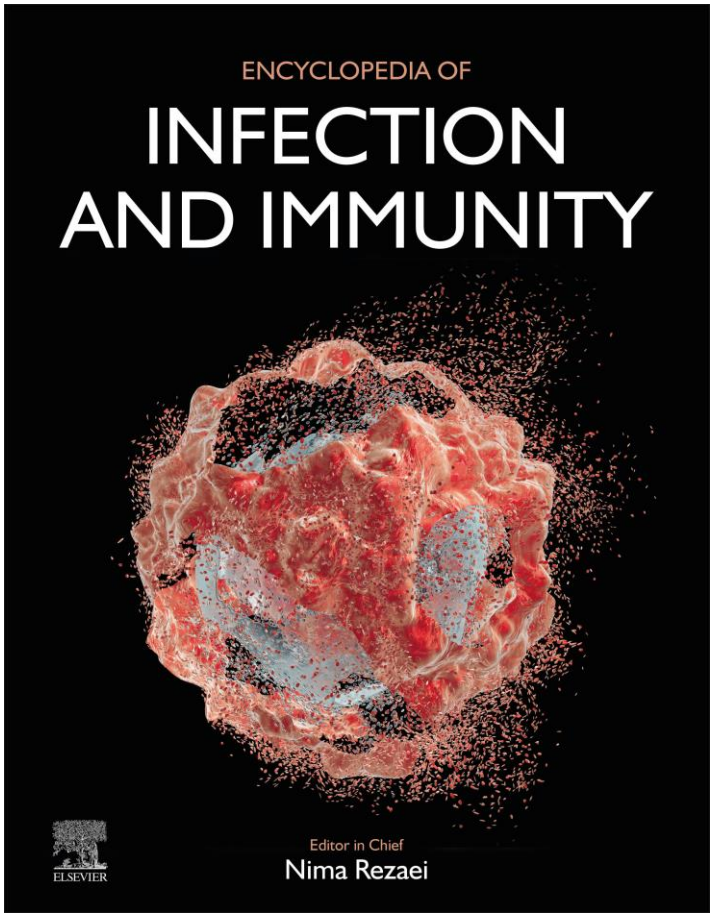

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Taeniasis and Cysticercosis

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Glossary

Anthelminthic Any chemotherapeutic substance directed against a helminth infection.
Carrier A host that harbors a particular pathogen without manifestations of disease.
Cysticercus The hollow fluid-filled larval stage of *Taenia,* containing a single invaginated scolex.
Definitive host The animal in which a parasite passes its adult existence and/or sexual reproductive phase.
Diheteroxenous Parasite requiring two hosts to complete its life cycle.
Intermediate host The animal that harbors the larval stage of the parasite.
Metacestode A collective term for any of the various larval stages of cestodes which are found in the intermediate host.

Oncosphere The motile, six-hooked embryo (hexacanth) of a tapeworm that is contained inside the egg membranes.
Proglottid One complete unit of a tapeworm, also called segment.
Scolex Attachment end of a tapeworm, commonly referred to as the anterior end which can bear suckers and hooks.
Strobila The chain of proglottids or segments of the tapeworm formed by budding.
Strobilization Process to produce proglottids from the neck region of tapeworms.
Zoonosis Infection or disease naturally transmitted between humans and other animals.

Agents and host involved

Both, taeniasis and cysticercosis are parasitic diseases caused by flatworms belonging to the class Cestoda (tapeworms), family Taeniidae, genus *Taenia*. The adult stages of *Taenia* species cause intestinal taeniasis in the definitive host whilst their larval stages or metacestodes (cysticerci) cause extra-intestinal cysticercosis in the intermediate host.

Humans are the only definitive hosts for the intestinal adults of three *Taenia* species, namely *Taenia solium* Linnaeus, 1758 (the pork tapeworm), *T. saginata* Goeze, 1782 (the beef tapeworm) and *T. asiaticus* n. n. Eom et al., 2020 (syn. *Taenia asiatica* Eom and Rim, 1993) (the Asian *Taenia*). In addition to the adult stage, humans are also intermediate hosts for *T. solium*, consequently suffering not only taeniasis but also cysticercosis. *T. solium* was included in the World Health Organization (WHO) neglected tropical disease (NTD) roadmap in WHO (2012) and this species is also the first on the list of the top 10 foodborne parasites elaborated by the Food and Agriculture Organization (FAO) in FAO (2014).

Other mammals involved in the three *Taenia* life cycles are pigs as intermediate hosts of *T. solium* and *T. asiaticus*, and cattle in the case of *T. saginata*. Cysticerci of *T. solium* have also been molecularly confirmed in dogs and bears (Ito et al., 2002; Theis et al., 1996). A strain of *T. saginata* uses reindeer (*Rangifer tarandus*) instead of bovids as intermediate hosts in northern Russia (Konyaev et al., 2017). There are other *Taenia* species also causing human cysticercosis (*T. crassiceps* or *T. martis* for instance), although these are only sporadically reported (Ntoukas et al., 2013; Eberwein et al., 2013). It has been suggested that *T. asiaticus* could also cause human cysticercosis, but there is no clear evidence so far (Galán-Puchades and Fuentes, 2013a).

Historical background

It is generally estimated that the origin of the association between humans and *Taenia* arose no more than 10,000 years ago, coincidental with the domestication of major food animals such as cattle and pigs and the advent of agriculture (Cox, 2002). Supposedly, at these early stages of animal husbandry, tapeworms circulating in synanthropic cycles between dogs and domesticated ruminants which were the source of *Taenia* parasites that first colonized and then diversified in humans. Another contrasting hypothesis, based on phylogenetic studies using mitochondrial genes, whole mitochondrial genomes, and select nuclear DNA sequences from modern specimens of *Taenia* species from humans and mammalian hosts, revealed that *T. solium* is most closely related to *Taenia* species infecting hyaenids, while *T. saginata* and *T. asiaticus* are most closely related to the species that infects lions (Terefe et al., 2014). This indicates that host switching that allowed *Taenia* spp. to infect humans was likely to be a result of hominids scavenging on the same animals as hyenas, in the case of *T. solium*, and large cats, in the case of *T. saginata*.

