), Vol 170(11), pp. 293–294.	No quantitative data on risk factors described
6	The neozoon raccoon dog as a new definitive host population for *Echinococcus multilocularis* in East Germany-a risk? Tackmann, K.; Goretzki, J.; Conraths, F.J. Schriftenreihe des Bundesministeriums fuer Verbraucherschutz, Ernaehrung und Landwirtschaft, Reihe A, Angewandte Wissenschaft (2003), No 498, pp. 176–181.	Case report
7	Infestation of water voles (*Arvicola terrestris*) with metacestodes of *Echinococcus multilocularis* in the canton of Freiburg (Switzerland). Schmitt, M.; Saucy, F.; Wyborn, S.; Gottstein, B. Schweizer Archiv fuer Tierheilkunde (1997), Vol 139(2), pp. 84–93.	No data on introduction or establishment
9	Prevalence of *Echinococcus multilocularis* tapeworm in red foxes in central Poland. Wystepowanie tasiemca *Echinococcus multilocularis* u lisow rudych na terenie centralnej Polski. Borecka, A.; Gawor, J.; Malczewska, M.; Malczewski, A. Medycyna Weterynaryjna (2007), Vol 63(11), pp. 1333–1335.	No quantitative data on risk factors described
10	Multi-locus microsatellite analysis supports the hypothesis of an autochthonous focus of *Echinococcus multilocularis* in northern Italy. Casulli, A.; Bart, J. M.; Knapp, J.; La Rosa, G.; Dusher, G.; Gottstein, B.; Di Cerbo, A.; Manfredi, M.T.; Genchi, C.; Piarroux, R.; Pozio, E. International journal for parasitology, (Jun 2009) Vol. 39(7), pp. 837–42.	No quantitative data on risk factors described
11	Endemic alveolar echinococcosis in Southern Belgium? Detry, O.; Honore, C.; Delwaide, J.; Demonty, J.; De Roover, A.; Vivario, M.; Thiry, A.; Hayette, M.P.; Belaiche, J.; Meurisse, M.; Honore, P. Acta gastro-enterologica Belgica, (Jan-Mar 2005) Vol. 68(1), pp. 1–4.	No data on introduction or establishment

ID	REFERENCE	REASON for EXCLUSION
12	Choropleth mapping of regional count data of *Echinococcus multilocularis* among red foxes in Lower Saxony, Germany. Berke, O. Preventative veterinary medicine, (Dec 2001) Vol. 52(2), pp. 119–31.	No data on introduction or establishment
13	Freedom from *Echinococcus multilocularis* : An Irish perspective. Murphy, T.M.; Wahlstrom, H.; Dold, C.; Keegan, J.D.; McCann, A.; Murphy, D.; Melville, J.; McAteer, W. Veterinary Parasitology, (Nov 2012) Vol. 190(1–2), pp. 196–203.	No data on introduction or establishment
14	Echinococcosis in pigs and intestinal infection with *Echinococcus* spp. in dogs in southwestern Lithuania. Bruzinskaite, R.; Sarkunas, M.; Torgerson, P.R.; Mathis, A.; Deplazes, P. Veterinary parasitology, (Mar 2009) Vol. 160(3–4), pp. 237–41.	No data on introduction or establishment
15	*Echinococcus multilocularis* in Europe - State of the art. Romig, T. Veterinary Research Communications, (2009) Vol. 33, No. SUPPL. 1, pp. S31-S34.	Not a primary research
16	Invasive tapeworm infections in Poland in 2011. Czarkowski, M.P.; Golab, E. Przeglad epidemiologiczny, (2013) Vol. 67(2), pp. 263–6, 365–7.	No data on introduction or establishment
17	Current data on the geographical distribution and epidemiology of *Echinococcus multilocularis*. Romig, T.; Bilger, B.; Mackenstedt, U. Deutsche Tierarztliche Wochenschrift, (Aug 1999) Vol. 106(8), pp. 352–357.	Not a primary research
18	Cystic echinococcosis in Poland in 2010. Tasiemczyce tkankowe w Polsce w 2010 roku. Waloch, M. Przeglad epidemiologiczny, (2012) Vol. 66(2), pp. 311–3.	No data on introduction or establishment
19	Significant increase of *Echinococcus multilocularis* prevalence in foxes, but no increased predicted risk for humans. Maas, M.; Dam-Deisz, W.D.C.; Takumi, K.; van der Giessen, J.W.B.; van Roon, A.M. Veterinary parasitology, (Oct 2014) Vol. 206(3–4), pp. 167–172.	No data on introduction or establishment
20	Rapid urbanisation of red foxes in estonia: distribution, behaviour, attacks on domestic animals, and health- risks related to zoonotic diseases. Plumer, L.; Davison, J.; Saarma, U. PloS one, (2014) Vol. 9(12), pp. e115124.	Not a primary research
21	Endoparasites in Eastern European stray dogs imported to Norway. Hamnes, I.S.; Klevar, S.; Davidson, R.K.; Hogasen, H.; Lund, A.; Grimm, F. Tropical Medicine and International Health, (Sept 2013) Vol. 18, Supp. 1, pp. 100. Abstract Number: O.6.4.005.	No data on introduction or establishment
22	Transmission ecosystems of *Echinococcus multilocularis* in China and Central Asia. Giraudoux, P.; Raoul, F.; Afonso, E.; Ziadinov, I.; Yang, Y.; Li, L.; Li, T.; Wang, Q.; Quere, J.-P.; Feng, X.; Wen, H. Ito, A. Craig, P.S. Parasitology, (Nov 2013) Vol. 140(13), Special. issue, pp. 1655–1666.	No data on introduction or establishment
23	Environmental determinants of the spatial distribution of *Echinococcus multilocularis* in Hungary. Sreter, T.; Tolnai, Z.; Szell, Z. Veterinary Parasitology, (Dec 2013) Vol. 198(3–4), pp. 292–297.	No data on introduction or establishment

APPENDIX II WP3 Request 6: *List of excluded articles*

ID	REFERENCE	REASON for EXCLUSION
4	Biological, epidemiological, and clinical aspects of echinococcosis , a zoonosis of increasing concern. Eckert, J.; Deplazes, P. Clinical microbiology reviews, (Jan 2004) Vol. 17(1), pp. 107–35.	Not a primary research
6	Potential risk factors for alveolar echinococcosis in humans in Poland. Gawor, J. Przeglad epidemiologiczny, (2011) Vol. 65(3), pp. 465–70.	No risk factor described
10	Impact of overgrazing on the transmission of *Echinococcus multilocularis* in Tibetan pastoral communities of Sichuan Province, China. Wang, Q.; Xiao, Y.; Vuitton, D.A.; Schantz, P.M.; Raoul, F.; Budke, C.; Campos-Ponce, M.; Craig, P.S.; Giraudoux, P. Chinese Medical Journal, (Feb 2007) Vol. 120(3), pp. 237–242.	No direct relationship to human cases
11	Investigation of *Echinococcus multilocularis* in red foxes and their possible relationship to human alveolar echinococcosis. Immelt, U.; Thelen, U.; Eskens, U. Tieraerztliche Umschau (2009), Vol. 64(4), pp. 199–212, 109.	No absolute numbers (raw data) provided, but p-values
13	*Echinococcus multilocularis* in south-eastern Europe (Romania). Siko, S.B.; Deplazes, P.; Ceica, C.; Tivadar, C.S.; Bogolin; I.; Popescu, S.; Cozma, V. Parasitology research, (May 2011) Vol. 108(5), pp. 1093–7.	No risk factor described
17	Grass height and transmission ecology of *Echinococcus multilocularis* in Tibetan communities, China. Wang, Q.; Xiao, Y.; Qiu, D.; Raoul, F.; Pleydell, D.; Giraudoux, P.; Budke, C.; Craig, P.S.;Vuitton, D.A.; Campos-Ponce, M. Chinese Medical Journal, (Jan 2010) Vol. 123(1), pp. 61–67.	No direct relationship to human cases
19	European echinococcosis registry: Human alveolar echinococcosis, Europe, 1982–2000. Kern, P.; Bardonnet, K.; Renner, E.; Auer, H.; Pawlowski, Z.; Ammann, R.W.; Vuitton, D.A. Emerging Infectious Diseases, (Mar 2003) Vol. 9(3), pp. 343–349.	Not a primary research
20	Water vole (*Arvicola terrestris* scherman) density as risk factor for human alveolar echinococcosis. Viel, J.F.; Giraudoux, P.; Abrial, V.; Bresson-Hadni, S. The American journal of tropical medicine and hygiene, (1999 Oct) Vol. 61, No. 4, pp. 559–65.	No case control or cross-sectional study
21	Age, season and spatio-temporal factors affecting the prevalence of *Echinococcus multilocularis* and *Taenia taeniaeformis* in *Arvicola terrestris*. Burlet, P.; Deplazes, P.; Hegglin, D. Parasites & vectors, (2011) Vol. 4, pp. 6.	No direct measure of risk for human
22	Is high prevalence of *Echinococcus multilocularis* in wild and domestic animals associated with disease incidence in humans? Gottstein, B.; Saucy, F.; Deplazes, P.; Reichen, J.; Demierre, G.; Busato, A.; Zuercher, C.; Pugin, P. Emerging infectious diseases, (May-Jun 2001) Vol. 7(3), pp. 408–12.	No risk factor described
24	Landscape dynamics and risk modelling of human alveolar echinococcosis. Danson, F.M.; Craig, P.S.; Man, W.; Shi, D.H.; Giraudoux, P. Photogrammetric Engineering and Remote Sensing, (Mar 2004) Vol. 70(3), pp. 359–366.	Risk modelling, but no risk factors described

