Universitat Autònoma de Barcelona

Epidemiology of taeniosis and cysticercosis in Europe

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Certifica:

Que la tesi doctoral tituada "**Epidemiology of taeniosis and cysticercosis in Europe**" presentada per **Minerva Laranjo González** per a l'obtenció del grau de Doctor en Medicina i Sanitat Animals s'ha realitzat sota la seva direcció a la UAB i al CReSA-IRTA, i autoritza la seva presentació perquè sigui valorada per la comissió establerta.

I perquè així consti als efectes oportuns, signa la present declaració a Bellaterra (Barcelona), a 16 de juliol de 2018.

Dr. Alberto Allepuz Palau

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Doctoranda

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CYSTINET

EUROPEAN NETWORK ON TAENIOSIS/CYSTICERCOSIS

cost

Aos meus pais

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LIST OF ABBREVIATIONS AND ACRONYMS

Ab	Antibody
AEMPS	Spanish Agency of Medicines and Medical Devices
Ag	Antigen
CBA	Cost-benefit analysis
CDC	Centers for Disease Control and Prevention
CEA	Cost-effectiveness analysis
CI	Confidence interval
CMBD-AP	“Conjunt mínim bàsic de dades d'atenció primària”
COI	Cost-of-illness
CYSTINET	European Network on Taeniosis/Cysticercosis
DALY	Disability-adjusted life year
DNA	Deoxyribonucleic acid
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
EFSA	European Food Safety Authority
ELISA	Enzyme-linked immunosorbent assay
EU	European Union
FAO	Agriculture Organization of the United Nations
GDP	Gross domestic product
GNI	Gross national income
ICD	International Classification of Diseases
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
MS	Member State
NCC	Neurocysticercosis
NPV	Net present value
OIE	World Organisation for Animal Health/Office International des Epizooties
OR	Odds ratio
PCR	Polymerase chain reaction
PECO	Population, Exposure, Comparator, Outcome

PICO	Population, Intervention, Comparator, Outcome
PIT	Population, Index test, Target condition
PO	Population, Outcome
RR	Relative risk
SCVMPH	Scientific Committee on Veterinary Measures relating to Public Health
SESC	Catalan Slaughterhouse Support Network
SMPH	Summary measures of population health
WHO	World Health Organization

ABSTRACT

Taenia solium and *Taenia saginata* are two zoonotic parasites that cause taeniosis in humans (definitive host) and cysticercosis in pigs and cattle (intermediate host), respectively. In Europe, *T. saginata* has been present for centuries but data showing the occurrence and burden of this zoonotic agent are scarce. *T. solium* is considered absent in Europe but data about this parasite in this region are limited. In consequence, data on *T. saginata* and *T. solium* occurrence in humans and animals in Europe are incomplete and fragmented. In this context, the general aim of this thesis was to advance the knowledge of the epidemiology of *T. saginata* and *T. solium* in Europe.

In study I a systematic review of studies published between 1990 and 2014 was conducted to present the current knowledge on the epidemiology, impact and control of bovine cysticercosis in Europe. The results of this study indicated that there is a lack of complete and updated epidemiological data in most countries, especially in eastern Europe. Moreover, it concluded that this lack of information is a limitation to guide risk-based interventions against the disease. Conducting studies on risk factors was recommended in order to guide such strategies.

In study II, the knowledge on the epidemiology of *T. saginata* and *T. solium* in humans and animals in western Europe was updated by undertaking a systematic review of scientific and grey literature published from 1990 to 2015. Additionally, data about disease occurrence were actively sought by contacting local experts in the different countries. The results of this study indicated that the detection and reporting of human taeniosis in western Europe needs to be improved. Furthermore, the study identified reports of *T. solium* tapeworm carriers, of suspected autochthonous cases of human cysticercosis and of suspected cases of *T. solium* in pigs without molecular confirmation. These findings, combined with the increased migration from *T. solium* endemic areas, may constitute a public health risk that deserves further attention. Moreover, in this study it was concluded that suspected cases of *T. solium* in pigs should be confirmed by molecular methods, that both taeniosis and human cysticercosis should be notifiable and surveillance and reporting in animals should be improved.

Study III of this thesis aimed to estimate the prevalence and spatial distribution of bovine cysticercosis (2008–2015) and the burden from *T. saginata* upon the animal and human sectors (2013–2015) in northeastern Spain (Catalonia). During 2008–2015 a mean prevalence of 0.010% was detected at slaughter. Cattle movement history was used to identify the place where cattle most likely became infected and to investigate its spatial distribution. Based on the farm where the infection was acquired with highest probability, two significant bovine cysticercosis clusters were detected in Catalonia. The number of patients diagnosed with taeniosis in primary care during the period 2013–2016 was low (41–63/year) suggesting that the public health risk of *T. saginata* in the study area is low. The economic impact of *T. saginata* in Catalonia during 2013–2015 was estimated considering costs of meat inspection, losses due to carcass condemnation and freezing and taeniosis-associated costs. The results obtained indicated that the economic impact due to *T. saginata* was mainly attributed to meat inspection and suggested that developing and implementing a risk-based surveillance is needed to lower these costs. Results also indicated that cattle movements need to be taken into account in the development of such a strategy.

RESUMEN

Taenia solium y *Taenia saginata* son dos parásitos zoonóticos que causan teniasis en personas (hospedador definitivo) y cisticercosis en cerdos y en ganado vacuno (hospedador intermediario), respectivamente. En Europa, *T. saginata* ha estado presente durante siglos, sin embargo hay poca información acerca de la ocurrencia e impacto de este agente zoonótico. *T. solium* se considera ausente en Europa pero los datos existentes sobre este parásito son escasos. En consecuencia, los datos sobre la incidencia y prevalencia de *T. saginata* y *T. solium* en personas y animales en Europa son incompletos y se encuentran fragmentados. En este contexto, la presente tesis tuvo por objeto general avanzar en el conocimiento de la epidemiología de *T. saginata* y *T. solium* en Europa.

El estudio I de esta tesis consistió en una revisión sistemática de estudios publicados entre 1990 y 2014 que tuvo como objetivo compilar el conocimiento actual sobre la epidemiología, impacto y control de la cisticercosis bovina en Europa. Los resultados de este estudio indicaron que existe una carencia de datos epidemiológicos completos y actualizados en la mayoría de países, especialmente en los países del Este de Europa. Además, se concluyó que la falta de información epidemiológica limita el desarrollo de estrategias de vigilancia basadas en riesgo y se recomendó la realización de estudios de factores de riesgo para guiar dichas estrategias.

En el estudio II se actualizó el conocimiento de la epidemiología de *T. saginata* y *T. solium* en personas y animales en Europa Occidental a través de una revisión sistemática de literatura científica y gris publicada entre 1990 y 2015. Así mismo, se realizó una búsqueda de datos sobre casos a través de expertos locales en los diferentes países. Los resultados indicaron que es necesario mejorar tanto la detección como la notificación de las teniasis humanas en Europa Occidental. Además, se identificaron casos de personas portadoras de la forma adulta de *T. solium*, casos de cisticercosis humana sospechosos de ser autóctonos y casos de *T. solium* en cerdos sin confirmación molecular. Estos hallazgos, junto con un aumento de la migración desde áreas donde *T. solium* es endémico, podrían constituir un riesgo para la salud pública y merecen una mayor atención. Además, este estudio concluyó que los casos sospechosos de *T. solium* en cerdos deberían confirmarse con técnicas moleculares, que tanto las teniasis como la cisticercosis humana deberían ser notificables y que se debería mejorar la vigilancia y notificación en animales.

El estudio III tuvo como objetivo estimar la prevalencia y distribución espacial de la cisticercosis bovina (2008–2015) y el impacto de *T. saginata* en sanidad animal y humana (2013–2015) en el noreste de España (Cataluña). Durante 2008–2015 se detectó una prevalencia en matadero de 0.010%. A partir de los registros de movimientos de bovino se identificó el lugar donde los animales se habrían infectado con mayor probabilidad y se investigó su distribución espacial. Teniendo en cuenta la granja en la que con mayor probabilidad se habría producido la infección, se detectaron dos conglomerados. El número de pacientes con diagnóstico de teniasis en atención primaria durante 2013–2016 fue pequeño (41–63/año) sugiriendo que el riesgo en salud pública de *T. saginata* en el área de estudio es bajo. El impacto económico de *T. saginata* en Cataluña durante 2013–2015 se calculó considerando los costes de la inspección postmortem, las pérdidas causadas por el decomiso y congelación de canales y los costes asociados a casos de teniasis. Los resultados obtenidos indicaron que el impacto económico de *T. saginata* se debe principalmente a la inspección postmortem y que el desarrollo de estrategias de vigilancia basadas en riesgo podría ser útil para reducir dicho coste. Los resultados también evidenciaron la importancia de tener en cuenta la trazabilidad de los animales para el desarrollo de dicha estrategia.

RESUM

Taenia solium i *Taenia saginata* són dos paràsits zoonòtics que causen teniasi en persones (hoste definitiu) i cisticercosi en porcí i boví (hoste intermediari), respectivament. A Europa, *T. saginata* ha estat present durant segles, tanmateix hi ha poca informació sobre l'ocurrència i impacte d'aquest agent zoonòtic. *T. solium* es considera absent a Europa però les dades existents sobre aquest paràsit són escasses. En conseqüència, les dades sobre la incidència i prevalença de *T. saginata* i *T. solium* en persones i animals a Europa són incompletes i es troben fragmentades. En aquest context, la present tesi va tenir per objectiu general avançar en el coneixement de l'epidemiologia de *T. saginata* i *T. solium* a Europa.

L'estudi I d'aquesta tesi va consistir en una revisió sistemàtica d'estudis publicats entre 1990 i 2014 que va tenir com a objectiu compilar el coneixement actual sobre l'epidemiologia, impacte i control de la cisticercosi bovina a Europa. Els resultats d'aquest estudi van indicar que existeix una mancança de dades epidemiològiques completes i actualitzades en la majoria de països, especialment en els països de l'Est d'Europa. A més a més, es va concloure que la falta d'informació epidemiològica limita el desenvolupament d'estratègies de vigilància basades en risc i es va recomanar la realització d'estudis de factors de risc per guiar aquestes estratègies.

En l'estudi II es va actualitzar el coneixement de l'epidemiologia de *T. saginata* i *T. solium* en persones i animals a Europa Occidental a través d'una revisió sistemàtica de literatura científica i grisa publicada entre 1990 i 2015. Igualment, es va realitzar una cerca de dades sobre casos a través d'experts locals en els diferents països. Els resultats van indicar que és necessari millorar tant la detecció com la notificació de les teniasis humanes a Europa Occidental. A més a més, es van identificar casos de persones portadores de la forma adulta de *T. solium*, casos de cisticercosi humana sospitosos de ser autòctons i casos de *T. solium* en porcí sense confirmació molecular. Aquestes troballes, juntament amb un augment de la migració des d'àrees on *T. solium* és endèmic, podrien constituir un risc per a la salut pública i mereixen una major atenció. A més a més, aquest estudi va concloure que els casos sospitosos de *T. solium* en porcs haurien de confirmar-se amb tècniques moleculars, que tant les teniasis com la cisticercosi humana haurien de ser notificables i que s'hauria de millora la vigilància i notificació en animals.

L'estudi III va tenir com a objectiu estimar la prevalença i distribució espacial de la cisticercosi bovina (2008–2015) i l'impacte de *T. saginata* en sanitat animal i humana (2013–2015) en el nord-est d'Espanya (Catalunya). Durant 2008–2015 es va detectar una prevalença a escorxador de 0.010%. A partir dels registres de moviments de bovins es va identificar el lloc on els animals s'haurien infectat amb una major probabilitat i es va investigar la seva distribució espacial. Tenint en compte la granja on la infecció s'hauria produït amb més probabilitat, es van detectar dos conglomerats. El nombre de pacients amb diagnòstic de teniasi en atenció primària durant 2013–2016 va ser petit (41–63/any) suggerint que el risc en salut pública de *T. saginata* en l'àrea d'estudi és baix. L'impacte econòmic de *T. saginata* a Catalunya durant 2013–2015 es va calcular considerant els costos de la inspecció postmortem, les pèrdues causades pel decomís i congelació de canals i els costos associats a casos de teniasis. Els resultats obtinguts van indicar que l'impacte econòmic de *T. saginata* s'atribueix principalment a la inspecció postmortem i que el desenvolupament d'estratègies de vigilància basades en risc podria ser útil per reduir aquest cost. Els resultats també van evidenciar la importància de tenir en compte la traçabilitat dels animals per al desenvolupament d'aquesta estratègia.

PUBLICATIONS

The studies presented in this thesis have been published in an international scientific peer-reviewed journal:

Study I: Epidemiology, impact and control of bovine cysticercosis in Europe: a systematic review.

Minerva Laranjo-González, Brecht Devleesschauwer, Sarah Gabriël, Pierre Dorny and Alberto Allepuz

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Study II: Epidemiology of taeniosis/cysticercosis in Europe, a systematic review: Western Europe

Minerva Laranjo-González, Brecht Devleesschauwer, Chiara Trevisan, Alberto Allepuz, Smaragda Sotiraki, Annette Abraham, Mariana Boaventura Afonso, Joachim Blocher, Luís Cardoso, José Manuel Correia da Costa, Pierre Dorny, Sarah Gabriël, Jacinto Gomes, María Ángeles Gómez-Morales, Pikka Jokelainen, Miriam Kaminski, Brane Krt, Pascal Magnussen, Lucy J. Robertson, Veronika Schmidt, Erich Schmutzhard, G. Suzanne A. Smit, Barbara Šoba, Christen Rune Stensvold, Jože Starič, Karin Troell, Aleksandra Vergles Rataj, Madalena Vieira-Pinto, Manuela Vilhena, Nicola Ann Wardrop, Andrea S. Winkler and Veronique Dermauw

Published in Parasites & Vectors, (2017) 10:349

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Study III: Epidemiology and economic impact of bovine cysticercosis and taeniosis caused by *Taenia saginata* in northeastern Spain (Catalonia)

Minerva Laranjo-González, Brecht Devleesschauwer, Famke Jansen, Pierre Dorny, Céline Dupuy, Ana Requena-Méndez and Alberto Allepuz

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1. General Introduction

1.1. Background on taeniosis/cysticercosis

Taeniosis refers to the intestinal infection of humans by the adult form of tapeworms of the genus *Taenia.* Three *Taenia* species can cause human taeniosis: *Taenia saginata*, *Taenia solium* and *Taenia asiatica* (Eom and Rim, 1993; Craig and Ito, 2007; Flisser et al., 2004). Humans act as the only definitive host for these three species. Cysticercosis refers to the tissue infection of the intermediate host (cattle for *T. saginata* and swine for *T. solium* and *T. asiatica*) with the metacestode larval stage (cysticercus) of these parasites (Galán-Puchades and Fuentes, 2016). *T. saginata* and *T. solium* primarily occur in cardiac and striated muscles whereas *T. asiatica* cysticerci are mainly found in pig viscera (Flisser et al., 2005). Humans acquire the infection by consuming raw or undercooked meat infected with cysticerci. In the case of *T. solium,* humans can also act as dead-end intermediate host and suffer from human cysticercosis (White, 1997). In humans, cysticerci have a tendency to establish in the central nervous system causing neurocysticercosis (NCC) (García et al., 2003).

T. solium and *T. saginata* have a cosmopolitan distribution; they have been known for centuries and are probably one of the oldest medical conditions recognised in humans (Grove, 1990; Hoberg, 2002). Moreover, they are among the most common causes of human intestinal cestodiasis worldwide (Craig and Ito, 2007). Conversely, *T. asiatica,* which had not been discovered until relatively recently (Eom and Rim, 1993; Craig and Ito, 2007; Galán-Puchades and Fuentes, 2013), has only been reported in South-East Asia, where it was recognised (Eom and Rim, 1993), and other countries in Asia like India or Nepal (Singh et al., 2016; Devleesschauwer et al., 2012). Due to the fact that the geographical distribution of *T. asiatica* seems to be restricted to Asian countries (Ale et al., 2014) and until now this *Taenia* species has not been reported in Europe (Dorny et al., 2010) this PhD thesis focused on *T. saginata* and *T. solium*.

1.1.1. Morphology and life cycle of *T. saginata* and *T. solium*

T. solium and *T. saginata* life cycles include three different developmental stages: the adult form, the egg and the larval stage (metacestode) (Figure 1-1).

The adult form, which is present in the definitive host, is a flat, ribbon-shaped, long and segmented tapeworm (Hoberg, 2002; Flisser et al., 2005). Its colour is opaque white or yellowish (Flisser et al., 2004) and it consists of a scolex (head), a neck and a strobila (body). The scolex is provided with structures for attachment to the human intestinal mucosa. The neck is a short (5–10 mm), undivided and narrow part that follows the scolex and from which the formation of the strobila begins (Ferrer and Gárate, 2014). The strobila is constituted of hundreds of hermaphroditic reproductive segments (proglottids) that mature and grow in size gradually (Gajadhar et al., 2006). Immature proglottids are the most proximal to the scolex and undergo continuous differentiation to form mature and gravid proglottids (the most distant segments). Mature proglottids possess fully developed male and female reproductive organs (Mayta et al., 2000). Gravid proglottids contain a large uterus filled with eggs (50,000 to 80,000) (Flisser et al., 2005).

Eggs are spherical and measure between 30 and 40µm in diameter (Wittner et al., 2011). Each egg contains an hexacant embryo (or oncosphere) which is surrounded by an embryophore (Ferrer and Gárate, 2014).

The metacestodal larval stage (or cysticercus) occurs in the tissue of the intermediate host. It consists of a translucent fluid-filled vesicle (cyst) that contains an invaginated scolex of the future tapeworm (Wittner et al., 2011).

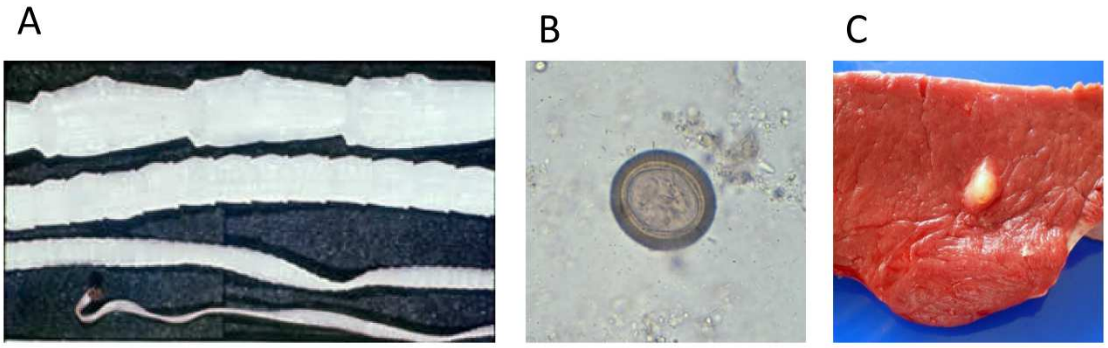

Figure 1-1 (A) *T. saginata* adult tapeworm; (B) *Taenia* spp. egg in unstained wet mounts; (C) *T. saginata* cyst in bovine myocardium (source of A and B: DPDx Parasites Image Gallery, Centers for Disease Control and Prevention (CDC); source of C: Catalan Slaughterhouse Support Network (SESC), http://www.cresa.cat/blogs/sesc/)

The life cycles of *T. saginata* and *T. solium* are complex and involve two mammalian hosts (Hoberg, 2002) (Figure 1-2, Figure 1-3). In the case of *T. saginata*, humans (sole definitive host) become infected through the consumption of raw or insufficiently cooked beef containing one or more viable cysticeri. The scolex evaginates and attaches to the intestinal mucosa and the parasite develops into the adult form in the human intestinal lumen (Flisser et al., 2005). The *T. saginata* adult worm usually measures between 4 and 6 m (Bogitsh et al., 2013), and may be composed of 1000–2000 proglottids (Wittner et al., 2011). It possesses a scolex with four suckers but no rostellum nor hooks. The strobilate tapeworm reaches sexual maturity in 10 to 12 weeks (Wittner et al., 2011) when gravid proglottids begin to detach from the distal part of the worm (Flisser et al., 2005). *T. saginata* gravid proglottids are excreted in faeces but they can also migrate spontaneously from the anus and be expelled through active migration: i.e. they can move independently between the legs, onto the clothes or bedding or fall to the ground while releasing eggs. After excretion, many of the eggs shed by the final host are fully embryonated and immediately infective for the intermediate host (Flisser et al., 2005). Eggs of the beef tapeworm are extremely resistant to a broad range of temperatures and may survive and remain viable for several weeks or months in suitable conditions (Gemmell et al., 1983; Hoberg, 2002). The eggs can be disseminated via flooding, surface waters, and effluents from water treatment plants. Cattle (i.e. the intermediate host) will acquire cysticercosis by ingesting eggs via contaminated pasture, feed or water (Dorny and Praet, 2007). Following ingestion of eggs, embryos hatch, activate under the effect of digestive fluids and penetrate the intestinal wall. Using the blood and lymphatic systems, oncospheres migrate to primarily striated and cardiac muscles where they develop into small vesicles of 6–10 mm (i.e. cysticercus stage). Cysticerci become infective after approximately 10 weeks (Flisser et al., 2005). They will normally degenerate and calcify after a few months, although infective/viable cysticerci may persist for several months or years (Gemmell et al., 1983). Cysticerci in different stages of development can be present in the animal at the same time. The life cycle is closed when humans consume meat containing cysticerci.

The life cycle of *T. solium* also consists of a two-host life cycle with humans as the only definitive host (Figure 1-3). In the case of *T. solium*, pigs are the natural intermediate host but humans can also act as accidental intermediate hosts (García and Del Brutto, 2000). Humans acquire taeniosis through the ingestion of undercooked pork infected with *T. solium* viable cysticerci. Adult *T. solium* tapeworms, which develop in the small human intestine, usually have a length of 2 to 4 m and approximately 1000 proglottids

(García and Del Brutto, 2005; Wittner et al., 2011). They have a scolex that possesses four suckers, a rostellum and a double crown of hooks (22–32) (Ferrer and Gárate, 2014). In the case of *T. solium,* gravid proglottids are generally expelled passively in the stools during defecation. Pigs acquire cysticercosis through the ingestion of faeces contaminated with eggs (Flisser et al., 2006). In pigs, *T. solium* larvae may invade muscles, viscera (i.e. liver, lungs), nervous tissue and, occasionally, subcutaneous tissue (Flisser, 1994). *T. solium* cysticerci measure around 8–15 mm (Flisser et al., 2005). Humans can acquire human cysticercosis upon accidental ingestion of eggs, acting as dead-end intermediate host for *T. solium*. This occurs through a human-to-human transmission via food contaminated with *T. solium* eggs, self-infection through inadequate personal hygiene or close contact with *T. solium* tapeworm carriers (Craig and Ito, 2007). In humans, *T. solium* oncospheres can migrate to subcutaneous tissue, striated and cardiac muscles, or the eyes but more commonly they migrate to the central nervous system (neurotropism) (Flisser, 1994). The infection of the central nervous system by *T. solium* cysticerci is known as neurocysticercosis.

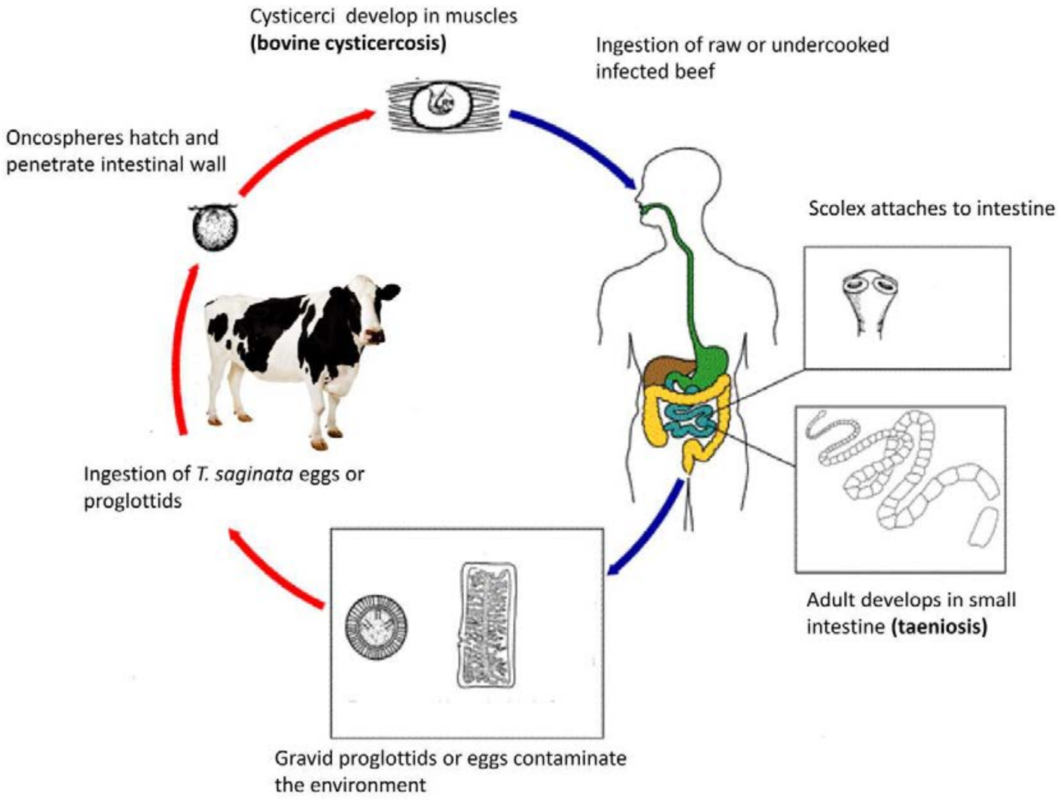

Figure 1-2 Life cycle of *T. saginata* (adapted from: https://www.cdc.gov/dpdx/az.html)

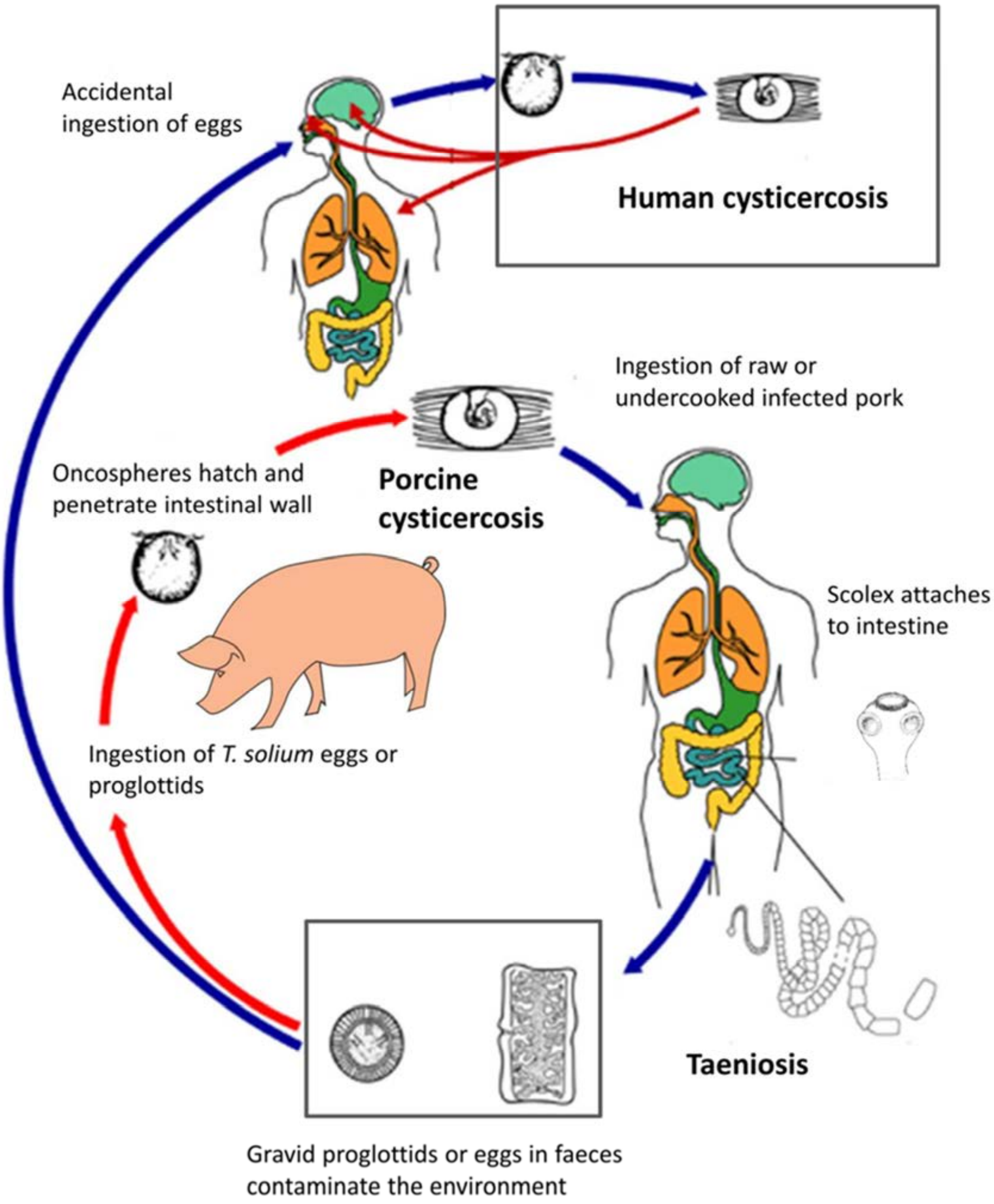

Figure 1-3 Life cycle of *T. solium* (adapted from: https://www.cdc.gov/dpdx/az.html)

1.1.2. Clinical presentation and diagnosis

1.1.2.1. Human taeniosis (*T. saginata* and *T. solium*)

1.1.2.1.1. Clinical presentation

T. saginata

Adult tapeworms absorb nutrients through the body surface and do not invade the intestinal mucosa (Craig and Ito, 2007). For this reason, patients suffering from taeniosis usually do not exhibit clinical signs. Occasionally, clinical signs such as pruritus ani, nausea, mild abdominal discomfort, diarrhoea, abdominal pain and weight loss are observed (Craig and Ito, 2007; Dorny and Praet, 2007; Dailey Garnes et al., 2018). The majority of *T. saginata* carriers feel an unpleasant sensation caused by the spontaneous migration of proglottids leaving the human host actively (Pawlowski and Schultz, 1972). More severe conditions such as appendicitis, peritonitis, cholangitis, intestinal perforation or obstruction, gall bladder perforation or biliary tract obstruction have been reported but occur very rarely (Sartorelli et al., 2005; Hakeem et al., 2012; Jongwutiwes et al., 2004; Karanikas et al., 2007; Uygur-Bayramiçli et al., 2012). *T. saginata* taeniosis can also be the cause of emotional distress due to the observation of the length of the worm and proglottids in the stools, which in addition are motile (Okello and Thomas, 2017).

T. solium

T. solium taeniosis can cause mild symptoms similar to those documented for *T. saginata*. However, most patients seem to be asymptomatic and most of them do not notice the passage of segments either as it occurs with *T. saginata* (García et al., 2003).