Phylogenetic evidence suggests that *Taenia* tapeworms began infecting hominids in sub-Saharan Africa 1–2.5 myr ago, prior to the domestication of animals (Ledger and Mitchell, 2019). Phylogenetic analyses indicate that *T. saginata* and *T. asiaticus* are putative sister species, unrelated to *T. solium*. The divergence between *T. saginata* and *T. asiaticus* is estimated to have taken place 0.78–1.71 myr ago in Africa or Eurasia (Hoberg et al., 2001). The biotic expansion from Africa into Eurasia may have resulted in the isolation and later divergence of *T. asiaticus* in Asia. Eight extant boar species have been identified in South-East Asia. This diversity of potential intermediate hosts in this area may have influenced the intermediate host switch in *T. asiaticus* from herbivore to swine. Therefore, the association of *T. asiaticus* with swine may have been established in Asia following divergence of host populations that later expanded into Europe, being consistent with the dominant distribution of this species in Asian countries (Hoberg, 2006; Michelet and Dauga, 2012).

Taenia spp. have been identified in human remains (pelvic soil and mummified remains) in several locations of Europe, Middle East, Africa and Asia, dated from 8300 BCE to 167 BCE (Ledger and Mitchell, 2019). Particularly in Egypt, the species *T. solium* was immunohistochemically diagnosed in a mummy being dated from the second to the first century BCE. This finding constitutes the oldest on record of the antiquity of this parasite (Bruschi et al., 2006). Likewise, one of the oldest and most famous possible patients suffering from neurocysticercosis (NCC), pathology due to the presence of the cysticerci of *T. solium* in the central nervous system (CNS) that can cause epilepsy, was Julius Caesars (100–44 BCE), who used to suffer headaches and epileptic crises (Bruschi, 2011).

Historically, until *T. asiaticus* was described in Eom and Rim (1993), only two *Taenia* species were considered to parasitize humans, *T. solium* and *T. saginata*. The reason is due to the fact that *T. asiaticus* was confounded with *T. saginata* for more than 200 years in Asia (Eom, 2006); an issue that will be addressed later.

In absence of any available molecular tool, scientists, two centuries ago, were finally able, after failed conclusions, to distinguish between *T. solium* and *T. saginata*. Authors, among others, Grove (1990), Cox (2002) or Wadia and Singh (2002), described the history of human *Taenia* infections in detail.

As already reviewed by Galán-Puchades and Fuentes (2013b), it was not until the mid-19th century that Küchenmeister recognized the differences between *T. solium* and *T. saginata* based on the morphology of the scolex. Leuckart was the first who experimentally showed that proglottids of *T. saginata* fed to cattle developed into cysticerci in calf muscles. Finally, Oliver was the first who discovered that "bladder worms" developed into adult *T. saginata* when ingested by humans.

The first person who demonstrated that pigs are the intermediate hosts of *T. solium* was the Belgian, van Beneden. In 1853, he gave *T. solium* eggs to a pig. When the pig was slaughtered at the abattoir four and a half months later, he found a large number of *T. solium* larvae (named *Cysticercus cellulosae*) in the muscles. Cysticercosis in humans due to *T. solium* was described by Rumler in 1558; however, the connection between tapeworms and cysticercosis had not been made at that time. Around 1850, Küchenmeister, largely criticized for his unethical practices, fed pork meat containing cysticerci of *T. solium* to humans awaiting execution in prison, and after they had been executed, he recovered developing and adult tapeworms in their intestines. By the mid-19th century, it was established that cysticercosis was caused by the ingestion of *T. solium* eggs. Another experimental infection was carried out in the 1930s by the Japanese scientist, Kozen Yoshino (1898–1965), and three more people, who voluntarily swallowed cysticerci from pigs in order to describe the outcomes of the infection (Ito et al., 2020).

The existence of the third *Taenia* species was not considered until the middle of the 20th century. In 1993, the South Korean scientist Keeseon Eom and colleagues provided descriptors of the new species, and have also recently published a complete historical overview of the species in which they proposed a new name for *T. asiatica*, specifically, *T. asiaticus*, according to the Code of Zoonotic Nomenclature (Eom et al., 2020). The origin of the discovery was an epidemiological incongruity observed in Taiwanese aborigines since, although the morphology of the expelled proglottids indicated *T. saginata*, the patients had not eaten beef—cattle being the natural intermediate host of *T. saginata*—but their diet was exclusively based on wild boars and pigs, the intermediate hosts for *T. solium* (Huang et al., 1966; Huang, 1967).

Morphology

Just as the others of the tapeworms belonging to the family Taeniidae, the species of the *Taenia* genus have three stages, two of them are parasite forms, i.e., the adult and the larval stage or metacestode, and the other one, the egg, is a free-living stage. In the definitive host, the intestinal adult stage produces eggs that leave the host and live in the environment for months. When ingested by the intermediate host, the egg turns into a cysticercus-type larva that, in turn, turns into the adult stage when the larva is ingested by the definitive host.

Adults

An adult *Taenia* tapeworm is made up of three parts: a fourth-sucker *scolex* at the anterior smaller part of the worm, behind a short *neck* followed by the *strobila*, a kind of chain comprising hundreds or thousands of hermaphroditic proglottids or segments. Macroscopically, the three species look alike. They are long whitish flat worms looking like tapes (hence tapeworms) (Fig. 1). *T. saginata* is the longest, measuring between 4 and 12 m. Table 1 shows some of the most relevant morphological characteristics of the adult stages of the three human *Taenia* species.

The only way to specifically distinguish them by their external morphology is by means of observing the 1–2 mm sized scolex under a stereomicroscope or a microscope, since only *T. solium* has hooks inserted in the rostellum, a cone-like muscular structure of the scolex that can protrude in some cestodes, but not in the case of *Taenia* species. The presence of hooks in *T. solium* made this species known as the "armed *Taenia*." Neither *T. saginata* nor *T. asiaticus* have hooks. Therefore, only *T. solium* could be differentiated from the two other unarmed species by the mere observation of a complete adult stage.

Fig. 2 illustrates the morphology of the three scolices; in *T. solium*, the hooks are arranged in two rows of 22–36 characteristically shaped hooks (like a cat claw), including small and large ones, measuring from 11 to 176 μm.