ID	REFERENCE	REASON for EXCLUSION
27	Epidemiology of human alveolar echinococcosis in China. Craig, P.S. Parasitology international, (2006) Vol. 55 Suppl, pp. S221–5.	Not a primary research
30	Vulpine tapeworm (*Echinococcus multilocularis*) infection (alveolar echinococcosis) in farmers as an occupational disease in accordance with BeKV no. 3102. Harbarth, S.; Nothdurft, H.D.; Sonnenburg, V.F. Arbeitsmedizin Sozialmedizin Umweltmedizin, (1995) Vol. 30(5), pp. 203–206.	No data on risk factors
31	Impact of anthropogenic and natural environmental changes on *Echinococcus* transmission in Ningxia Hui Autonomous Region, the People's Republic of China. Yang, Y.R.; Clements, A.C.A.; Grey, D.J.; Atkinson, J.A.; Williams, G.M.; Barnes, T.R.; McManus, D.P.; Yang, Y.R. Parasites and Vectors (Jul 2012), Vol. 5(146).	Not a primary research
34	A model for the transmission of *Echinococcus multilocularis* in Hokkaido, Japan. Ishikawa, H.; Ohga, Y.; Doi, R. Parasitology research, (Dec 2003) Vol. 91(6), pp. 444–51.	No risk factor described
36	*Echinococcus multilocularis* in foxes in Vienna and surrounding territories. Duscher, G.; Steineck, T.; Gunter, P.; Prosl, H.; Joachim, A. Wiener Tierarztliche Monatsschrift, (2005) Vol. 92(1), pp. 16–20.	No risk factor described
37	Risk factors for human alveolar Echinococcosis in Germany. Kern, P.; Ammon, A.; Kron, M.; Sinn, G.; Sander, S.; Peterson, L.R.; Gaus, W. American Journal of Tropical Medicine and Hygiene, (Sept 2003) Vol. 69(3) Supplement, pp. 366–367.	Not a primary research
38	Exposure to *Echinococcus multilocularis*, *Toxocara canis*, and *Toxocara cati* in Austria: A Nationwide Cross-Sectional Seroprevalence Study. Poeppl, W.; Herkner, H.; Tobudic, S.; Faas, A.; Mooseder, G.; Burgmann, H.; Auer, H. Vector borne and zoonotic diseases (Larchmont, N.Y.), (Oct 2013).	No risk factors reported or determined
39	Spatial modelling and ecology of *Echinococcus multilocularis* transmission in China. Danson, F.M.; Giraudoux, P.; Craig, P.S. Parasitology international, (2006) Vol. 55 Suppl, pp. S227–31.	Not a primary research
41	Fox tapeworm *Echinococcus multilocularis*, an underestimated threat: a model for estimating risk of contact. Koenig, A.; Romig, T. Wildlife Biology (2010), Vol. 16(3), pp. 258–266.	No risk factor described
42	Emergence of a new opportunistic infection in europe: Hepatic alveolar echinococcosis . A fifty-case report. Chauchet, A.; Grenouillet, F.; Knapp, J.; Richou, C.; Delabrousse, E.; Capelle, S.; Di Martino, V.; Blagosklonov, O.; Vuitton, D.A.; Bresson-Hadni, S.; Deconinck, E.; Dentan, C. Journal of Hepatology, (Apr 2013) Vol. 58, Supp. 1, pp. S381	No risk factor described
43	Increased risk of infection by *Echinococcus multilocularis* for people living in the endemic region Schwaebische-Alb West Germany? Muehling. A.; Kimmig, P. Zentralblatt fuer Bakteriologie Mikrobiologie und Hygiene Abt 1 Originale B Hygiene Umwelthygiene Krankenhaushygiene Arbeitshygiene Praeventive Medizin, (1985) Vol. 181(1–2), pp. 24.	Not a primary research

ID	REFERENCE	REASON for EXCLUSION
44	Invasive tapeworm infections in Poland in 2011. Czarkowski, M.P.; Golab, E. Przeglad epidemiologiczny, (2013) Vol. 67(2), pp. 263–6, 365–7.	No risk factor described
47	(Risk of alveococcosis for humans in Poland.) Zagrozenie bablowica wielojamowa (alweokokoza) dla ludzi w Polsce. Gawor, J.; Malczewski, A.; Stefaniak, .; Nahorski, W.; Paul, M.; Kacprzak, E.; Myjak, P. Przeglad epidemiologiczny, (2004) Vol. 58(3), pp. 459–65.	No risk factor described
50	Parasitism of red fox *Vulpes vulpes* by *Echinococcus multilocularis* in Lorraine France and their consequences on human contamination. Aubert, M.; Jacquier, P.; Artois, M.; Barrat; M.J.; Basilea, A.M. Recueil de Medecine Veterinaire de l'Ecole d'Alfort, (1987) Vol. 163(10), pp. 839–843.	No risk factor described for human
51	Transmission ecology of *Echinococcus multilocularis*: What are the ranges of parasite stability among various host communities in China? Giraudoux, P.; Pleydell, D.; Raoul, F.; Quere, J.P.; Wang, Q.; Yang, Y.R.; Vuitton, D.A.; Qiu, J.M.; Yang, W.; Craig, P.S. Parasitology International, (2006) Vol. 55, Supp. [S], pp. S237-S246.	Not a primary research
52	Pasture types and *Echinococcus multilocularis* , Tibetan Communities. Wang, Q.; Xiao, Y.; Yang, W.; Vuitton, D.A.; Raoul, F.; Giraudoux, P.; Budke, C.M.; Campos-Ponce, M.; Schantz, P.M.; Craig, P.S. Emerging Infectious Diseases, (2006) Vol. 12(6), pp. 1008–1010.	No relationship to human cases
53	Tradition and Transition: Parasitic Zoonoses of People and Animals in Alaska, Northern Canada, and Greenland. Jenkins, E.J.; Castrodale, L.J.; de Rosemond, S.J.C.; Dixon, B.R.; Elmore, S.A.; Gesy, K.M.; Hoberg, E.P.; Polley, L.; Schurer, J.M.; Simard, M.; Thompson, R.C.A. Adv. Parasitol., (2013) pp. 33–204. Advances in Parasitology, Vol 82.	Not data driven
54	Does the risk of *Echinococcus multilocularis* (EM) infection increase with increasing populations of infected foxes in Swiss cities? A retrospective analysis of the cohort of the Swiss Echinococcosis Study Group (SESG) 1976–1999. Renner-Schneiter, E.C.; Deplazes, P.; Ammann, R.W.; Renner, E.L. Hepatology, (Oct 2000) Vol. 32(4 Pt. 2), pp. 625.	Case study, no data on risk factors
55	Cystic and alveolar echinococcosis transmission and risk factors in Ningxia Hui Autonomous Region of China: Current situation and evolusion. Yang, Y.R.; Craig, P.S.; Sun, T.; Williams, G.M.; Vuitton, D.A.; Giraudoux, P.; Jones, M.K.; McManus, D.P. American Journal of Tropical Medicine and Hygiene, (Nov 2006) Vol. 75(5), Suppl. S, pp. 205.	Not a primary research
56	Ecological epidemiology: landscape metrics and human alveolar echinococossis. Graham, A.J.; Danson, F.M.; Giraudoux, P.; Craig, P.S. Acta Tropica, (Aug 2004) Vol. 91(3), pp. 267–278.	Landscape modelling, but no risk factors described