1.1.2.1.2. Diagnosis

The classical method to diagnose taeniosis is the direct microscopic examination of *Taenia* spp. eggs shed in faeces (stool microscopy) (Ferrer and Gárate, 2014). *T. solium* and *T. saginata* eggs look identical under the light microscope (Craig and Ito, 2007). Therefore this technique only enables identification of *Taenia* eggs at genus level (i.e. *Taenia* spp.). Macroscopic examination is based on the search of *T. solium* or

T. saginata proglottids in faeces (Dorny et al., 2005). Morphological microscopic examination of gravid proglottids, if well preserved, can enable species identification (Mayta et al., 2000). This is usually done by counting the number of unilateral uterine branches of gravid proglottids (7 to 15 in *T. solium* and 15 to 30 in *T. saginata*) (Ferrer and Gárate, 2014). This number in some cases may overlap between the two *Taenia* species leading to inconclusive results. These techniques have a low sensitivity due to intermittent nature of shedding of eggs (García et al., 2003; Mwape and Gabriël, 2014). Techniques for detection of DNA such as PCR can be used to confirm the *Taenia* species (i.e. *T. saginata* or *T. solium*) (González et al., 2000; González et al., 2002). Alternative immunodiagnostic assays in faeces or serum (e.g. coproantigen-detection ELISA and antibody-detection ELISA) have also been developed but they are not widely used or commercially available (García et al., 2003; Mwape and Gabriël, 2014; Gómez-Morales et al., 2017).

1.1.2.2. Human neuro/cysticercosis (*T. solium*)

1.1.2.2.1. Clinical presentation

Clinical manifestations and disease severity depend on the location, size, number, developmental stage of cysts (viable, degenerating, calcified), and intensity of the host's immune response (García et al., 2014; Carabin et al., 2011; Webb and White, 2016). When cysts establish outside the central nervous system cysticercosis is usually asymptomatic. Few exceptions may occur in cases of ocular cysticercosis or in infrequent cases of massive muscular infection (García and Del Brutto, 2005). In the case of NCC, the infection of the central nervous system by the larval stage of *T. solium*, can have a wide range of clinical manifestations and disease severity. NCC can manifest itself as a completely asymptomatic infection but also as a mild to a severe and even fatal disease. According to a systematic review by Carabin et al. (2011) the most common clinical manifestation of NCC is seizures or epilepsy, followed by headaches, focal deficits and signs of increased intracranial pressure (Carabin et al., 2011).

1.1.2.2.2. Diagnosis

Diagnosis of NCC presents normally a challenge as clinical manifestations are non-specific, most neuroimaging findings are not pathognomonic and serological tests may have limitations in terms of sensitivity and specificity (White, 2000; Del Brutto et al., 2001). Commonly, definitive diagnosis of NCC cannot be reached (Nash et al., 2005). However, a series of diagnostic criteria combining immunological, epidemiological, clinical, and imaging data have been proposed (Del Brutto et al., 2001) and have been proved useful (Del Brutto, 2012a) in facilitating diagnosis of NCC. Its interpretation allows reaching two types of diagnostic levels: definitive and probable (Del Brutto, 2012a).

1.1.2.3. Bovine cysticercosis (*T. saginata*) and porcine cysticercosis (*T. solium*)

1.1.2.3.1. Clinical presentation

Bovine cysticercosis is usually subclinical in naturally acquired infections (Dorny et al., 2000). Nevertheless, clinical signs have been recorded in bovines that had been experimentally infected with *T. saginata* eggs (Oryan et al., 1998; Blazek et al., 1985). In the case of *T. solium* porcine cysticercosis, pigs have been generally considered to be asymptomatic. However, recent studies indicate that naturally infected pigs with NCC can present clinical signs and suffer from seizures. It has also been reported that NCC can be responsible for behavioural changes in infected sows (Trevisan et al., 2016; Trevisan et al., 2017a).

1.1.2.3.2. Diagnosis

The main procedure for the diagnosis of cysticercosis in animals is meat inspection (i.e. post-mortem examination). Meat inspection is based on visual (macroscopic) examination of the intact and cut surfaces of the carcass and organs (OIE, 2017). *T. saginata* and *T. solium* cysts are identified based on their morphological appearance. In the European Union (EU), the official post-mortem inspection is enforced through Regulation (EC) No 854/2004 of the European Parliament and of the Council of 29 April 2004 laying down specific rules for the organisation of official controls on products of animal origin intended for human consumption (European Parliament and Council of the European Union, 2004). The minimum procedures required for the inspection of bovine and porcine cysticercosis are described in Chapter I and IV of Section IV of Annex I to this regulation and apply to bovine animals over 6 weeks old and swine. For cattle, these procedures consist in the examination of the external masseters, in which two incisions must be made parallel to the mandible, and the internal masseters (internal pterygoid muscles), which must be incised along one plane; visual inspection and palpation of the tongue; inspection of oesophagus; visual inspection of the pericardium and heart, the latter being incised lengthways so as to open the ventricles and cut through the interventricular septum; and visual inspection of the diaphragm. Regarding swine, the legislation was relatively recently amended to eliminate the requirement of palpation and incisions in pigs subject to routine slaughter and, at present, it only prescribes visual inspection of the carcass and offal (European Commission, 2014). Additional examinations, such as palpation and incision of parts of the carcass and offal and laboratory tests, are to take place whenever considered necessary to reach a definitive diagnosis or to detect the presence of the disease. If cysticerci are found during post-mortem inspection the meat and offal of generally infected carcasses are to be condemned. In case of localised infections, the parts that are not infected may be approved for human consumption after having undergone a cold treatment.

Cysts detected during meat inspection can be found at different stages of development but frequently a very high proportion of them are dead (Geerts et al., 1980). During meat inspection mistaken identification of *T. saginata* and *T. solium* cysts may occur. This can be due to similarities in the appearance of lesions caused by taeniid or other parasites and due to cyst degeneration (González et al., 2006). In case of doubtful cysts or suspect lesions, diagnosis can be confirmed by histopathology (Van der Logt and Gottstein, 2000; Ogunremi et al., 2004). Furthermore, molecular tools (PCR) can be used to reach a definitive identification of the parasite (González et al., 2006; Geysen et al., 2007). The main drawbacks of such techniques are that they are labour intensive, costly and require specialist facilities (Dorny et al., 2010).

Current official meat inspection has a poor sensitivity (i.e. estimated to be <30%), especially in case of light infections, and therefore it is not able to detect all infected carcasses (Walther and Koske, 1980; Dorny et al., 2004; Dorny et al., 2010). For this reason, official prevalence figures normally underestimate real prevalence of these diseases (i.e. porcine and bovine cysticercosis) (Geerts et al., 1980; Van Knapen, 1981; Dorny et al., 2000; Jansen et al., 2018). In the case of cattle, current legislation (Regulation (EC) No 854/2004) also allows the use of alternative methods, namely serological tests. Specifically, it states that the incision of the masseter muscles in bovines older than 6 weeks of age can be omitted when serology is used and also when the animal has been raised on a holding officially certified to be free of cysticercosis. However, serology is not currently being used for this purpose (Blagojevic et al., 2017). The available serological tests are only used in epidemiological studies and not as an alternative to routine post-mortem inspection. The main reason for this is the fact that the performance characteristics (i.e. sensitivity or specificity) of the existing serological tests are not available or have not yet reached an adequate level (Ogunremi and Benjamin, 2010; Blagojevic et al., 2017). Presently visual post-mortem inspection remains the only technique that is feasible for routine application at the slaughterhouse (Dorny et al., 2010). Serological tests detecting circulating antigens (Ag) and antibodies (Ab) of *T. saginata* and *T. solium* in cattle and pigs, respectively, have been developed. The common characteristic of the existing Ab detecting methods is that they do not differentiate between current and past infections (Ogunremi and Benjamin, 2010; Deckers and Dorny, 2010). On the other hand, Ag detecting tests only detect viable cysts (i.e. infective cysts) and therefore are able to identify current infections. In the case of porcine cysticercosis, serological tests identifying circulating antigens have been validated and are commercially available (Deckers and Dorny, 2010).

1.1.3. Treatment and immunoprophylaxis

1.1.3.1. Human taeniosis (*T. saginata* and *T. solium*)

The two modern drugs currently used to treat taeniosis are niclosamide (2g/person orally in a single dose for adults) and praziquantel (5–10 mg/kg orally in a single dose) (Okello and Thomas, 2017). These treatments have shown an efficacy of approximately 85% (niclosamide) and 95% (praziquantel) (Pawlowski et al., 2005). Usually niclosamide is the drug of choice because it is not absorbed from the gastrointestinal tract (García et al., 2003). Other cestodicidals such as albendazole (at a triple dose of 400 mg/person) have also demonstrated to be efficacious (Steinmann et al., 2011).

1.1.3.2. Human neuro/cysticercosis (*T. solium*)

Treatment has to be adapted to each individual case. Therapeutic measures may include symptomatic medication (e.g. analgesics, anti-inflammatory drugs, and antiepileptic drugs), surgery and anthelmintic treatment (García et al., 2003; García et al., 2014).

1.1.3.3. Bovine cysticercosis (*T. saginata*) and porcine cysticercosis (*T. solium*)

Anthelminthic chemotherapy against the larval stage of *T. solium* and *T. saginata* in pigs and cattle, respectively, has been principally used experimentally (Parkhouse and Harrison, 2014). In pigs, different anthelmintics have been tested and, among them, oxfendazole has shown the best efficacy (Mkupasi et al., 2013). Oxfendazole has been authorised for the treatment of porcine cysticercosis in many countries (Okello and Thomas, 2017). Treatment of pigs (30 mg/kg of oxfendazole) is recommended by the World Health Organization (WHO) as an approach to be combined with other interventions for the control of *T. solium* transmission (WHO, 2018). In cattle, praziquantel has demonstrated efficacy in killing *T. saginata* cysticerci (Pawlowski et al., 1978). However, at present this drug is too costly to be used as a routine treatment in cattle (Parkhouse and Harrison, 2014).

Vaccines against *T. solium* in pigs and *T. saginata* in cattle have been successfully developed (Lightowlers, 2006). Immunoprophylaxis against these two parasites is seen more as a control measure to prevent infection in humans than in animals as such. In pigs, the TSOL18 vaccine has demonstrated to be effective against *T. solium* natural infections (Lightowlers, 2010) and has been recently commercialised (Okello and Thomas, 2017). In endemic countries, vaccination of pigs is recommended as a tool to be used in *T. solium* control and prevention programs by the WHO (WHO, 2018). In the case of cattle, a highly effective vaccine against *T. saginata* larval infection (TSA9/TSA18) has been developed (Lightowlers et al., 1996). However, there is a lack of interest in its commercialisation from veterinary pharmaceutical companies (Silva and Costa-Cruz, 2010).

1.1.4. Burden of *T. saginata* and *T. solium*

As previously described the clinical effects of human taeniosis are relatively minimal and the infection can be easily treated with anthelmintics. Therefore, the public health burden of *T. saginata* is very limited. Nevertheless, in the European society acquiring a tapeworm infection through beef consumption is not acceptable (Dorny et al., 2010). Consequently, meat inspection (i.e. official post-mortem inspection of carcasses at the slaughterhouse) is being implemented as the main measure to prevent *T. saginata* infection in humans. The sanitary measures that are taken following the detection of an infected carcass can lead to significant economic losses to farmers and the cattle industry. These losses result from the downgrading and the freezing treatment of infected carcasses to inactivate cysticerci (in localised infections), and the condemnation of carcasses and offal (in generalised infections) (Yoder et al., 1994; Hashemnia et al., 2015; Rossi et al., 2016; Gemmell et al., 1983). Apart from financial losses for the livestock sector, *T. saginata* also incurs costs associated with the pharmacological treatment(s), medical consultations and laboratory diagnoses of *T. saginata* infections in humans (Blagojevic et al., 2017). Nevertheless, very few studies evaluate the economic burden of *T. saginata* and they normally take into account only the monetary losses in the animal health sector (i.e. losses due to condemnation and downgrading of carcasses). Recent estimates on the economic impact of bovine cysticercosis in Europe are lacking and the costs associated with *T. saginata* human infections in European countries have not been estimated. Furthermore, implementation of meat inspection is costly and time-consuming. The cost of post-mortem inspection that is specifically attributable to bovine cysticercosis in European countries has not yet been determined either (Blagojevic et al., 2017).

T. solium is a major public health concern in low-income countries where the parasite is endemic. However, it is also being recognised as a problem in non-endemic countries associated with immigration and international travels from endemic regions (Carabin et al., 2011; García et al., 2014; White, 2000). *T. solium* incurs a high public health burden principally due to human NCC. NCC is the most important cause of acquired epilepsy in most endemic countries and it has been estimated that around 30% of the people with epilepsy in countries of Latin America, Sub-Saharan Africa and Southeast Asia suffer from NCC (Ndimubanzi et al., 2010). In the last years, efforts have been made to estimate the global burden of epilepsy attributable to NCC. In 2015, the WHO's Food-borne Disease Burden Epidemiology Reference Group identified *T. solium* as a leading cause of deaths from food-borne diseases. The study estimated for 2010 that more than 370,000 individuals suffered from NCC-associated epilepsy and that NCC was the cause of more than 28,000 deaths in endemic areas, resulting in a total of 2.8 million (UI: 2.1 to 3.6 million) disability-adjusted life-years (DALYs) globally (Torgerson et al., 2015). Apart from the human health burden, *T. solium* can be responsible for a significant monetary impact. In endemic countries, *T. solium* porcine cysticercosis is the cause of economic losses due to condemnation and reduction of the economic value of infected pigs (Zoli et al., 2003; Phiri et al., 2003; Atawalna et al., 2015). Additionally, this zoonosis incurs considerable costs associated with the treatment, diagnosis and hospitalisation of NCC cases as well as productivity and income losses resulting from disability of affected individuals (Webb and White, 2016). In the United States, for example, hospital charges linked to NCC cases for 2003–2012 were estimated at >US $908 million (O'Neal and Flecker, 2015). Studies assessing the societal burden (i.e. considering both the health and economic burden in humans and pigs) in endemic countries show that human and porcine cysticercosis contribute to a considerable cost and to a reduced economic and societal wellbeing (Trevisan et al., 2017b; Trevisan et al., 2018).

1.1.5. Epidemiological situation

1.1.5.1. *Taenia saginata*

T. saginata is the most common and widely distributed human *Taenia* tapeworm (Craig and Ito, 2007). It has a global distribution and affects both low and high-income countries with the highest prevalence in developing regions (Dorny et al., 2000; Gajadhar et al., 2006). It is estimated that 60,000,000 people are infected throughout the world (Andreassen, 2005). *T. saginata* infection is particularly important in Africa, Latin America, Asia and some Mediterranean countries (Murrell, 2005). However, it also occurs in many European countries and sporadically in the USA, Canada, Australia and New Zealand (OIE, 2017).

In Europe, despite obligatory and systematic meat inspection, *T. saginata* is still present. However, the knowledge on epidemiological data in cattle and humans is limited (Dorny et al., 2010). Data on occurrence and geographic distribution of bovine cysticercosis originates principally from official meat inspection reports. Based on official meat inspection in several European countries, by the end of twentieth century the prevalence of bovine cysticercosis was low varying between 0.007% and 6.8% (SCVMPH, 2000). The infection seemed to be more frequent in Eastern Europe than in other European countries (Murrell, 2005). Nevertheless, these figures underestimate the actual prevalence due to the low sensitivity of meat inspection (Dorny et al., 2000). Only heavily infected cattle are likely to be detected but most infected cattle in Europe suffer from light infections. At present, the available data on bovine cysticercosis prevalence in Europe are fragmentary (Dorny and Praet, 2007; Dorny et al., 2010) and not sufficient to compare the epidemiological situation between countries. Cysticercosis is included in the Annex I of Directive 2003/99/EC of the European Parliament and of the Council on the monitoring of zoonoses and zoonotic agents as a zoonosis that should be monitored according to the epidemiological situation (European Parliament and Council of the European Union, 2003). However, few countries report their data to the Commission (which shall send it to the European Food Safety Authority). Furthermore, epidemiological studies at farm level on factors responsible for *T. saginata* infection in cattle are scarce (SCVMPH, 2000; Dorny et al., 2000). In consequence, the knowledge on its epidemiology in Europe is limited.

The occurrence of *T. saginata* infection in humans in Europe is unknown. Nevertheless, it is presumed to be relatively low (SCVMPH, 2000). Prevalence and incidence figures are very scarce and frequently based on sales figures of specific cestodicidals (namely praziquantel and niclosamide). Prevalence data of taeniosis in Europe extracted from a review of papers published from 1973 to 2000 ranged between <0.01 and 10% with the highest levels being found in Slovakia and Turkey (Cabaret et al., 2002). Available data on taeniosis are not accurate principally due to low pathogenicity which leads to cases not being reported by patients or not identified by doctors and due to the fact that there is not mandatory reporting. Since humans have an essential role in maintaining the life cycle data on *T. saginata* in humans are necessary. Improving the epidemiological knowledge on the infection of *T. saginata* in both man and cattle in Europe is needed.

1.1.5.2. *Taenia solium*

T. solium is also world-wide distributed but absent or rare in high-income countries (Torgerson and Macpherson, 2011). It is endemic in most countries of Latin America, Africa and Asia, in regions with poor sanitation and free-ranging, scavenging pigs and where pork is consumed (García et al., 2003). This parasite is usually associated with low economic development (Sciutto et al., 2000). In countries with adequate sanitation, mandatory meat inspection and modern pig husbandry practices that prevent pigs from having access to human faeces the life cycle cannot be maintained (SCVMPH, 2000).

In 2015, the map used by the WHO exhibiting the endemicity status of *T. solium* in the world was updated (Donadeu et al., 2016) (Figure 1-4). This update was done based on literature and also on other data that were used as indicators of likely transmission of *T. solium* in different countries (Donadeu et al., 2016). This map illustrates endemic regions in sub-Saharan Africa, Latin America and East, South and South-east Asia. Regarding Europe, a few Eastern European countries are classified as endemic and some others (including Spain, Austria and several eastern European countries) are categorised as having few pigs with risk factors meaning that there is suspicion of full parasite transmission but there is a very small number of pigs exposed to risk factors.

In Europe, *T. solium* was eradicated from most countries as a result of socio-economic development, meat inspection and modern pig husbandry systems (Dorny and Praet, 2007). However, isolated foci of human cysticercosis cases acquired locally appeared to still exist (Overbosch et al., 2002). Several recent publications have indicated that incidence of NCC may be considered to be increasing in Europe (Del Brutto, 2012b; Fabiani and Bruschi, 2013). Although autochthonous NCC cases have been described, the majority of NCC cases diagnosed in Europe are identified as imported cases (Overbosch et al., 2002) probably due to increased immigration and travelling from endemic areas (Fabiani and Bruschi, 2013). NCC is being recognised as an emerging disease in high-income countries (Fabiani and Bruschi, 2013; Sciutto et al., 2000). Tapeworm carriers coming from endemic regions can transmit the infection to other individuals. Therefore, there is a risk for re-introduction of the infection.

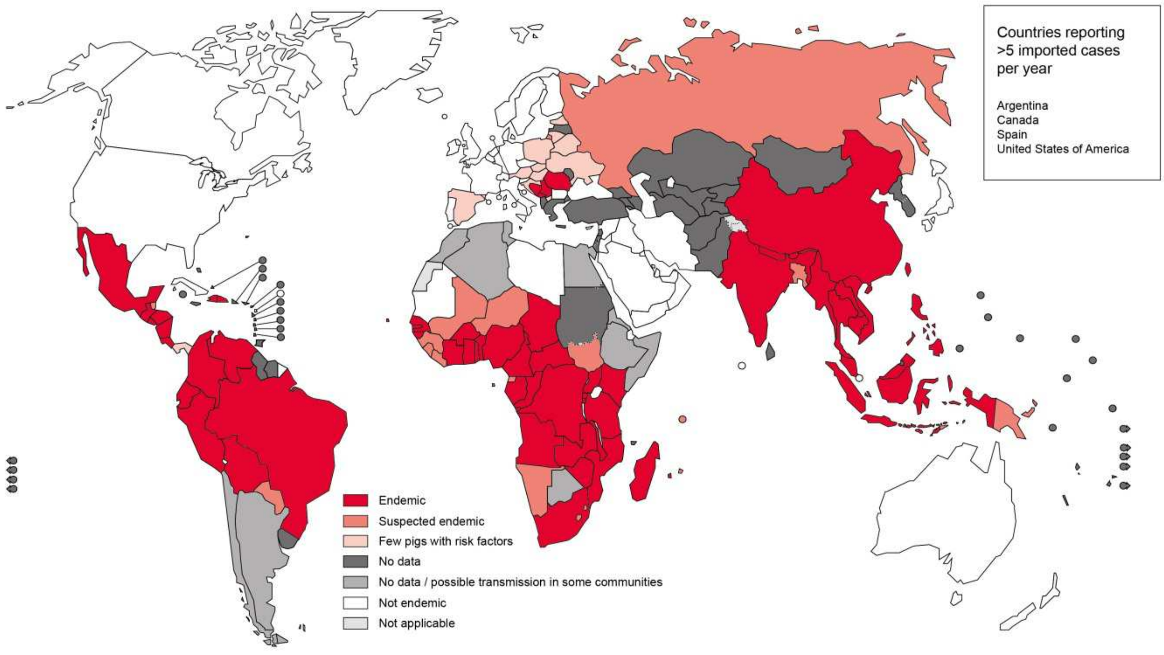

Figure 1-4 Global distribution of *Taenia solium,* 2015 (Donadeu et al., 2016)

At present, data on NCC in Europe are scarce and incomplete (Fabiani and Bruschi, 2013; Del Brutto, 2012b) and many cases reported in local non accessible journals (part of lost science) may be missed (Del Brutto, 2012b).

Surveillance of *T. solium* cysticercosis in pigs in the EU is based on official post-mortem inspection. As previously described for *T. saginata*, based on Directive 2003/99/EC of the European Parliament and of the Council, *T. solium* cysticercosis in pigs should also be monitored according the epidemiological situation. Nevertheless, since it is assumed that *T. solium* in pigs is absent (EFSA, 2011), little attention is paid to its monitoring (SCVMPH, 2000). According to a scientific report submitted to EFSA by Dorny et al. (2010), data on porcine cysticercosis are lacking for more than a third of the EU Member States (Dorny et al., 2010). Although the results obtained in this study were incomplete, from the available data it was concluded that active transmission of *T. solium* would still occur, probably in some Eastern European countries, and that it would be virtually eradicated in North, West and South of Europe.

As is the case for *T. saginata* taeniosis, the extent of *T. solium* taeniosis in Europe is unknown. There is no mandatory reporting for *T. solium* taeniosis in European countries (Gabriël et al., 2015). In addition, it is very difficult to evaluate the prevalence of

T. solium taeniosis, because the coproscopical methods used for survey are inadequate and usually cannot differentiate between *T. solium* and *Taenia saginata* infections (Murrell, 2005).

1.2. Knowledge synthesis methods

Knowledge synthesis refers to the summary of all pertinent studies on a specific question or topic using reliable, reproducible and explicit methods to inform research end-users (Kastner et al., 2012; Whittemore et al., 2014; Grimshaw, 2010; Young et al., 2014). The rationale for using knowledge synthesis methods is diverse. One of the reasons is the fact that results of individual studies may be misleading due to bias in their conduct or random variations in findings (Tricco et al., 2011). By integrating findings from different individual research studies knowledge synthesis can provide a more accurate and reliable assessment (a clearer picture) of the state of knowledge about a topic (Young et al., 2014; Sargeant et al., 2006). It can also describe the consistency or lack of consistency in diverse evidence (O'Connor and Sargeant, 2015) and identify gaps in research evidence to target future research (Kastner et al., 2012). Additionally, applying formal knowledge synthesis may result in avoiding unnecessary repetition of individual research studies (Grimshaw, 2010).

Research end-users include policy-makers, practitioners and other decision-makers (Young et al., 2014). They often need to make evidence-based informed decisions. In this context, knowledge synthesis is key to transfer knowledge from research into policy and practice (known as knowledge transfer and exchange) (Young et al., 2014) as it serves as a link between research and decision-making (Tricco et al., 2011).

The terminology around the science of knowledge synthesis is still evolving. Some authors use the terms knowledge synthesis, research synthesis and evidence synthesis as synonyms. In the literature, research synthesis is also referred to as a summary of research studies while knowledge synthesis is referred to as a broader tool that also includes non-research based knowledge (e.g. local knowledge) (O'Connor and Sargeant, 2015).

The common feature of all knowledge synthesis methods is that all of them use a systematic and auditable methodology (i.e. using reliable, reproducible and explicit methods). This includes having an explicit aim; having a methodological protocol; applying a comprehensive search strategy to find relevant studies; evaluating quality and potential risk of bias in individual studies; and collecting and synthesizing data (Whittemore et al., 2014).

Several knowledge synthesis methods have been developed and applied across different fields for decades (Young et al., 2014). Systematic reviews, for example, have been very commonly used in human health research. In the field of agri-food public health (i.e. veterinary public health, food safety, and "One Health") knowledge synthesis methods, and in particular systematic reviews and meta-analysis, started to be formally implemented a decade ago and since then they have been increasingly used (Young et al., 2014; Sargeant et al., 2005). The same trend can be seen in veterinary medicine (Sargeant and O'Connor, 2014). They have been adopted to answer questions about interventions efficacy, risk factors for infection or disease, prevalence of outcomes, and diagnostic test accuracy in different areas. In addition to systematic reviews and meta-analysis, other synthesis methods have been recently developed for the health and social sciences and they have started to be adapted to the agri-food public health sector as well. They include scoping reviews, structured rapid reviews, and mixed studies reviews and qualitative reviews (Young et al., 2014).

1.2.1. Scoping reviews

Scoping reviews aim to rapidly map the literature available on a topic to identify the key concepts on the area, sources of evidence available (quantity and type of evidence) and gaps in the literature (Grimshaw, 2010). They can be conducted as an exploratory project on their own. However, they are often conducted prior a full systematic review to determine the feasibility of undertaking it (EFSA, 2010; Young et al., 2014). This occurs when it is unclear whether enough evidence on a topic exists or when it is thought that the literature is too diverse and extensive (Grimshaw, 2010). By identifying gaps in the existing literature scoping reviews help in determining focused questions for future systematic reviews (Young et al., 2014). Scoping reviews seek to answer broader questions than other synthesis types such as systematic reviews (Whittemore et al., 2014).

1.2.2. Structured rapid reviews

Rapid reviews are modified systematic reviews that follow an accelerated process to provide knowledge on a topic in a very short time frame. They typically result from the urgent demand of end-users to acquire advice for decision-making with limited time and resources (Ganann et al., 2010). To accelerate the review process, rapid reviews follow a methodology that has several limitations compared to systematic reviews. This includes using only one reviewer during the entire process, limiting the search strategy, etc. In consequence, rapid reviews should always report in detail the methods followed and the potential limitations of the review in terms of strength of evidence, risk of bias and credibility of the findings (Young et al., 2014).

1.2.3. Mixed studies reviews and qualitative reviews

Mixed studies reviews and qualitative reviews also follow a modified systematic review process but their goal is to analyse contextual information such as stakeholder attitudes, values, and opinions and other socio-behavioural mechanisms affecting the success or failure of interventions (Young et al., 2014). The knowledge sources used in these knowledge synthesis methods include qualitative and quantitative studies and other sources of information such as review articles, reports, and policy documents (Mays et al., 2005).

1.2.4. Systematic reviews

A systematic review is "an overview of existing evidence pertinent to a clearly formulated question, which uses pre-specified and standardised methods to identify and critically appraise relevant research, and to collect, report and analyse data from the studies that are included in the review. Statistical methods to synthesize the results of the included studies (meta-analysis) may or may not be used in the process" (EFSA, 2010).

Systematic reviews are employed to appraise and summarise large quantities of research studies (Sargeant et al., 2005); support decision-making by making the most relevant evidence on a topic accessible; and, particularly, to identify knowledge gaps and target future research (EFSA, 2010; Sargeant et al., 2006).

1.2.4.1. Principles of systematic reviews

The principles of systematic reviews can be summarized as follows: methodological rigour and coherence in the selection of studies, the assessment of the methodological quality of the studies and the synthesis and interpretation of the results; and the transparency and reproducibility of the review process (EFSA, 2010).

These principles make systematic reviews different from traditional narrative reviews. Systematic reviews address specific review questions, seek to identify as many relevant studies as possible and use explicit methods to limit bias at all stages of the process (Sargeant et al., 2006). Bias in the identification and inclusion of studies is reduced by employing a systematic and a pre-specified search strategy and pre-specified criteria for studies inclusion. In systematic reviews, the risk of bias of the included studies is evaluated and the results are objectively summarised (Sargeant and O’Connor, 2014). In systematic reviews the results of all relevant studies are fully reported and the methodology used during the entire process is documented and reported so that others can reproduce, update and critically appraise the review (EFSA, 2010). On the other hand, traditional narrative reviews often have a broad scope, the search is not always extensive and they do not normally report the use of scientific methods to identify, assess and synthesize the evidence available on a topic under review (EFSA, 2010; Sargeant and O’Connor, 2014; Mulrow, 1987). Usually, little details are provided on how the review was conducted, how and why the included studies were selected and how representative they are of available evidence (O’Connor and Sargeant, 2015). Traditional narrative reviews are written by experts in the field of interest who might have preconceived opinions on the topic of interest (Grimshaw, 2010). Therefore, the resulting review might be biased and subject to the author’s views (Grimshaw, 2010).

1.2.4.2. Systematic review process

The systematic review process consists of eight fundamental steps (EFSA, 2010) (Figure 1-5). Documenting the review process is key to ensure transparency and reproducibility. The review process can be documented and reported following guidelines such as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

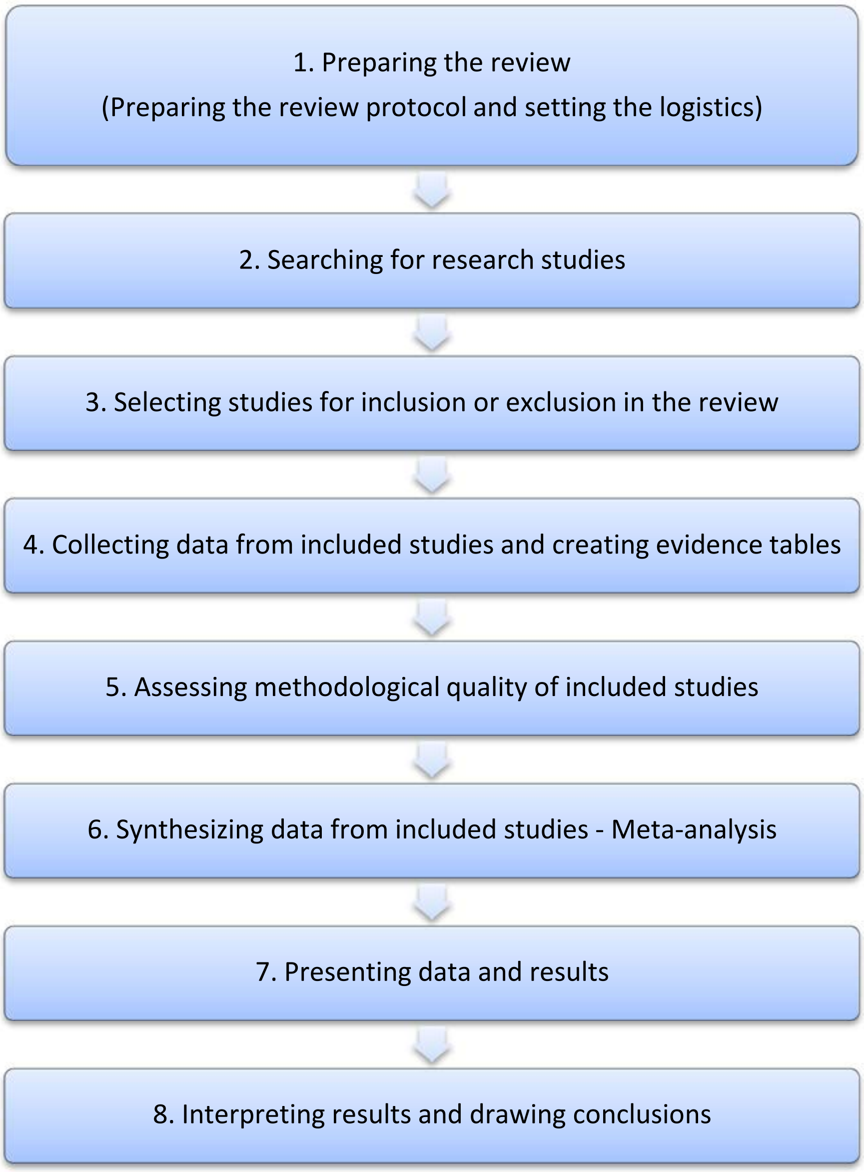

Figure 1-5 Key steps of a systematic review process (EFSA, 2010)

Step 1: Preparation of the review

The preparation of the review includes developing a review protocol in advance and planning the logistics for conducting the review. The protocol is prepared a priori and clearly defines the review question and the scope of the review, includes the background on the review question, and pre-defines eligibility criteria for inclusion or exclusion of studies. The protocol describes the methodology to be followed in each stage of the process (i.e. the methods for searching research studies, selecting the studies, collecting the data, assessing the methodological quality of the included studies, and synthesizing the data collected). Following the protocol minimizes the risk of bias during the process. Planning the logistics include setting up the review team and establishing the time frame and resources for conducting the review (EFSA, 2010).