The neck, the part immediately behind the scolex, is the region of growth from where the proglottids of the body, that constitute the strobila, are continuously generated. Actually, a strobila is a kind of factory aimed at the production of eggs. According to the age of the proglottid, the production still has not started (young and immature segments near the neck), the production is in operation (sexually mature proglottids in the middle of the chain) and, finally, at the end of the strobila, the gravid and oldest proglottids, are full of already formed eggs. These latter proglottids are expelled on a daily basis and can be found in human feces. Fig. 3. shows the general internal morphology of a sexually mature proglottid as well as that of the three gravid segments which, once processed at the laboratory (see "Diagnosis" section), by means of counting the number of lateral branches, would allow to distinguish between *T. solium* and *T. saginata/T. asiaticus* [these two species present a similar number of branches (Table 1)].

Eggs

The eggs of the three human *Taenia* species have the same morphology (in fact, the eggs of any tapeworm of the family Taeniidae) and, therefore, do not permit species identification. In gravid proglottids, the uterus is full of spherical eggs, measuring 31–43 μm in

Fig. 1 Detail of a fragment of the strobila of *Taenia saginata*.

Table 1 Morphological characteristics of the adult stages of *Taenia* species.

	Taenia solium	Taenia saginata	Taenia asiaticus
Length (m)	1–5	4–12	4–8
Scolex	Armed rostellum	Rostellum absent	Unarmed rostellum
Number of Proglottids	$\leq$1000	>1000	<1000
Number of testes	350–600	800–1200	320–1200
Ovary	Three lobes	Two lobes	Two lobes
Vaginal sphincter	Absent	Present	Present
Number of lateral branches in uterus	7–13	14–32	16–21
Branching pattern	Dendritic	Dichotomous	Dichotomous

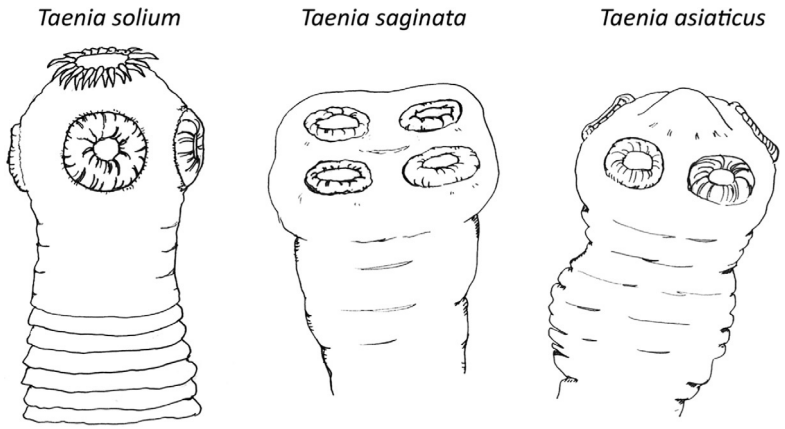

Fig. 2 Scolex morphology of the three human *Taenia* species (illustration by Angela Debenedetti, PhD).

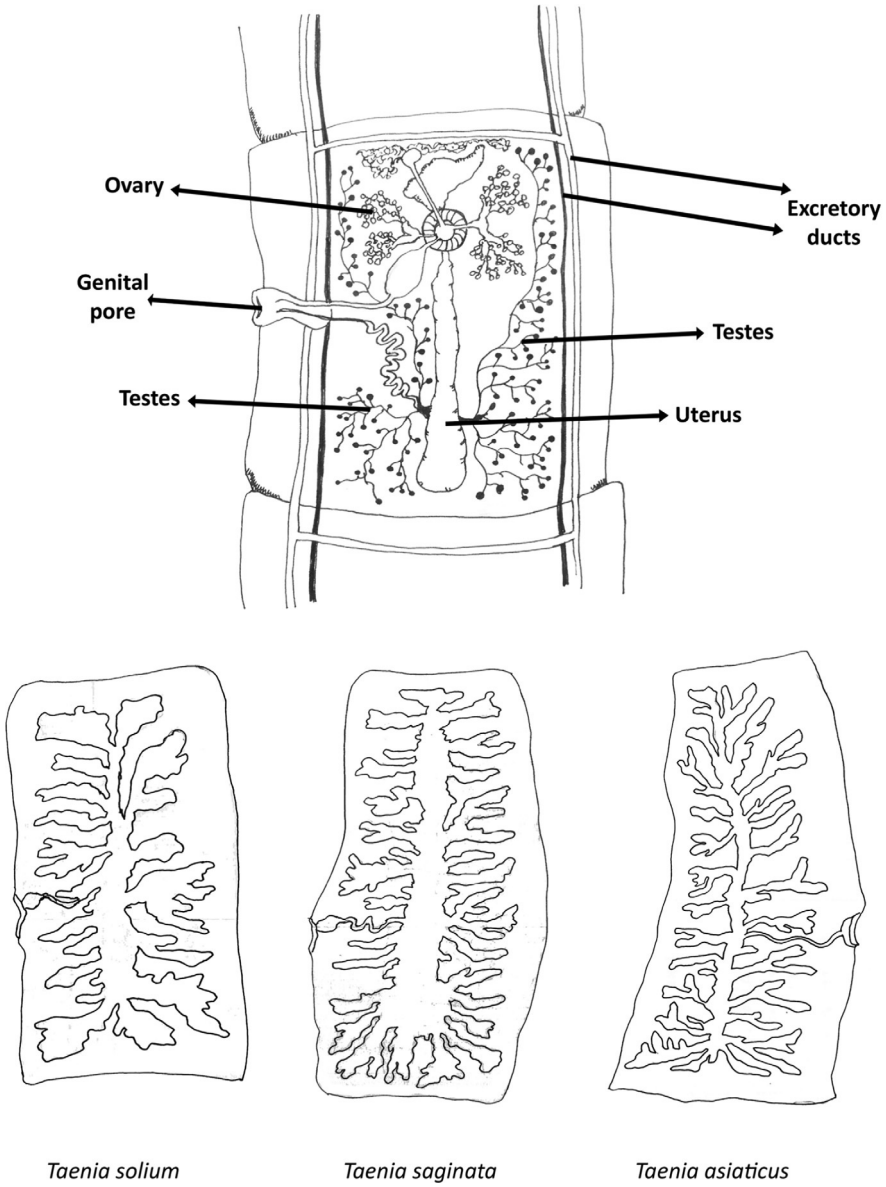

Fig. 3 Up: General morphology of a sexually mature proglottid of *Taenia* spp.; below: uterus morphology of the three human *Taenia* species in the gravid proglottids (illustrations by Angela Debenedetti, PhD).

diameter, presenting an outer embryophore, made up of keratin blocks cemented together, which is thick and radially striated protecting a fully-developed embryo, the oncosphere. This embryo is surrounded by several membranes and possesses three pairs of hooklets, the reason why the oncosphere is also known as hexacanth embryo (Fig. 4, left). The color of the eggs varies between pale yellow and brown.