ID	REFERENCE	REASON for EXCLUSION
59	Investigations on a Swiss area highly endemic for *Echinococcus*. Gottstein, B.; Saucy, F.; Wyss, C.; Siegenthaler, M.; Jacquier, P.; Schmitt, M.; Brossard, M.; Demierre, G. Applied parasitology, (Jun 1996) Vol. 37(2), pp. 129–36.	No risk factor described for human
60	Risk assessment of infection with *Echinococcus multilocularis* in a highly endemic focus of Switzerland. Gottstein, B.; Saucy, F.; Deplazes, P.; Teuscher, F.; Demierre, G.; Ducrot, H. Schweizerische Medizinische Wochenschrift, (Sept 1997) Vol. 127(39), pp. 1629.	No risk factor described for human
62	Epidemiology of alveolar echinococcosis , with reference to St Lawrence Island, Bering Sea. Rausch RL, Fay FH. Proceedings of the NATO Advanced Research Workshop on cestode zoonoses: echinococcosis and cysticercosis: an emergent and global problem, Poznan, Poland, 10–13 September 2000 (2002), pp. 309–325.	Not a primary research, no quantitative data on risk factors
63	Risk of transmission of fox tapeworm. Kratzer, W.; Kern, P. Internistische Praxis, (2001) Vol. 41(3), pp. 693.	Not a primary research
64	Control of echinococcosis and cysticercosis: a public health challenge to international cooperation in China. Ito, A.; Urbani, C.; Jiamin, Q.; Vuitton, D.A.; Dongchuan, Q.; Heath, D.D.; Craig, P.S.; Zheng, F.; Schantz; P.M. Acta Tropica, (Apr 2003) Vol. 86(1), pp. 3–17.	No risk factor described
65	Epidemiology and control of echinococcosis in central Asia, with particular reference to the People ‘s Republic of China. Zhang W.; Zhang Z.; Shi B.; Li J.; Wen H.; McManus D.P. Acta tropica, (Jan 2015) Vol. 141(Pt B), pp. 235–43.	Not a primary research
66	Surveillance of *Echinococcus* isolates from Qinghai, China. Ma J.; Wang H.; Li C.; Ma X.; Cai H.; Liu P.; Wang, Y.; Lin, G.; Zhao, F.; Zhang, T.; Zhang, Y.; Hou, Z. Veterinary parasitology, (2015 Jan 15) Vol. 207, No. 1–2, pp. 44–8.	No relationship to human cases
67	Dynamics of the force of infection: insights from *Echinococcus multilocularis* infection in foxes. Lewis Fraser I.; Otero-Abad B.; Torgerson P.R.; Hegglin D.; Deplazes P. PLoS neglected tropical diseases, (Mar 2014) Vol. 8(3), pp. e2731.	No risk factor described
69	Echinococcosis and cysticercosis in Poland in 2012. GolAb E.; Czarkowski M.P. Przeglad epidemiologiczny, (2014) Vol. 68(2), pp. 279–82, 379–81.	No distinction between Eg and Em
70	Review of risk factors for human echinococcosis prevalence on the Qinghai-Tibet Plateau, China: a prospective for control options. Wang Q.; Huang Y.; Huang L.; Yu W.; He W.; Zhong B.; Li W.; Zeng X.; Vuitton D.A.; Giraudoux P.; Craig P.S.; Wu W. Infectious diseases of poverty, (2014) Vol. 3(1), pp. 3.	Not a primary research
71	Detecting nested clusters of human alveolar echinococcosis. Said-Ali, Z.; Grenouillet, F.; Knapp, J.; Bresson-Hadni, S.; Vuitton, D.A.; Raoul, F.; Richou, C.; Millon, L.; Giraudoux, P. Parasitology, (Nov 2013) Vol. 140(13), pp. 1693–700.	No risk factor described

ID	REFERENCE	REASON for EXCLUSION
72	A random forest approach for predicting the presence of *Echinococcus multilocularis* intermediate host *Ochotona* spp. presence in relation to landscape characteristics in western China. Marston, C.G.; Danson, F.M.; Armitage, R.P.; Giraudoux, P.; Pleydell, D.R.J.; Wang Q.; Qui J.M.; Craig, P.S.; Wang, Q.; Qui, J.M. Applied Geography (2014) , Vol. 55, pp. 176–183.	No risk factor described
73	Alveolar echinococcosis in a highly endemic area of northern Slovakia between 2000 and 2013. Antolova, D.; Miterpakova, M.; Radonak, J.; Hudackova, D.; Szilagyiova, M.; Zacek, M. Eurosurveillance, (Aug 2014) Vol. 19(34), arn. 20882.	No useful data on risk factor

APPENDIX II WP3 Request 7: *List of excluded articles*

ID	REFERENCE	REASON for EXCLUSION
1	Incidence prevalence and geographic distribution of human alveolar echinococcosis in austria from 1854 to 1990. Auer, H.; Aspock, H. Parasitology Research, (1991) Vol. 77(55), pp. 430–436.	Case report
3	Alveolar echinococcosis (*Echinococcus multilocularis*) and other forms of echinococcosis (*Echinococcus vogeli* and *Echinococcus oligarthrus*). Eckert, J. Zoonoses: biology, clinical practice and public health control. (1998), pp. 689–716.	Not a primary research
4	Environmental changes impacting *Echinococcus* transmission: research to support predictive surveillance and control. Atkinson, J.M.; Grey, D.J.; Clements, A.C.A.; Barnes, T.S.; Mcmanus, D.P.; Yang, Y.R. Global change biology, (Mar 2013) Vol. 19(3), pp. 677–88.	Not a primary research
5	Survey of public knowledge about *Echinococcus multilocularis* in four european countries: need for proactive information. Hegglin, D.; Deplazes, P.; Bontadina, F.; Gloor, S.; Romig, T.; Kern, P. BMC Public Health, (2008) Vol. 8. arn. 247.	No quantitative data on risk factors described
6	Base line prevalence and spatial distribution of *Echinococcus multilocularis* in a newly recognised endemic area in the Netherlands. Van Der Giessen, J.W.B.; Rombout, Y. Teunis, P. Veterinary parasitology, (Jan 2004) Vol. 119(1), pp. 27–35.	No quantitative data on risk factors described
7	Transmission dynamics of *Echinococcus multilocularis*; its reproduction number, persistence in an area of low rodent prevalence, and effectiveness of control. Takumi, K.; Van Der Giessen, J. Parasitology, (Jul 2005) Vol. 131(Pt 1), pp. 133–40.	No quantitative data on risk factors described
9	Investigations and actions taken during 2011 due to the first finding of *Echinococcus multilocularis* in Sweden. Wahlstrom, H.; Lindberg, A.; Osterman, L.E.; Agren, E.O.; Widgren, S.; Carlsson, U.; Christensson, D.; Elvander, M.; Lindh, J.; Wallensten, A.; Barragan, A.; Hjertqvist, M.; Lindqvist, R.; Plym-Forshell, L.; Cedersmyg, M.; Lindstrom, E.; Olsson, G.E.; Hornfeldt, H.; Davelid, C. Eurosurveillance, (Jul 2012) Vol. 17(28), pp. 1–7.	No quantitative data on risk factors described
10	Role of pet dogs and cats in the transmission of helminthic zoonoses in Europe, with a focus on echinococcosis and toxocarosis. Deplazes, P.; Schweiger, A.; Van Knapen, F.; Overgaauw, P.A.M. Veterinary Parasitology, (Nov 2011) Vol. 182(1), pp. 41–53.	No quantitative data on risk factors described
11	*Echinococcus multilocularis* infection in foxes (*Vulpes vulpes*) in Lorraine. implications for man. Aubert, M.; Jacquier, P.; Artois, M.; Barrat, M.J.; Basile, A.M. Recueil de Medecine Veterinaire (1987), Volume 163(10), pp. 839–843	No quantitative data on risk factors described
12	Investigations on a Swiss area highly endemic for *Echinococcus multilocularis*. Gottstein, B.; Saucy, F.; Wyss, C.; Siegenthaler, M.; Jacquier, P.; Schmitt, M.; Brossard, M.; Demierre, G. Applied Parasitology, (1996) Vol. 37(2), pp. 129–136.	No quantitative data on risk factors described