Defining the review question

Defining the review question(s) is a fundamental step because all the elements of the review process will be defined based on that question (Sargeant et al., 2005). The review may have one or more questions to be answered. However, not all the questions are answerable through a systematic review. Systematic reviews are particularly effective to answer specific questions. Specific questions (or closed-framed questions) are “well-structured questions for which it is possible to envisage a primary study design that would answer the question” (EFSA, 2010). If the question to address is broad, it might be possible to break it into several specific questions.

A useful tool to determine if a question can be answered through a systematic review is to identify certain key elements in the structure of the question. Open-framed questions (i.e. questions for which some key elements are missing) sometimes may be transformed into specific questions by determining the missing elements. There are three types of question structures and each of them has specific key elements to determine (EFSA, 2010):

- For questions on the effects of an intervention or exposure the key elements are population (P), intervention (I) or exposure (E), comparator (C), and outcome (O) (represented by the acronyms PICO or PECO). Population refers to the population of interest (e.g. group of animals); intervention and exposure refer to the factor to which the population is exposed (e.g. vaccine or eradication method); comparator is the scenario against which the intervention or exposure is compared (e.g. lack of exposure to the factor of interest); and the outcome is a measurable property in the population that indicate the consequence of the factor to which the population was exposed (e.g. presence or absence of a parasite).

- For questions on test accuracy the key elements are population (P), index text(s) (I) and target condition (T) (represented by the acronym PIT). In the case of diagnostic tests accuracy the population can be an animal species; the index test would be the test for which the performance is being evaluated; and the target condition is the disease or condition whose presence/absence or level is to be detected or measured by the test.
- For descriptive questions on prevalence, incidence and occurrence of a condition in a given population (e.g. prevalence of an animal pathogen in a geographic area) the key elements are population (P) and outcome (O) (represented by the acronym PO). Population refer to the organism or setting in which the outcome of interest is measured (e.g. animal species). The outcome refers to what is measured in the population (e.g. a disease) (EFSA, 2010).

Identifying these components also helps to define the criteria that will be used for including studies in the review, focus the search strategy and plan the type of data that will be collected.

Developing the eligibility criteria for including studies

Eligible studies should concern the key elements of the review question(s). Additionally, other reports characteristics such as years of publication, language, publication status, publication types (e.g. letters), and study design can be used as eligibility criteria. The set of inclusion/exclusion criteria for selecting studies needs to include a statement of study designs that would be eligible to address the question. The eligible study design will be identified after considering which study design might have been used in primary studies, which designs will produce the best evidence or which designs are available, even if the design is weaker.

Step 2: Search of research studies

An essential step of systematic reviews is conducting an extensive search (or sensitive search) to identify as many studies as possible relevant to the review question. This is done by searching a range of different information sources and using a specific search strategy. The search strategy is developed by identifying a range of synonyms and related terms to be searched in different fields of database records. This process involves four stages: identifying information sources from which relevant studies can be retrieved; developing a search strategy (by combining different search terms or keywords); managing the references and documents retrieved; and documenting and reporting the search process (with a flow chart and narrative description) to ensure transparency and reproducibility.

An extensive search includes searching multiple databases, hand searching for additional material and including unpublished studies (e.g. dissertations, theses, conferences abstracts, collection of reports or working papers) and studies in languages other than English (Tricco et al., 2008). This helps to minimize bias such as publication bias (e.g. positive results may be more likely to be published than negative results) and for compensating for limitations of research reporting and indexing (EFSA, 2010).

Step 3: Selection of studies for inclusion or exclusion in the review

The studies retrieved during the study search are selected for inclusion in the review based on the pre-specified eligibility criteria. Normally this process is done in two stages: first, through screening of titles and abstracts and second, by assessing full-text records. The records that are examined by full-text are those records that, based on titles and abstract, were considered relevant (i.e. eligible) or for which a definitive decision could not be reached.

In order to avoid introducing personal errors and biases, the selection process should be conducted by more than one reviewer independently. It is important that at least one reviewer has expertise in the topic of interest. The selection process should be validated in advance in a sub-sample of studies to ensure reproducibility and reliability.

The results of the selection process (i.e. number studies included) have to be reported using, for example, a flow diagram. The studies not included in the review based on full text should also be listed and the reason for exclusion should be reported. Each of the steps of the study selection process has to be carefully documented to enable it to be reproduced and evaluated (EFSA, 2010).

Step 4: Collection of data from the included studies and creation of evidence tables

Data from each of the included studies are systematically collected to ensure reproducibility. The aim of the data collection is to retrieve the study findings and to report characteristics of the study that may be relevant to interpret the results or to explain heterogeneity in the effect measure (e.g. characteristics of the population studied in animal production studies such as species, age, production system, country or information on the detection method in studies determining the prevalence of a disease) (Sargeant et al., 2005). The information to be collected will depend on the review question and the outcome(s) pre-specified in the review protocol. The protocol also should include the analyses planned to be conducted and describe the procedure for data collection (e.g. number of reviewers collecting data). The information collected may be numerical or text. Usually data are collected in a pre-defined data collection form. This form should be described when reporting the systematic review, if possible (EFSA, 2010).

Step 5: Assessment of the methodological quality of included studies

The methodological quality of the included studies should be assessed to determine the degree to which they may be susceptible to bias. The assessment should be done in a standardized way. Assessment tools such as checklist are used to identify characteristics of the study design, conduct or analysis that could introduce bias. Common types of bias occurring in different study designs include selection, performance, detection, attrition and reporting biases (EFSA, 2010).

Step 6: Synthesis of data from included studies – Meta-analysis

The aim of data synthesis is to summarise the results from the individual included studies, using qualitative or quantitative methods (Sargeant et al., 2006). The type of methods to be used will depend on the data collected. In case of qualitative analysis the results of each study may be presented using tables or charts according to study characteristics and described through a narrative synthesis (Sargeant et al., 2006; Tricco et al., 2011). Quantitative data synthesis or meta-analysis may sometimes be used.

Meta-analysis is the process of combining evidence from separate individual studies by using statistical methods to determine overall effects and magnitude of effect size (Glass, 1976). Using meta-analysis the uncertainty or confidence of a parameter estimate may be calculated; and sensitivity analyses may be applied, to understand the contribution of a particular study on the overall outcome (EFSA, 2010). Meta-analysis may not always be possible or appropriate. This is the case when individual studies do not yield sufficient quantitative data or if there is a high heterogeneity (due to differences in the study designs, quality, study population, etc.) in the results across the studies (Sargeant, et al., 2006).

Step 7: Presentation of data and results

The results to be presented include the screening process, characteristics of the included studies, the data collected and results of the analysis performed (Tricco et al., 2011). The results of any bias assessment that may have been conducted should also be presented (Tricco et al., 2011). The results need to be presented in a clear way to ensure transparency and correct interpretation (EFSA, 2010). Tabular and graphical presentations may be used, but at least a narrative description of the results has to be provided (Tricco et al., 2011). The screening process might be described textually or using a flow diagram (Tricco et al., 2011). The characteristics of the studies (e.g. authors, publication year, study type, location, and key elements such as population or intervention) are usually presented in tabular or textual form.

Step 8: Interpretation of results and drawing of conclusions

Systematic reviews should include a well-structured discussion and a clear presentation of the reviewer’s conclusions (EFSA, 2010). Reference could be made to the quantity (e.g. number of documents found and included) and quality of evidence; interpretation of results (e.g. interpretation of sources of heterogeneity), any potential limitation of the review or the studies included (e.g. poor quality in the conduct or reporting of studies); conflicting results with other studies (EFSA, 2010; Tricco et al., 2011; Young et al., 2014). Conclusions should be drawn based on the available evidence only (EFSA, 2010). Knowledge gaps found in the review should be reported and priorities for future research may be given (Young et al., 2014).

1.3. Assessment of disease burden

The aim of burden assessment is to generate estimates of the health and economic impact of diseases. These estimates can be used to assess and quantitatively compare the relative magnitude of diseases (Lake et al., 2014) and to create a baseline against which effects of interventions can be evaluated (Devleesschauwer et al., 2018). Overall, burden assessment aids decision-making in setting priorities and allocating economic resources. It helps to prioritise effective interventions and evaluate their cost-effectiveness (Devleesschauwer et al., 2014).

Estimating the burden of a disease entails evaluating the effects of morbidity and mortality on the affected individuals or populations and considering the time and economic expenditures linked to treat or prevent the concerned disease (Shaw, 2009). In the case of zoonotic diseases, because the human health, animal production and other sectors of the society may be affected, burden assessment may involve a higher level of complexity. In this case, the monetary and non-monetary impacts on human and animal health and other sectors need to be considered. Moreover, assigning a monetary value to human health is ethically questionable and complex (Shaw, 2009).

1.3.1. Burden of disease in humans

The burden of human health can be assessed following two approaches: a non-monetary approach (health impact assessment) and a monetary approach (economic impact assessment). The non-monetary approach avoids costing the impact of the disease in monetary terms and can be more useful when the interest is just the human host (Carabin et al., 2004). The monetary approach is more useful to estimate the total economic burden to the society because it can be combined with the economic impact of the disease in animals (Carabin et al., 2004).

1.3.1.1. Health impact assessment (Non-monetary approach)

In human health, a series of non-financial indicators to quantify the burden of the disease have been developed (Shaw, 2009). They are often known under the umbrella term of health-adjusted life years (Carabin et al., 2005) and consist of summary measures of population health (SMPH) that take into account occurrence and impact of morbidity and mortality into one metric (Mangen et al., 2015). The Disability-Adjusted Life Year (DALY) is the most widely used SMPH and the one preferred by the World Health Organization (Polinder et al., 2012). DALYs estimates can be used to quantify and compare the burden of diseases with different health outcomes within and across countries (Murray and Acharya, 1997; Mangen et al., 2015; Devleesschauwer et al., 2018). The total number of DALYs measures the gap between the present health of a population and an idealised health situation (Mathers et al., 2007) as they represent the number of years of healthy life lost due to a disease (Murray, 1994). They result from adding the number of years lived with a disability (weighted by the severity of the disability) due to the disease and the number of years of life lost due to premature mortality (Devleesschauwer et al., 2018).

1.3.1.2. Economic impact assessment (Monetary approach)

In humans, the economic impact of a disease is typically estimated by calculating the "cost-of-illness" (COI). The COI is the monetary value of the effect of the disease in individuals or the society (Lake et al., 2014). It is calculated as the sum of healthcare and non-healthcare costs and the productivity losses associated to morbidity or premature mortality. These cost components are typically classified into direct and non-direct costs (Carabin et al., 2005) (Figure 1-6). Direct healthcare costs are costs borne by the healthcare system (e.g. costs of treatment, diagnosis, medical visits, and hospitalisation). Direct non-healthcare costs are costs paid by the patients themselves (e.g. travel expenses to health facilities, over the counter drugs, and other patient co-payments). Indirect non-healthcare costs relate to productivity losses due to absenteeism or job loss resulting from the inability of patients and their caregivers to perform paid work (e.g. loss of future income due to premature death). Finally, indirect healthcare costs correspond to all medical costs in life-years gained. However, the latter are frequently not included in cost-of-illness assessments (Van Baal et al., 2011).

Other non-healthcare costs may also be incurred. In the context of food-borne zoonotic diseases, for example, there might be costs associated to surveillance and other regulatory measures to prevent infection but these costs are often not estimated either (Lake et al., 2014).

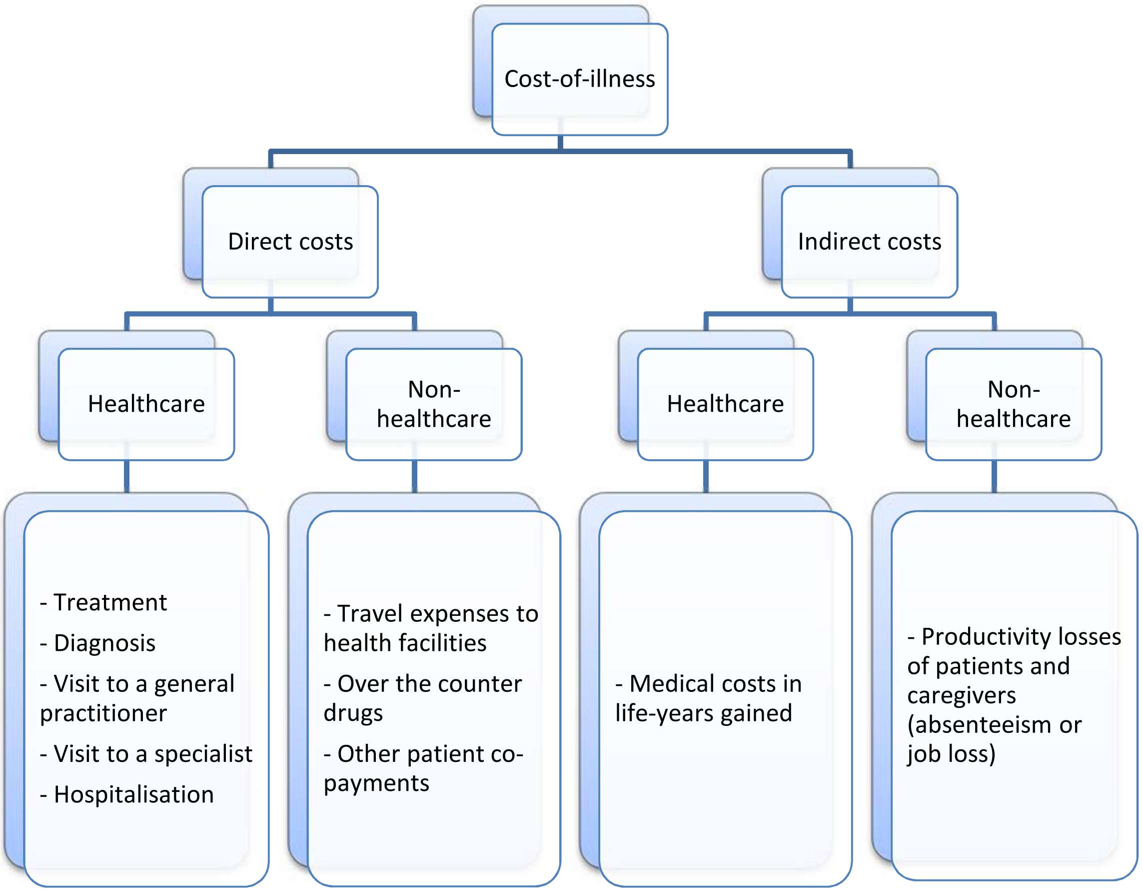

Figure 1-6 Cost components included in human health economic impact studies (adapted from Devleesschauwer et al., 2018)

1.3.2. Burden of disease in animals

In the livestock sector, health economics has become increasingly important to aid decision-making on how to best allocate resources for disease management (Otte and Chilonda, 2001). Nowadays, providing sound economic justification for any proposed animal health intervention is of major importance for those who need to finance them (Otte and Chilonda, 2001). Such decisions may need to be taken at different levels ranging from the individual animal or farm to regional or national levels (Perry and Randolph, 1999). Animal health economics addresses three main aspects: quantifying the financial effects of animal diseases, developing methods for optimizing decisions when animals, herds or populations are affected and determining the costs and benefits of disease control interventions (Dijkhuizen et al., 1995).

1.3.2.1. Framework to assess the economic impact of animal diseases and their control

The first step of an economic analysis in animal health is to calculate the cost of a disease. The cost of a disease typically considers the impacts of the disease in terms of reduction of productivity and costs of control (Perry and Randolph, 1999). Rushton et al. (1999) classify the disease impacts into direct and indirect (Figure 1-7). Direct impacts refer to production losses (i.e. reduction on the output) (McInerney et al., 1992). Indirect impacts refer to expenditures resulting from human reactions to the presence and/or risk of a disease. Direct losses can be visible losses that have immediate impacts (e.g. death of animals, lower milk yield, lower egg production, reduced quality of hides) or invisible losses that usually go unnoticed and often relate to fertility management issues (e.g. fertility problems, change in the herd structure, delay in the sale of animals and products). Indirect losses or impacts include additional costs which relate to control measures (e.g. vaccination or treatments) and forgone revenue. Forgone revenue refers to revenue lost due to the presence of the disease (e.g. opportunity lost due to denied access to better markets) (Rushton, 2013).

The overall impact or cost of a disease (C) can be calculated as the sum of the production losses (L) and the control expenditures (E), which in mathematical notation is expressed as $C = L + E$ (McInerney et al., 1992).

The overall economic impact of a disease as such does not inform on how to best allocate limited resources or if anything should be done to change the situation (McInerney et al., 1992). However, it can be used as a baseline to assess an animal health intervention (Rushton, 2013). The information that is useful to guide decision-making is the avoidable cost of the disease. The avoidable cost of a disease is the difference between the total cost incurred with a particular strategy and the cost incurred with an "optimal" strategy (Martin et al., 1987; Otte and Chilonda, 2001).

By determining the relationship between the two cost components of the cost of a disease (i.e. L and C) we can identify the optimal point of expenditure. This economically optimum point would be the combination of losses and control expenditures at which total cost is kept to a minimum (i.e. where an additional monetary unit spent yields the same additional monetary unit in return) (McInerney et al., 1992).

Therefore, economic analyses should answer whether it is worth investing funding and resources on a proposed strategy. This is done by comparing different alternative strategies considering their expected benefits and costs as well as the distribution of these benefits and costs over time (Otte and Chilonda, 2001).

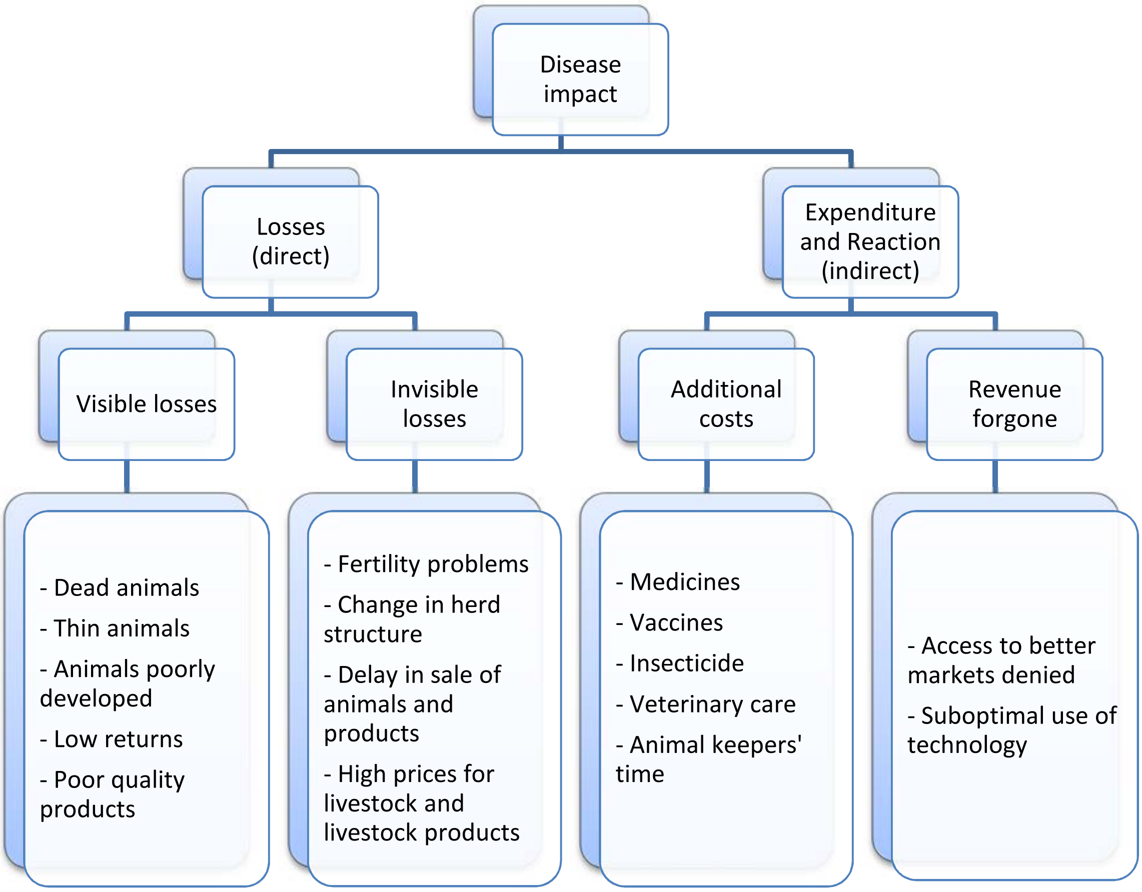

Figure 1-7 Elements required for animal diseases impact assessments (adapted from Rushton et al., 1999; and from Rushton, 2013)

The costs of a disease may be experienced by individual farmers or livestock sectors (private funds) or by the society as a whole (public costs). For example, additional costs may be incurred by veterinary public health services when involved in diagnosis, prevention and control of animal diseases (e.g. post-mortem inspection at the slaughterhouse) (Shaw, 2009). Therefore, in any economic assessment we need to determine the target group (e.g. farmer, a livestock sector, society) and the level of analysis (e.g. individual animal or farm or national or international levels) (Rushton et al., 1999).

Zoonotic diseases may also affect companion animals and wildlife. Direct losses due to these diseases and the costs related to treatment and prevention can be calculated in monetary terms. Additionally, non-monetary losses such as the value of an endangered species to society or the value of a companion animal to their owner may also exist (Shaw, 2009).

There is a wide range of economic methods that can be used to perform Animal Health economic analyses at different levels (FAO, 2016; Dijkhuizen et al., 1995). Some of the main techniques are described below:

Gross margin analysis and enterprise budget

Gross margins and enterprise budgets are useful to compare profitability of different enterprises and for assessing enterprise productivity (Martin et al., 1987; Rushton et al., 1999). An enterprise gross margin is defined as the enterprise outcome minus variable costs directly attributable to that enterprise. It does not consider fixed costs. The gross margin measures the contribution of that enterprise to the farm profit. Because fixed costs are ignored the profitability of the enterprise is not directly measured. To determine the profit of an enterprise the enterprise budget can then be estimated. An enterprise budget is defined as the enterprise output minus the fixed and variable costs (or gross margin minus fixed costs) (Rushton et al., 1999).

Partial budget analysis

Partial budget analysis is a method used to estimate the economic viability of a new intervention on a small scale (farm o enterprise level) over a short period of time (Rushton, 2009). This technique evaluates the economic consequences of a relatively small change (i.e. a change that does not affect the total farm management) in the existing system (Martin et al., 1987; FAO, 2016). The analysis compares the benefits (new revenue and costs saved) with the costs (new costs and revenue foregone) resulting from adopting a new disease control procedure (Martin et al., 1987). If the benefits are higher than the costs the proposed change would be advantageous, whereas if the costs equal or exceed the benefits the existing system is better (Rushton et al., 1999). One limitation is that it enables comparison between strategies but it does not necessarily provide optimum solutions. It is based on expected values and do not incorporate uncertainty or risk (Rushton et al., 1999).

Decision analysis

Decision analysis is a method for formally analysing complicated decisions involving a sequential series of actions and chance events (Rushton, 2009). It is used at farm or higher levels (e.g. sector, national). Decision tree analysis is the most common technique for decision analysis (Dijkhuizen et al., 1995). A decision tree is defined as a graphical method of expressing, in chronological order, the alternative actions available to the decision-maker and the choices determined by chance (Dijkhuizen et al., 1995). The goal is to obtain an expected monetary value for each alternative action by combining calculated costs (output values) with the probabilities of chance events. The preferred action is that with the highest expected monetary value (Rushton, 2009).

Cost-benefit analysis

Cost-benefit analysis (CBA) is a method for assessing the economic viability of a proposed course of action (e.g. animal health programs and projects) over an extended period of time. It is typically the analytical tool used when dealing with long-term disease control programs (Dijkhuizen et al., 1995). CBA compares total discounted benefits of a strategy with the total discounted costs, both expressed in monetary terms (Häsler et al., 2013). The main indicator used in cost-benefit analysis is the net present value (NPV) (total discounted costs minus total discounted benefits). If the NPV is greater than or equal to zero, then the proposed investment is economically viable at the discount rate applied. The reason for which the values of benefits and costs are "discounted" is because benefits and costs of different alternatives may occur at different points in time. Discounting of these values results in the present value of costs and benefits and makes them comparable (Dijkhuizen et al., 1995). CBA can be used to estimate the viability of a proposed project (appraisal) or a project that is already ongoing or completed (evaluation). CBA can be applied at different levels of intervention, ranging from the farm or sector level to regional or national levels. For example, CBA may be undertaken at a sector level to appraise a proposed control strategy and decide whether they benefit from it or not or at farm level to decide whether investing in a strategy would be financially viable.

Cost-effectiveness analysis

Cost-effectiveness analysis (CEA) is a method used to determine the economic viability of a course of action when the costs are estimated in monetary terms and the benefits expressed as a chosen outcome (FAO, 2016). The result of this analysis is the cost per unit of an effectiveness measure (i.e. the chosen outcome). Like CBA, CEA can be applied before and after the implementation of an intervention and used at different levels (i.e. from farm or sector to national or international level). CEA is the suitable technique to assess interventions when the benefits are difficult to quantify (e.g. benefits to human health of the control of a zoonotic disease); when the production losses incurred under different control scenarios are the same; and when, for a particular reason (e.g. political), it has been decided that a given intervention should be implemented (Martin et al., 1987). The final aim of the CEA is to know how we can reach a chosen goal at minimal cost. This can be done by comparing the cost of achieving the same level of result with different strategies, or the cost of reaching different levels of the chosen outcome (Krupnik, 2004). CEA has been more frequently used in human health than in animal health (Babo Martins and Rushton, 2014). In human health, an including zoonotic diseases, it is common to compare costs of a programme with non-monetary benefits such lives saved, DALYs averted or individuals treated (Krupnik, 2004; Narrod et al., 2012).

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2. Objectives

The general aim of this PhD thesis was to advance the knowledge of the epidemiology of taeniosis/cysticercosis zoonotic complexes (due to *T. saginata* and *T. solium*) in Europe.

The specific objectives of this PhD thesis were the following:

- To compile the existing knowledge on the epidemiology, impact and control measures of bovine cysticercosis in Europe.
- To update and compile the current knowledge on the epidemiology of *T. solium* and *T. saginata* in western Europe (both in humans and animals).
- To assess the epidemiology and burden of the *T. saginata* taeniosis/bovine cysticercosis disease complex in the animal and human sectors in Catalonia (Spain).

3. Study I

Epidemiology, impact and control of bovine cysticercosis in Europe: a systematic review

Parasites & Vectors, (2016) 9:81

3.1. Abstract

Introduction: Bovine cysticercosis in Europe has been known for centuries but the data showing the occurrence of this zoonosis are scarce. The aim of this paper is to review and present the current knowledge on bovine cysticercosis in Europe.

Methods: We conducted a systematic review of studies published between 1990 and November 2014. Qualitative and quantitative data on prevalence, risk factors, burden and interventions were extracted and analysed.

Results: Reports on prevalence were available for 23 European countries, mostly from western and central Europe; for a few of these only data before 1990 were available. Prevalence based on meat inspection was generally low (below 6.2% in 95% of the records) and varied between and within countries. Serology and detailed meat inspection provided a higher prevalence range (0.41–14%). Only few studies analysing risk factors were identified. Reported factors related to access to pastures and risky waters, dairy production and uncontrolled human defecation in the proximity of the farm among others. Only one estimate of the economic impact of the disease could be identified. Recommended interventions were focused on increasing diagnostic tests sensitivity or the application of risk-based surveillance strategies.

Conclusions: There is a lack of complete and updated data on most countries, especially in eastern Europe. Further risk factors studies might be needed together with estimates on the burden of the disease in all European countries. Risk-based interventions are being encouraged but current data are limited to guide this approach.

3.2. Introduction

Bovine cysticercosis is a parasitic infection of cattle caused by the larval stage (cysticercus) of the cestode *Taenia saginata*. Humans are the definitive host and harbour the adult form of the parasite in their intestines. Terminal segments containing eggs are detached from the adult parasite and millions of eggs may be released daily to the environment [1]. Cattle acquire the infection through the ingestion of eggs [2]. The parasite migrates to metabolically active muscles where it develops into cysticerci and humans get infected by consuming raw or undercooked meat containing infective cysticerci.

In cattle, natural infections are normally asymptomatic but they cause financial losses to the cattle industry due to downgrading, condemnation, extra handling, refrigeration and transport of the infected carcasses [3]. The main intervention to control bovine cysticercosis in Europe is meat inspection, followed by condemnation or freezing treatment when necessary, as prescribed by European legislation [4]. However other measures such as thorough cooking of meat and the compliance with the regulations on the treatment and use of wastewater and sludge are determinant to prevent parasite transmission.

The current knowledge of the epidemiological situation of bovine cysticercosis in Europe is mainly based on the detection of cysticerci in the carcasses of bovine animals during meat inspection at the slaughterhouse. In the European Union meat inspection is enforced through Regulation (EC) No 854/2004 which prescribes a visual inspection of specific muscles and incisions in the internal and external masseter muscles (not applicable to animals under six weeks of age) and a lengthwise incision of the heart in cattle of all ages. Carcasses and offal of heavily infected animals (generalised infections) are to be condemned. In the case of lightly infected cattle (localised infections) the affected parts are condemned and the rest of the carcass must undergo a freezing treatment that inactivates the cysticerci [4].

Bovine cysticercosis is distributed worldwide and affects developing and industrialised countries [5]. Official meat inspection reports are considered to be an underestimation of the real prevalence as meat inspection has a low sensitivity for the detection of cysts in muscles [5]. The precision of the visual identification is also questionable, as the cysticerci can be confused with lesions caused by infections with *Sarcocystis* spp. and *Actinobacillus* spp. or with other local alterations [6].

In Europe, the presence of *T. saginata* has been known for centuries, yet data on the occurrence of this zoonosis are scarce, fragmentary and inaccurate with variations regarding the levels of infection in the different countries and regions. The aim of this paper is therefore to review and present the current knowledge of bovine cysticercosis in Europe.