The eggs of *T. asiaticus* were analyzed by means of electron microscopy and TEM (transmission electron microscopy) as well as SEM (scanning electron microscopy) images, which showed the presence of small vesicles consistent with extracellular vesicles (exosomes and ectosomes) (Galán-Puchades et al., 2016).

The eggs of *T. saginata* (Fig. 4, right) only infect cattle, causing bovine cysticercosis, those of *T. asiaticus* apparently only cause pig cysticercosis. However, the eggs of *T. solium* are infective to pigs as well as to humans, causing not only pig but also human cysticercosis.

Metacestodes

Cysticerci are rounded or oval extra-intestinal metacestodes visible to the naked eye. They are whitish bladders measuring, depending on the *Taenia* species, between 0.2 and 1.5 cm in diameter (Fig. 5). The fluid-filled vesicle has an invaginated scolex which can be seen as a kind of small eccentric and solid granule. In the case of *T. solium*, the vesicular fluid consists of water but also contains calcium, glycoproteins, cholinesterase, and coproporphyrin (Cervantes et al., 1986).

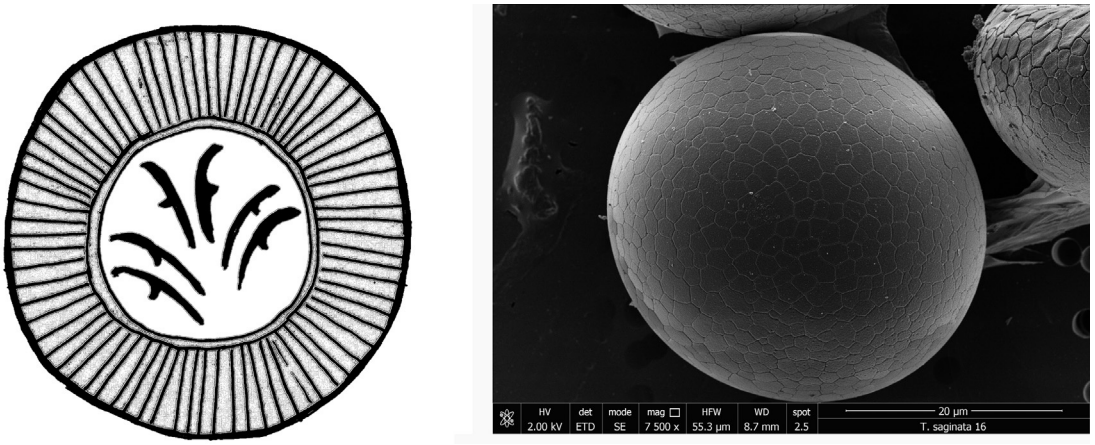

Fig. 4 Left: *Taenia* egg (illustration by Angela Debenedetti, PhD); right: SEM image of a *T. saginata* egg.

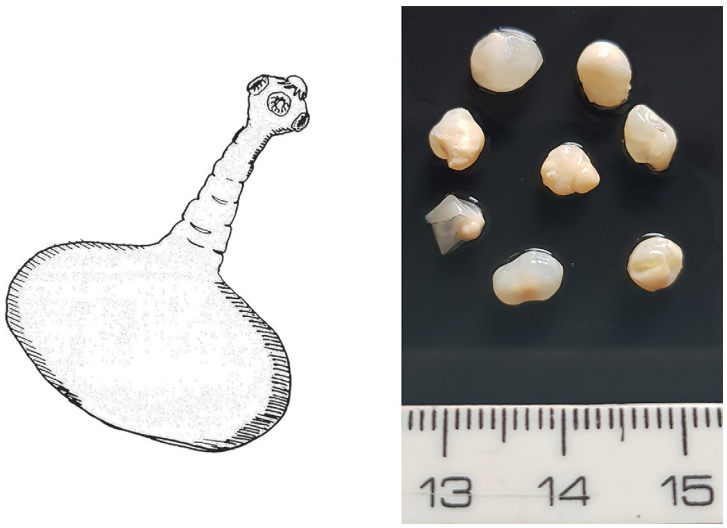

Fig. 5 Left: Morphology of a *Cysticercus cellulosae* with the scolex evaginated (illustration by Angela Debenedetti, PhD); right: Cysticerci of *Taenia solium* from a pig brain.

Having different specific names for the cysticercus and for the adult stage of the human *Taenia* species is an established habit. The cysticercus of *T. solium* is known as *Cysticercus cellulosae*, *C. bovis* that of *T. saginata* and *C. viscerotropica* for *T. asiaticus.* In the case of *T. solium* and *T. saginata*, when the cysticerci in the intermediate hosts were matched with the adult stages in humans, both had already been differently named, which has remained the same ever since. In the case of *T. asiaticus*, when the species was described, the cysticercus was named differently to keep this habit.

The nature of the intermediate host distinguishes *C. bovis* (cattle) from the porcine cysticerci (*C. cellulosae* and *C. viscerotropica*). *C. bovis*, with a size of 7–10 mm, contains the unarmed scolex of the future adult stage. In the case of cysticerci from pigs, the organ in which the metacestode is found as well as the size and the internal morphology are noticeable. *C. viscerotropica* shows a clear liver tropism, although other less frequent locations should not be ruled out (Singh et al., 2016). The cysticercus of *T. asiaticus* is the smallest, measuring 1.9–3.0 mm in maximum length. Up to 37 rudimentary hooklets on the rostellum can be observed in about 17% of the larval stage of (Eom et al., 2020). *C. cellulosae*, measuring 0.5–1.5 cm, exhibits no defined tropism (Fan et al., 1994), thus developing in muscles and other organs in pigs. Contrary to *C. viscerotropica*, *C. cellulosae* has an armed scolex with the two rows of hooks of the future adult stage in the interior of the cysticercus.

Life cycle

Fig. 6 illustrates the life cycles of the three *Taenia* species and Table 2 shows certain peculiarities of each one of these three cycles.