ID	REFERENCE	REASON for EXCLUSION
13	Cystic and alveolar echinococcosis in turkey. Altintas, N. Annals of Tropical medicine and parasitology, (Sep 1998) Vol. 92(6), pp. 637–42.	Not a primary research
14	*Arvicola terrestris* an intermediate host of *Echinococcus multilocularis* in France epidemiological consequences. Houin, R.; Deniau, M.; Liance, M.; Puel, F. International Journal for Parasitology, (1982) Vol. 12(6), pp. 593–600.	No quantitative data on risk factors described
15	*Echinococcus multilocularis* in Estonia [1]. Moks, E.; Saarma, U.; Valdmann, H. Emerging Infectious Diseases, (Dec 2005) Vol. 11, No. 12, pp. 1973–1974.	No quantitative data on risk factors described
16	Echinococcosis: transmission biology and epidemiology. Craig, P.S.; Mcmanus, D.P. Parasitology, (2003) Vol. 127, No. Suppl, pp. S1.	No quantitative data on risk factors described
17	Growing importance of prevention and control of alveolar echinococcosis. Fujikura, T. World Health Forum, (1991) Vol. 12(2), pp. 146–150.	Not a primary research
18	Distribution of *Echinococcus multilocularis* in Southwest Germany Zeyhle, E. Molecular and Biochemical Parasitology, (1982) No. Suppl, pp. 258.	No quantitative data on risk factors described
19	Echinococcosis and other larval cestode infections. Eckert, J.; Gemmel, M.A.; Wikerhauser, T. Review Of Advances In Parasitology; Proceedings Of The 4th International Congress Of Parasitology, Warsaw, Poland (1981) p 365–391	Not a primary research
20	Towards global control of cystic and alveolar hydatid diseases. Gemmell, M.A.; Lawson, J.R.; Roberts, M.G. Parasitology Today, (1987) Vol. 3(5), pp. 144–151.	Not a primary research
21	The global burden of alveolar echinococcosis. Torgerson, P.R.; Keller, K.; Magnotta, M.; Ragland, N. PLoS Neglected Tropical Diseases, (Jun 2010) Vol. 4(6). arn. e722.	Not a primary research
22	Genetic diversity of *Echinococcus* spp. in Russia. Special issue: control of cestode zoonoses in Asia: role of basic and applied science. Konyaev, S.V.; Yanagida, T.; Nakao, M.; Ingovatova, G.M.; Shoykhet, Y.N.; Bondarev, A.Y.; Odnokurtsev, V.A.; Loskutova, K.S.; Lukmanova, G.I.; Dokuchaev, N.E.; Spiridonov, S.; Alshinecky, M.V.; Sivkova, T.N.;Andreyanov, O.N.; Abramov, S.A.; Krivopalov, A.V.; Karpenko, S.V.; Lopatina, N.V.; Dupal, T.A.; Sako, Y.; Ito, A. Parasitology (2013), Vol. 140(13), pp. 1637–1647.	No quantitative data on risk factors described
23	Human echinococcosis: a neglected disease? Craig, P.S.; Budke, C.M.; Schantz, P.M.; Li, T.Y.; Qiu, J.M.; Yang, Y.R.; Zeyhle, E.; Rogan, M.T.; Ito, A. Tropical Medicine and Health (2007), Vol. 35(4), pp. 283–292.	Not a primary research
24	Hydatid and the arctic international workshop of alveolar hydatid disease anchorage Alaska USA june 7–8 1990. Schantz, P.M.; Gottstein, B.; Ammann, R.; Lanier, A. Parasitology Today, (1991) Vol. 7(2), pp. 35–36.	Not a primary research

ID	REFERENCE	REASON for EXCLUSION
25	Significant increase of *Echinococcus multilocularis* prevalence in foxes, but no increased predicted risk for humans. Maas, M.; Dam-Deisz, W.D.C.; Takumi, K.; van der Giessen, J.W.B.; van Roon, A.M. Veterinary parasitology, (Oct 2014) Vol. 206(3–4), pp. 167–172.	No quantitative data on risk factors described
26	Review of risk factors for human echinococcosis prevalence on the Qinghai-Tibet Plateau, China: a prospective for control options. Wang Q.; Huang Y.; Huang L.; Yu W.; He W.; Zhong B.; Li W.; Zeng X.; Vuitton D.A.; Giraudoux P.; Craig P.S.; Wu W. Infectious diseases of poverty, (2014) Vol. 3(1), pp. 3	Not a primary research

APPENDIX II WP4 Request 8: *List of excluded articles*

ID	REFERENCE	REASON for EXCLUSION
2	Detection of *Echinococcus multilocularis* in Carnivores in Razavi Khorasan Province, Iran Using Mitochondrial DNA. Beiromvand, M.; Akhlaghi, L.; Massom, S. H. F.; Mobedi, I.; Meamar, A. R.; Oormazdi, H.; Motevalian, A.; Razmjou, E. PloS Neglected Tropical Diseases, (Nov 2011) Vol. 5(11).	One technique used, no comparison
3	*Echinococcus multilocularis* adaptation of a worm egg isolation procedure coupled with a multiplex PCR assay to carry out large-scale screening of red foxes (*Vulpes vulpes*) in Norway. Davidson, R.K.; Oines, O.; Madslien, K.; Mathis, A. Parasitology research, (Feb 2009) Vol. 104(3), pp. 509–14.	One technique used
6	A real-time multiplex-nested PCR system for coprological diagnosis of *Echinococcus multilocularis* and host species. Dinkel, A.; Kern, S.; Brinker, A.; Oehme, R.; Vaniscotte, A.; Giraudoux, P.; Mackenstedt, U.; Romig, T. Parasitology research, (Aug 2011) Vol. 109(2), pp. 493–8.	No data to perform a 2x2 comparison table
8	The red fox (*Vulpes vulpes L.*) as a source of zoonoses. Letkova, V.; Lazar, P.; Curlik, J.; Goldova, M.; Kocisova, A.; Kosuthova, L.; Mojzisova, J. Veterinarski Arhiv, (2006) Vol. 76, Suppl. S, pp. S73-S81.	No result or comparison of/between different tests
10	Detection of *Echinococcus* coproantigens by enzyme-linked immunosorbent assay in dogs from Cluj county. Seres, S.; Radoi, L.B.; Gherman, B. I.; Cozma, V. Lucrari Stiintifice - Universitatea de Stiinte Agronomice si Medicina Veterinara Bucuresti. Seria C, Medicina Veterinara (2008), Vol. 53, pp. 460–467.	One technique used
19	Assessment of the epidemiological status of *Echinococcus multilocularis* in foxes in France using ELISA coprotests on fox faeces collected in the field. Raoul, F.; Deplazes, P.; Nonaka, N.; Piarroux, R.; Vuitton, D.A.; Giraudoux, P. International journal for parasitology, (Dec 2001) Vol. 31(14), pp. 1579–88.	No data to perform a comparison between different tests
22	*Echinococcus multilocularis* and *Toxocara canis* in urban red foxes (*Vulpes vulpes*) in Brussels, Belgium. Brochier, B.; De Blander, H.; Hanosset, R.; Berkvens, D.; Losson, B.; Saegerman, C. Preventative veterinary medicine, (Jun 2007) Vol. 80(1), pp. 65–73.	One technique used
26	Epidemiology and risk factor analysis for canine echinococcosis in a Tibetan pastoral area of Sichuan. Huang, Y.; David, H.D.; Yang, W.; Qiu, J.M.; Chen, X.W.; Yang, Y.; Wang, Q.; Li, T.Y.; Xiao, Y.F.; Qiu, D.C.; Xiao, N.; Chen, F.X.; Ge, S.; Se, D. Chinese Journal of Parasitology and Parasitic Diseases (2008), Vol. 26(4), pp. 245–252.	No useful data
29	Latent-class methods to evaluate diagnostics tests for *Echinococcus* infections in dogs. Hartnack, S.; Budke, C.M.; Craig, P.S.; Qiu, J.; Boufana, B.; Campos-Ponce, M.; Torgerson, P. R. PloS Neglected Tropical Diseases, (Feb 2013) Vol. 7(2).	Not a primary research