3.3. Methods

3.3.1. Search strategy

We conducted a systematic review of peer-review papers published from 1990 to November 2014 on the occurrence, risk factors, control measures and burden of bovine cysticercosis in Europe. We followed the PRISMA guidelines for reporting systematic reviews [7] Additional file 1 (Annex I).

In a first step, specific review questions were defined in order to accomplish the scope of the review. The key elements of these review questions were the population (i.e. cattle), exposure (i.e. risk factors or burden), intervention (i.e. control measures) and outcome (i.e. bovine cysticercosis). The search was performed in three international bibliographic databases: PubMed, (on 15 November 2014) and Scopus and Web of Science (on 16 November 2014). The literature search was performed in English using the following set of keywords: ((cattle OR bovine OR beef) AND (cysticerc* OR taeni* OR tapeworm OR tapeworms)) OR “saginata”. For each bibliographic database the search strategy was adapted as follows: in PubMed and Scopus the search was done in “All Fields” and in the Web of Science, it was done in “Topic Field” which includes Title, Abstract and Author Keywords. Retrieved records were exported to an Excel file. Other records reviewed included records obtained through citation searching (publications cited in papers included in the systematic review), the proceedings of the European Network on Taeniosis/Cysticercosis (CYSTINET) meetings, documents published by international institutions (i.e. the European Food Safety Authority publications; Codex Alimentarius guidelines) and unpublished work (i.e. master’s thesis).

In a first screening of all retrieved records, duplicate records were excluded. The titles and abstracts of all unique documents were then screened for relevance to the scope of the review. If the eligibility of the document could not be assessed from the abstract and title only, the full text was screened to exclude or include the document. The exclusion criteria were: (i) publication date before 1990; (ii) wrong agent (other than Cysticercus bovis or *T. saginata*); (iii) wrong host (other than bovine); (iv) providing epidemiological information from outside Europe; (v) providing information different than occurrence, risk factors for *T. saginata* bovine infection and its burden or control measures; and (vi) book chapters. Figure 3-1 shows the steps applied in the search.

Papers included at this stage were selected for full text revision and assessed for eligibility. Records for which the full text was not available were excluded. Yet, ten of these records provided relevant information in the abstract. This information was included in the review. Records in languages other than Spanish and English were translated with Google Translate (https://www.google.es).

At this step, the screening process was independently assessed by two other reviewers and disagreement about eligibility was discussed among the three reviewers until a consensus was reached. A list with the references included in the review is provided in the Additional file 2 (Annex I).

3.3.2. Data collection and analyses

For each eligible study, quantitative and qualitative data were extracted. Quantitative data regarding prevalence and risk factors were stored in a predefined spread sheet document. Recorded data included information about the country, year of publication, year to which the data belonged, prevalence and 95% confidence interval (if provided), level of data collection (i.e. national or regional) or measures of association among others. In the case of prevalence, both original and non-original data were collected from the included papers. If the same data were reported in more than one paper these were taken into account only once to avoid duplications. If non-original data were lacking details (e.g. collection date or location), the original source, although not initially included in the review (e.g. study prior to 1990), was consulted unless it was not available.

Data from reports such as the European Food Safety Authority (EFSA) zoonoses reports were used when original source providing the same data (e.g. prevalence for a country in a specific year) had not been included in the review. If the year when the prevalence data were collected was not available the year of the publication of those data was considered instead. Whenever prevalence data corresponded to an interval of years for the purpose of representing it in bar plots only the first year was considered. All the descriptive analyses were performed using R 3.2.0 (https://www.r-project.org/).

Qualitative data on occurrence, risk factors, burden and control measures were extracted and compiled in tables along with the bibliographic reference. These qualitative data were classified according to the type of information given: source of infection in outbreaks, risk factors, protective factors. Identified risk factors were further classified into categories. Relevant information on burden was extracted and summarised in a narrative form. Information on control measures was extracted and grouped into broad categories (i.e. methods to improve sensitivity, measures to destroy eggs, measures to apply to positive farms or preventive measures at farm level among others).

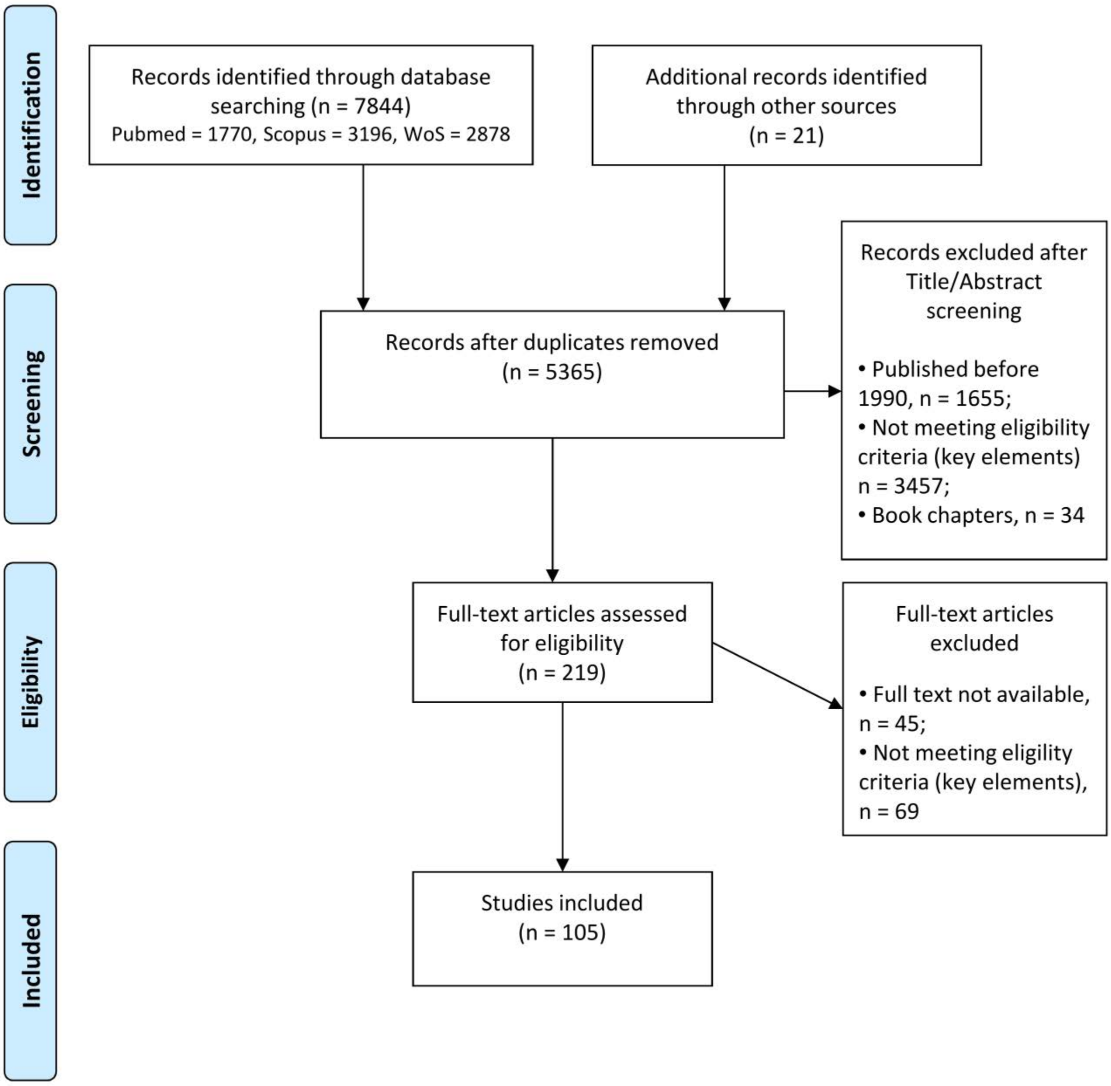

Figure 3-1 Flow diagram: search strategy steps

3.4. Results

3.4.1. Prevalence

We identified bovine cysticercosis prevalence reports for 23 out of the 49 European countries. Most of the data originated from routine inspection and just a few studies reported results based on other diagnostic techniques such as serological tests or detailed meat inspection. A table displaying all the prevalence data identified through the review is provided in Additional file 3 (Annex I).

In total we collected data from 50 different sources reporting bovine cysticercosis prevalence in Europe based on meat inspection. The number of published reports and/or personal communications per year was quite low with no more than three reports in most of the years. Reports showed that bovine cysticercosis has been present in Europe for decades and is still present today (Figure 3-2). Most of the data referred to the situation after 1990, since only reports published after 1990 were selected for inclusion. Nevertheless, from the included records we identified data on prevalence from 1918 until 2013 and for some countries such as Greece, Hungary, The Netherlands, Slovenia and Serbia we could only identify reports referring to prevalence prior to 1990 (Figure 3-3). The level of prevalence reported by routine meat inspection was generally low across Europe as the prevalence was below 6.2% in 95% of the records and below 4.3% in 90% of the records.

Few sources provided the age of the animals inspected. Only in a few cases prevalence was given for different groups of age. Results showed higher rates for adult animals than for calves. In a Croatian abattoir during 2005–2010 the prevalence detected in calves (0.014%) was lower than in steers (0.093%) and much lower than in cows (0.69%) [8]. In the UK, during 2008–2011 the prevalence detected in calves and adults was 0.008 and 0.032%, respectively [9]. These results are in line with the epidemiological situation observed in Belgium where positive cattle are normally adult cattle and calves are generally negative at meat inspection (P. Dorny, personal communication).

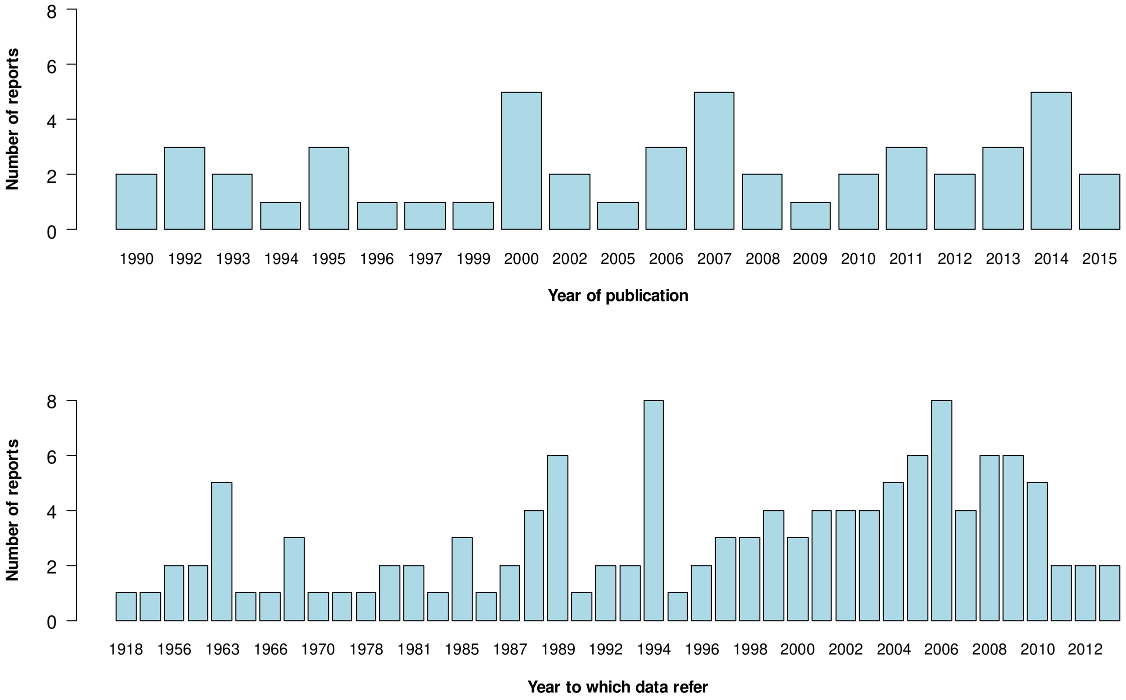

Figure 3-2 Number of sources reporting prevalence per year of publication and per year of data collection. If data are collected for an interval or years only the value for the first year is presented in the graph

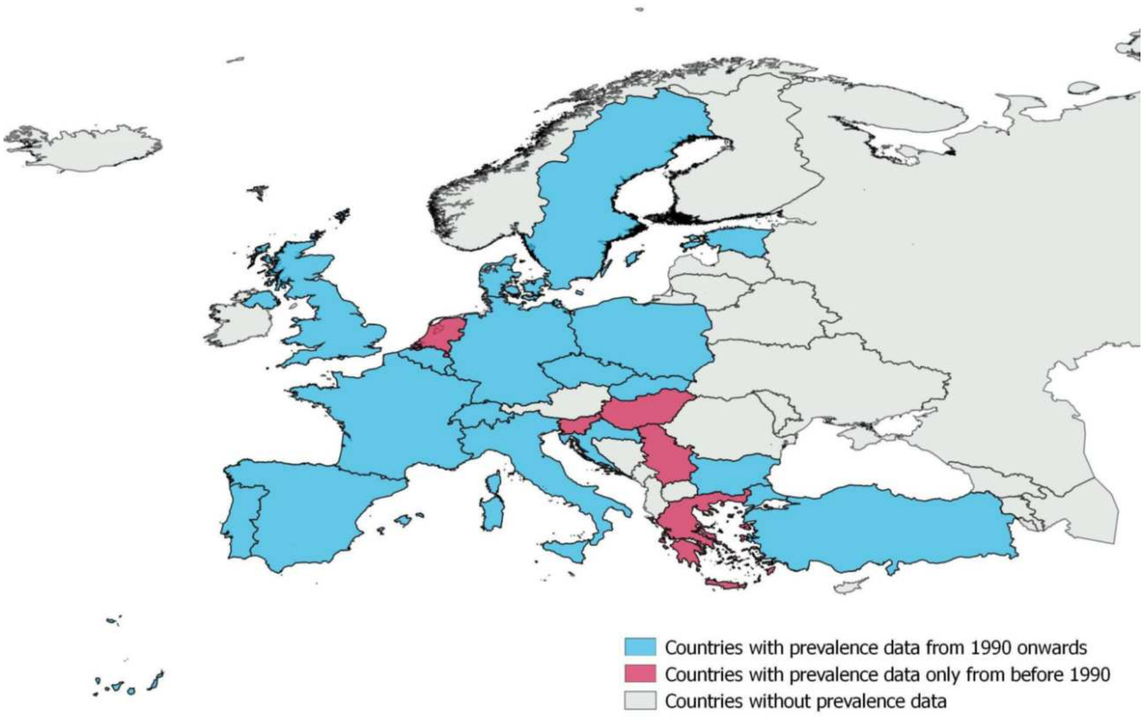

Figure 3-3 Map of Europe representing availability of prevalence data per country

Before 1990 the highest rates, based on routine meat inspection, were reported for Turkey, Germany and Poland. In Turkey, the prevalence detected at a regional level ranged from 0.3 to 30% between 1957 and 1990 [10]. In Eastern Germany and in the province of Olsztyn in Poland prevalences of 3.5–6.8% and 3.6%, respectively, were reported during 1974–1989 [11, 12]. After 1990, the highest prevalence levels were reported in one abattoir of Germany (i.e. 6.5%) in 1992 [13] and in the Autonomous Region of Madeira (i.e. 2.0–5.8%) during 1993–2005 [14].

The lowest prevalence was identified for Estonia, which reported no positive cases to EFSA for 2006, 2008, 2009 and 2010 [15–17]; followed by Sweden and the UK with a range of $2*10^{-4}$–$1*10^{-3}$ and $8*10^{-3}$–$4*10^{-2}$%, respectively [9, 18–20]. In the remaining countries, the prevalence was below 2.0% with few exceptions (i.e. Italy and The Netherlands). In most of the cases it was below 1.0%, although the variability between and within countries was very high (Figure 3-4).

Few studies reported results based on more sensitive inspection methods such as serology or detailed meat inspection. Studies carried out in Belgium [5] and northeastern Spain [21] have detected, through antigen ELISA (enzyme-linked immunosorbent assay), a prevalence level 3 to 55 times higher than the prevalence obtained through meat inspection. Also, in Germany, Abuseir et al. [22] performed a regional epidemiological study and detected an antibody titre level of 8.8%, which is higher than any prevalence level reported through meat inspection in Germany. In Turkey, a prevalence of 14% resulting from an Indirect fluorescent antibody test (IFA) was reported in the area of Iç Anadolu Bölgesi, City of Konya [10]. Reports based on detailed meat inspection have been reported in Spain, Switzerland and Belgium and show prevalences around 2 to 50 times higher than the prevalence obtained by routine meat inspection [1, 23, 24]. In France, in the Brittany region, in 1973 and 1974 the prevalence by meat inspection was less than 1% and increased to 9% when the heart was cut into 2–3 mm thick slices [25]. Finally, Eichenberger et al. [26] using latent class analysis estimated a prevalence of 16.5% (95% CI: 12.5–21.2%) in dairy cows. This result contrasts with the much lower prevalence estimates resulting from routine meat inspection in Switzerland (Further details presented in Additional file 3 of Annex I).

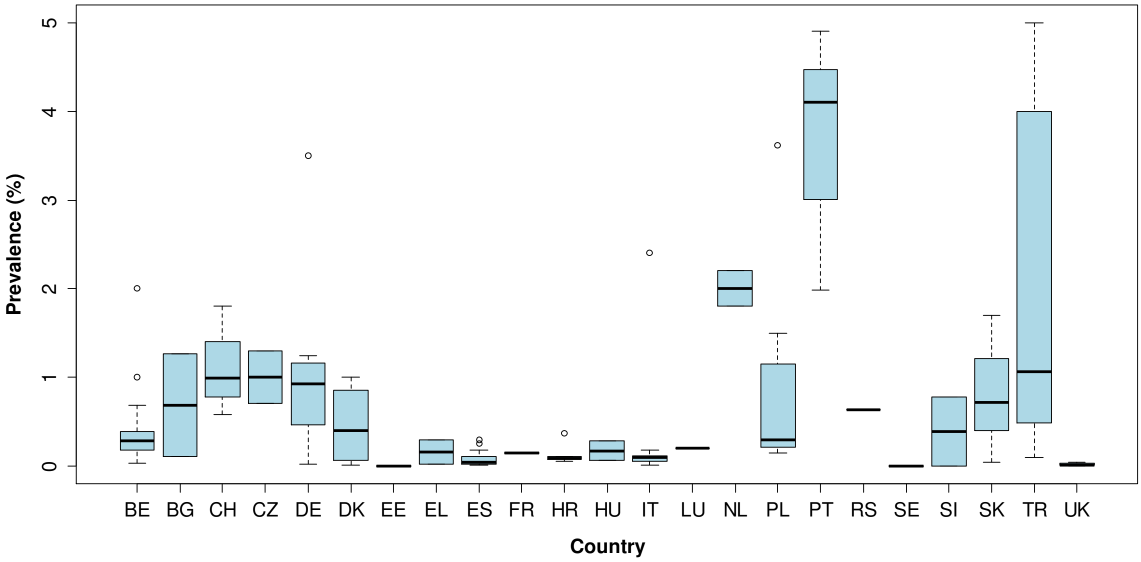

Figure 3-4 Prevalence levels (%) based on meat inspection reported per country. Prevalences higher than 5% are not presented in the figure. These data correspond to a few regional records reported in Turkey between 1963 and 1989 (prevalence range 9.7–30%), one report from the Autonomous Region of Madeira in 2006 (5.8%) and two reports from Germany (6.5% in 1992 and 6.8% between 1974 and 1989). Legend: BE, Belgium; BG, Bulgaria; CH, Switzerland; CZ, Czech Republic; DE, Germany; DK, Denmark; EE, Estonia; EL, Greece; ES, Spain; FR, France; HR, Croatia; HU, Hungary; IT, Italy; LU, Luxembourg; NL, The Netherlands; PL, Poland; PT, Portugal; RS, Serbia; SE, Sweden; SI, Slovenia; SK, Slovakia; TR, Turkey; UK, United Kingdom

A recent study performed in Belgium revealed a prevalence of 23% and 9% in animals negative to meat inspection by complete cutting of the predilection sites and by antigen ELISA, respectively. Taking into account the sensitivity and specificity of these techniques the authors concluded that around 38.4% of all carcasses of adult cattle were probably infected with cysticerci (Unpublished observations, Jansen et al., 2015).

3.4.2. Risk factors

In total, we have found 12 studies that analysed risk factors [5, 8, 23, 27–35]. These studies were conducted in 7 countries, with most studies being conducted in Denmark (3) followed by Belgium, France and Switzerland (2 each) and Croatia, Italy and Spain (1 each).

Six of these studies have identified risk factors through the quantification of measures of association (odds ratio or relative risk) between a given factor and the occurrence of cysticercosis. The risk factors at herd level identified in these studies and their level of association with the occurrence of bovine cysticercosis are presented in Figure 3-5 (95% CI represented in most cases). The 95% CI should be interpreted with caution as small sample sizes might produce wide CI. Further details on the identified risk factors are shown in Table 3-1.

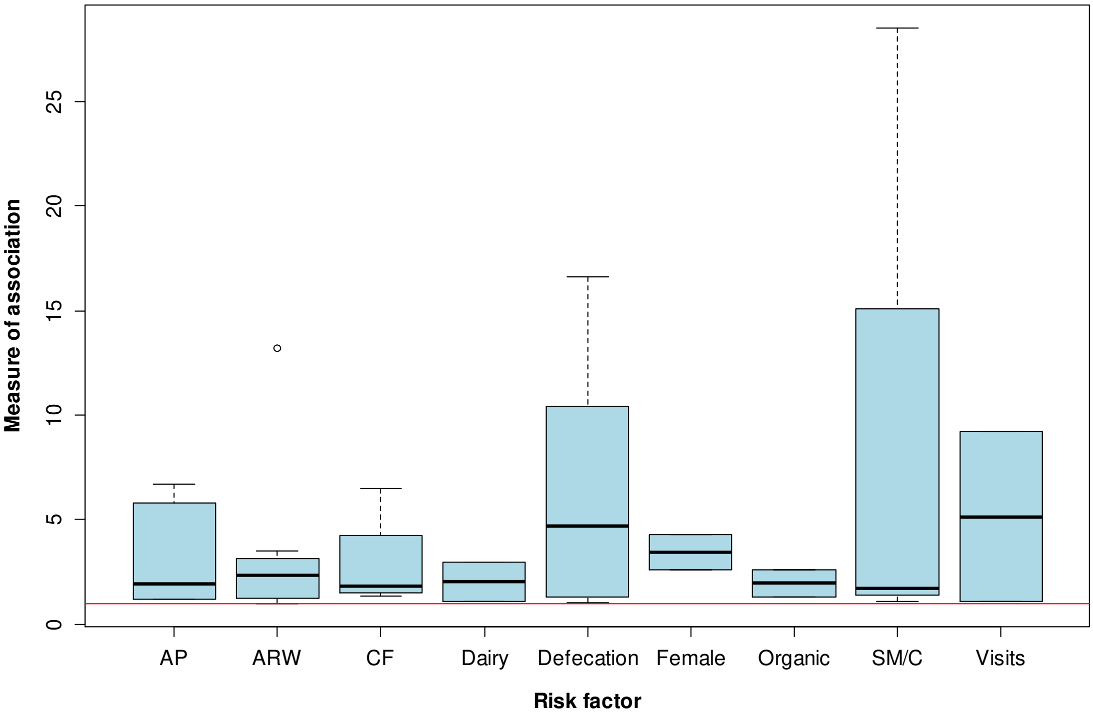

Figure 3-5 Representation of the degree of association (OR and RR) per each risk factor identified**.** Only factors associated with a higher risk of infection are represented. The red line sets the point along the Y-axis where the degree of association equals 1. Legend: AP, Access to pastures; ARW, Access to risky water sources; CF, Access to potentially contaminated feed; Dairy, Dairy animals; Defecation, Proximity to uncontrolled human defecation; Female, Being female; Organic, Organic farming; SM/C, Sharing machinery or hiring contractors; Visits, Having visitors on farm

Eight studies identified other than previously presented risk factors (Figure 3-5; Table 3-1) and for which no association measure was calculated. These risk factors include age and gender [5, 8, 23, 32]. Increasing age and being female have been positively correlated with the occurrence of bovine cysticercosis. At herd level, an increased risk has also been associated with the number of slaughtered animals, the herd size and the location of the herd. Boone et al. [28] observed that the number of slaughtered animals was, among other factors, linked to the occurrence of bovine cysticercosis in a herd. Allepuz et al. [27], Kyvsgaard et al. [36] and Boone et al. [28] found that infected herds had a larger number of animals than uninfected herds.

Contradictory results were found in a case–control study conducted by Calvo-Artavia et al. [29] showing that larger herds were less at risk than smaller herds in Denmark. According to the authors, this contradictory result could be due to the fact that in Denmark larger herds are normally kept indoors.

Some studies have investigated the existence of a spatial pattern in the distribution of infected herds. For instance, Allepuz et al. [27] identified two statistically significant clusters in Catalonia, northeastern Spain. In Belgium, one province was four times less likely to have one infected herd than the three other provinces [28]. In Italy, Cassini et al. [31] identified two significant clusters and Dupuy et al. [33] identified three areas in France with a higher risk of bovine cysticercosis. The reason for disease cluster presence in these areas was attributed to factors such as grazing in mountainous areas with access to risky water sources, movement of infected animals from one infected herd to several herds in the same area or proximity to areas with a high demographic pressure.

In addition to the above mentioned studies, other publications merely hypothesised potential risk factors for bovine cysticercosis without performing any specific study [2, 37, 38]. These factors were related to: (i) access of cattle to contaminated water and/or pastures; (ii) fertilization with potentially contaminated materials; (iii) human defecation in the proximity of grazing areas; (iv) lack of fly and bird control; (v) persistence of eggs in waste water after treatment; (vi) presence of tapeworm carriers in the farm; and (vii) high intensification of agriculture (involving high concentration of cattle and increased irrigation).

Factors linked to a lower probability of cattle becoming infected have also been identified in the literature. Interestingly, Kyvsgaard et al. [35] observed in a case–control study in Denmark a lower risk of infection if sewage sludge was spread on neighbouring land than if no spreading occurred or if the spreading was done on own land. They also identified lower risk if the distance to a sewage treatment plant was ≤100 m (in comparison with being at a larger distance) and also being closer than 100 m to a railway track. This last finding is in contrast to the findings of a study conducted in Switzerland where the presence of a railway track along or through farm land was found to increase the risk of infection [34].

Table 3-1 Categories of risk factors for bovine cysticercosis represented in Figure 3-5

Abbreviation	Risk factor	Subcategories included
AP	Access to pastures	Grazing - organic
		Grazing - conventional (i.e. non-organic)
		Grazing next to streams with single outlets (without direct access to water)
		Grazing next to streams with sewage effluent (without direct access to water)
ARW	Access to risky water sources	Free access to surface water (rivers, lakes, canals)
		Proximity of wastewater effluent (< 200 m)
		Access to risky water with sewage treatment plant effluent in proximity[a]
		Access to risky water with no sewage treatment plant effluent in proximity[a]
		Drinking from streams with sewage outlets from single households
		Flooding of pastures
CF	Access to contaminated feed	Feeding of freshly harvested grass on stable to dairy cows
		Purchased roughage
		Sewage sludge spread on own land
Dairy	Dairy animals	Dairy as production type
Female	Being female	Being female
Organic	Organic farming	Organic farming
SM/C	Sharing machinery or hiring contractors	Use of machinery (that had been used for emptying septic tanks) for spreading liquid animal manure
		Sharing machinery or hiring contractors
		Spreading of liquid manure (with machinery that had been used for emptying septic tanks) partially done by contractors
Defecation	Proximity to uncontrolled human defecation	Car park in the proximity of grazing areas
		Leisure activities in the proximity of grazing areas
		Railway line in the proximity of grazing areas
		Distance to camping site ≤100 m
Visits	Having visitors on farm	Having visitors on farm

[a] Risky water sources could be streams, lakes or ponds.

3.4.3. Source of infection

Some studies have performed outbreak investigations to assess potential sources of infection. In Scotland, five outbreaks (1976–1979) were traced back to the application of sludge on grazing fields [39]. However, another survey (1980–1983) investigated affected farms and showed that only in 4.3% of them sludge had been used, indicating the existence of other routes of infection [20]. A study conducted in Denmark [40] found illegal application of sludge from septic tanks on pasture or crops (in some cases after having been mixed with animal slurry) as the most frequent source of infection. In Spain, by using epidemiological questionnaires and a risk scoring system proposed by EFSA (2004) [24] Allepuz et al. [27] identified that water supply was the most likely source of infection in 23 out of the 55 investigated farms. In Norway, bovine cysticercosis outbreaks have been traced to foreign tourists and seasonal farm workers, and to farm equipment used to handle sewage sludge carrying infected matter [41].

3.4.4. Burden

According to the literature review, bovine cysticercosis may inflict substantial economic costs to the cattle industry [28, 42, 43] but its impact to public health seems to be less relevant. The clinical importance of *T. saginata* in humans is limited because symptoms are generally mild and it is easily treated [44]. However, severe symptoms can occasionally occur and people carrying a tapeworm can suffer from psychological stress. The main economic losses in the cattle sector are due to extra handling, condemnation, freezing treatment, weight loss after freezing (2–5%) and loss of value of frozen meat of affected bovines which are reported to be around 30 to 45% of the value of the carcasses [1]. There is a scarcity of studies quantifying economic burden due to cysticercosis in cattle. In England the costs due to bovine cysticercosis, including condemnation, downgrading, refrigeration, handling, and transport have been estimated at around £100 per carcass or £4.0 million annually [45].

3.4.5. Interventions

In addition to general control measures described in Reg. (EC) No 854/2004 [4], the systematic review revealed other measures that can be applied. Other measures in place include sewage treatment and the establishment of rules for the agricultural use of sewage and sludge [39] and monitoring of bovine cysticercosis [46]. At farm level, the suggested interventions are to: search for tapeworm carriers among the farm staff [2]; conduct epidemiological studies to find the source of infection in affected farms [8, 31]; and monitor the effectiveness of control measures and provide education and information to farmers. The application of pharmacological treatment to infected herds has also been described as a potential control measure as cattle can be efficiently treated against cysticercosis [47]. However, authors question the feasibility of applying it as the economic cost is high and the degenerated cysticerci can still be present in the carcasses up to two years later. Vaccination has also been proven as an effective tool to protect cattle [48] but vaccines are not commercially available [49] and the cost-benefit is also questioned [50, 51]. Biological control using antagonistic fungi to eliminate *T. saginata* eggs from the environment has been suggested to have potential as a control tool in the future [51].

Due to the very low sensitivity of the current meat inspection procedure the need of applying more sensitive techniques to detect infected cattle has been also highlighted in different studies. Serological tests (based on antibody or antigen detection) provide a better sensitivity. The main downside of antibody detection tests is that they do not distinguish between animals harbouring cysticerci and animals that have been exposed to eggs without establishment of cysticerci (P. Dorny, personal communication). Moreover, low levels of antibodies, antigenic cross-reactivity between parasites and shortage of parasite material as a source of antigen [52] may also occur. Antigen detection tests, detect animals harbouring infective (live) metacestodes [53] but they do not succeed in detecting all light infections, which are the most common type of infection in Europe [5]. Serology is more time consuming than meat inspection but it could be a useful screening test at herd level [47]. AbELISA kits to detect bovine cysticercosis antibodies are currently being commercialised but AgELISA kits are only available for the diagnosis of cysticercosis in humans and pigs and not for cattle. Sensitivity can also be increased, according to previous studies, through increasing the number of incisions in the carcass or in the heart (enhanced meat inspection) [1, 23]. The first would lead to carcass mutilation [21] and to a higher risk of microbiological contamination [21]. The latter, however, would be feasible in the daily practice and useful in low cyst burden areas [23]. A recent study conducted in Belgium showed, however, that performing additional incisions to the heart did not increase the sensitivity of the technique sufficiently to be considered profitable (Jansen et al., 2015, unpublished observations).