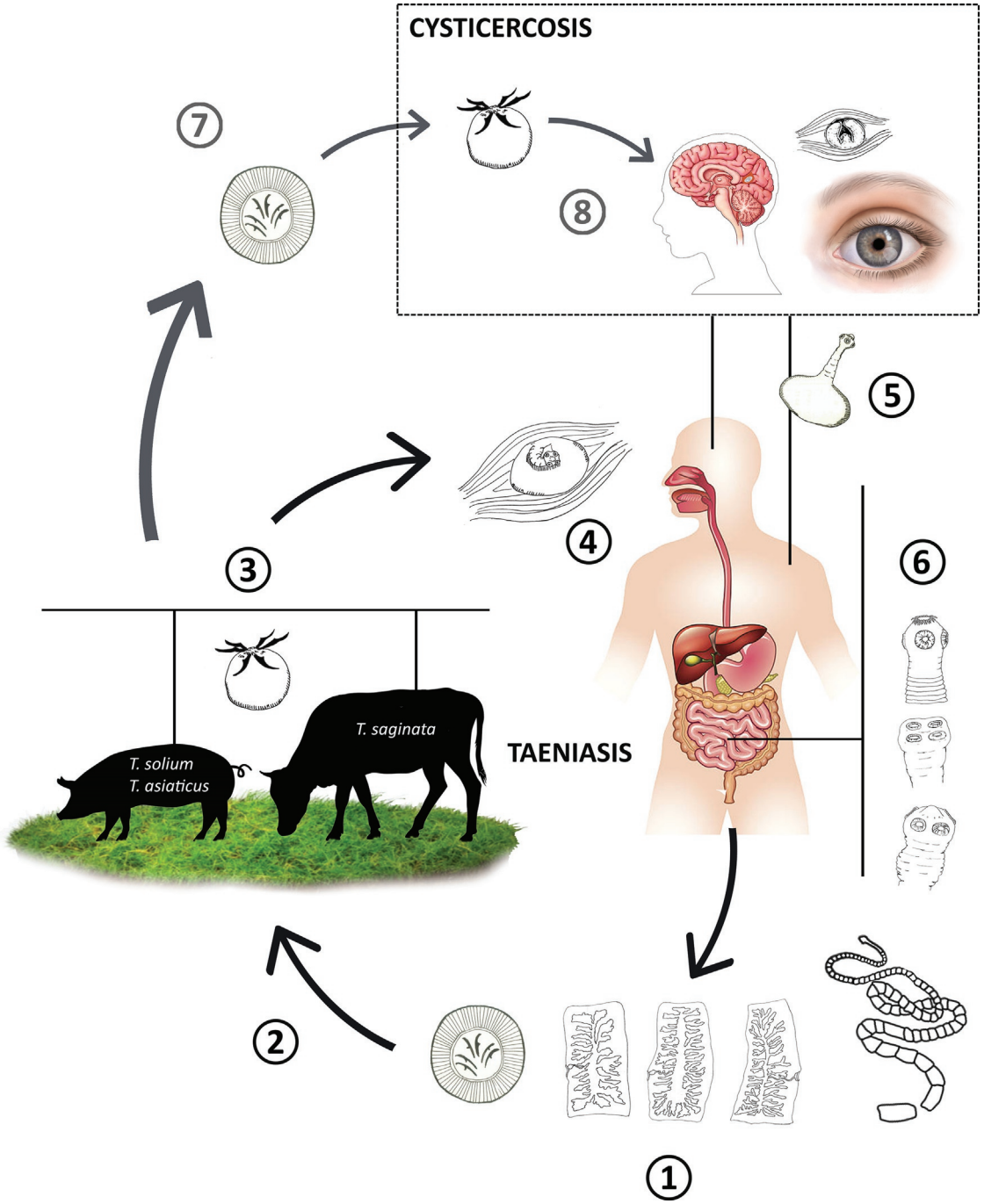

Fig. 6 Human *Taenia* life cycle: (1) gravid proglottids are shed in feces; (2) pigs (*T. solium, T. asiaticus*) and cattle (*T. saginata*) become infected by ingesting the eggs which contaminate water and food; (3) oncospheres from eggs turn into cysticerci in the intermediate hosts (IH); (4) humans acquire taeniasis ingesting raw/undercooked infected meat and/or viscera of the IH with cysticerci; (5) cysticerci turn into adult tapeworms in the human intestine; (6) the adult stage remains in the small intestine where the scolex attaches itself; (7) humans develop cysticercosis through the accidental ingestion of *T. solium* eggs: (8) cysticerci can develop in any organ but most commonly in subcutaneous tissue, the brain (NCC) and eye (ophtalmocysticercosis) (illustration by Angela Debenedetti, PhD).

The three species have a similar diheteroxenous life cycle. They require two mammalian hosts in order to complete them. Humans are the only known definitive host harboring the intestinal adult stage. In general, on a daily basis or two or three times per week, eggs are shed in the feces of the taeniasis individual, either free or in the interior of gravid proglottids. Gravid proglottids of *T. saginata* and *T. asiaticus* are motile, able to actively force their way out through the anal sphincter, independent of human defecation.

Table 2 Features of human *Taenia* life-cycles.

	Taenia solium	Taenia saginata	Taenia asiaticus
Gravid proglottids release	In short chains of 3–5 segments	Isolated segments	Isolated segments
Movement of the proglottids	No	Yes	Yes
Alternative intermediate hosts	Wild boar, dogs, bears	Reindeer	Wild boar
Larval development (in weeks)	9–10	10–12	4–8
Larval survival	3–6 years	1 year	1–2 months

The eggs can survive in the environment, water or soil, for months, depending on temperature and moisture (see section "Epidemiology and distribution"). A survival of 413 days was reported for *T. saginata* eggs on pasture in Kenya (Duthy and van Someren, 1948).

Once the eggs are ingested by the intermediate host, cattle in the *T. saginata* life cycle and pigs in the case of *T. solium* and *T. asiaticus*, and in contact with hydrochloric acid, digestive enzymes and bile, the blocks of the embryophore become unglued, thus liberating the oncosphere which penetrates the intestinal wall reaching the blood or lymphatic vessels of the mesentery. Subsequently, these post-oncospheres are passively transported to several host tissues in which they will develop into the larval or metacestode stage, the cysticerci, in several weeks (Table 2). When humans eat raw or undercooked infected meat or viscera of intermediate hosts (beef and pork), in the upper part of the small intestine, the scolex evaginates out of the cysticercus, becomes attached to the mucosa with the aid of the suckers (and hooks in *T. solium*), and by gradual strobilization develops into adults in several weeks.