ID	REFERENCE	REASON for EXCLUSION
39	*Echinococcus multilocularis* in north Italy. Manfredi, M.T.; Casulli, A.; La Rosa, G.; Di Cerbo, A.R.; Trevisio, K.; Genchi, C.; Pozio, E. Parassitologia, (Jun 2006) Vol. 48(1–2), pp. 43–6.	No data to perform a comparison
43	Prevalence of *Echinococcus multilocularis* in red foxes in the Slovak Republic. Dubinsky, P.; Varady, M.; Reiterova, K.; Miterpakova, M.; Turcekova, L. Helminthologia (Bratislava), (Dec 2001) Vol. 38(4), pp. 215–219.	No data to perform a comparison between different tests
44	Diagnosis of *Echinococcus multilocularis* infection in definitive host by detection of coproantigens. Sakashita, M. Japanese Journal of Veterinary Research (1992), Volume 40(1), 57.	Not a primary research
49	Magnetic resonance imaging and immunoblot analyses in rats with experimentally induced cerebral alveolar echinococcosis. Asanuma, T.; Matsumoto, Y.; Takiguchi, M.; Inanami, O.; Nakao, M.; Nakaya, K.; Ito, A.; Hashimoto, A.; Kuwabara, M. Comparative medicine, (Dec 2003) Vol. 53(6), pp. 649–56.	No data to perform a comparison between different tests
54	Application of EKITTO.RTM., a new immunochromatography kit for the detection of canine *Echinococcus multilocularis* coproantigen in vulpine faeces. Irie, T. Japanese Journal of Veterinary Research (2010), Volume 58(1), 54.	No data to perform a comparison between different tests
56	Parasitological and immunological methods for the detection of *Echinococcus multilocularis* in foxes. Eckert, J.; Deplazes, P.; Ewald, D.; Gottstein, B. Mitteilungen der Oesterreichischen Gesellschaft fuer Tropenmedizin und Parasitologie (1991), Vol. 13, pp. 25–30.	Not a primary research
57	Predictive values and quality control of techniques for the diagnosis of *Echinococcus multilocularis* in definitive hosts. Eckert, J. Acta tropica, (Feb 2003) Vol. 85(2), pp. 157–63.	Not a primary research
58	Immunological and molecular techniques for diagnosing the *Echinococcus multilocularis* infection in definitive and intermediate hosts. Eckert, J.; Deplazes, P. Acta Parasitologica, (Jan 2001) Vol. 46(1), pp. 1–7	Not a primary research
59	Molecular tools for studies on the transmission biology of *Echinococcus multilocularis*. Deplazes, P.; Dinkel, A.; Mathis, A. Parasitology, (2003) Vol. 127 Suppl, pp. S53–61.	Not a primary research
60	Diagnosis of the *Echinococcus multilocularis* infection in final hosts. Deplazes, P.; Eckert, J. Applied parasitology, (Dec 1996) Vol. 37(4), pp. 245–52.	Not a primary research
61	Echinococcosis: diagnosis and diagnostic interpretation in population studies. Torgerson, P.R.; Deplazes, P. Trends in parasitology, (Apr 2009) Vol. 25(4), pp. 164–70.	Not a primary research
62	Copro-DNA tests for diagnosis of animal taeniid cestodes. Mathis, A.; Deplazes, P. Parasitology international, (2006) Vol. 55 Suppl, pp. S87–90.	Not a primary research
64	Control of *Echinococcus multilocularis*: strategies, feasibility and cost–benefit analyses. Hegglin, D.; Deplazes, P. International journal for parasitology, (Apr 2013) Vol. 43(5), pp. 327–37.	Not a primary research

ID	REFERENCE	REASON for EXCLUSION
65	Detection of cestode infections in definitive hosts: present status and future advances. NATO Science Series: Life and Behavioural Sciences, Volume 341 Fraser, A.; Elayoubi, F.; Craig, P. S. Proceedings of the NATO Advanced Research Workshop on cestode zoonoses: echinococcosis and cysticercosis: an emergent and global problem, Poznan, Poland, 10–13 September 2000 (2002), pp. 157–175.	Not a primary research
66	WHO/OIE manual on echinococcosis in humans and animals: a public health problem of global concern. Eckert, J.; Gemmell, M.A.; Meslin, F.X.; Pawowski, Z.S. WHO/OIE manual on echinococcosis in humans and animals: a public health problem of global concern (2001), pp. i-xvii + 265 pp.	Not a primary research
67	Coproantigens in taeniasis and echinococcosis. Allan, J.C.; Craig, P.S. Parasitology International, (2006) Vol. 55, No. Suppl., pp. S75-S80.	Not a primary research
68	Immunodiagnostic and molecular approaches for the detection of taeniid cestode infections. Ito, A.; Craig, P.S. Trends in Parasitology, (Sept 2003) Vol. 19(9), pp. 377–381.	Not a primary research
70	*Echinococcus multilocularis* infection: immunology and immunodiagnosis. Gottstein, B. Advances in parasitology, (1992) Vol. 31, pp. 321–80.	Not a primary research
71	Trial of two new ELISA kits: 'Echinococcus serology', specific to the genus *Echinococcus*, and *'Echinococcus multilocularis'*, specific to the species *Echinococcus multilocularis*. Delaunay, P.; Petithory, J.C. Bulletin de la Societe Francaise de Parasitologie (1994), Vol. 12(1), pp. 23–28.	Study on human
72	Serodiagnosis of alveolar echinococcosis: detection of antibody against EM18 in patients and rodents. Akira, I. The Southeast Asian journal of tropical medicine and public health, (1997), Vol. 28 Suppl 1, pp. 117–24.	Study mostly on human, part on rodents no useful data
73	Potential remedy against *Echinococcus multilocularis* in wild red foxes using baits with anthelmintic distributed around fox breeding dens in Hokkaido, Japan. Tsukada, H.; Hamazaki, K.; Ganzorig, S.; Iwaki, T.; Konno, K.; Lagapa, J.T.; Matsuo, K.; Ono, A.; Shimizu, M.; Sakai, H.; Morishima, Y.; Nonaka, N.; Oku, Y.; Kamiya, M. Parasitology, (Aug 2002) Vol. 125(Pt 2), pp. 119–29.	No data to perform a comparison between different tests
75	The prevalence of *Echinococcus multilocularis* infection in wildlife carnivores in an area of Germany .1. Parasitological analysis of wild carnivores for determination of pathogen prevalence. Tackmann, K. Tierarztliche Umschau, (Aug 1993) Vol. 48(8), pp. 498–503.	One technique used
76	Development of latex agglutination test for the detection of *Echinococcus multilocularis* coproantigens in the definitive hosts. Shimizu, M. Japanese Journal of Veterinary Research, (May 2000) Vol. 48(1), pp. 68–69.	Not a primary research