Post-mortem laboratory confirmation of *T. saginata* is based on macroscopic, microscopic, histological and molecular assessment of putative lesions. If the lesion is a degenerated cyst or a macroscopically similar lesion caused by other parasites (e.g. *Sarcocystis* spp.) incorrect diagnosis may occur. Different improved post-mortem diagnostic techniques developed for this purpose identified during the review include antigen ELISA in meat juice [54], immunohistochemical methods [6, 55] and biomolecular assays [54, 56].

The interventions to be applied on infected carcasses focus on the destruction of cysts. They include temperature treatment (freezing or cooking of meat) and irradiation. According to an EFSA Scientific Opinion it has been concluded that freezing of cattle carcasses at −10 °C for 10 days kills the cysticerci [57]. It is also generally accepted that cooking meat properly all the way through kills the cysts [57]. Regarding irradiation, the results of a study conducted by Geerts et al. [58] indicated that cysticerci of *T. saginata* lose their infectivity after being irradiated with gamma rays at doses of 0.3, 0.4 and 0.6 kGy.

On the other hand, since classical meat inspection is time-consuming, costly and with low detection sensitivity, several authors have assessed and suggested the application of a risk-based surveillance in order to improve meat inspection sensitivity [25, 30]. This system would consist in implementing a higher priority of surveillance resources in those animals or areas that present higher risk of infection. In this sense, it has been proposed to use more sensitive diagnostic procedures such as the reinforcement of meat inspection (e.g. by using antigen detection serology or increasing the number of incisions in the heart) in high risk areas or animals previously identified as such [33]. For example, in Denmark, Calvo-Artavia et al. [29] proposed including data for the identification of low or high-risk animals in the Food Chain Information document, e.g. gender, age and grazing practices in the case of Denmark, to enable meat inspectors to apply a risk-based inspection. In addition to the use of risk-based surveillance, Dupuy et al. [33] also suggested the application of specific control measures in high-risk areas depending on the risk factors identified (e.g. increasing the control of sewage sludge in areas identified as high-risk areas). Following this approach a Codex Alimentarius document providing guidance on the application of risk-based measures for the control of *T. saginata* in cattle has been recently developed [59].

3.5. Discussion

The high variability in the prevalence levels among and within countries identified through this review could be attributed to different factors. Firstly, real differences might exist due to heterogeneity in the exposure to risk factors among and within countries (e.g. differences in gender, age, herd size, breeding systems, etc.). Secondly, the reported data were collected at different levels (for a whole country, a region, or in one or few abattoirs). For some countries most of the records were recorded at regional level (e.g. Spain or Croatia) whereas in others the prevalence was described mainly at national level (e.g. Belgium or Sweden). In the cases when the level of data collection was not specified, the approach taken was assuming that data belonged to the whole country but this assumption could lead to inaccurate information/interpretation. Thirdly, there were differences in time frames of data collection. This varied extensively between countries and within a country. Some sources provided a mean prevalence for a long period (e.g. years). In other cases an annual follow-up was given and therefore consecutive annual prevalence data were available (e.g. Belgium). Fourthly, data were extracted from routine official meat inspection reports and from scientific studies. The accuracy of the data derived from a particular scientific study might be higher than the data obtained through official routine meat inspection procedures. Finally, factors influencing the level of detection by routine meat inspection included the training, expertise, motivation of the meat inspector [2], the level of infection (number of cysts), the location of cysts in other muscles than those routinely inspected, the stage of degeneration of the cysts [44], the level of compliance with the officially established meat inspection protocols [4] and also the characteristics of the facilities where the meat inspection is carried out (i.e. speed of slaughter line, lighting, etc.).

Meat inspection sensitivity has been estimated to be between 10 and 30% [2, 5, 23]; therefore, the data collected underestimate the real prevalence. In order to know the current epidemiological context of bovine cysticercosis the use of more sensitive surveillance strategies is needed and data collection and reporting throughout the years for all of the countries is essential. Monitoring and reporting occurrence of Cysticercus bovis in the European Union is recommended by Directive 2003/99EC (on the monitoring of zoonoses and zoonotic agents) [46], but it is not compulsory and only very few countries annually report their data to the European Commission and European Food Safety Authority.

Only few studies identifying risk factors have been carried out and mostly in western European countries. Since the type of cattle production, farming management and other factors may vary between different parts of Europe, conducting risk factors analysis in Eastern European countries should be encouraged. Also studies based on more sensitive techniques would be needed in order to avoid possible biases due to misclassification of cases [28].

The fact that bovine cysticercosis is present in Europe indicates that the transmission between cattle and humans is taking place and serves also as an indicator of poor hygiene [37, 60]. Human taeniosis is not a notifiable disease and reported prevalences are only indicative [39]. Estimates have indicated that in Europe 11 million people suffer from taeniosis caused by *T. saginata* [61]. Without accurate data on the number of human cases, although the global burden is considered to be low [42, 62], the relevance of bovine cysticercosis as a public health problem is difficult to assess [21] and has not yet been quantified [42]. Few authors have reported estimates of the number of affected humans potentially infected from undetected carcasses during routine meat inspection with variable results. In the UK it was estimated that one human case could originate from between 30–100 undetected bovine cases [9]. In France, however, it was estimated that one undetected carcass could potentially infect between eight and 20 humans [25]. Human taeniosis generally causes mild symptoms (abdominal discomfort, mild diarrhoea, weight loss and anal pruritus) and psychological distress. Only occasionally severe symptoms such as appendicitis occur but no fatalities have been reported. Therefore it is considered that interventions such as meat inspection avert very few Disability-Adjusted Life Years (DALYs) [42]. The only direct cost of human taeniosis is the payment of medical visits, treatment and laboratory tests, which are reported to be very low and reasonable in terms of cost-benefit ratio [42].

There are almost no studies estimating the economic impact of bovine cysticercosis on the meat and cattle industry and in some cases the data are outdated. Earlier research estimated economic losses due to bovine cysticercosis in industrialised countries at 234 US$ for a whole carcass (updated to 1990 US$ prices) [63] but no specific estimates for Europe were provided in that study. In Europe we identified only one estimate on economic impact in England. Therefore, in order to assess the relevance of this animal parasitosis, studies on its economic impact in Europe are needed.

Despite these current control measures, bovine cysticercosis is still present in Europe, which proves that the interventions in place are not sufficient for the successful control of this zoonosis [37]. The current recommendations are to continue performing visual meat inspection until validated serological tests are commercially available for routine practice [37]. In order to better control this parasitosis and also to evaluate the control/prevention tools accurate prevalence data on animals and humans are necessary.

Several authors have suggested the application of risk-based surveillance and control systems to improve the detection sensitivity and to avoid measures that are not proportionate to the level of risk reduction achieved [59]. In order to apply such approaches, classification of areas, herds and animals at low risk, together with the epidemiological data supporting this risk classification are needed. Sources of these data could be records from post-mortem inspection at the slaughterhouses and results from laboratory tests, results from farm investigations, records from human health surveillance and data on human treatments. At present sufficient information to implement such systems are hardly available in Europe, especially in the eastern countries. The quality of data and data reporting of *T. saginata* cysticercosis cases in Europe should be improved. Studies identifying risk factors should be conducted in different countries and for different production systems. This information should allow a better understanding of the epidemiological situation and identification of factors determining level of risk and therefore the implementation of risk-based approaches.

3.6. Conclusions

The available prevalence data for bovine cysticercosis in Europe are scarce and of low quality. This lack of data is especially notable in the eastern countries. There is hardly any knowledge on the economic impact of bovine cysticercosis in Europe. Since current control measures based on meat inspection may not be proportionate to the risk posed according to the epidemiological situation a risk-based surveillance and control approach is currently encouraged. However, the currently available data are limited to guide such an approach.

3.7. Authors' contributions

MLG conducted the systematic review of the literature, extracted and analysed data and drafted the first version of the manuscript. AA and BD contributed to the screening of papers, the design of the study, interpretation of data and collaborated in the writing of the first draft. PD and SG contributed to the writing of the paper. All authors read and approved the final version of the manuscript.

3.8. Acknowledgements

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4. Study II

Epidemiology of taeniosis/cysticercosis in Europe, a systematic review: Western Europe

Parasites & Vectors, (2017) 10:349

4.1. Abstract

Introduction: *Taenia solium* and *Taenia saginata* are zoonotic parasites of public health importance. Data on their occurrence in humans and animals in western Europe are incomplete and fragmented. In this study, we aimed to update the current knowledge on the epidemiology of these parasites in this region.

Methods: We conducted a systematic review of scientific and grey literature published from 1990 to 2015 on the epidemiology of *T. saginata* and *T. solium* in humans and animals. Additionally, data about disease occurrence were actively sought by contacting local experts in the different countries.

Results: Taeniosis cases were found in twelve out of eighteen countries in western Europe. No cases were identified in Iceland, Ireland, Luxembourg, Norway, Sweden and Switzerland. For Denmark, Netherlands, Portugal, Slovenia, Spain and the UK, annual taeniosis cases were reported and the number of detected cases per year ranged between 1 and 114. Detected prevalences ranged from 0.05 to 0.27%, whereas estimated prevalences ranged from 0.02 to 0.67%. Most taeniosis cases were reported as *Taenia* spp. or *T. saginata*, although *T. solium* was reported in Denmark, France, Italy, Spain, Slovenia, Portugal and the UK. Human cysticercosis cases were reported in all western European countries except for Iceland, with the highest number originating from Portugal and Spain. Most human cysticercosis cases were suspected to have acquired the infection outside western Europe. Cases of *T. solium* in pigs were found in Austria and Portugal, but only the two cases from Portugal were confirmed with molecular methods. Germany, Spain and Slovenia reported porcine cysticercosis, but made no *Taenia* species distinction. Bovine cysticercosis was detected in all countries except for Iceland, with a prevalence based on meat inspection of 0.0002–7.82%.

Conclusions: Detection and reporting of taeniosis in western Europe should be improved. The existence of *T. solium* tapeworm carriers, of suspected autochthonous cases of human cysticercosis and the lack of confirmation of porcine cysticercosis cases deserve further attention. Suspected cases of *T. solium* in pigs should be confirmed by molecular methods. Both taeniosis and human cysticercosis should be notifiable and surveillance in animals should be improved.

4.2. Introduction

Taenia solium and *Taenia saginata* are zoonotic tapeworm species that cause taeniosis in humans (definitive host) and cysticercosis in pigs and cattle (intermediate hosts), respectively. Humans can also acquire cysticercosis after accidentally ingesting *T. solium* eggs. Cysticerci in humans often establish in the central nervous system causing neurocysticercosis (NCC) [1].

Human taeniosis causes few or no symptoms [2] although it can cause psychological stress [3]. Animal cysticercosis is normally asymptomatic, particularly if infections are light. However, cases are responsible for substantial economic losses to the meat sector [4]. NCC may be asymptomatic, but it can cause neurological manifestations such as seizures, headaches, focal neurological deficits, signs of increased intracranial pressure and deaths [5, 6] and is a leading cause of acquired epilepsy in endemic areas [7].

Taenia solium is considered to be endemic in parts of Asia, sub-Saharan Africa and South and Central America [8]. In Europe, industrialisation of pig rearing systems and improved sanitation are believed to have eliminated the parasite [9, 10]. However, gaps regarding the true endemicity status of *T. solium* in Europe still remain [10]. According to a map on *T. solium* endemicity, recently updated by the World Health Organization [8], some countries in western Europe still have some pig herds at risk of *T. solium* transmission. Furthermore, the epidemiological situation in eastern Europe is unclear since there are countries classified as endemic, with some pig herds at risk, and countries from which data are lacking [8]. In addition, *T. solium* in humans has been emerging as a public health concern in Europe due to the increased number of diagnosed NCC cases in recent decades. These have been linked to increased travels and migratory movements towards and from endemic countries [11–14].

Taenia saginata is distributed worldwide [15], and has been found in cattle in countries of western and eastern Europe. However, the available data are limited and often of low quality [16]. Data on taeniosis due to *T. saginata* are scarce, and among the data that do exist, its prevalence is sometimes estimated from the sales of anthelmintic drugs [17].

Taeniosis and human cysticercosis are not notifiable in Europe as stated by Gäbriel et al. [9] and therefore it is difficult to assess the epidemiology of these zoonoses in the region. Detection and reporting of animal cysticercosis cases is mainly based on official meat inspection. Porcine cysticercosis has to be notified to the World Organisation for Animal Health (OIE), but there is no mandatory reporting for bovine cysticercosis. Despite the European Directive 2003/99/EC [18] that recommends monitoring animal cysticercosis according to the epidemiological situation, few countries report these cases [16, 19].

Based on the need for useful estimates for taeniosis/cysticercosis surveillance and control activities, as well as to advance the knowledge and awareness of these zoonotic disease complexes, the aim of this review was to update and compile the current knowledge on the epidemiology of *T. solium* and *T. saginata* in western Europe (both in humans and animals). This review is one of two systematic reviews: the present review covers western Europe and a second review will cover eastern Europe.

4.3. Methods

4.3.1. Study design

We conducted a systematic review supplemented by a search of local and unpublished sources for information on the occurrence, prevalence, incidence and the geographical distribution of human and animal *T. saginata* and *T. solium* infections in western Europe published from 1990 to 2015. This area was defined, based on gross domestic product/gross national income (GDP/ GNI) and regional proximity, as including the following countries: Austria, Belgium, Denmark, Finland, France, Germany, Iceland, Ireland, Italy, Luxembourg, Norway, the Netherlands, Portugal, Slovenia, Spain, Sweden, Switzerland and the United Kingdom; and excluding overseas territories and mini-states (e.g. Liechtenstein).

4.3.2. International databases

We searched the following online international databases: PubMed, ISI Web of Knowledge, CABDirect, OAIster and OpenGrey for all published data on the topic and followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for reporting systematic reviews (Additional file 1: Table S1 of

Annex II). The following search phrase was used: (cysticerc* OR cisticerc* OR neurocysticerc* OR neurocisticerc* OR “C. bovis” OR “C. cellulosae” OR taenia* OR tenia* OR saginata OR solium OR taeniosis OR teniosis OR ténia OR taeniid OR cysticerque) AND (Austria OR België OR Belgiën OR Belgique OR Belgium OR Denmark OR Deutschland OR Éire OR England OR España OR Finland OR France OR Germany OR Iceland OR Ireland OR Ísland OR Italia OR Italy OR Luxembourg OR Nederland OR Netherlands OR Norway OR Österreich OR Portugal OR Schweiz OR Scotland OR Slovenia OR Slovenija OR Spain OR Suisse OR Svizzera OR Sweden OR Switzerland OR United Kingdom OR Wales). The databases were searched for papers published from 1st January 1990 up to 1st December 2015 (even if containing data older than 1990). Papers were excluded if at least one of the following criteria were met: (i) studies did not concern *T. saginata* and/or *T. solium*; (ii) studies did not report data from within the specified area; (iii) studies published before 1990 or after 1st December 2015; (iv) studies reported results outside the scope of the study questions (including general reviews on the topic). Papers were initially screened for eligibility primarily based on title and abstract, and, if necessary, the full paper was assessed. If the full text was not available, relevant data provided in the abstract were included. From each eligible document, data were collected in predefined tables.

4.3.3. Local sources

We distributed country sheets (Additional file 2 of Annex II) to members of the European Network on Taeniosis/Cysticercosis (CYSTINET, COST Action TD1302) and other experts, requesting them to list relevant national journals, epidemiological bulletins, MSc/PhD dissertation databases, national institutes, and registries, and to translate relevant search terms. Due to ethical constraints, unpublished hospital or laboratory data were requested at an aggregated level. In addition, we searched for relevant records in meeting proceedings of CYSTINET and the European Network for Food-borne Parasites (Euro-FBP, COST Action FA1408). Finally, we explored the references listed in recent topic-specific reviews [12–14, 16] to identify any additional eligible documents. We applied the same inclusion and exclusion criteria and followed the same data collection approach for all eligible sources. Personal communications received after 1st of December 2015 were allowed to be included when describing data from within the study period.

4.3.4. Data collection and analyses

Three independent reviewers (VD, MLG, CT) performed the data collection. For data analysis, cases reported as case reports providing information on individual characteristics of the patient were defined as individual cases. Cases provided at aggregated level with no individual information were defined as aggregated cases. Predefined tables summarising individual cases included year of diagnosis, age, gender, country of origin or nationality, and reported risk factors, and reference (i.e. author and publication year). Tables summarising aggregated cases or prevalence included country, level of data collection (e.g. national/regional), timeframe, number of cases (or prevalence), *Taenia* species, risk factors (e.g. immigration/ travel history) if available, and reference.

For description of risk factors, we applied the following definitions: (i) Endemic region: Asia, Africa, South and Central America (including Caribbean islands), and eastern European countries; (ii) Immigrant: any person born in or native from an endemic region, or reported to have moved from an endemic region; (iii) Travelled/ stayed in endemic region: having travelled, stayed, or resided in an endemic region reported in their epidemiological history; (iv) No history of travels to endemic areas or immigration (autochthonous): information on risk factors provided, but no history of travel/immigration (outside western Europe) is reported.

In those cases where the existence of duplicates was probable (e.g. cases included in two retrospective studies on the same area/hospital, covering overlapping time periods, cases diagnosed in the same hospital in the same timeframe but reported in different sources, etc.) cases were only presented once. Descriptive analyses and graphics were performed in Excel and the R software environment for statistical computing (R Core Team, 2016).

4.4. Results

4.4.1. Search results

The steps followed in the search strategy are presented in Figure 4-1. A total of 442 relevant references were identified and included in the review: 208 were retrieved through online international databases (Additional file 3: Table S2 of Annex II) and 234 were made available through local sources (Additional file 4: Table S3 of Annex II).

The countries for which we identified relevant data or cases of *T. saginata* or *T. solium* in humans or animals are shown in Figure 4-2. Data were retrieved from peer-reviewed papers, governmental and scientific reports (e.g. EFSA reports), epidemiological bulletins, dissertations, conference abstracts, and from sources providing unpublished data (e.g. registries and personal communications).

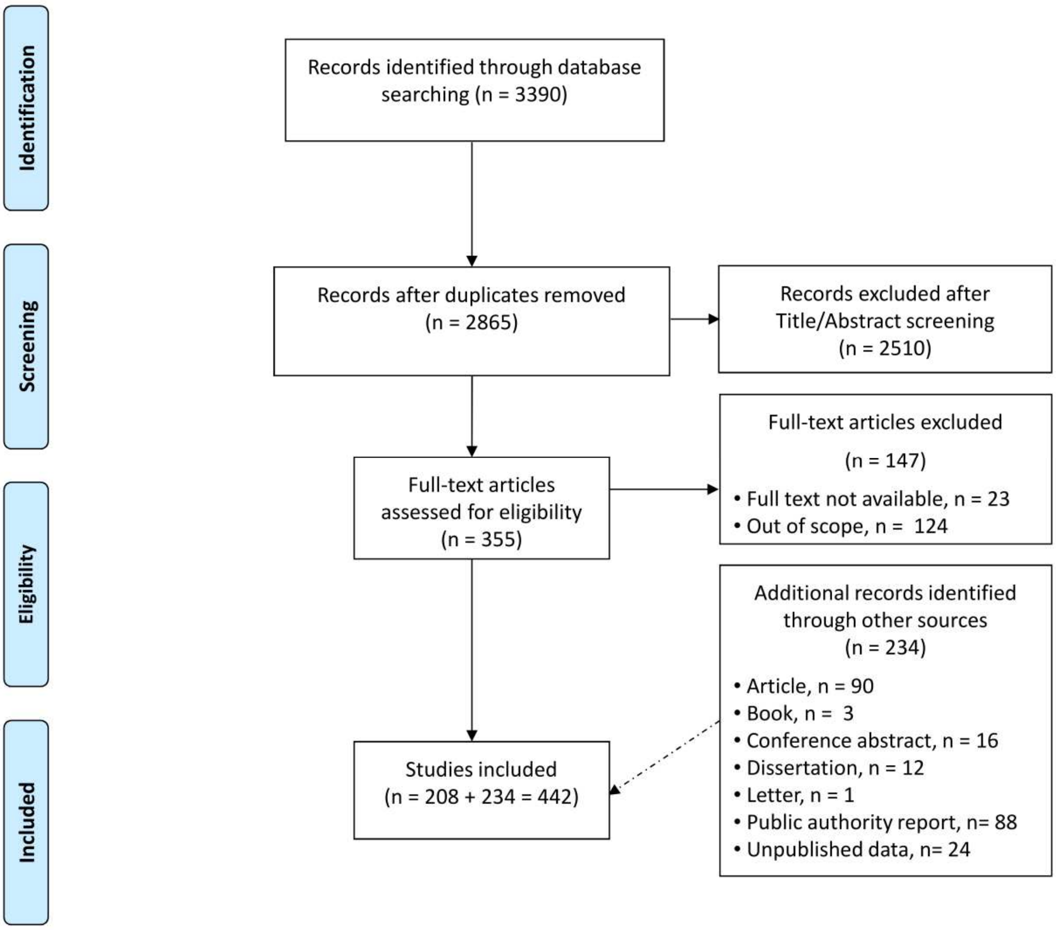

Figure 4-1 Flow diagram of the search strategy steps

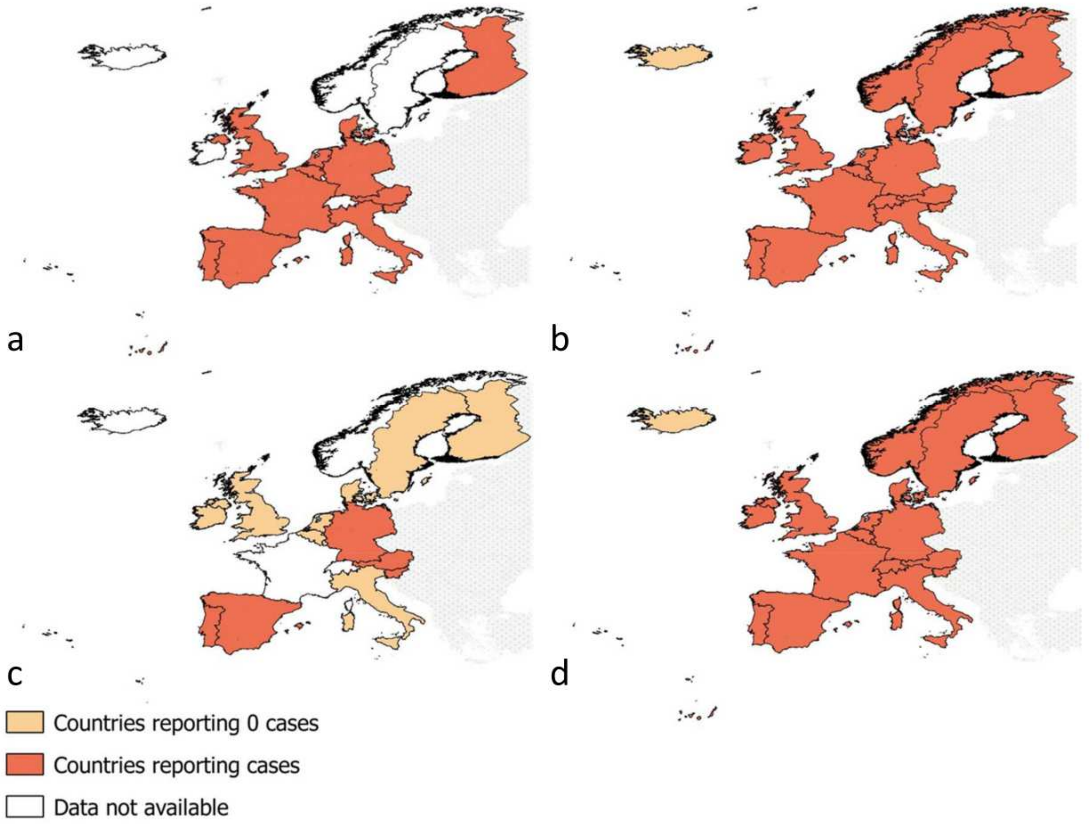

Figure 4-2 Summary of identified data on human taeniosis and cysticercosis in western Europe (1990–2015). a Taeniosis. b Human cysticercosis. c Porcine cysticercosis. d Bovine cysticercosis

4.4.2. Taeniosis

We identified 86 sources providing unique information for twelve countries: 21 records reporting 22 individual cases and 65 providing information on aggregated cases or prevalence. For Finland, the only information found indicated that a handful of taeniosis cases are diagnosed in HUSLAB yearly (*T. solium* being less common than *T. saginata*) [20, 21]. No reports of taeniosis could be found for Iceland, Ireland, Luxembourg, Norway, Switzerland and Sweden.

4.4.2.1. Taeniosis case reports

In total, 22 individual cases were reported in seven countries (Additional file 5: Table S4 of Annex II). Almost all were reported as *T. saginata* (11 cases) or *Taenia* spp. (8 cases, one of them suspected to be *T. saginata*) (Figure 4-3). Two case reports of *T. solium* were found, one in Spain (in a 19 year-old Spanish woman who had consumed raw pork) and one in Italy (a post-mortem diagnosis in a 26-year old farmer in 1985). A *T. solium* case was suspected in Corsica (France) in a 55 year-old woman who had consumed a Corsican traditional dish made with uncooked pig intestine [22] although Galán-Puchades and Fuentes [23] later suggested that *Taenia asiatica* could have been the causative agent. None of the *T. solium* case reports provided details on how the species identification was achieved. In half of the cases, consumption of raw meat was mentioned as a risk factor. It was not mentioned whether the taeniosis cases could be autochthonous or imported except for one patient who had recently returned from a prolonged stay in Ivory Coast.

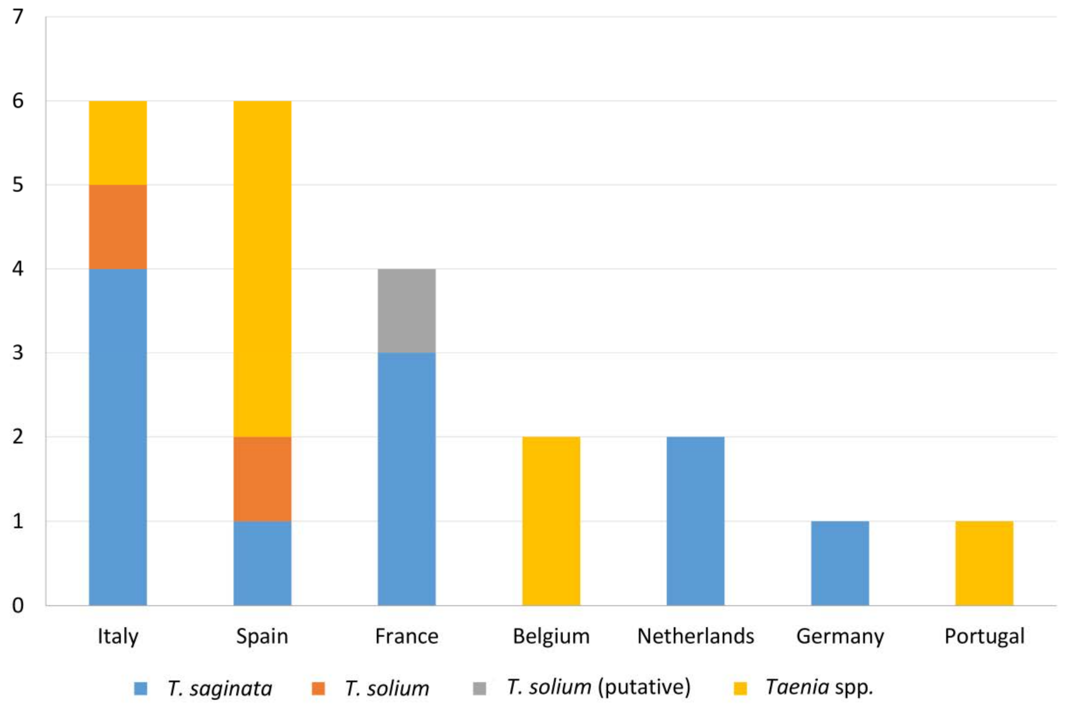

Figure 4-3 Number of identified taeniosis cases in case reports in western Europe (1990–2015)

4.4.2.2. Aggregated taeniosis cases

Aggregated taeniosis cases were obtained from authorities'reports, epidemiological bulletins, or national registries (Additional file 5: Table S5 of Annex II) and from hospitals/laboratories and epidemiological studies (Additional file 5: Table S6 of Annex II).

Data from authorities' reports, epidemiological bulletins or national registries were available for six countries covering different years. The number of cases reported per year by each country was variable, with the UK and Spain reporting the highest number of annual cases (Figure 4-4). Most cases were reported as *Taenia* spp. or *T. saginata*; however, eight *T. solium* cases in Spain (reported in different years between 2001 and 2008), eight in Portugal (reported in different years between 2000 and 2011), five in Slovenia (detected in different years between 1997 and 2011), and two in the UK (one case reported in 2002 and another in 2003) were identified. According to Hill et al. [24] around 98% of the cases recorded by the Health Protection Agency in the UK in the last years were *T. saginata*. For most cases, no information was available in relation to nationality, risk factors, or sources of infection. Of all aggregated taeniosis cases reported in the UK, one case reported having eaten raw beef and 46 cases were connected with overseas travels. The total number of cases per *Taenia* species and country is shown in the Additional file 5: Table S5 (Annex II).

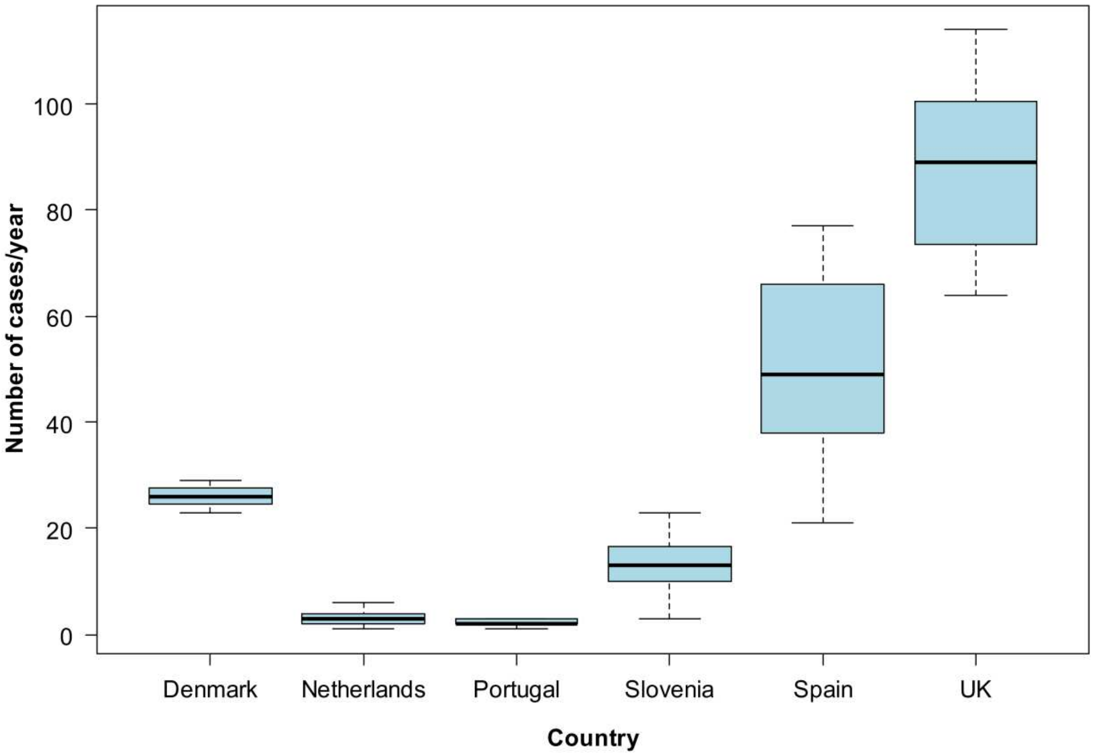

Figure 4-4 Number of aggregated taeniosis cases/year reported in authorities' reports, epidemiological bulletins and national registries in western Europe (1990–2015). Data from Portugal do not include the autonomous regions of Madeira and Azores

Aggregated taeniosis cases identified from laboratory/ hospital data and epidemiological studies (e.g. retrospective studies in hospitals) were identified for seven countries (Figure 4-5). Further details are presented in the Additional file 5: Table S6 (Annex II).