The adult life span of *Taenia* species is not clearly known. The life span of *T. solium* is controversial. Although longevity of up to 25 years was accepted for years (Hoberg, 2002), a shorter life span of less than 5 years has also been suggested (Lightowlers, 2010; García et al., 2014). In the case of *T. saginata* and *T. asiaticus*, cases in which infections persisted for decades have been recorded (Wright and Jain, 1984; Eom et al., 2020).

In addition to taeniasis, humans may develop cysticercosis by means of the ingestion of *T. solium* eggs, acting then as intermediate hosts. Unfortunately, the CNS is one of the main target organs of cysticerci in humans; this infection produces a complex disease, NCC.

Epidemiology and distribution

There are numerous articles in the literature that describe a great variety of aspects of the epidemiology of human taeniasis/cysticercosis. Only considering those most generalist published in the last 20 years, is worth mentioning the papers by Eom and Rim (2001), Flisser (2002), Hoberg (2002), Pawlowski (2002), Ito et al. (2003), Murrell (2005), Devleesschauwer et al. (2012), Zammarchi et al. (2013), Coral-Almeida et al. (2015), Ito et al. (2016), Laranjo-Gonzalez et al. (2017), Wu et al. (2017), Braae et al. (2018), Trevisan et al. (2018), Bucur et al. (2019), Dixon et al. (2019), Abraham et al. (2020), Eichenberger et al. (2020), among others, are noteworthy.

The epidemiology of the human *Taenia* species depends on two basic factors: the natural ecology of the life cycle and the artificial changes introduced by humans in that ecology. The high biotic potential of the adult stages (great ability to produce eggs), the increase of host populations (humans, pigs and cattle), changes in livestock production, high consumption rates of undercooked meat, as well as the inherent consequences of globalization, i.e., progressively more intensified contacts between hosts due to human migratory movements, in addition to the role of international trade, make taeniasis a progressive zoonosis.

Parasite populations of these three species comprise three subpopulations: The adult stage in humans, the released eggs in the environment and the metacestodes in the intermediate hosts. Therefore, three epidemiological factors determine the geographical distribution of taeniasis/cysticercosis: (a) the human factor; (b) the environment; and (c) the type of livestock.

Taenia solium distribution

The pork tapeworm has a cosmopolitan distribution being infrequent in those regions where pork is not consumed. *T. solium* is an endemic parasitic disease in many countries of Central and South America, South Africa and Asia. Its prevalence varies according to the epidemiological factors, i.e., the level of sanitation, pig husbandry practices (pigs scavenging for food), limited veterinary meat inspection and eating habits. In endemic regions, large portions of the population may be infected. In these areas up to 6% of people may harbor intestinal worms at a given time and serve as a source of infectious eggs that cause cysticercosis (Allan et al., 1996).

Out of more than 190 countries analyzed by WHO, only 20% were non-endemic (there is no data from 47% of the countries) (https://apps.who.int/gho/data/node.main.NTDTSOL1?lang=es; last updated 2018-12-12). Worldwide about 66 million people are estimated to be infected with *T. solium*, mainly in Sub-Saharan Africa, Latin America and South and South-East Asia (Pal et al.,

2018). According to a systematic review carried out in endemic countries in 2015, the estimates for the prevalence of circulating *T. solium* antigens or antibodies for Africa, Latin America and Asia were: 7.30%, 4.08% and 3.98%, respectively. Seroprevalence estimates of *T. solium* antibodies were 17.37%, 13.03% and 15.68%, respectively. Taeniasis reported prevalences ranged from 0% to 17.25% (Coral-Almeida et al., 2015).

Since routine diagnostic methods to identify human taeniasis lack specificity and usually cannot differentiate among the three species (see "Diagnosis" section), the true burden of *T. solium* taeniasis estimated by those techniques can only be an approximation. On the contrary, if serodiagnostic methods are employed, its prevalence may be an overestimate of its real prevalence due to transient antibodies. In fact, and due to its public health importance, the NCC burden has been analyzed by two different research groups. NCC-associated epilepsy Disability Adjusted Life Years (DALYs) were estimated at 0.5 million by The Global Burden Disease. However, the WHO's Foodborne Disease Burden Epidemiology Reference Group obtained a much larger estimate at 2.8 million (Carabin et al., 2017). The total number of people suffering from NCC, including symptomatic and asymptomatic cases, is estimated to be between 2.56 and 8.30 million (OPS, 2019). These contrasting results reveal uncertainties regarding the epidemiology of *T. solium*.

Improved pig rearing conditions seem to have eliminated the parasite in most Western European countries. However, little is known about the current true endemicity status of *T. solium* throughout Europe. Although autochthonous *T. solium* taeniasis/cysticercosis may be possible in Europe, peer-reviewed literature does not provide sufficient information on the current endemicity status of *T. solium* in Europe (Devleesschauwer et al., 2017). Indeed, only a few case reports were available from Eastern European countries.

According to Cantey et al. (2014), data on the prevalence of taeniasis, or adult tapeworm infection, in the United States is scarce. The few population-based taeniasis studies suggest prevalence may be 0.5–3% in selected populations. Moreover, there is also a lack of data on the seroprevalence of cysticercosis in the United States. The limited understanding of the NCC burden is caused by multiple factors, including the fact that the disease is only reportable in Arizona, California, New Mexico, Oregon, and Texas.

Although *T. solium* is no longer endemic in industrialized nations, where livestock is raised commercially with regulations to ensure minimal contact with human feces, the prevalence there has been increasing in recent years due to immigration. Also, specific identification has increased due to improved diagnostic techniques.

Taenia solium epidemiology

The human factor

The tapeworm life cycle is propagated via foodborne and fecal-oral transmission (Fig. 7). Consumption of uninspected pork meat is the major source of human *T. solium* taeniasis. To circumvent the requisition of infected pigs, owners of a small number of pigs, especially in rural areas, use them for their own consumption or they are illegally sold, thereby escaping control (Murrell, 2005). In addition to an inadequate inspection of pork, other risk factors for infection include age, open sewers and improper disposal of human feces, poor education, and the inability to recognize infected pigs. Local techniques for food preparation can also influence the spread of the disease.