ID	REFERENCE	REASON for EXCLUSION
78	A coprological survey of intestinal helminthes in strain dogs captured in Osaka prefecture, Japan. Kimura, A.; Morishima, Y.; Nagahama, S.; Horikoshi, T.; Edagawa, A.; Kawabuchi-Kurata, T.; Sugiyama, H.; Yamasaki, H. The Journal of veterinary medical science /the Japanese Society of Veterinary Science, (Oct 2013) Vol. 75(10), pp. 1409–11.	No useful data
79	Immunodiagnosis of parasite infections by elisa echinococcosis and trichinellosis. Jacquier, P.; Gottstein, B.; Petavy, A.F.; Danis, M.; Nozais, J.P.; Pagelot, F.; Percebois, G. Immunobiology, (1986) Vol. 173(2–5), pp. 247–248.	Study on human
80	Diagnostic value of a Western Blot using a crude larval antigen from *Echinococcus multilocularis*. Piarroux, R.; Janin, V.; Bresson-Hadni, S.; Vuitton, D.A.; Houin, R.; Liance, M. Acta Parasitologica, (Jul 2000) Vol. 45(3), pp. 196.	Study on human
81	Efficient serological methods for detecting *E. multilocularis* infection in different Old World monkey species. Proceedings of the Institute for Zoo and Wildlife Research, Berlin, No.5. Tappe, D.; Blankenburg, A.; Brehm, K.; Frosch, M.; Maetz-Rensing, K.; Kaup, F.J. Erkrankungen der Zootiere: Verhandlungsbericht des 41. Internationalen Symposiums ueber die Erkrankungen der Zoo- und Wildtiere, Rome, Italy, 28 May - 1 June, 2003 (2003), 421 p.	No useful data
87	Egg intensity and freeze–thawing of faecal samples affect sensitivity of *Echinococcus multilocularis* detection by PCR. Klein, C.; Liccioli, S.; Massolo, A.Parasitology research, (Oct 2014) Vol. 113(10), pp. 3867–73.	No data to perform a comparison
88	*Echinococcus multilocularis* infections in dogs from urban and peri-urban areas in France. Umhang, G.; Comte, S.; Raton, V.; Hormaz, V.; Boucher, J.-M.; Favier, S.; Combes, B.; Boue, F. Parasitology research, (Jun 2014) Vol. 113(6), pp. 2219–22.	No data to perform a comparison between different tests
99	Reinfection studies of canine echinococcosis and role of dogs in transmission of *Echinococcus multilocularis* in Tibetan communities, Sichuan, China. Moss, J.E.; Chen, X.; Li, T.; Qiu, J.; Wang, Q.; Giraudoux, P.; Ito, A.; Torgerson, P.R.; Craig, P.S. Parasitology, (Nov 2013) Vol. 140(13), pp. 1685–92.	The comparison test is genus specific, even Eg infection could be detected
100	Nutrias and muskrats as bioindicators for the presence of *Echinococcus multilocularis* in new endemic areas. Umhang, G.; Richomme, C.; Boucher, J.-M.; Guedon, G.; Boue, F. Veterinary parasitology, (Oct 2013) Vol. 197(1–2), pp. 283–7.	No data to perform a comparison
102	*Echinococcus* infections in Chinese dogs: A comparison of coproantigen kits. Huang, Y.; Yi, D.Y.; Huang, L.; Yu, W.J.; Wang, Q.; Qiu, D.C.; Liu, L.L.; Li, Y.Q.; Han, X.M.; Wang, H.; Xiao, N.; Wu, W.P.; Heath, D.D. Journal of Helminthology, (2014) Vol. 88(2, pp. 189–195.	Study focused on Eg

ID	REFERENCE	REASON for EXCLUSION
103	Noninvasive detection of *Echinococcus multilocularis* tapeworm in Urban Area, Estonia. Laurimaa, L.; Davison, J.; Plumer, L.; Suld, K.; Oja, R.; Moks, E.; Keis, M.; Hindrikson, M.; Kinkar, L.; Laurime, T.; Abner, J.; Remm, J.; Anijalg, P.; Saarma, U. Emerging Infectious Diseases, (2015) Vol. 21(1), pp. 163–164.	No data to perform a comparison
104	Ghost-hunting-is *Echinococcus multilocularis* really absent from mainland Norway? Davidson, R.; Oines, O.; Albin-Amiot, C.; Hopp, P.; Madslien, K.; Hagstrom, A.; Isaksson, M. Tropical Medicine and International Health, (Sept 2013) Vol. 18(Supp. 1), pp. 97.	Not a primary research
105	Updates on the surveillance program on parasites of raccoon dogs and foxes in Denmark 2011–2012. Al-Sabi, M.N.S.; Enemark, H.L.; Chriel M.; Jensen, T.H. Tropical Medicine and International Health, (2013) Vol. 18(Supp. 1), pp. 96.	Not a primary research
106	Development of a highly sensitive semi-automated capture probe DNA extraction method and real-time PCR diagnosing *E. multilocularis*. Juremalm, M. Tropical Medicine and International Health, (Sept 2013) Vol. 18(Supp. 1), pp. 48	Not a primary research
107	Echinococcus species from red foxes, corsac foxes, and wolves in Mongolia. Ito, A.; Chuluunbaatar, G.; Yanagida, T.; Davaasuren, A.; Dorjsuren, T.; Nakao, M.; Sako, Y.; Chuluunbaatar, G.; Sumiya, B.; Davaasuren, A.; Davaajav, A.; Asakawa, M.; Ki, T.; Nakaya, K.; Dorjsuren, T. Parasitology, (Nov 2013) Vol. 140(13), Sp. iss., pp. 1648–1654.	No data to perform a comparison

APPENDIX II WP4 Request 9: *List of excluded articles*

ID	REFERENCE	REASON for EXCLUSION
6	Surgical and chemotherapeutic treatment of alveolar echinococcosis in a dog. Haller, M.; Deplazes, P.; Guscetti, F.; Sardinas, J.C.; Reichler, I.; Eckert, J. Journal of the American Animal Hospital Association, (Jul-Aug 1998) Vol. 34(4), pp. 309–14.	No drug described
11	*Echinococcus multilocularis* in dogs, Japan. Morishima, Y.; Sugiyama, H.; Arakawa, K.; Kawanaka, M. Emerging Infectious Diseases (2006), Vo. 12(8), pp. 1292–1294.	No useful data
14	Experimental results with praziquantel (Embay 8440) in cestodiasis and cysticercosis. Thomas, H. Boletin Chileno de Parasitologia (1977), Vol. 32(1-2), pp. 2–6.	Not a primary research
15	Veterinary aspects of alveolar echinococcosis-A zoonosis of public health significance. Deplazes, P.; Eckert, J. Veterinary Parasitology, (Jul 2001) Vol. 98(1–3), pp. 65–87.	Not a primary research
16	Helminths in dogs and cats in Germany - aims and strategies of therapy. Epe, C. Tieraerztliche Umschau (2007), Vol. 62(4) special issue, pp. 43–48.	Not a primary research
17	Echinococcosis in animals: clinical aspects, diagnosis and treatment. Eckert, J.; Deplazes, P.; Craig, P.S.; Gemmell, M.A.; Gottstein, B.; Heath, D.; Jenkins, D. J.; Kamiya, M.; Lightowlers, M. WHO/OIE manual on echinococcosis in humans and animals: a public health problem of global concern (2001), pp. 72–99.	Not a primary research
18	FAO/UNEP/WHO guidelines for surveillance, prevention and control of echinococcosis/hydatidosis. Eckert, J.; Gemmell, M.A.; Soulsby, E.J. L. FAO/UNEP/WHO guidelines for surveillance, prevention and control of echinococcosis/hydatidosis. (1981), ix + 147 p	Not a primary research
19	Epidemiology and risk factor analysis for canine echinococcosis in a Tibetan pastoral area of Sichuan. Huang, Y.; David, H. D.; Yang, W.; Qiu, J.M.; Chen, X.W.; Yang, Y.; Wang, Q.; Li, T.Y.; Xiao, Y.F.; Qiu, D.C.; Xiao, N.; Chen, F.X.; Ge, S.; Se, D. Chinese Journal of Parasitology and Parasitic Diseases (2008), Vol. 26(4), pp. 245–252.	No useful data
20	Praziquantel-a new cestocide. Thomas, H.; Andrews, P. Pesticide Science (1977), Vol. 8(5), pp. 556–560.	Not a primary research
21	Helminths in the dog and cat. Epe, C. Kleintierpraxis, (Mar 2011) Vol. 56(3), pp. 136.	No drug described
22	*Echinococcus multilocularis* infections in dogs from urban and peri-urban areas in France. Umhang, G.; Comte, S.; Raton, V.; Hormaz, V.; Boucher, J.-M.; Favier, S.; Combes, B.; Boue F. Parasitology research, (Jun 2014) Vol. 113(6), pp. 2219–22.	No useful data
24	Reinfection studies of canine echinococcosis and role of dogs in transmission of *Echinococcus multilocularis* in Tibetan communities, Sichuan, China. Moss, J.E.; Chen, X.; Li, T.; Qiu, J.; Wang, Q.; Giraudoux, P.; Ito, A.; Torgerson, P.R.; Craig, P.S. Parasitology, (Nov 2013) Vol. 140(13), pp. 1685–92.	Not a primary research

ID	REFERENCE	REASON for EXCLUSION
25	Broadline efficiency, a new endectocide for cats against external parasites. Leon Artozqui, M. Argos - Informativo Veterinario (2014), No 157, pp. 76–77	No data on Em
26	*Echinococcus multilocularis*: a political zoonosis. AU Wright, I. Companion Animal (2013), Vol.18(8), pp. 368, 370–371.	Not a primary research
27	Epidemiological Study and Control Trial of Taeniid Cestode Infection in Farm Dogs in Qinghai Province, China. Nonaka, N.; Guo, Z.; Irie, T.; Kirino, Y.; Horii, Y.; Li, W.; Peng, M.; Duo, H.; Shen, X.; Fu, Y.; Gan, T.; Nasu, T.; Horii, Y. Journal of veterinary medical science, (Mar 2014) Vol. 76(3), pp. 395–400.	No useful data