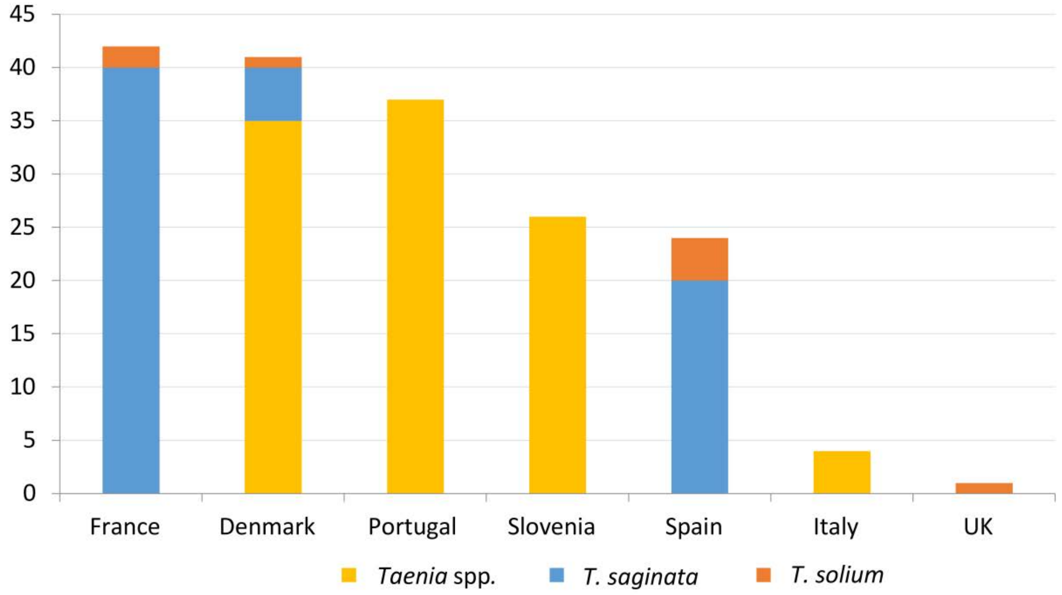

Figure 4-5 Number of aggregated taeniosis cases reported at hospital/laboratory level in western Europe (1990–2015). Data for Portugal correspond to the Autonomous Region of Madeira

4.4.2.3. Taeniosis prevalence data

Prevalence data were reported in regional epidemiological studies conducted at hospital or laboratory level. These studies were conducted in five countries at different time periods and reported *T. saginata* or *Taenia* spp. prevalences ranging between 0.05 and 0.27% (Additional file 5: Table S7 of Annex II).

Based on anthelmintic drugs sales, several authors have estimated the number of taeniosis cases or prevalence in a given region or country (Additional file 5: Table S8 of Annex II). The estimated number of *Taenia* cases occurring annually in Belgium and France was 11,350 and 64,495, respectively [25, 26]. Estimated prevalences range from 0.02 to 0.67%, with the highest being reported in Germany (0.33–0.67%) and Belgium (0.35–0.46%) and the lowest in Denmark (0.02%) and Italy (0.02–0.04%). In France, based on the quantification of taeniid egg contents in sludge, Barbier et al. [27] deducted that *T. saginata* taeniosis prevalence in the Caen urban area ranged from 1.5 to 2.7% (1987–1989).

4.4.3. Human cysticercosis

We identified 243 relevant sources providing unique information on human cysticercosis in all 18 countries.

4.4.3.1. Human cysticercosis case reports

A total of 275 individual cysticercosis cases were reported in 17 countries (Figure 4-6). No case reports were identified for Iceland. Spain (72 cases) and France (54 cases) recorded the highest number of cases. The average number of cases published per year was 10.6 with 2014 being the year with the highest number (25) and 1997 the year with the lowest number (1) reported, respectively, among all 17 countries. The age of patients ranged from 2 to 94 years; 129 were female and 127 male (gender unknown in 19 cases).

Information on risk factors was reported in most cases (Additional file 5: Table S9 of Annex II). In 82% of cases the infection was probably acquired outside western Europe (61% due to immigration and 21% due to travels or stays in endemic regions). Among infected immigrants, the highest number of cases had emigrated from Latin America (77), followed by Asia (39) and Africa (35), whereas 15 cases originated from eastern Europe (e.g. Albania, Bosnia and Herzegovina, former Yugoslavia). For 5% of cases, the infection appeared to be acquired autochthonously (no travel/immigration history reported) (Table 4-1, Figure 4-6). For the remaining cases (13%), there was no information on nationality or risk factors that could be linked with the infection.

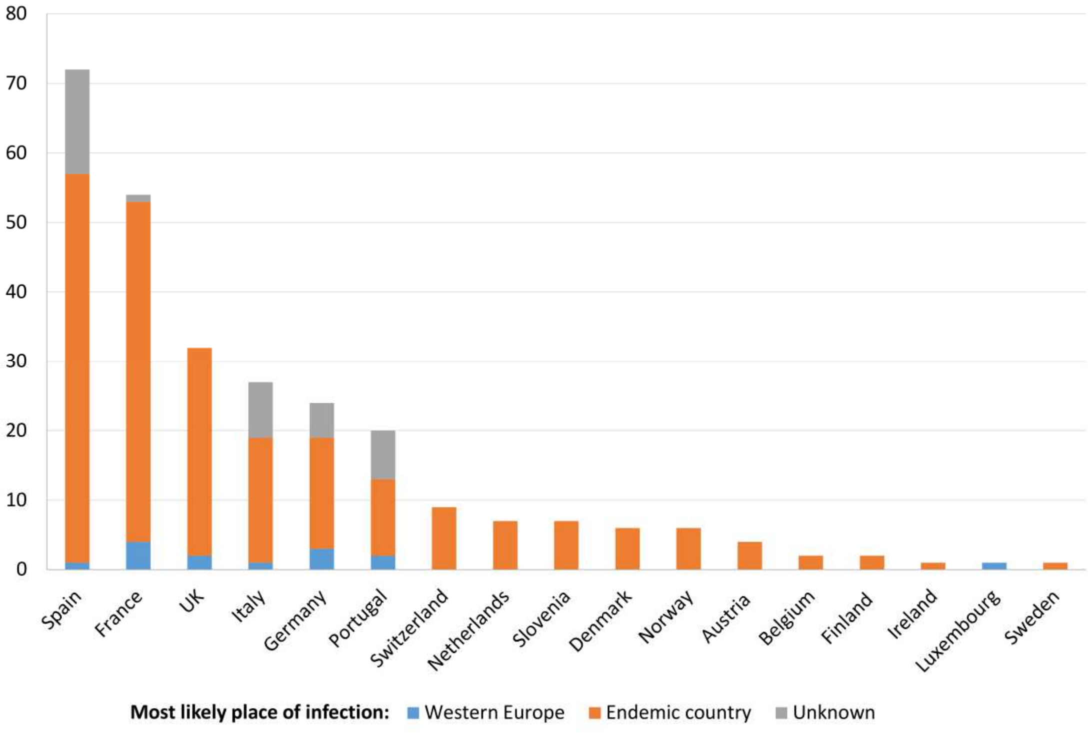

Figure 4-6 Number of identified human cysticercosis cases in case reports in western Europe (1990–2015)

Table 4-1 Suspected autochthonous human cysticercosis cases from case reports

Country	No. cases	Background	Age (yrs)
France	4	1 case: had never left Europe 1 case: had never left metropolitan France 1 case: no history of travel to endemic areas 1 case: had never left France	44–69
Germany	3	3 cases: no history of travel to foreign countries	6–69
UK	2	1 case: no history of travelling outside Europe 1 case: lack of travel to endemic areas	3–21
Portugal	2	1 case: without relevant personal background 1 case: no history of travelling abroad	57–71
Italy	1	1 case: had never visited endemic areas for cysticercosis	61
Luxembourg (infection could have been acquired in Spain)	1	1 case: born in Spain, moved to Luxembourg 8 years prior diagnosis (annual visits to Spain)	20
Spain	1	1 case: without background of interest except for that he was a pig breeder	70

4.4.3.2. Aggregated human cysticercosis cases

Aggregated human cysticercosis cases were obtained from authorities' reports or registries (Additional file 5: Table S10 of Annex II) and from hospital/laboratories or epidemiological studies (Additional file 5: Table S11 of Annex II).

Data from authorities' reports and registries were available for six countries over different periods. The highest number of cases was reported in Spain, with 1702 hospitalised cases with diagnosis of cysticercosis at hospital discharge between 1997 and 2014 (range of 45–169 hospitalisations per year), following ICD-coding systems [28]; Portugal with 1120 hospitalised cysticercosis cases between 1993 and 2004 and 357 NCC hospitalized cases between 2006 and 2013 (mean of 45 cases per year) following ICD-coding systems [29, 30]; and Italy with 540 hospitalisations for cysticercosis between 2001 and 2010 (range of 40–53 per year) based on ICD-coding systems [31]. In Denmark, the national inpatient diagnosis register recorded 32 cases during 2012–2014 and in the Netherlands there were 24 hospitalisations with cysticercosis as primary diagnosis (following ICD codes) during 1986–1990. In Iceland, based on governmental reports there were no cases notified in 2013–2014 [32].

Cases based on laboratory/hospital data or epidemiological studies were retrieved for 13 countries. The highest numbers of cysticercosis cases were diagnosed in Portugal (476) and Spain (282), followed by a lower number in the Netherlands (147), France (135) and Italy (90) (Figure 4-7). Of these cases, 38 [diagnosed in France (18), Italy (17), Spain (2) and Portugal (1)] had most likely acquired the infection in western Europe based on the travel/immigration history reported. The 18 cases diagnosed in France were reported to have acquired the infection mainly in the Iberian Peninsula in 1978–1988. Further details are shown in Additional file 5: Table S11 (Annex II).

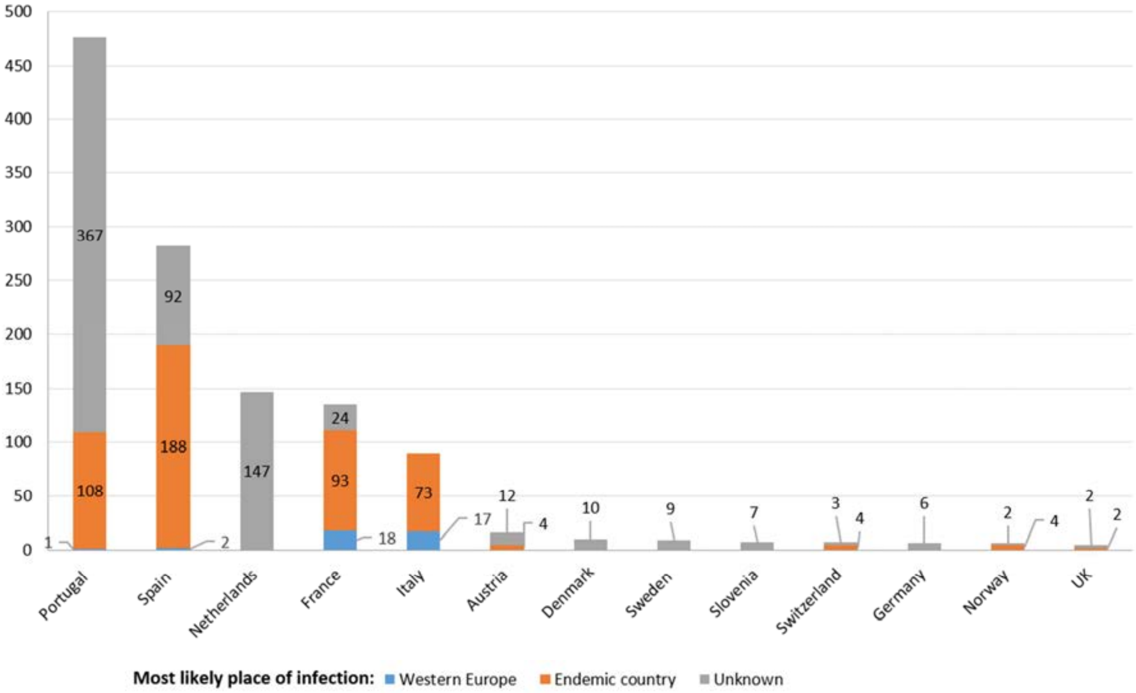

Figure 4-7 Number of aggregated human cysticercosis cases reported at hospital/laboratory level in western Europe (1990–2015)

4.4.4. Porcine cysticercosis

We identified 39 relevant references providing unique information on 14 countries: 25 provided cases and 14 provided prevalence data. No information could be obtained for France, Iceland, Norway and Switzerland (Additional file 5: Table S12 of Annex II).

Based on the available information, no cases of porcine cysticercosis were identified during meat inspection at slaughter in Belgium, Denmark, Finland, Ireland, Italy, Luxembourg, the Netherlands, Sweden and the UK. According to public authorities, *T. solium* in pigs has not been reported for many years in the UK [33]. In Denmark, the last report of cysticerci in pork dated back to 1894 [34] and in Italy, according to Tamburrini et al. [35], porcine cysticercosis cases were only occasionally observed (e.g. in Basilicata) in the past.

Porcine cysticercosis was reported during meat inspection at slaughter in Austria, Germany, Portugal, Slovenia and Spain. Important to note, reports from Germany did not differentiate between cases of *Taenia hydatigena* and *T. solium* cysticercosis and Spain and Slovenia reported porcine cysticercosis with no further information on the causative species. Therefore, it is not possible to assess whether these cases were of public health importance. Slovenia notified only one case of porcine cysticercosis in 2007 (2007–2014), but it was not confirmed by any laboratory diagnostic method [36]. The reported prevalence in Germany ranged from 0 to 0.0023% (2009–2012). In Spain, the prevalence ranged from 0 to 0.20% in domestic pigs (1999–2014); 0.16 to 0.43% in home-slaughtered pigs (2011–2013), and 0 to 0.19% In wild boar (2009–2013).

In Extremadura (Spain), García Vallejo [37] analysed samples of 689 Iberian pigs raised on extensive breeding farms and could not identify any infected with *T. solium* cysticerci.

Austria was the only country where the veterinary authority had been annually (between 1998 and 2002) reporting cases of *T. solium* [reported as "*Cysticercus cellulosae*": 10–40 cases/year (1999–2002); 0 cases in 1998] [38–42]. Most of these cases were described as light infections (65 light and 23 heavy infections during 1999–2002).

In Portugal, two confirmed cases of generalised cysticercosis due to *T. solium* were detected in 2004. One case was a pig bought and raised for home consumption on a farm located near Coimbra (Unpublished data, Correia da Costa, 2016). The second case, a pig of the Bisaro breed (traditionally raised outdoors), was detected and confirmed at an abattoir in Vinhais (northern Portugal) [43, 44]. More recently, and according to official data from 2008 to 2015, no cases of *T. solium* cysticercosis were detected in Portugal (unpublished data, DGAV, 2016).

4.4.5. Bovine cysticercosis

In our review we identified 85 sources providing unique information (prevalence or number of cases) from all (18) countries. Prevalence data or number of cases were mainly based on routine meat inspection (Regulation (EC) No 854/2004) [45]. Prevalence data of bovine cysticercosis was identified in fifteen out of the eighteen countries (Figures 4-8, 4-9). For few countries and specific years, we retrieved the number of positive cases detected per year (prevalence data was not available) (Additional file 5: Table S13 of Annex II). Prevalence data based on more sensitive methods than routine meat inspection (i.e. serology or a more detailed meat inspection) [46, 47] were only available for six countries (Additional file 5: Table S14 of Annex II). In Iceland it has been never detected. However, it should be noted that incisions in the heart and masseter muscles are not routinely performed as part of meat inspection in Iceland [48].

The majority of bovine cysticercosis cases identified were detected after 1990. Figures 4-8 and 4-9 show the reported prevalence detected at slaughter before 1990 and after 1990, respectively. Prevalence reported before 1990 ranged from 0.03% (Belgium in 1969–1989 and Norway in 1989) to 6.80% (Former German Democratic Republic in 1974–1989). After 1990, the prevalence ranged from 0% (some regions of Spain in 2009–2014, one abattoir in Belgium in 2003, the UK in 2006 and mainland Portugal during 2008–2015) up to 7.82% (Madeira, Portugal, in 2010). After 1990, 95% of the prevalence data reported were below 4.87% and 50% were below 0.07%. The highest prevalence was reported in Madeira (7.82%). Although no positive cases were found in the Portuguese Autonomous region of Azores, at least part of the cases detected in Madeira seemed to have acquired the infection in Azores [49].

For Ireland and Norway, only one prevalence record before 1990 was available: 0.62% in Ireland (1977–1980) [50] and 0.03% in Norway (1989) [51]. However, individual cases were reported in Norway after this date [52, 53]. For Finland, no prevalence data could be retrieved, but 2 cases were reported: one in 1996 and one in 2002 (Additional file 5: Table S13 of Annex II).

In some reports on bovine cysticercosis, information on the degree of infection was available. The percentage of heavily infected cases ranged from 0.59 to 6.06% in Austria (1998–2003), 0.49–1.61% in Belgium (2002–2013), 5.30–6.47% in Germany (2009–2012) and 6.29–12.68% in Madeira (2007–2013).

Prevalence data based on more sensitive methods (i.e. serology, detailed meat inspection or modelling) ranged from 0.54 to 38.4% (Additional file 5: Table S14 of Annex II). Data on the occurrence of bovine cysticercosis according to the age of the animal was available for four countries: the prevalence in calves and adult cattle ranged between 0 and 0.55% and 0.03–1.68%, respectively (Additional file 5: Table S15 of Annex II).

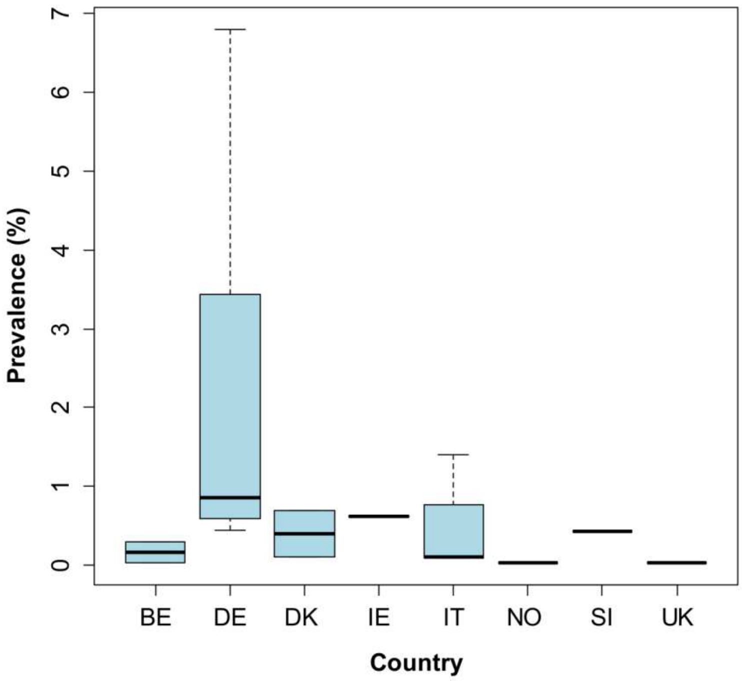

Figure 4-8 Prevalence of bovine cysticercosis based on routine meat inspection detected in western Europe before 1990. Prevalence estimates are from individual studies, and not the estimated prevalence for the entire country. Abbreviations: BE, Belgium; DE, Germany; DK, Denmark; IE, Ireland; IT, Italy; NO, Norway; SI, Slovenia; UK, United Kingdom

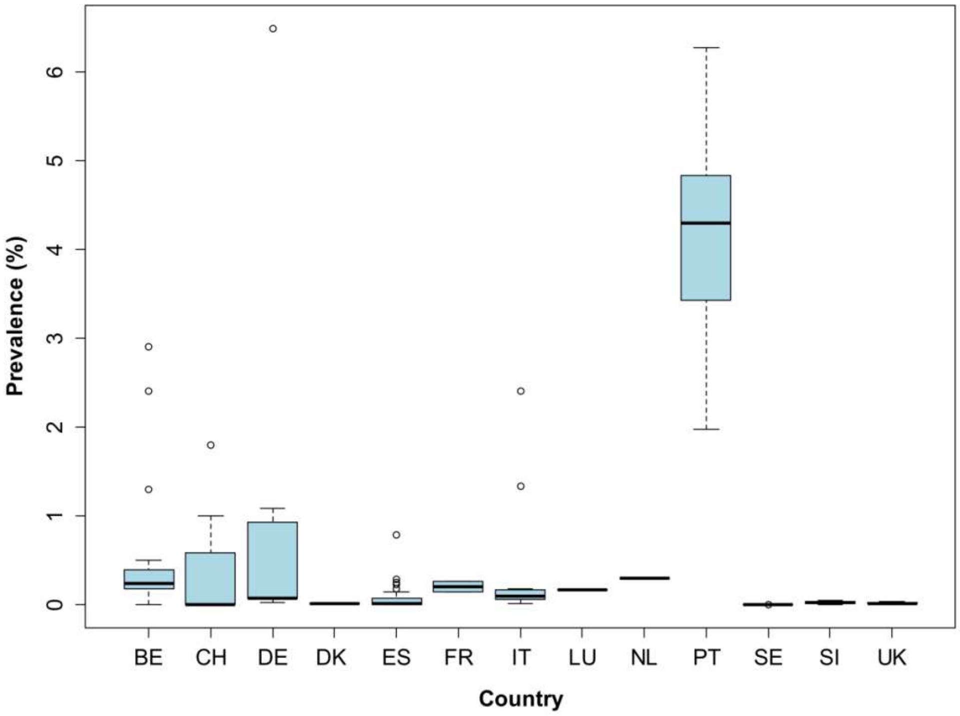

Figure 4-9 Prevalence of bovine cysticercosis based on routine meat inspection detected in western Europe after 1990. Prevalence estimates are from separate local studies. Data for Portugal correspond to the Autonomous Region of Madeira. Prevalences higher than 6.5%, which correspond to prevalences up to 7.82% detected in Madeira (2010), are not presented in the figure. Abbreviations: BE, Belgium; CH, Switzerland; DE, Germany; DK, Denmark; ES, Spain; FR, France; IT, Italy; LU, Luxembourg; NL, The Netherlands; PT, Portugal; SE, Sweden; SI, Slovenia; UK, United Kingdom

4.5. Discussion

The aim of the current study was to collect epidemiological data on *T. saginata* and *T. solium* in human and animal hosts in western Europe. Human taeniosis cases were identified in two thirds of the countries included in the search. Overall, the number of sources providing data was limited and the annual number of taeniosis cases found equally low for most countries, except for the UK and Spain. However, estimates based on anthelmintic sales (e.g. niclosamide) [25, 26, 54–58] or detection of Taeniidae eggs in sewage [27], although approximate, suggest that the true number of taeniosis cases is far from negligible. Indeed, we assume a serious underestimation, due to the fact that taeniosis is not a notifiable disease, the perceived low health impact, and a possible low awareness among medical doctors about the potential presence of *T. solium* carriers [14, 59] with a high public health impact. We further hypothesize that, as a consequence, the diagnosis is often based exclusively on patient's reporting shedding of proglottids without any laboratory confirmation. Our results also highlight that species differentiation is rarely performed for taeniosis cases, reflected by the high proportion of cases reporting "*Taenia* spp." as the causative agent. Next to the reasons discussed previously related to the perceived low health impact of the disease, diagnostic limitations might play a role for those cases for whom stool examination was performed. Indeed, *Taenia* spp. eggs are morphologically identical, and while differentiation can be made based on the number of uterus branches of expelled proglottids, such material is not always available. Furthermore, stool examination by molecular methods is not often performed [60]. Overall, given the lack of species differentiation in addition to the overall assumed underestimation of cases, it is difficult to estimate the true number of taeniosis cases caused by either *T. saginata* or *T. solium* in western Europe.

Taenia saginata is responsible for continuous economic losses for the meat industry, due to the condemnation or freezing of affected carcasses [3, 61] as prescribed in the European Regulation (EC) No 854/2004 [45]. Carriers of *T. saginata* contribute to these financial losses by sustaining the parasite's life-cycle. In our search, *T. saginata* taeniosis cases were identified in Austria, Belgium, Denmark, Finland, France, Germany, Italy, Netherlands, Portugal, Spain, Slovenia and the UK. The presence of bovine cysticercosis was reported in nearly all countries included in the search, at different prevalence levels. As most of the data on *T. saginata* in cattle retrieved were based on meat inspection, a hugely insensitive detection method (reported sensitivity of 15.6%; [62]), we assume an underestimation of cases [46, 63]. A few false positive cases could also be present, as other causes of macroscopic lesions (e.g. abscesses, *Sarcocystis* cysts) could be confused with calcified cysticerci by meat inspection [59, 64]. Thus, more sensitive diagnostic tools should be implemented and species differentiation should be done in case of doubt. Furthermore, data reporting should be improved. Austria, for example, used to report findings on *T. saginata* at slaughter (1998–2003) but at present any (unspecified) cysts found in cattle are reported under the term "echinococcosis" [65–71]. For some countries (e.g. Norway, Finland) only sporadic cases of bovine cysticercosis were reported, which could be due to the lack of good reporting systems, as well as to the low prevalence or even absence of the parasite, due to the lack of favourable conditions for its transmission in these areas (e.g. lack of raw meat consumption, or lack of environmental factors such as use of sewage sludge on pastures).

Taenia solium taeniosis cases were reported in Denmark, France, Italy, Portugal, Spain, Slovenia and the UK, but the diagnostic methods used for identifying the *Taenia* species were often not clearly described [72]. On the individual level, identification of *T. solium* taeniosis cases is extremely relevant as one tapeworm carrier, if not treated, can pose a significant health risk to both themselves and to people in contact, as ingestion of infective eggs can lead to cysticercosis [11]. From the available data, it was not clear whether any of the reported *T. solium* taeniosis cases could have been acquired within western Europe through consumption of infected pork. However, as we can assume that most *T. solium* taeniosis cases were imported, prevalence studies in risk groups, such as travellers and immigrants, would be recommended. Furthermore, the epidemiological situation of *T. solium* in pigs was found to be unclear for many countries in western Europe: only five countries reported porcine cysticercosis cases and they usually did not report the causative species (i.e. cysticerci could also be *T. hydatigena*). Moreover, current reporting systems are often not consistent. For instance, in Austria similar to the cattle data previously discussed, nowadays only unspecified cysts are being reported for pigs [65–71]. Given the public health impact of *T. solium*, and because cysts of different *Taenia* spp. may not be distinguishable in the early stages [9], molecular confirmation should be performed in suspected porcine cysticercosis cases and the reporting should be made at species level, as recommended by EFSA [73]. Only Portugal reported two cases of *T. solium* in pigs, confirmed by molecular methods, one pig being raised outdoors and another bought for home consumption) (Correia da Costa, pers. com., 2016) [43, 44] supporting the hypothesis that in some rural areas in western Europe, favourable conditions might still exist for *T. solium* transmission (e.g. outdoor pig farming and contact with faeces from tapeworm carriers). In theory, increasing immigration and travels, combined with increasing outdoor pig farming (e.g. organic pig farming) may contribute to a future re-establishment of *T. solium* local transmission in many areas [9, 10] and we may expect there to be a rise in porcine cysticercosis cases in western Europe in the near future [9, 10].

Humans can act as dead-end host for *T. solium*, upon ingestion of eggs shed by a *T. solium* tapeworm carrier. The burden of human cysticercosis, especially in cases of NCC, is massive and it is believed to be the food-borne parasitic infection incurring the largest number of disability adjusted life years globally [74]. We found human cysticercosis cases in all western European countries included in the search, except Iceland. In some countries (e.g. Belgium, Finland, Ireland, Luxembourg, Norway, Sweden and Switzerland) included in our search, a cysticercosis case seemed to be a rare finding, whereas in countries like France, and especially the most southern countries in our search (Spain and Portugal), cases were more frequently observed. Based on the available epidemiological information, it was apparent that most human cysticercosis cases diagnosed in western Europe were linked to immigration or travel to endemic countries. The absolute number of cases in immigrants appear to have increased in recent years, with a large number of cases originating from Latin America and the Caribbean, possibly due to a rapid increase in immigration from this area towards Europe, mostly to the southern European countries, around the transition from the 20th to the twenty-first century [75]. Immigration from Africa has increased throughout the last decade and is expected to increase further [76]; we might therefore observe a rise in imported cases from African countries in the coming years. In addition, some cysticercosis cases originated from eastern Europe where favourable conditions for local *T. solium* transmission also seem to exist [8, 10]. Increased mobility, possibly associated with the introduction of the Schengen zone [9], could thus also result in a rise of imported cases from that region. In our review, we identified few human cysticercosis cases suspected to be autochthonously acquired. However, the exact place and time of infection and whether local transmission from an imported *T. solium* tapeworm carrier might have occurred could not be determined from the available data. Overall, although false positive cases of cysticercosis are possible in serological tests due to crossreactions [77], the number of NCC cases identified in our search is probably lower than the actual number, as some NCC cases might not exhibit symptoms [78], the serological reference test exhibits a low sensitivity in case of single viable or calcified lesions [79], and clinicians in these non-endemic areas lack experience with the disease and therefore might not recognize it [59].

4.6. Conclusions

The fact that both taeniosis and human cysticercosis are mainly non-notifiable diseases implies the absence of systematic data collection and reporting, leading to fragmented data. Overall, due to the economic impact of *T. saginata* and the potential impact on public health of *T. solium*, the improved detection and reporting of human taeniosis cases is extremely relevant for control and surveillance purposes. By maintaining the parasite life-cycle, *T. saginata* tapeworm carriers contribute to continuous economic losses in the meat sector. Furthermore, despite the low health impact, acquiring *T. saginata* taeniosis should not be acceptable from a food safety perspective. The existence of *T. solium* tapeworm carriers, combined with the presence of suspected autochthonous cases of human cysticercosis as well as the lack of confirmation of porcine cysticercosis cases in most countries, deserves further attention. We might see a rise in imported human cysticercosis in the near future due to increased migration from endemic countries. Species identification of taeniosis cases should be encouraged and epidemiological investigations carried out to detect whether local transmission of *T. solium* may occur. Furthermore, suspected cases of *T. solium* in pigs should be confirmed by molecular methods. Both taeniosis and human cysticercosis should be notifiable and surveillance and reporting in animals should be improved.

4.7. Authors' contributions

MLG, CT and VD conducted the systematic review of the literature and extracted data. MLG analysed data and drafted the first version of the manuscript. AA, BD, CT, MLG, SSo and VD contributed to the design of the study, interpretation of data and writing of the first draft. The rest of co-authors contributed to data collection and/or writing of the paper. All authors read and approved the final manuscript.