Although humans usually harbor only one intestinal adult, multiple infections can be higher than 40%, reinfection being a common phenomenon in meat eaters. Although it has been accepted that taeniasis is more frequent among individuals between

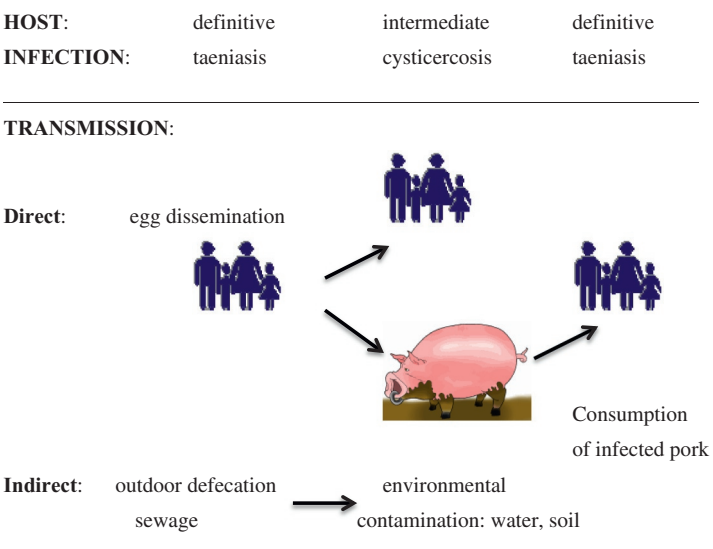

Fig. 7 Graphical scheme of *Taenia solium* transmission.

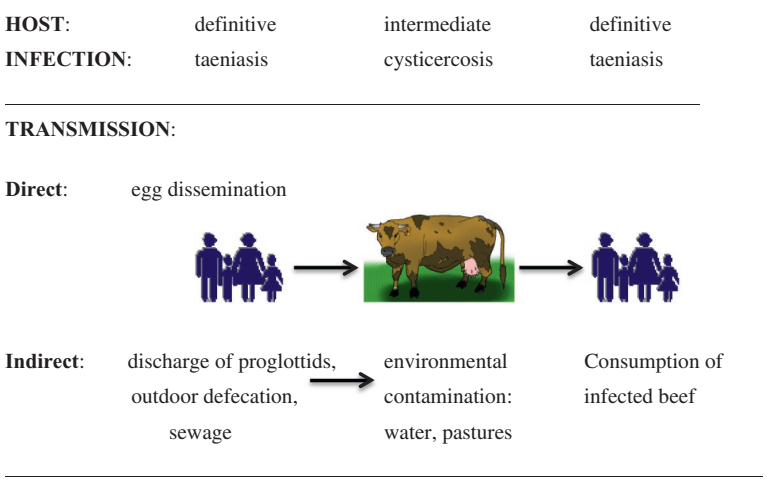

Fig. 8 Graphical scheme of *Taenia saginata* transmission.

20 and 40 years of age, a study in the Democratic Republic of Congo revealed that the highest positivity was found in the 5–10 year age group (Madinga et al., 2017).

Human travel and migration undoubtedly favor the spread of the parasite considering that human taeniasis usually occurs asymptomatically. Infected individuals may even be unaware of their condition, since gravid proglottids are shed only by defecation, therefore, probably being unnoticed by the patient.

Cysticercosis, in pigs as well as in humans, occurs following the ingestion of eggs. The very high fecundity of the tapeworms facilitates this transmission, that in the case of human-to-human (Fig. 8), can be caused by the accidental ingestion of eggs contaminating food and water as well as by eggs directly ingested via dirty hands. This person-to-person transmission explains the presence of human cysticercosis cases among people who, for religious or dietary reasons, do not consume pork (Schantz et al., 1992).

Regarding NCC, the majority of infected individuals is between 20 and 50 years of age (Hoberg, 2002). People do not need to harbor an intestinal worm to acquire cysticercosis since it is caused by the ingestion of eggs, but about 15% of patients with NCC do harbor a tapeworm at the time of diagnosis (García et al., 1999; Gilman et al., 2000) and 25% report having had one at some point (Dixon and Lipscomb, 1961). External auto-infection (anus-hand-mouth) seems to be more probable than internal auto-infection by reverse peristalsis of the intestine (Murrell, 2005), although prevalence of antibodies to oncospheres suggests that this may occur more frequently than previously thought (Bowman et al., 2006). Extraordinarily, cysticercosis can even be acquired by bizarre medical practices that ignore the infective ability of the eggs (Bourke and Petana, 1994).

The environment

The uterus of a gravid proglottid of *T. solium* can harbor up to 55,000 eggs. The segments are detached from the strobila in groups (Table 2). Thereby, *T. solium* can shed up to 300,000 eggs per day into the environment (Pawlowski, 2002).

According to the Environmental Classification of excreta-related infections elaborated by WHO (2004), *T. solium* and *T. saginata* belong to Category IV, i.e., latent and persistent infection; pigs and cattle as intermediate hosts and successful transmission.

The survival of parasites outside the gastrointestinal tract of the host depends on the environmental conditions. There are many abiotic and biotic variables that affect the eggs. Among them there are physical factors (temperature, sunlight, humidity, etc.), chemical ones (ammonia, salt, acids, etc.) as well as biological ones (fungi, protozoa, and invertebrates) (WHO, 2004). Factors influencing egg survival and infectivity have been studied in several members of the genus *Taenia*. Infective *Taenia* eggs can survive for up to 9 months in the environment. However, temperatures above 60 °C, pH 12 and desiccation lead to rapid death of the eggs. Conversely, humidity and temperatures above 10 °C and room temperature favor egg survival. A number of agents such as wind, water and some invertebrates and birds are believed to aid taeniid egg dispersal (Pawlowski, 2002). *Taenia* eggs are able to survive in sludge. As a consequence, a potential route of transmission is the irrigation of pasture with wastewater or using domestic sludge as fertilizer for soil.