APPENDIX II WP5 Request 3: *List of excluded articles*

ID	REFERENCE	REASON for EXCLUSION
9	Risk assessment of the presence of *Echinococcus multilocularis* and *Toxocara canis* in foxes from Brussels. Saegerman, C.; Blander, H. de; Hanosset, R.; Berkvens, D.; Losson, B.; Brochier, B.; de Blander, H. Epidemiologie et Sante Animale (2006), No 50, pp. 97–104. Conference: La grippe aviaire. Journee D'Epidemiologie AESA-AEEMA 18 mai 2006.	Not a primary research, same data as ID 5
15	Dog ownership, dog behaviour and transmission of *Echinococcus* spp. in the Alay Valley, southern Kyrgyzstan. Special Issue: Control of cestode zoonoses in Asia: role of basic and applied science. Kesteren, F.; van; Mastin, A.; Mytynova, B.; Ziadinov, I.; Boufana, B.; Torgerson, P.R.; Rogan, M. T.; Craig, P.S.; van Kesteren, F. Parasitology (2013), Vol. 140(13), pp. 1674–1684.	Not from EU or AC
16	Controlling *Echinococcus multilocularis*-ecological implications of field trials. Hansen F.; Tackmann K.; Jeltsch F.; Wissel C.; Thulke H.-H. Preventative veterinary medicine, (Jul 2003) Vol. 60(1), pp. 91–105.	Modelisation
21	Control of *Echinococcus multilocularis*: strategies, feasibility and cost–benefit analyses. Hegglin D.; Deplazes P. International journal for parasitology, (Apr 2013) Vol. 43(5), pp. 327–37.	Not a primary research
25	Ecology and epidemiology of *Echinococcus multilocularis* in Europe. Deplazes P. Parassitologia, (Jun 2006) Vol. 48(1–2), pp. 37–9.	Not a primary research
26	The present situation of echinococcosis in Europe. Romig T.; Dinkel A.; Mackenstedt U. Parasitology international, (2006) Vol. 55 Suppl, pp. S187–91.	Not a primary research
38	Urbanisation of wild animals changes in the behavioural biology of the red fox (*Vulpes vulpes*) in conjunction with the dimension of human alveolar echinococcosis . Janko, C. BfN - Skripten (Bundesamt fuer Naturschutz) (2012), No 309, pp. 131–135.	No useful data
40	A fifteen-year-investigation on the prevalence of *Echinococcus multilocularis* in the red fox population of Lower Saxony - An overview. von Keyserlingk-Eberius, M. Journal Fur Verbraucherschutz Und Lebensmittelsicherheit-Journal Of Consumer Protection And Food Safety, (Nov 2008) Vol. 3(4), pp. 421–428.	Not a primary research, same data as ID 43
41	*Echinococcus multilocularis* in the Iberian Peninsula. Considerations sur l'existence du cestode *Echinococcus multilocularis* dans la peninsule Iberique. Carvalho-Varela, M. Anais da Escola Superior de Medicina Veterinaria, Lisboa (1986), Vol. 23–24, pp. 102–117.	No useful data
54	Statistics and sample design in epidemiological studies of *Echinococcus multilocularis* in fox populations. Conraths, F. J.; Tackmann, K.; Staubach, C.H. Acta Tropica, (Feb 2003) Vol. 85(2), pp. 183–189.	Modelisation

ID	REFERENCE	REASON for EXCLUSION
55	Echinococcosis and hydatidosis in Bulgaria. Kamenov, Y.; Atanassov, A.; Prelesov, P.; Kalinova, K.; Rasheva, G. Wiadomosci Parazytologiczne (1998), Vol. 44(2), pp. 217–226, 22.	Data on *E. granulosus*
60	*Echinococcus multilocularis* and possible cycles in UK wildlife. Medlock, J.M.; Leach, S. Veterinary Record (2009), Vol. 164(25), pp. 789–790.	No useful data
65	*Echinococcus multilocularis* in Svalbard, Norway: Microsatellite genotyping to investigate the origin of a highly focal contamination. Knapp, J.; Staebler, S.; Deplazes, P.; Bart, J.M.; Stien, A.; Yoccoz, N.G.; Yoccoz, N.G.; Drogemuller, C.; Gottstein, B. Infection, Genetics and Evolution, (Aug 2012) Vol. 12(6), pp. 1270–1274.	No useful data
71	Environmental changes impacting *Echinococcus* transmission: research to support predictive surveillance and control. Atkinson, J.-A.M.; Grey, D. J.; Clements, A.C.A.; Mcmanus, D.P.; Yang, Y.R.; Barnes, T.S. Global Change Biology, (Mar 2013) Vol. 19(3), pp. 677–688.	Not a primary research
72	Infestation of water voles (*Arvicola terrestris*) with metacestodes of *Echinococcus multilocularis* in the canton of Freiburg (Switzerland). Schmitt, M.; Saucy, F.; Wyborn, S.; Gottstein, B. Schweizer Archiv fuer Tierheilkunde (1997), Vol. 139(2), pp. 84–93.	Not a primary research, same data as ID 56
74	Predictive values and quality control of techniques for the diagnosis of *Echinococcus multilocularis* in definitive hosts. Eckert, J. Acta tropica, (Feb 2003) Vol. 85(2), pp. 157–63.	Not a primary research
80	FAO/UNEP/WHO guidelines for surveillance, prevention and control of echinococcosis/hydatidosis. Eckert, J.; Gemmell, M.A.; Soulsby, E.J.L. FAO/UNEP/WHO guidelines for surveillance, prevention and control of echinococcosis/hydatidosis. (1981), ix + 147 p., Document VPH/81.28.	Not a primary research
82	Demonstrating freedom from *Echinococcus multilocularis* in Sweden, Finland and mainland Norway using species specific design prevalences. Wahlstroem, H.; Isomursu, M.; Hallgren, G.; Christensson, D.; Cedersmyg, M.; Wallensten, A.; Hjertqvist, M.; Uhlhorn, H.; Davidson, R.; Hopp, P. Epidemiologie et Sante Animale (2011), No 59/60, pp. 75–77.	Not a primary research
85	Helminthozoonoses the current situation in Slovakia. Letkova, V. Folia Veterinaria (2006), Vol. 50(4), pp. 201–204.	Not a primary research
88	Technical specifications for monitoring community trends in zoonotic agents in foodstuffs and animal populations. EFSA Journal (2010), Vol. 8(3), Article 1530 p.	No useful data
94	Epidemiology and control prospects of foodborne parasitic zoonoses in the European Union. Pozio E. Parassitologia, (Jun 2008) Vol. 50(1–2), pp. 17–24.	Not a primary research