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5. Study III

Epidemiology and economic impact of bovine cysticercosis and taeniosis caused by *Taenia saginata* in northeastern Spain (Catalonia)

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5.1. Abstract

Introduction: In Catalonia (north-eastern Spain), *Taenia saginata* has been described in cattle but its occurrence in humans is unclear. Moreover, whether cattle acquired the infection in Catalonia or outside Catalonia and its economic impact have not been investigated. This study aimed to estimate the prevalence and spatial distribution of bovine cysticercosis in Catalonia (2008–2015), and the burden from *T. saginata* upon the animal and human sectors in Catalonia (2013–2015).

Methods: Data on cattle diagnosed with cysticercosis at meat inspection were collected and analysed. Cattle movement history was used to identify the most likely place of bovine cysticercosis infection and to investigate its spatial distribution. Data on taeniosis treatment (niclosamide and praziquantel) costs and their supply in Catalonia as well as data on patients attending primary care with diagnosis of taeniosis were collected. The financial impact associated with *T. saginata* due to carcasses condemned and frozen, meat inspection and human taeniosis was estimated.

Results: During 2008–2015, between 18 and 107 cattle were found positive for cysticercosis each year (prevalence at slaughter of 0.010%). Movement history was available for 44% of the infected cattle and in 53% of them Catalonia was identified as the place where the infection was acquired with highest probability. Two significant bovine cysticercosis clusters were detected. The number of patients diagnosed with taeniosis in primary care during the period 2013–2016 was 41–63/year. The overall economic impact of *T. saginata* (2013–2015) amounted to 154,903 €/year (95% CI: 113,075–196,762). Meat inspection accounted for 81.9% (95% CI: 75.8–86.2%) of the costs, followed by costs due to carcass condemnation and freezing (9.4%; 95% CI: 6.9–12.8%), and taeniosis-associated costs (8.7%; 95% CI: 6.7–11.6%). Costs due to freezing and condemnation of carcasses reached 19,442 €/year (95% CI: 17,528–21,391) (509 €/lightly infected carcass and 1,140 €/heavily infected carcass). Taeniosis-associated costs were estimated at 12,848.5 €/year (237 €/patient).

Conclusions: The public health risk of *T. saginata* in the area seems to be low. The economic impact due to *T. saginata* was mainly attributed to meat inspection. The cost due to carcass condemnation and freezing was limited compared to the revenue of the beef sector. Developing and implementing risk-based surveillance is needed to lower

the costs of meat inspection. Considering cattle movements might be useful in the development of such a strategy.

5.2. Introduction

Taenia saginata is a food-borne parasite that infects humans (definitive host) and bovines (intermediate host). Humans acquire the infection (taeniosis) by consuming raw or undercooked beef containing infective cysticerci (*T. saginata* metacestode larval stage). The adult tapeworm develops in the human intestine and produces gravid proglottids that are shed in the stools or leave the anus spontaneously [1]. Bovines acquire the infection (bovine cysticercosis) by accidentally ingesting water, pasture or fodder contaminated with *T. saginata* ova originating from human faeces [2]. Following ingestion, the eggs hatch and release oncospheres that migrate, through the circulatory system, mainly to muscular tissues where they establish and develop into cysticerci. In the muscles they will remain infective for months or even years before undergoing degeneration and calcification [3]. Bovine cysticercosis in naturally infected cattle does not cause clinical signs [4].

The main preventive measure to control *T. saginata* is based on the detection of cysticerci and implementation of sanitary measures during meat inspection. In the European Union (EU), Regulation (EC) No 854/2004 [5] establishes that all bovines over six weeks-old are to be individually examined for bovine cysticercosis through visual examination, incision and palpation of several muscular tissues. Carcasses found to be heavily infected (generalised infection) are to be condemned. However, if the infection is not generalised (light infection), the parts not infected can be declared fit for human consumption after undergoing a cold treatment.

Human taeniosis is generally asymptomatic and easily treated with anthelmintics [2]. However, symptoms such as anal pruritus, abdominal discomfort, weight loss, diarrhoea, nausea, epigastric pain and vomiting have been described [1, 4]. Despite its low impact on public health [6], it is generally assumed that *T. saginata* incurs a high economic impact for the beef sector due to condemnation and downgrading of carcasses [3, 7]. Additionally, resources involved in routine meat inspection are being invested [8]. However, the economic significance of this parasite in European countries is not well known and there are no recent estimates quantifying the economic impact [9–11]. Moreover, the impact on public health is difficult to assess as taeniosis is not notifiable and there are no systematic data collection and reporting systems. The number of taeniosis cases is often estimated from sales figures of niclosamide and praziquantel [12]. In Europe, a risk-based surveillance and control approach is encouraged [8, 13] but current knowledge on the epidemiology and impact of bovine cysticercosis is too limited to guide such an approach [4].

In north-eastern Spain (Catalonia) bovine cysticercosis has been detected every year with a prevalence based on meat inspection ranging between 0.015–0.022% since 2005 and with a clustered distribution of infected farms [14]. Previous analyses have not taken into account the movement of animals and the fact that cattle could have been infected in a different location than the last farm that sent the animals to the slaughterhouse. Therefore, these previous estimates might be useful to assess human exposure to *T. saginata* but might be biased if the interest is to assess the burden of bovine cysticercosis in this region. In addition, there are no published data on the number of cases of taeniosis in humans and there are no estimates of the economic impact of bovine cysticercosis in north-eastern Spain (Catalonia).

The aim of this paper was to assess the epidemiology and burden of the *T. saginata* taeniosis/bovine cysticercosis disease complex in the animal and human sectors in Catalonia. We specifically aimed to (i) estimate the prevalence of bovine cysticercosis in cattle slaughtered in Catalonia between 2008 and 2015; (ii) estimate the prevalence and spatial distribution of bovine cysticercosis in Catalonia between 2008 and 2015 (based on the Catalan farm where cattle most likely became infected); and (iii) calculate the economic burden from *T. saginata* upon the animal and human sectors in Catalonia for the years 2013–2015.

5.3. Methods

5.3.1. Data collection and analysis

5.3.1.1. Bovine cases

The number of cattle in which cysticerci had been detected (i.e. positive animals) during routine post-mortem inspection at the slaughterhouse (Regulation (EC) No 854/2004) [5], the year of detection and the slaughterhouses reporting cases, were provided by the Public Health Agency of Catalonia. Data on all cattle farms (i.e. geographical coordinates, census and production type), the identification of farms that have sent positive animals for slaughter, together with the individual identification codes of the positive animals (when available) and cattle movement history were provided by the Department of Agriculture, Livestock, Fisheries and Food of the Autonomous Government of Catalonia. The number of cattle slaughtered annually in Catalonia was obtained from "Encuesta de sacrificio de Ganado" [15] published by the Spanish Ministry of Agriculture.

5.3.1.1.1. Identification of the farm where cattle most likely became infected

The movement history of positive animals was used to identify those farms where cattle could have been most likely infected. Individual identification codes of positive cattle were used to retrieve, from the cattle movements database, their age and the time period during which each animal had been on every farm in their movement history. Details on movements occurring outside Catalonia are not kept in this database and therefore it was not possible to calculate the time spent by positive animals on farms outside our area of study. For those movements, based on the date the animal had left or arrived to Catalonia and their date of birth, we calculated the overall time period that each animal had been outside this area.

For each cattle farm the "probability" that the animal had acquired the infection on it was calculated as follows:

$$P_{ij} = \frac{(T_{ij})}{(Age_i - 42)}$$

where i is the individual cattle code; j is the cattle farm code (for farms outside Catalonia the code would be "outside"); P_{ij} is the probability with which an animal "i" had acquired the infection on a location "j"; T_{ij} is the time spent by animal "i" on location "j" (days); Age_i is the age of the animal "i" (days).

We assumed that the infection could not have been acquired in the last 6 weeks (i.e. 42 days) before slaughter as it is considered that a cyst develops and becomes readily visible and easily detected during post-mortem inspection six weeks after infection [16, 17]. Therefore, we deducted 42 days from the time spent by the infected animal on the last farm (or farms if the time spent on the last one was lower than 42 days).

For each infected animal, the case farm was defined as the farm in their movement history with the highest P_{ij} value that was located in Catalonia. For the positive animals for which we did not have the individual cattle code and therefore could not obtain movement data, we assumed that the infection could have been acquired on the last farm sending the animals for slaughter (i.e. case farm). In these cases if the last farm was located out of this region these animals were discarded for further spatial analysis. Bovine cysticercosis cases for which both the movement history and the farm sending animals to slaughter were inaccessible were also discarded for further spatial analysis.

5.3.1.1.2. Estimation of bovine cysticercosis prevalence

The apparent prevalence of bovine cysticercosis at slaughterhouse level was calculated as the number of positive cases detected during meat inspection divided by the total number of slaughtered animals. The apparent prevalence of bovine cysticercosis acquired in the region of Catalonia was calculated as the number of animals that would have most likely been infected in Catalonia divided by the number of cattle slaughtered in Catalonia not coming from farms outside this region. The specificity (100%) and sensitivity (27% for animals with a low level of infestation [18]) of meat inspection were taken into account to calculate the true prevalence of the disease. Specificity was assumed to be 100% since when doubts about the final diagnosis exist, samples of bovine cysticercosis suspected cases are usually sent to the laboratory for confirmation. The true prevalence was calculated using the following formula [19]:

$$True\ prevalence = \frac{AP - (1 - Sp)}{1 - [(1 - Sp) + (1 - Se)]} = \frac{AP + Sp - 1}{Se\ + Sp - 1}$$

where AP is the apparent prevalence; Se is the sensitivity (ranging from 0 to 1); and Sp is the specificity (ranging from 0 to 1).

5.3.1.1.3. Spatial analysis

A spatial analysis to detect geographical clusters of bovine cysticercosis in Catalonia was performed using the free software SaTScan v.9.4.4 (http://www.satscan.org). We ran a purely spatial analysis for clusters with high rates of bovine cysticercosis cases detected from 2008 to 2015. Based on the exact geographical coordinates of each farm, we used a Bernoulli model in which cattle farms were classified as case/control. Case farms were those cattle farms where the infection could have been acquired with the highest probability (based on previous analysis), while controls were the remaining cattle farms.

Details about the spatial scan statistic can be found in Kulldorf et al. [20]. Briefly, this method generates circular zones of continuously varying radii that range from zero up to a maximum cluster size (50% of the population at risk in our case). For each location and window size, a likelihood ratio test is computed based on the number of observed and expected cases within and outside the circular window and compared with the likelihood under the null hypothesis. Under the null hypothesis the expected number of cases in each area is proportional to its population size. The significance of the clusters is assessed using a Monte Carlo hypothesis test (999 replications). A 5% significance level was established. Results from the spatial scan statistics were represented using the free software QGIS v.2.12.2 [21].

5.3.1.2. Human cases

The number of niclosamide and praziquantel treatments prescribed and distributed in Catalonia to treat taeniosis, was made available from the Spanish Agency of Medicines and Medical Devices (AEMPS) for 2015 and 2016. Data on consultations to primary care of patients who, during the period 2013–2016, had a diagnosis of taeniosis (*T. saginata* or unspecified taeniosis) following the ICD-9-CM (International

Classification of Diseases, Ninth Revision, Clinical Modification) codes (i.e. 123.2: "*Taenia saginata* infection"; 123.3: "Taeniasis, unspecified") were retrieved from the database "Conjunt mínim bàsic de dades d'atenció primària" (CMBD-AP) [22]. The CMBD-AP is a registry managed by the Catalan Health Department that gathers information on the pathology seen by primary healthcare services classified according to the ICD. Duplicate records (i.e. patients seen more than once with the same diagnosis date) were discarded using the patient identification code. Consultations of the same patient with a different diagnosis date were considered to be different taeniosis cases. The extracted data included a patient identification code, county of residency, the *Taenia* species diagnosed, date of diagnosis and date of consultation. The majority of the cases recorded in CMBD-AP [22] were recorded as *Taenia* spp. cases. We assumed that all of them were *T. saginata* as this is, among the three species causing human taeniosis (*T. saginata*, *T. asiatica* and *T. solium*), the only species endemic in Europe.

5.3.1.3. Assessment of the economic impact of *T. saginata* in Catalonia

We estimated the financial impact associated with *T.saginata* by taking into account three components: (i) costs for the cattle owners due to condemnation and freezing of carcasses (2012–2015); (ii) costs for the official veterinary authorities due to the implementation of meat inspection associated with bovine cysticercosis (2012–2015); and (iii) costs associated with human taeniosis (data for human cases belonged to the period 2013–2016). The overall annual cost due to *T. saginata* in Catalonia was estimated only for the period 2013–2015 which are the years for which data on both bovine cysticercosis and human taeniosis were available. The different parameters used to estimate the economic impact of *T. saginata* are described in Tables 5-1, 5-2 and explained below.

5.3.1.3.1. Model implementation

The models were run using the mc2d package [23], implemented in R (R Development Core Team 2008) [24]. Monte Carlo simulations (10,000 and 1001 iterations for modelling uncertainty and variability, respectively) were performed and all non-fixed input parameters were included as uncertain or variable parameters.

The parameters for which the experts provided a minimum and maximum value with no further information on whether a value within that range could occur with a higher or lower probability were modelled as a uniform distribution. This kind of distribution is defined by the minimum and maximum values obtained from the experts and, between those limits, a continuous spectrum of values occurs with the same probability. For the only parameter for which experts provided a range of values and also the most likely value (i.e. "time taken by official veterinarians in scenario 3") we used a PERT distribution, which is defined by a minimum, most likely and maximum values. The parameters used as fixed values with no distribution were those parameters for which we obtained a unique fixed value from data providers with no further detail on whether these values could vary or not.

Table 5-1 Parameters used to estimate the economic losses attributable to *T. saginata* in Catalonia

	Parameter	Value	Source
Costs for the cattle owner due to condemnation and freezing of carcasses	No. of types of infection		
	Generalised	4	Personal communication (Catalan Public Health Agency)
	Localised	144	
	No. of positive animals per age group		
	8–12 months	44	Personal communication (Agriculture Department)
	12–24 months	82	
	>24 months	22	
	Average carcass weight (kg) per age (months) category annually		
	2012		[25]
	8–12	232.9	
	12–24	274.9	
	>24	294.1	
	2013		
	8–12	227.0	
	12–24	273.7	
	>24	294.9	
	2014		

Parameter	Value	Source
8–12	230.1	
12–24	278.1	
>24	295.2	
2015		
8–12	225.7	
12–24	283.3	
>24	293.0	
Average weekly carcass price per age category (€/100kg) annually[a]		
2012		[26]
8–12	Normal (μ = 369.1, σ = 4.6)	
12–24	Normal (μ = 385.7 , σ = 9.5)	
>24	Normal (μ = 224.4, σ = 18.9)	
2013		
8–12	Normal (μ = 369.1, σ = 4.6)	
12–24	Normal (μ = 396.7, σ = 5.0)	
>24	Normal (μ = 227.1, σ = 26.5)	
2014		
8–12	Normal (μ = 369.1, σ = 4.6)	
12–24	Normal (μ = 387.2, σ = 17.6)	
>24	Normal (μ = 220.4, σ = 25.7)	
2015		
8–12	Normal (μ = 369.1, σ = 4.6)	
12–24	Normal (μ = 371.8 = , σ = 5.7)	
>24	Normal (μ = 215.6, σ = 21.6)	
Costs of carcass disposal (€/kg)	0.198	Personal communication (rendering company)

	Parameter	Value	Source
	Loss of value of a frozen carcass (%)	Uniform (min = 48, max = 60)	Expert's opinion (five slaughterhouses)
Costs for the official veterinary authorities due to the implementation of meat inspection associated with bovine cysticercosis	Time taken by meat inspection official auxiliaries in scenario 1		
	Seconds spent per animal to detect bovine cysticercosis through routine inspection (i.e. animals coming from farms where positive animals have never been detected)	Uniform (min = 20, max = 55)	Expert's opinion (official veterinary teams)
	Time taken by meat inspection official auxiliaries in scenario 2		
	Seconds spent per animal to detect bovine cysticercosis through detailed inspection (i.e., animals coming from farms where positive animals have been detected at some point in time)	Uniform (min = 110, max = 115)	Expert's opinion (official veterinary teams)
	Time taken by official veterinarians in scenario 2		
	Seconds spent per animal during supervision/inspection of cattle coming from farms where positive animals have been detected at some point in time	Uniform (min = 60, max = 120)	Expert's opinion (official veterinary teams)
	Time taken by official veterinarians in scenario 3		
	Hours spent per animal when a positive animal is detected during post-mortem inspection	PERT (min = 0.5, mode = 1.75, max = 3)	Expert's opinion (official veterinary teams)
	Cost of service of meat inspection official auxiliaries (€/hour)	19	Personal communication (Catalan Public Health Agency)
	Cost of service of official veterinarians (€/hour)	37	Personal communication (Catalan Public Health Agency)
	Cost of anatomo-pathological diagnosis (€/unit) (2012–2015)		
	2012	31	Personal communication (Veterinary Pathology Diagnostic Service, Autonomous University of Barcelona)
	2013	31	
	2014	33.1	
	2015	34.7	
	No. of suspect samples sent for anatomo-pathological examination (2012–2015)		
	2012	31	SESC [24]
	2013	18	

	Parameter	Value	Source
	2014	15	
	2015	14	
Costs associated with human taeniosis	No. of cases with a taeniosis diagnosis in primary care during the period 2013–2016 based on ICD-codes	217	[22]
	No. of medical consultations per patient		
	To primary care	1	Expert’s opinion (medical specialist)
	To a specialist	1	Expert’s opinion (medical specialist)
	Therapeutical options used (%)		
	Niclosamide	60	Unpublished data
	Praziquantel	40	Unpublished data
	Cost of medical consultation (€/unit)		
	Primary care consultation	40	[28]
	Specialist consultation	137	Personal communication (Hospital Clínic de Barcelona)
	Diagnostic tests used (%)		
	Microscopy: concentration techniques for intestinal parasites, helminth eggs and cystic forms	50	See text
	Macroscopy: morphological identification of parasites	50	See text
	Cost of diagnostic test (€/unit)		
	Microscopy: concentration techniques for intestinal parasites, helminth eggs and cystic forms	15.3	[28]
	Macroscopy: morphological identification of parasites	9.8	[28]
	Cost of medical treatment (€/unit)		
	Treatment (niclosamide)	5	Personal communication (AEMPS)
	Treatment (praziquantel)	79.3	Personal communication (AEMPS)
	No. of stool samples tested (per patient)	2	Expert’s opinion (medical specialist)

[a] Carcass price of bovines aged 8–12 months was available only for 2015

Table 5-2 Number of animals inspected (2012–2015)

Year	Scenario 1[a]	Scenario 2[b]
2012	458,042	19,507
2013	462,172	21,066
2014	448,210	22,831
2015	475,487	23,682

[a]Animals coming from farms where positive animals have never been detected
[b]Animals coming from farms where positive animals have been detected at some point in time

5.3.1.3.2. Costs for the cattle owners due to condemnation and freezing of carcasses

This component was calculated as the sum of the cost of all generalised (i.e. condemned carcasses) and localised infections (i.e. frozen carcasses) detected in Catalan slaughterhouses during 2012–2015. The value of the carcasses was estimated based on the average annual carcass weight [25] and the mean weekly carcass price [26] for the different age categories.

Data on the age of the animals were obtained from the Agriculture Department of the Catalan Government. The age of the positive animals was available in just 26% of the cases (38 out of 148). The age of the remaining cases was estimated based on the age distribution of the positive animals detected between 2008 and 2015 for which the age was accessible (167 out of 382). Positive cattle were classified into three age categories (8–12 months; 12–24 months; and > 24 months). The carcass price and weight assigned to each of these categories was based on the market price and weight for various categories (e.g. bovines aged between 8–12 months, uncastrated males of 12–24 months and female bovines that have calved, other female bovines aged over 12 months), which are freely available on the Agriculture Department's website [25, 26]. A normal distribution was used in order to take into account the variability of the weekly carcass price for each age category along the year. The mean and standard deviation were calculated based on the average weekly carcass price for each age category each year.

The price (per unit of weight) of carcass disposal was provided by a rendering company and included as a fixed parameter in the model. The cost of carcass disposal was calculated based on the weight of the condemned carcasses. The cost of transporting condemnations from the slaughterhouse to the rendering plant was not included as condemned carcasses are usually transported with other animal by-products that are regularly collected in slaughterhouses.

The percentage of value loss of the frozen carcasses was provided by five slaughterhouses of the region. The costs of handling, transport to freezing facilities, freezing treatment and the weight loss of the carcass after freezing were included in the percentage value loss, together with the meat depreciation, as stated by the experts from the slaughterhouses providing the information. In order to take into account the variability in the answers around value loss given by the five slaughterhouses, we included this parameter in the model as an uncertain parameter by using a uniform distribution.

In the case of localised infections, during the entire period (2012–2015), there was only one carcass part condemned (partial condemnation). As details on the weight, size and value of this part were not available, this was not included in the cost estimate. A total of 31 heads and 116 hearts were also condemned. For comparison with other studies, the losses due to rejected offal, heads and hearts were not included in our overall economic burden analysis.

The cost due to condemnation and freezing of carcasses was calculated as follows for each year:

$$CO = \sum_j GI_j * \left(CC_j + CCD_j\right) + \sum_j LI_j * \ CC_j * LV$$

where *CO* is the cost for the cattle owners; *j* is the indicator of the age category (i.e. 8–12 months; 12–24 months and >24 months); *GI* is the number of generalised infections for each “j” age category; *CC* is the value of the carcass for each “j” age category; *CCD* is the cost of carcass disposal for each “j” age category; *LI* is the number of localised infections for each “j” age category; *LV* is the percentage of loss of value of the frozen carcass.

5.3.1.3.3. Costs for the official veterinary authorities due to the implementation of meat inspection associated with bovine cysticercosis

The costs of meat inspection associated with bovine cysticercosis were calculated taking into account three different scenarios: (i) routine inspection: animals coming from farms where positive animals have never been detected (referred to as scenario 1); (ii) detailed inspection: animals coming from farms where positive animals have been detected at some point in time (referred to as scenario 2); and (iii) detection of a positive case (referred to as scenario 3). In scenario 1, routine meat inspection is conducted by meat inspection official auxiliaries. In scenario 2, official veterinarians also intervene either by supervising meat inspection or conducting meat inspection themselves. Carcasses and predilection sites are inspected more carefully, and extra slicing of the heart is performed resulting in a longer period of time dedicated per animal. In scenario 3, the official veterinarian dedicates time to different activities such as carefully examining the carcass, taking samples to send for confirmatory diagnosis, retaining and sending the carcass to be frozen, preparing official documentation or verifying that the carcass has been frozen.

Time dedicated to meat inspection in the different scenarios was collected from official veterinary teams from three of the biggest cattle slaughterhouses in Catalonia (accounting for 60% of the total number of slaughtered animals). Specifically, we collected information on the time dedicated to the inspection of the heart, masticatory muscles, diaphragm, oesophagus, carcass and tongue per animal inspected. The uncertainty around these times provided by the different veterinary teams was taken into account by using uniform distributions (scenarios 1 and 2). In scenario 3 experts provided a minimum, most likely and maximum value for the time dedicated; a PERT distribution was therefore used.

The cost of the official auxiliary and official veterinary services per hour was provided by the Catalan Public Health Agency. The number of animals coming from farms where positive animals have been detected at some point in time were estimated based on number of animals that these farms send to Catalan slaughterhouses in a year. These data were extracted from cattle movement records provided by the Agriculture Department of the Catalan Government.

The number of suspect samples sent for confirmation was provided by the Catalan Slaughterhouse Support Network [27]. The price of one anatomo-pathological exam was obtained from the Veterinary Pathology Diagnostic Service from the Autonomous University of Barcelona.

The cost attributed to meat inspection was calculated as follows:

$$MI_j = \ TA_j * CTA * AN_j \ + TOV_j * CTOV * AN_j \ + \ \mathrm{SS} * \mathrm{DG}$$

where j is the indicator of the scenario (1 to 3); TA is the time dedicated to meat inspection associated to bovine cysticercosis by meat inspector official auxiliaries in each "j" scenario per animal (for official auxiliaries only scenario 1 and 2 were considered); *CTA* is the cost of the meat inspector official auxiliaries service by unit of time; *AN* is the number of animals inspected in each "j" scenario; *TOV* is the time dedicated to meat inspection associated to bovine cysticercosis by official veterinarians in each "j" scenario per animal (for official veterinarians only scenario 2 and 3 were considered); *CTOV* is the cost of the official veterinary service by unit of time; *SS* is the number of bovine cysticercosis suspect samples sent for confirmatory diagnosis; *DG* is the cost of anatomo-pathological diagnosis.

5.3.1.3.4. Costs associated with human taeniosis

Human taeniosis-associated costs were estimated using the number of cases diagnosed with taeniosis during 2013–2016 (i.e. ICD-9-CM Codes 123.2: "*Taenia saginata* infection"; 123.3: "Taeniasis, unspecified") retrieved from the CMBD-AP [22]. Additionally, the following assumptions were made: (i) each patient consulted a primary care physician and a specialist, once each; (ii) for each patient 2 stool samples were tested; (iii) 50% of the samples were tested through macroscopic examination and 50% through microscopy (the proportion of cases in which proglottids are found is unknown therefore it was assumed that in half of the cases proglottids would be available for macroscopic examination); (iv) all patients were treated; (v) patients were treated only once; and (vi) 60% of the cases were treated with niclosamide and 40% with praziquantel. These last data were obtained from a questionnaire sent to seven hospital pharmacies of Catalonia in which the most frequent therapeutic option used to treat taeniosis was asked (unpublished data).

The costs of a medical consultation to primary care and to a specialist were obtained from the Catalan Health Service [28] and the Clinic Hospital of Barcelona (personal communication), respectively. The cost of the diagnostic tests was obtained from the Catalan Health Service [28]. The price of niclosamide and praziquantel was made available from the AEMPS (personal communication).

Accordingly, the cost associated with human taeniosis (HT) was calculated as follows:

$$HT = NC * (CVP + CVE + DGI + DGA) + 0.6 * NC * CN + 0.4 * NC * CP$$

where *NC* is the number of cases; *CVP* is the cost of a medical consultation by a primary care doctor; *CVE* is the cost of a medical consultation by a specialist; *DGI* is the cost of the microscopic parasitological examination; *DGA* is the cost of the macroscopic parasitological examination; *CN* is the cost of niclosamide; *CP* is the cost of praziquantel.

5.3.1.3.5. Costs not considered in our analysis

Other specific costs not considered in our analysis include outbreak investigations, measures taken at farm level (i.e. changing filters in the water supply system or parasitological controls of farm staff), training for meat inspectors, research projects, costs associated with transport to obtain diagnosis and treatment or opportunity costs associated with obtaining healthcare. Complications associated to *T. saginata* taeniosis such as appendicitis or gastrointestinal perforations have been described occasionally [29]. As these conditions are very rare any possible costs related to them (e.g. hospitalisation) have not been considered in the analysis.

5.4. Results

5.4.1. Bovine cases

5.4.1.1. Prevalence of bovine cysticercosis in cattle slaughtered in Catalonia between 2008 and 2015

The number of positive animals detected in Catalan slaughterhouses between 2008 and 2015 is shown in Table 5-3. The apparent prevalence detected at slaughterhouse was low (0.010%) and ranged between 0.004–0.022%. Taking into account the low sensitivity of meat inspection the true prevalence was estimated at 0.037%, ranging between 0.014–0.080%.

Table 5-3 Cattle diagnosed by meat inspection with bovine cysticercosis in slaughterhouses in Catalonia (2008–2015)

Year	Positive animals	Animals slaughtered in Catalonia	Apparent prevalence (%)	True prevalence (%)
2008	107	492,678	0.022	0.080
2009	62	473,842	0.013	0.048
2010	40	480,685	0.008	0.031
2011	25	477,388	0.005	0.019
2012	67	477,549	0.014	0.052
2013	18	483,238	0.004	0.014
2014	19	471,041	0.004	0.015
2015	44	499,169	0.009	0.033
Total	382	3,855,590	0.010	0.037

5.4.1.2. Prevalence and spatial distribution of bovine cysticercosis most likely acquired in Catalonia between 2008 and 2015

5.4.1.2.1. Farm where cattle most likely became infected

Movement history could be retrieved and analysed for 167 cattle, out of a total of 382 meat inspection positives, for which individual identification was available. Based on the probability with which each positive animal acquired the infection on each location of their movement history, 53% (i.e. 88 out of 167) most likely became infected in

Catalonia. Out of these, the infection was certainly acquired on a Catalan farm in 21 cattle (13% of the positives) as they never left Catalonia.

In 47% of the cases (79 out of 167) the infection was most likely acquired outside the study area, and 62 out of these (37%) definitely acquired the infection outside as they came to Catalonia only to be slaughtered. Out of the 79 animals that would have acquired the infection outside, in 63 cases the infection would have taken place in other parts of Spain, in 10 cases in other EU countries (1 in Belgium, 8 in France and 1 in Romania) and for 6 the location of the case farm was unknown.

The 88 animals that most likely acquired the infection in Catalonia had been on average on two farms in Catalonia during their lifetime (range of 1–4 farms). The average time that each animal spent on each farm was highly variable depending on the type of farm. While in assembly centres the animals stayed on average 3 days, in production farms they stayed on average 419 days (median of 247 days and a range of 3–4955 days). Of note, in 84% of these cases (74 out of 88 animals) the farm identified as the most likely place of infection was also the last farm sending the animals to slaughter.

Information on the number of times that a farm sent at least one positive animal for slaughter was available for 311 out of the total 382 positive cattle detected. During 2008–2015 the majority (88%) of the farms sending at least one positive animal to slaughter sent positive animals only once, 11% of the farms sent positive batches between 2 and 3 times, and one farm sent positive animals on eight different occasions.

5.4.1.2.2. Prevalence of bovine cysticercosis in cattle coming from Catalan farms and that were most likely infected in Catalonia

When taking into account only cattle that did not come from farms located outside Catalonia and the cases that had been most likely infected in this area, the apparent prevalence of bovine cysticercosis by meat inspection between 2008 and 2015 was 0.007% and ranged between 0.003–0.015% (Table 5-4). The calculated true prevalence was 0.025% (range of 0.009–0.054%).

Table 5-4 Cattle diagnosed by meat inspection with bovine cysticercosis that were most likely infected in Catalonia (2008–2015)

Year	Animals infected in Catalonia	Slaughtered animals coming from Catalan herds	Apparent prevalence (%)	True prevalence (%)
2008	54	364,582	0.015	0.054
2009	31	350,643	0.009	0.033
2010	20	355,707	0.006	0.021
2011	13	353,267	0.004	0.013
2012	34	353,386	0.009	0.035
2013	9	357,596	0.003	0.009
2014	10	348,570	0.003	0.010
2015	22	369,385	0.006	0.022
Total	191	2,853,137	0.007	0.025

5.4.1.2.3. Spatial distribution of bovine cysticercosis in Catalonian farms

The spatial analysis identified two significant clusters of bovine cysticercosis (Figure 5-1). The largest cluster was located in the north-east of Catalonia and had a radius of 5.74 km and a relative risk (RR) of 12.8. It comprised 52 farms and had eight observed case farms vs 0.70 expected. The case farms were 7 fattening herds and one beef breeding herd and involved 22 positive animals (1–6 per farm). The mean age of the infected cattle (unknown in two cases) was 1.2 years (range of 9.3 months to 3.3 years). These positive cattle had been detected at slaughter at different points in time from the end of 2008 until the end of 2011 (11 cases at the end of 2008, 5 at the beginning of 2010 and 6 from mid to end of 2011). One of these farms had also sent two positive animals to the slaughterhouse 1.5 years before (May 2007). One other farm also sent positive animals on 3 different occasions during 2007. However, these cases were not included in the spatial analysis as the study period included only cases from 2008 to 2015.

A second cluster, located in the west of the study area, had a radius of 0.17 km and a RR of 58.2. It involved four herds (3 cases *vs* 0.054 expected). All three case farms were dedicated to fattening. The total number of positive animals was three (one per farm) and had been detected at different points in time from the beginning of 2008 to mid-2009. The age of the infected cattle (unknown in one case) was around one year-old.

Figure 5-1 Spatial distribution of significant high rate clusters of bovine cysticercosis identified using a Bernoulli model with a maximum scanning window of 50% of the population at risk (2008–2015). Triangles, case farms; circle, first cluster; arrow, second cluster

5.4.2. Human cases

Table 5-5 Number of patients attending primary care with diagnosis of taeniosis (2013–2016) and number of taeniosis cases treated with niclosamide and praziquantel (2015–2016) in Catalonia

Year	Taeniosis cases seen at primary healthcare			Taeniosis cases treated with niclosamide or praziquantel		
	T. saginata	***Taenia* spp.**	**Total**	**Niclosamide**	**Praziquantel**	**Total**
2013	2	39	41	na	na	na
2014	0	63	63	na	na	na
2015	1	61	62	6	16	22
2016	0	51	51	9	10	19
Total	3	214	217	15	26	41

Abbreviation: na, not available

The number of patients treated for taeniosis in Catalonia (using either niclosamide or praziquantel) was 22 in 2015 and 19 in 2016 (Table 5-5). Based on the consultations recorded in the CMBD-AP database the number of cases attending primary healthcare diagnosed with taeniosis during 2013–2016 was 217 (41–63 /year) (Table 5-5).

5.4.3. Assessment of the economic impact of *T. saginata* in Catalonia

The overall annual mean economic impact of *T. saginata* in Catalonia during the period 2013–2015 amounted to 154,903 € (95% CI: 113,075–196,762 €). The costs of the different components during the period 2013–2015 are shown in Figure 5-2. The major contribution was attributed to the surveillance of bovine cysticercosis at the slaughterhouse as it accounted for 81.9% (95% CI: 75.8–86.2%) of the total costs. The cost for the beef sector due to condemnation and freezing of carcasses was responsible for 9.4% (95% CI: 6.9–12.8%) while the costs associated to human taeniosis accounted for 8.7% (95% CI: 6.7–11.6%) of the total economic impact.

The cost of meat inspection targeting bovine cysticercosis (2012–2015) (mean of 127,566 €/year, 95% CI: 85,818–169,203) (Table 5-6) was estimated at 0.2 € (95% CI: 0.1–0.3 €) per animal inspected through routine meat inspection, at 1.5 € (95% CI: 1.2–1.8 €) per animal inspected through a detailed meat inspection (originating from farms that have sent positive animals to slaughter at some point in time), and at 99 € (95% CI: 66.3–131.5 €) for the procedures following the detection of a positive.

The cost due to condemnation and freezing of carcasses (2012–2015), reached a mean of 19,442 €/year (95% CI: 17,528–21,391) (Table 5-7). Costs due to lightly infected carcasses amounted to 18,301 €/year (95% CI: 16,388–20,250), corresponding to 509 € (95% CI: 455–563 €) per lightly infected carcass. Costs due to heavily infected carcasses (including value loss and disposal cost) were estimated at 1140 €/year (95% CI: 1089–1191), which corresponded to 1140 € (95% CI: 1089–1193 €) per heavily infected carcass; the disposal costs amounted only to 52.2 €/carcass. Considering average prices provided by experts, the value of rejected heads (31) and hearts (116) during the study period amounted to just 358 € (95% CI: 347–369 €).

The costs associated to taeniosis were estimated at 12,848.5 €/year corresponding to 236.8 € per patient (25.1 € for diagnosis, 177 € for medical consultations and 34.7 € for treatment).

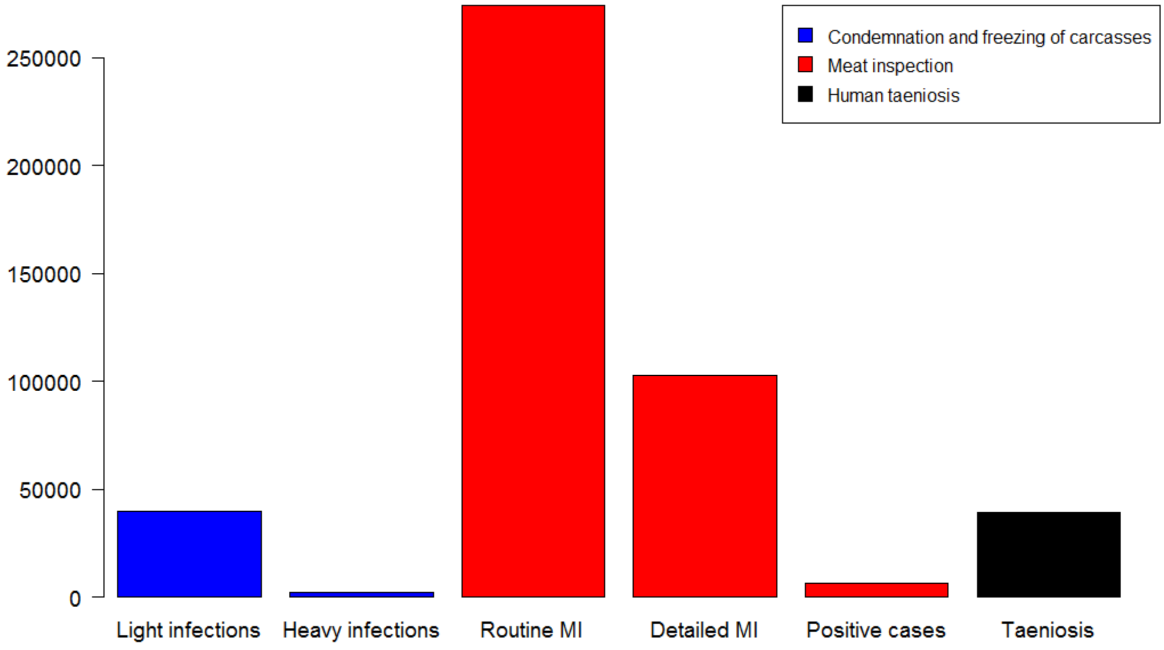

Figure 5-2 Average costs (€) of the different components associated to *T. saginata* during the period 2013–2015. Abbreviations: MI, meat inspection

Table 5-6 Costs (€) for the Official Veterinary services due to meat inspection targeting bovine cysticercosis

Year	MI, routine		MI, detailed		MI, detection of positive carcasses	
	Mean	**95% CI**	**Mean**	**95% CI**	**Mean**	**95% CI**
2012	90,903	50,658–130,827	29,624	23,916–35,350	5323	3129–7524
2013	91,723	51,115–132,007	31,992	25,827–38,176	1744	1155–2335
2014	88,952	49,571–128,019	34,672	27,991–41,374	1711	1089–2335
2015	94,365	52,587–135,810	35,965	29,035–42,916	3290	1849–4735

Abbreviation: MI, meat inspection, CI, confidence interval

Table 5-7 Costs (€) for the beef sector due to freezing and condemnation of infected carcasses

Year	Generalised infections (value loss and disposal costs)		Localised infections (value loss)	
	Mean	95% CI	Mean	95% CI
2012	1996	1937–2058	33,161	29,694–36,692
2013	0	0	9261	8293–10,247
2014	2565	2363–2747	8715	7804–9643
2015	0	0	22,068	19,761–24,418

5.5. Discussion

Previous research conducted on *T. saginata* in north-eastern Spain (Catalonia) [14, 30] focussed only on bovine cysticercosis; the current study therefore provides a more complete picture of the burden of the *T. saginata* taeniosis/bovine cysticercosis complex in this region. This approach is in line with the One Health concept (http://www.onehealthinitiative.com) which promotes an interdisciplinary approach to tackle diseases. Previous research [30] found a seroprevalence of bovine cysticercosis using an antigen ELISA about 50 times higher than the prevalence obtained by visual inspection. However, the public health risk derived from not detecting all the infected carcasses was unclear due to the lack of available data on human taeniosis at that moment. The results of this study suggest that the public health risk might be low as the number of taeniosis cases diagnosed in primary care ranged between just 41 and 63 per year. Surprisingly, the number of taeniosis cases estimated from the supply of niclosamide and praziquantel was even lower (19–22/year). In Spain these drugs cannot be supplied and have to be requested through the Spanish Medicines Agency and prescribed by a specialist. Therefore the number of niclosamide and praziquantel treatments requested and supplied to treat taeniosis could be indicative of the number of taeniosis cases. The difference between the number of cases diagnosed and treated could be due to the use of a different anthelmintic despite the fact that niclosamide and praziquantel are the most frequently used drugs to treat taeniosis [31–33]. The main strength of using the CMBD-AP dataset [22] to retrieve the number of taeniosis cases is the fact that it is an exhaustive compilation of all the primary care activity provided by the Catalan Health System which covers a population of around 7,500,000 [34]. One limitation is the fact that taeniosis is not a notifiable disease and it could be possible that not all taeniosis cases were properly registered. The results of our study contrast with what has been reported in other countries. For example, in Belgium, around 11,000 taeniosis cases have been estimated to occur annually [35]. These differences in the human health impact might be related to differences in the prevalence of bovine cysticercosis. Indeed, in 2013, Belgium reported a prevalence in cattle of 0.12% [36] whereas in Catalonia it was much lower (i.e. 0.004%). Such differences could be partially attributed to different culinary habits, production systems and climate. Risk factors for bovine cysticercosis infection that have been reported include having access to pastures, to risky water sources or to contaminated feed [9]. In Catalonia, most of the animals are kept indoors and therefore, they may be less exposed to *T. saginata* eggs in the environment. In addition, annual precipitation in Catalonia is lower than in countries like Belgium, which may lead to a shorter egg survival time. In our study, it was not known whether the taeniosis cases were acquired from infected animals not detected at meat inspection or imported from elsewhere in Spain or abroad. The place where the taeniosis infection is acquired is normally unknown. Consequently, it is difficult to know if this also plays an important role in the difference between taeniosis prevalence estimated in different countries.

Reported prevalences of bovine cysticercosis are usually based on meat inspection and it is rarely specified whether the cases are autochthonous or not [37]. Our results indicated that half of the affected animals most likely acquired the infection outside the study area. Therefore the true prevalence of bovine cysticercosis in Catalonia, based on cattle not coming from farms outside Catalonia and on the cases that most likely acquired the infection in Catalonia, would be slightly lower (around 0.025% between 2008–2015) than the true prevalence based on all the cases detected in all cattle slaughtered in Catalan slaughterhouses (around 0.037%). Despite some limitations (i.e. movement history not being accessible for all positive cases) the spatial analysis identified two areas with a higher risk of infection taking into account the farm where cattle most likely became infected. The presence of disease clusters has also been reported in studies performed in France and Italy [17, 37]. Disease clusters could be explained by an epidemiological link between farms. Unfortunately, we did not have results of any epidemiological investigation. Other factors involved could be a higher risk of exposure to *T. saginata* eggs through pastures, water or feed in these areas or direct contamination from human tapeworm carriers (e.g. farm workers). Furthermore, research in these areas might be desirable in order to elucidate the chain of infection and try to adopt preventive measures to reduce the risk of infection.

Recent publications highlight the usefulness of implementing risk-based surveillance in areas with low prevalence of bovine cysticercosis [18, 38, 39]. It has been proposed that information on risk factors (e.g. grazing practices in the herd, location of the herd or gender) could be provided, as food chain information, by the farmer prior to slaughter [40], to identify high- and low-risk herds (or animals) [39, 41]. Our results showed that in the majority of the cases, similar to that observed by Dupuy et al. [17] in France, the infection occurred on the last farm before slaughter, but in some cases the infection could have occurred on a different farm. Therefore, the fact that not all animals may become infected on the last farm should be taken into account if a risk-based surveillance is to be implemented in the future. In line with this, based on a study conducted in the UK, Marshall et al. [42] also concluded that cattle movement history could be used to support a more targeted meat inspection strategy.

The assessment of the economic impact revealed that the highest cost associated with *T. saginata* was due to meat inspection (82% of the cost). In Catalonia, a detailed meat inspection of animals originating from farms that have sent positive animals to slaughter at some point in time is performed. The total cost incurred by routine meat inspection (i.e. inspection of animals originating from farms that have not previously sent positive animals to slaughter) was higher than the detailed meat inspection. However, the cost per animal was higher for detailed meat inspection (1.5 €) than for routine meat inspection (0.20 €). Taking into account that most farms sent positive animals to slaughter only once, and that the infection seems not to always occur on the last farm prior to slaughter, not performing detailed meat inspection in the way it is currently performed could reduce the economic cost without losing sensitivity on the surveillance of the disease.

Calculating the costs of meat inspection associated with bovine cysticercosis was challenging. This was due to the fact that the meat inspectors also perform procedures targeting other diseases (e.g. tuberculosis) [5]. To address this, we asked for the time dedicated exclusively to searching and applying sanitary measures related to bovine cysticercosis, but obviously the uncertainty around this estimate is high. Despite that, the time dedicated to routine meat inspection addressing bovine cysticercosis was very similar to what has been found in a similar study performed in Belgium [35].

Overall, the annual costs for the bovine meat sector in Catalonia due to *T. saginata* were not high compared to the revenue generated by the Catalan beef sector (e.g. revenue generated by 124,500 tons of beef that were produced in 2015) [43]. Compared to the costs estimated in other countries (437,730 € in 2016 in mainland France [44] and 3,579,335 €/year in Belgium [35]), the costs in Catalonia were much lower. Nevertheless, these figures are not directly comparable as they are influenced by the prevalence and number of animals slaughtered. In the case of Belgium, costs also included an insurance paid to cover the losses due to bovine cysticercosis that does not exist in Catalonia. Without including insurance costs, the costs per carcass (including value loss and disposal costs) were similar: 509 € and 1140 € per lightly and heavily infected carcasses, respectively, in Catalonia, *versus* an average of 586 € and 998 € per lightly and heavily infected carcasses, respectively, in Belgium [35]. These recent estimates are higher than costs estimated in earlier studies. According to Murrell (1991) [10] losses in industrialised countries amounted to 234 US$ per infected carcass and in England they reached up to £100 per infected carcass [11]. However, caution should be taken when comparing costs between countries and years due to differences in price levels or differences in factors included in the analysis.

In the present study we might have underestimated some costs for the meat sector. For example, the preventive immobilization of a suspect case, until laboratorial results are available, may incur losses for commercial reasons that are difficult to quantify. Additionally, according to experts, when a carcass is frozen it is difficult to find a client willing to buy it and there might be the need to leave it in a freezing room for up to several months. If the carcass cannot be sold, the majority of it will be used for meat preparations (e.g. burgers) resulting in extra costs due to processing.

The costs associated with taeniosis were estimated at 236.8 € per patient, including medical consultation, diagnosis and treatment. In Belgium, these costs were lower ranging between 6.29 € and 72.4 € per patient depending on whether patients consulted a physician or not [35]. In our study, the costs were estimated based on the patients consulting primary care but the number of cases could be underreported as it is not a notifiable disease. In the USA, older estimates of treatment costs (111 US$/patient) [10] were higher than in the present study (34.7 €/patient), but it is not specified whether medical consultations and diagnosis were accounted for in these estimates.

Our estimates of the taeniosis-associated costs are only approximate due to several limitations. When estimating this component we assumed that all the taeniosis cases registered in the CMBD-AP had been treated with praziquantel or niclosamide. However according to the AEMPS the number of cases treated with these drugs per year was lower. It could be possible that an extra 30–40 cases/year diagnosed but not treated with these anthelmintics were treated with another treatment regime. However, we do not know which other treatment could have been used, the number of doses prescribed or the price of this other therapy. Additionally, it could also be possible that some of the extra cases registered in the CMBD-AP were recorded as taeniosis cases as a result of miscoding. These types of errors have been reported to occur when using ICD coding systems. In the same way, it might have been possible that some taeniosis cases had not been registered as such in the database, especially when it is not a notifiable disease. Overall we believe that these limitations do not have a major impact on the results due to the very low number of cases being diagnosed each year.

5.6. Conclusions

Through this study we believe to provide a relatively complete picture of the *T. saginata* taeniosis/bovine cysticercosis disease complex in north-eastern Spain. The public health risk derived from failing to detect every bovine cysticercosis infected carcass seems to be low in the area of study as there were a very low number of taeniosis cases. The economic impact associated with *T. saginata* was mainly attributed to meat inspection and borne by the public veterinary services. The cost for the beef sector was much lower and relatively limited compared to the revenue generated by the sector. The cost for the public veterinary services might be reduced through some changes in the surveillance of this disease and further efforts in this direction might be desirable. Possible changes could include the suppression of the detailed meat inspection and the development of a risk-based surveillance strategy. The identification of the most likely farm where cattle became infected shows that animal movements need to be taken into account in the development of such strategy.

5.7. Authors' contributions

MLG, BD, FJ, PD, CD and AA (members of the CYSTINET task force on the economic impact of *T. saginata* in Europe) designed a methodological protocol to assess the economic impact of the disease applicable to other European countries. All of them discussed the methods used and the preliminary results of the analysis. AR contributed to information and data collection. MLG and AA designed the study, collected and analysed data. MLG performed the definitive data analysis and drafted the first version of the manuscript. All authors contributed to interpretation of results and provided inputs in writing the final manuscript. All authors read and approved the final manuscript.

5.8. Acknowledgments

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5.9. Ethical approval

Data on human cases were obtained from a database (CMBD-AP) held by the Health Department of the Catalan Government. Researchers can request data from CMBD-AP by filling and signing a form in which a signed Confidentiality Commitment is required. Data provided to researchers is anonymised. For these reasons, this study did not need individual ethics approval.

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6. General Discussion

The motivation for performing the two first studies of this PhD was the fact that the available data of *Taenia* spp. in Europe was insufficient to give a correct idea about the epidemiology and impact of these zoonoses (SCVMPH, 2000; Cabaret et al., 2002; Dorny and Praet, 2007). Based on a survey among European Union (EU) Member States (MSs) conducted in 2010, for more than a third of the countries data on bovine and porcine cysticercosis were lacking (Dorny et al., 2010). In the EU, following Directive 2003/99/EC, MSs must collect relevant data on zoonoses and zoonotic agents and assess trends and sources of these agents. This information has to be submitted yearly to the European Commission (EC) and is made available to the public in an annual report prepared by EFSA and ECDC. In the case of animal cysticercosis, which is included in the Part B of Annex I of Directive 2003/99/EC (under the term "cysticercosis and agents thereof"), monitoring should be done if the epidemiological situation requires so. However, very few countries submit data on bovine or porcine cysticercosis.

In the case of swine, porcine cysticercosis (infection due to *T. solium*) is included in the World Organisation for Animal Health (OIE) list of notifiable diseases and therefore the disease has to be notified. Despite this, and concerning European countries, not all of them report data on porcine cysticercosis and those that do report information normally do it based on morphology, without molecular confirmation. As a matter of fact, Spain reported around 330 cases of porcine cysticercosis to the OIE between 2005 and 2014, but most likely they were *T. hydatigena* and not *T. solium* (Devleesschauwer et al., 2017). The fact that cases are officially reported to the OIE without having been confirmed is worrying and indicates that the surveillance and reporting systems for this parasite are not adequate. Likewise, nearly all the data on porcine cysticercosis generated in study II of the thesis were not recorded at species level. Noteworthy, although such data mostly resulted from findings during official meat inspection at the slaughterhouse, these were retrieved from grey literature and contact with experts as they are not made available at a European level (i.e. reported to the EC and EFSA). The fact that information on the epidemiological situation of *T. solium* in pigs is not reported at a European level is probably due to the assumption that the disease is not present in western Europe and consequently little or no attention has been paid to its surveillance (SCVMPH, 2000).

The lack of a correct surveillance of porcine cysticercosis in western Europe suggests therefore a lack of awareness of the public health risk posed by this parasite. It might be desirable to devote more efforts to the surveillance of this parasite especially in areas with extensive pig rearing conditions. Increased awareness of this zoonosis and better training of meat inspectors and veterinarians working in the slaughterhouse is recommended. In addition, porcine cysticercosis cases should be confirmed by molecular methods. Nevertheless, the current surveillance system is already limited by the fact that the sensitivity of meat inspection to detect porcine cysticercosis, unless there is a heavy infection, is low (estimated at 0.221 by Dorny et al., 2004).

In a ranking of parasitic diseases developed by the Food and Agriculture Organization of the United Nations (FAO), *T. solium* cysticercosis was ranked first -as the most important food-borne parasite globally- due to the health impact of human neurocysticercosis-related epilepsy (FAO/WHO, 2014). More recently, *T. solium* was also included in a ranking of food-borne parasites at a European level and ranked as the 10th most relevant food-borne parasite in Europe (Bouwknegt et al., 2018). The difference between the importance given to *T. solium* globally and in Europe lies on the fact that *T. solium* is considered virtually absent in this region. The life cycle of *T. solium* is maintained in areas with low sanitation standards and where pigs can have access to human contaminated faeces (i.e. pigs roam free and open-air defecation takes place). In consequence, *T. solium* taeniosis/cysticercosis zoonotic complex is mainly a problem in rural communities of sub-Saharan Africa, Asia and Latin America. In Europe, it is believed that *T. solium* has been eliminated due to an improvement of the pig rearing conditions and sanitation conditions (Del Brutto, 2012) but, large uncertainties do exist about these statements (Devleesschauwer et al., 2017). Indeed, in study II of this PhD it was evidenced that in western Europe there are reports of *T. solium* tapeworm carriers and of human cysticercosis cases that are suspected to be autochthonous (i.e. acquired locally in western European countries). Moreover, two confirmed cases of porcine cysticercosis (caused by *T. solium*) were also identified. Nevertheless, the evidence made available in this study was insufficient to completely understand the epidemiological situation of *T. solium* in western Europe.

The identification of *T. solium* in pigs would be indicative of *T. solium* full cycle transmission. As suggested in study II, the fact that two confirmed cases of *T. solium* porcine cysticercosis were identified in two different places in Portugal would support the hypothesis that there might still be certain areas in western Europe with favourable conditions for local *T. solium* transmission. Nevertheless, these could be two isolated cases in specific rural areas where pigs have been exposed to risk factors for *T. solium* porcine cysticercosis (e.g. open-air defecation and backyard or other outdoor farming systems).

In the EU, an increasing number of neurocysticercosis cases are being diagnosed (Del Brutto, 2012; Fabiani and Bruschi, 2013; Zammarchi et al., 2013). As indicated in study II, a high proportion of the human cysticercosis cases that have been described in western Europe appeared to be linked to immigration, travels or stays in endemic areas. Nevertheless, few suspected autochthonous cases of human cysticercosis (i.e. acquired locally) were also identified. The available information was insufficient to determine the time and source of infection but a number of suspected autochthonous cases of human cysticercosis could have become infected in the past and diagnosed years later as suggested by Zammarchi et al. (2013). These cases could have acquired the infection in certain rural areas where *T. solium* full cycle transmission still occurred and become infected via *T. solium* carriers that acquired taeniosis through local consumption of infected pork. Nevertheless, autochthonous cases may also be the result of an infection from a *T. solium* tapeworm carrier originating from an endemic region. The evidence made available in study II was insufficient to determine whether *T. solium* human-to-human transmission from imported tapeworm carriers might be taking place in western Europe.

T. solium tapeworm carriers arriving from endemic countries to a virtually free country (e.g. migrant workers, asylum seekers, international travellers) may transmit the infection to humans but also to pigs (SCVMPH, 2000). The risk of *T. solium* infection in pigs is probably very low in intensive pig farming but the risk might be slightly higher in extensive pig production systems. Currently, the establishment of *T. solium* full life cycle in western European countries seems unlikely provided that the majority of the pigs in this region are raised under controlled housing conditions (i.e. with no access to environment contaminated with human faeces) and due to improved sanitation (Gabriël et al., 2015). Furthermore, although the true number of *T. solium* carriers in western Europe is unknown (as evidenced in study II) we could think that the probability that a *T. solium* tapeworm carrier contaminates a farm where pigs are raised outdoor is not high. Nevertheless, due to increasing immigration with possible entrance of *T. solium* tapeworm carriers from endemic areas (e.g. immigrants, asylum seekers) and growing trend towards outdoor pig production (e.g. organic pig farming) (Gabriël et al., 2015; Park et al., 2017) the epidemiological situation of *T. solium* in Europe could change.

In this context, it would be desirable to make human cysticercosis a notifiable disease and develop a register of human cysticercosis cases. Such system could serve as an early warning system for re-emergence of *T. solium* in Europe while contributing to the awareness of this disease of both medical and veterinary sectors.

With respect to bovine cysticercosis, the disease is no longer included in the OIE list which suggests that the interest in this parasitosis might have been lowered. At a European level, as previously mentioned, monitoring of the disease should be done depending on the epidemiological situation. The results obtained through the two first studies of this thesis have evidenced that prevalence data of bovine cysticercosis in Europe are still scarce and of low quality, which is particularly notable in eastern countries. This fact raises questions about the capacity of the country to assess their epidemiological situation and the quality of the surveillance system.

A number of factors could explain the scarcity of readily available data on bovine cysticercosis at a European level. On one hand, in some cases the surveillance system for bovine cysticercosis might be deficient. This could be the result of a lack of interest in the disease (due to low public health impact) and/or a lack of meat inspectors with sufficient experience and/or training to detect this particular disease combined with the extremely low sensitivity of routine meat inspection. On the other hand, the system might be adequate but findings during official meat inspections may be recorded and kept at a lower level (e.g. slaughterhouse level or even regional or national level) and not made public or reported at a European level.

Concerning human taeniosis, data on occurrence are very scarce and when available, such data are usually only indicative (Cabaret et al., 2002; Dorny and Praet, 2007). Study II has advanced the knowledge on the epidemiology of taeniosis in western Europe. However, it has shown that the amount and quality of evidence are still limited (e.g. the lack of notification most likely leads to underestimated and fragmented data, species differentiation is often not performed and/or diagnostic methods are often not clearly defined). The improvement of the surveillance and reporting systems for taeniosis cases might be the cornerstone to improve data quality but the low impact on public health of *T. saginata* (ignoring the psychological stress caused due to an infestation by this parasite) might hinder its improvement.

In this PhD we were also able to provide estimates of the economic impact of the *T. saginata* taeniosis/cysticercosis complex in Catalonia. In Europe, there was hardly any knowledge on the economic impact of bovine cysticercosis, as evidenced in study I of this thesis. In the case of Catalonia, based on the estimates generated in study III the losses for the beef sector seemed not to be high compared to the revenue generated by the sector. The largest proportion of the total economic impact of *T. saginata* in Catalonia was incurred by meat inspection activities. Overall, the results of study III suggested that current costs attributed to bovine cysticercosis in Catalonia could be lowered by implementing changes in the current approach of meat inspection for bovine cysticercosis. Based on this, future research could be targeted at designing a more cost-effective surveillance and control strategy. Currently in the EU meat inspection is undergoing a modernisation process and the application of visual-only inspection (omitting incisions and palpations) in cattle is expected in the future (Blagojevic et al., 2017). The sensitivity to detect bovine cysticercosis with this new approach is expected to be even lower (EFSA, 2013). At the same time, latest studies highlight that the resources invested in controlling the disease might not be proportionate to the risk that this parasite poses and advocate for the implementation of risk-based approaches. In this context, to be able to apply a risk-based surveillance and control approach and to evaluate new strategies to control the disease, acquiring good epidemiological data is essential. However, as concluded in study I, current available epidemiological data in Europe are limited to guide this approach. In this regard, summarising all the available evidence on the epidemiology of this zoonosis in European countries (as has been done in the first two studies of this thesis) might have partially covered this gap, and have contributed to understanding its epidemiological situation. Nevertheless, implementing specific studies in the country to explore different risk-based meat inspection activities (e.g. see Chengat Prakashbabu et al., 2018 and Calvo-Artavia et al., 2013) is desirable.

Performing economic studies in order to take also into account the cost-effectiveness ratio is also highly relevant (Jansen et al., 2018).

6.1. References

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7. General Conclusions

1. Epidemiological data about bovine cysticercosis in Europe are scarce and of low quality. This lack of information is a limitation to guide the development of risk-based surveillance strategies against this disease.

2. In western Europe, the existence of *T. solium* tapeworm carriers, combined with the presence of suspected autochthonous cases of human cysticercosis, the lack of confirmation of porcine cysticercosis cases and the rise of migration from endemic countries may be a public health risk that deserves further attention.

3. Species identification of taeniosis cases together with epidemiological investigations of human cysticercosis cases to detect whether local transmission of *T. solium* might have occurred in western Europe should be encouraged. Furthermore, suspected cases of *T. solium* in pigs should be confirmed by molecular methods.

4. The absence of systematic data collection and reporting on both taeniosis and human cysticercosis makes it very difficult to have an accurate evaluation of the public health risk driven by *T. saginata* and *T. solium* zoonotic complexes. Making taeniosis and human cysticercosis notifiable diseases is desirable. Surveillance and reporting in animals should be improved.

5. In Catalonia, the economic impact associated with *T. saginata* was mainly attributed to meat inspection and borne by the public veterinary services. This cost could be reduced through some changes in the meat inspection such as the suppression of the detailed meat inspection in animals coming from farms where cases have been previously detected and the development of a risk-based surveillance.

6. If a risk-based surveillance for bovine cysticercosis is to be implemented in Catalonia, animal movements should be taken into account in the development of such strategy.

Annexes

Annex I: Additional files (Study I)

All additional files of Study I (listed below) can be accessed at the following link: https://doi.org/10.1186/s13071-016-1362-3

Additional file 1: PRISMA 2009 Checklist.

Additional file 2: List of references for the records included in the review.

Additional file 3: Prevalence data extracted from the included records.

Annex II: Additional files (Study II)

All additional files of Study II (listed below) can be accessed at the following link: http://dx.doi.org/10.1186/s13071-017-2280-8

Additional file 1: Table S1. PRISMA 2009 Checklist.

Additional file 2: Country sheets template.

Additional file 3: **Table S2**. List of references included in the review retrieved through online international databases.

Additional file 4: **Table S3**. List of references included in the review made available through local sources.

Additional file 5: **Table S4**. Identified taeniosis cases in case reports in western Europe (1990–2015). **Table S5**. Aggregated taeniosis cases reported in authorities' reports, epidemiological bulletins, and national registries in western Europe (1990–2015). **Table S6**. Aggregated taeniosis cases reported at hospital/laboratory level in western Europe (1990–2015). **Table S7**. Taeniosis prevalence data reported in epidemiological studies (1990–2015). **Table S8**. Taeniosis estimates published in western Europe (1990–2015). **Table S9**. Identified human cysticercosis cases in case reports in western Europe (1990–2015). **Table S10**. Aggregated human cysticercosis cases identified in registries and reports in western Europe (1990–2015). **Table S11**. Aggregated human cysticercosis cases reported at hospital/laboratory level in western Europe (1990–2015).

Table S12. Porcine cysticercosis cases and prevalence reported in western Europe (1990–2015) based on meat inspection. **Table S13**. Bovine cysticercosis cases reported (when prevalence not available) in western Europe (1990–2015) based on meat inspection. **Table S14**. Bovine cysticercosis prevalence detected in western Europe (1990–2015) by more sensitive methods than routine meat inspection. **Table S15**. Bovine cysticercosis prevalence data per age reported in western Europe (1990–2015) based on routine meat inspection.