ID	REFERENCE	REASON for EXCLUSION
96	The raccoon dog (*Nyctereutes procyonoides*) in Germany-an established Neozoon as host and vector for parasites and other pathogenes. Sutor, A.; Schwarz, S.; Conraths, F.J. Berliner Munchener Tierarztliche Wochenschrift, (Nov-Dec 2011) Vol. 124(11–12), pp. 457–464.	No useful data
97	Zoonotic diseases in wildlife and the importance of surveillance. Neimanis, A. Animals, health, food hygiene. Proceedings of Conference on "Current events in veterinary research and practice", Jelgava, Latvia, 22–23 November 2012 (2012), 240 p.	No useful data
99	Research on targeting sources of alveolar echinococcosis in Japan. Kamiya, M.; Trinipil, L.J.; Oku Y. Comparative immunology, microbiology and infectious diseases, (Sep 2007) Vol. 30(5–6), pp. 427–48.	Not a primary research
100	Towards the control of *Echinococcus multilocularis* in the definitive host in Japan. Nonaka, N.; Kamiya, M.; Oku, Y. Parasitology international, (2006) Vol. 55 Suppl, pp. S263–6.	No useful data
101	Transmission dynamics of *Echinococcus multilocularis*; its reproduction number, persistence in an area of low rodent prevalence, and effectiveness of control. Takumi, K.; Van der Giessen, J. Parasitology, (Jul 2005) Vol. 131(Pt 1), pp. 133–40.	Modelisation
102	Modelling the spatial distribution of *Echinococcus multilocularis* infection in foxes . Pleydell, D.R.J.; Danson, F.M.; Raoul, F.; Giraudoux, P.; Tourneux, F.; Graham, A.J.; Craig, P.S. Acta Tropica, (Aug 2004) Vol. 91(3), pp. 253–265.	Modelisation
111	Fox baiting against *Echinococcus multilocularis*: contrasted achievements among two medium size cities. Comte, S.; Raton, V.; Raoul, F.; Hegglin, D.; Giraudoux, P.; Deplazes, P.; Favier, S.; Gottschek, D.; Umhang, G.; Boue, F.; Combes, B. Preventative veterinary medicine, (Aug 2013) Vol. 111(No. 1–2), pp. 147–55.	No data on monitoring or surveillance
112	A semi-automated magnetic capture probe based DNA extraction and real-time PCR method applied in the Swedish surveillance of *Echinococcus multilocularis* in red fox (*Vulpes vulpes*) faecal samples. Isaksson, M.; Hagstrom, Ang.sa; Armua-Fernandez, M.; Wahlstrom, H.; Ang.gren, E.; Mille,r A.; Holmberg, A.; Lukacs, M.; Casulli, A.; Deplazes, P.; Juremalm, M. Parasites & vectors, (Dec 2014) Vol. 7(1), pp. 583.	No data on monitoring or surveillance
114	Present status of *Echinococcus multilocularis* in Sweden. Wahlstrom, H.; Osterman Lind, E.; Christensson, D.; Agren, E.O.; Botero-Kleiven, S.; Cedersmyg, M. Tropical Medicine and International Health, (Sept 2013) Vol. 18, Supp. 1, pp. 96–97.	No original data

APPENDIX II WP5 Request 5: *List of excluded articles*

ID	REFERENCE	REASON for EXCLUSION
4	Baiting red foxes in an urban area: A camera trap study. Hegglin, D.; Bontadina, F.; Gloor, S.; Romer, J.; Mueller, U.; Breitenmoser, U.; Deplazes, P. Journal of Wildlife Management, (Oct 2004) Vol. 68(4), pp. 1010–1017.	No Data Baiting strategy
6	A model for the control of *Echinococcus multilocularis* in France. Roberts M.G.; Aubert M.F. Veterinary parasitology, (Jan 1995) Vol. 56(1–3), pp. 67–74.	No Data Mathematical model
7	Echinococcoses of animals and humans in the Russian Federation. NATO Science Series: Life and Behavioural Sciences, Volume 341. Bessonov, A.S. Proceedings of the NATO Advanced Research Workshop on cestode zoonoses: echinococcosis and cysticercosis: an emergent and global problem, Poznan, Poland, 10–13 September 2000 (2002), pp. 91–98.	Review No data
8	Experience gained and evaluation of the echinococcosis/hydatidosis eradication programmes in Cyprus 1971-1999. NATO Science Series: Life and Behavioural Sciences, Volume 341. Economides, P.; Christofi, G. Proceedings of the NATO Advanced Research Workshop on cestode zoonoses: echinococcosis and cysticercosis: an emergent and global problem, Poznan, Poland, 10–13 September 2000 (2002), pp. 367–379.	Data on E. granulosus
11	*Echinococcus multilocularis* in foxes in Vienna and surrounding territories. Duscher, G.; Steineck, T.; Guenter, P.; Prosl, H.; Joachim, A. Wiener Tieraerztliche Monatsschrift (2005), Vol. 92(1), pp. 16–20	No Data
14	Transmission dynamics of *Echinococcus multilocularis* ; its reproduction number, persistence in an area of low rodent prevalence, and effectiveness of control. Takumi K.; Van der Giessen J. Parasitology, (Jul 2005) Vol. 131(Pt 1), pp. 133–40.	No Data Mathematical model
15	Control of *Echinococcus multilocularis*: strategies, feasibility and cost–benefit analyses. Hegglin D.; Deplazes, P. International journal for parasitology, (2013 Apr) Vol. 43, No. 5, pp. 327–37.	Review No data
16	[Baiting intervals and duration of control of the small fox tapeworm: a simulation study]. Hansen, F.; Tackmann, K.; Jeltsch, F.; Thulke, H.-H. Berliner und Munchener tierarztliche Wochenschrift, (Jul-Aug 2003) Vol. 116(7–8), pp. 299–305.	No Data Mathematical model
20	Habitat model for baiting foxes in suburban areas to counteract *Echinococcus multilocularis*. Koenig, A.; Janko, C.; Barla-Szabo, B.; Fahrenhold, D.; Heibl, C.; Perret, E.; Wermuth, S. Wildlife Research, (2012) Vol. 39(6), pp. 488–495.	No Data Mathematical model
22	[Fenbendazole therapy of experimental larval echinococcosis. I. The effect of fenbendazole on worm burden and protoscolex development of *Echinococcus multilocularis*]. Hinz, E. Zentralblatt fur Bakteriologie, Parasitenkunde, Infektionskrankheiten und Hygiene. Erste Abteilung Originale. Reihe A: Medizinische Mikrobiologie und Parasitologie, (Jun 1978) Vol. 240(4), pp. 542–8.	No data animal experimentation

ID	REFERENCE	REASON for EXCLUSION
23	Echinococcosis world distribution and prospects for control. Schantz, P.M. Report of the the PAHO/WHO Working Group on perspectives and possibilities of control and eradication of hydatidosis (2002), pp. 62–74.	No Data Mathematical model
24	FAO/UNEP/WHO guidelines for surveillance, prevention and control of echinococcosis/hydatidosis. Eckert, J.; Gemmell, M.A.; Soulsby, E.J.L. FAO/UNEP/WHO guidelines for surveillance, prevention and control of echinococcosis/hydatidosis. (1981), ix + 147 p., Document VPH/81.28; 27 contributors	Review No data
27	Current control strategies targeting sources of echinococcosis in Japan. Kamiya, M.; Lagapa, J.T.G.; Nonaka, N.; Ganzorig, S.; Oku, Y.; Kamiya, H. Revue scientifique et technique (International Office of Epizootics), (Dec 2006) Vol. 25(3), pp. 1055–65.	Review No data
29	Perspective on control options for *Echinococcus multilocularis* with particular reference to Japan. Ito, A.; Romig, T.; Takahashi, K. Parasitology, (2003) Vol. 127 Suppl, pp. S159–72.	Review No data

ABBREVIATIONS

AC	adjacent country
AE	alveolar echinococcosis
ANSES	French Agency for Food, Environmental and Occupational Health and Safety
CI	confidence interval
CSIC	Agencia Estatal Consejo Superior de Investigaciones Cientificas
DCF	Data Collection Framework
DH	definitive host
EFSA	European Food Safety Authority
ELISA	enzyme-linked immunosorbent assay
EM	*Echinococcus multilocularis*
ESCAPP	European Scientific Counsel Companion Animal Parasites
EU	European Union
EURLP	European Union Reference Laboratory for Parasites
EVIRA	Finnish Food Safety Authority
FLI	Federal Research Institute for Animal Health
HLA	human leucocyte antigen
HU	Hohenheim University
IH	intermediate host
IM	intramuscular
IPB	Institute of Parasitology of Bern
IPZ	Institute of Parasitology of Zurich
ISS	Istituto Superiore di Sanità
IST	intestinal scraping technique
LR	likelihood ratio
LR-	negative likelihood ratio
LR+	positive likelihood ratio

MS	Member State
NOS	Newcastle–Ottawa Scale
NRL	National Reference Laboratory for Parasites
NUT	Nomenclature des Unites Territoriales statistique
NVH	Norwegian School of Veterinary Science
NVRI	National Veterinary Research Institute
PCR	polymerase chain reaction
Q-PCR	quantitative-PCR
RD	risk difference
RIVM	National Institute of Public Health and the Environment
ROC	receiver operating characteristic
rRNA	ribosomal RNA
SC	subcutaneous
SCT	sedimentation and counting technique
snRNA	small nuclear RNA
SSCT	segmented sedimentation and counting technique
STN	Scientific & Technical Information Network
SVT	shaking in a vessel technique
UU	University Hospital of Ulm
WP	Work Package