Livestock: Pigs

The third link of the epidemiological chain is livestock as reservoir of the disease. Pig cysticercosis considerably affects pork meat quality and entails substantial economic losses in the affected areas where *T. solium* is endemic. In these endemic areas, *T. solium* porcine infections have been associated with poverty, absence of latrines and free access of scavenging pigs to human feces. In many low income countries, pigs are usually poorly fed, are not confined and are allowed, and even encouraged, to roam about free in search of food. These free roaming pigs, in combination with the generalized practice of open-air fecalism that prevails, end up ingesting a significant amount of human feces, some of which are contaminated with *T. solium* eggs. In the worst social conditions, pigs are deliberately placed to graze in terrains used for public defecation or near rural out-houses. In rural areas, piglets become

infected at the age of 4 weeks, i.e., immediately after weaning. In tropical areas, infection in piglets is higher during the dry and hot season; this paradox arises from adult animals being reluctant to move at high temperatures, whilst piglets remain active (De Aluja et al., 1998), and, as a consequence, have easy access to fecal material during the hot season.

The prevalence of porcine cysticercosis in endemic countries usually varies between 0% and 56.6%, 1% and 61%, and 0.02% and 77% in Africa, Latin America and Asia, respectively (Murrell, 2005; Wu et al., 2017). *T. solium* has been eradicated in the European Union (EU), primarily due to the change toward industrial pig farming, in which the animals are raised in controlled housing conditions with no outside access. Thereby, the probability of pigs feeding on human feces is very low. However, since 2007, according to the European Food Safety Authority (EFSA), cysticerci consistent with *T. solium* have been detected in pigs slaughtered in five countries of the EU (Austria, Estonia, Lithuania, Poland and Romania) (EFSA, 2010). The entry of tapeworm carriers into the EU seems a lot more plausible than the import of infected pork (Gabriel et al., 2015).

Taenia saginata distribution

The most common and widely distributed human *Taenia* tapeworm is *T. saginata*. Infection in humans has been reported in 45 countries and 45–60 million people are affected (Pal et al., 2018). *T. saginata* is common in cattle-breeding areas of the world. The areas with the highest prevalence (up to 27%) are found in Central Asia, the Near East, and Central and East Africa. Areas of lower prevalence (<1%) are found in Europe, Southeast Asia, Central America, and South America. Consumption of "measly" (cyst-infected) raw or undercooked beef is the usual means of transmission. Rare steak or kebabs and steak tartare are dishes typically associated with *T. saginata* infection.

Data published between 1990 and 2017 on *T. saginata* taeniasis and cysticercosis occurrence and prevalence in Europe, America, Asia and Africa has been gathered by The European Network on Taeniosis/Cysticercosis (CYSTINET) (https://www.biomedcentral.com/collections/GDTS).

Taenia saginata epidemiology

The human factor

As in the case of *T. solium*, the tapeworm life cycle is propagated via foodborne and fecal-oral transmission (Fig. 8). Unlike *T. solium*, the eggs of *T. saginata* are only infective for cattle and not for humans. Therefore, taeniasis *saginata* in humans is not the serious public health threat that taeniasis *solium* is, although the economic burden of bovine cysticercosis should not be underestimated.

Human taeniasis results from the consumption of contaminated beef that has not been frozen or thoroughly cooked containing viable *Cysticercus bovis*. In pastoral societies raw or rare meat is part of the normal diet, however, *T. saginata* taeniasis is, in many developed countries, also associated with the increased consumption of raw and rare beef.

Taenia saginata has been reported in children below 1 year of age as well as in adults over 80, although infection is most common in the 20–40-year age group.

There are three main patterns of transmission of *T. saginata*: (i) hyperendemic, characterized by pastoral farming in areas with a high prevalence of human *T. saginata* taeniosis and bovine cysticercosis; (ii) endemic, characterized, by the existence of a small number of human carriers, a wide dispersal of eggs in the environment and a moderate prevalence of bovine cysticercosis mostly of low intensity; and (iii) epidemic, characterized by feedlot situations in which a single human carrier, whose close contact with a herd of susceptible cattle can result in a massive outbreak of bovine cysticercosis (Murrell, 2005).

The environment

In the epidemiology of *T. saginata*, the presence of eggs in perianal zones, clothes, hands, as well as the shedding of gravid proglottids independent of defecation (up to five to 15 per day) cause humans to contaminate the environment to a greater extent than in the case of *T. solium* taeniasis.

T. saginata eggs have been found to survive in the environment for several months. In a damp temperate climate, the eggs of *T. saginata* can survive in the environment for about 10 months, remaining viable for 130 days in water, which represents a major way of dissemination of the eggs (Murrell, 2005). Eggs could be activated after 4 months of being kept in a stream of water at temperatures ranging from—10 °C to 17 °C, as well as after 1 week of constant freezing at −18 °C, or repeated freezing and thawing from −6 °C to 5 °C. Therefore, *T. saginata* eggs can survive in cold environments, such as the Northern European winter, and pose a significant risk of transmission (Bucur et al., 2019).

There are several ways in which the eggs of *T. saginata* can become available to cattle through sewage. In systems which use primary settling tanks, grit tanks, sedimentation tanks or aeration tanks, eggs in the effluent will pass through these systems into rivers or farms using sewage. Flooding of the rivers will ensure that the eggs are dispersed onto livestock pastures. If the outlet falls directly into the sea from a raw sewage collection plant, segments will be present and the eggs can then be disseminated onto pastures by birds.

Livestock: Cattle

According to Taylor et al. (2007), in cattle, there are two quite distinct epidemiological patterns found in low income and industrialized countries, respectively. In certain parts of Africa, Asia and South America cattle are reared on an extensive scale, frequently human sanitation is poorly developed and cooking fuel is expensive, which leads to a high level of human infection with

T. saginata (up to 20%). As a consequence, cattle are usually infected in early life, often within the first few days after birth. Based on routine carcass inspection, the infection rate is often around 30–60%, although the real prevalence is considerably higher.

In industrialized countries (mainly countries of Europe, North America, Australia and New Zealand), the standards of sanitation are high and meat is carefully inspected and generally thoroughly cooked before consumption. In such countries, the prevalence of bovine cysticercosis is low, being less than 1% of carcasses inspected. Occasionally however, a cysticercosis "storm," in which a large proportion of cattle is infected, has been reported on certain farms. In Britain and Australia, this has been associated with the use of human sewage on pasture as a fertilizer in the form of sludge, i.e., sedimented or bacterial-digested feces. Other causes of a sudden high incidence of infection on certain farms are due to a tapeworm infection in a stockman occurring either as a random event or as the result of the presence of migrant labor from a country with a high prevalence of infection.

Taenia asiaticus distribution

So far, *Taenia asiaticus*, also known as the Asian *Taenia*, shows a geographical distribution exclusively linked to the Asian continent, and was primarily found only in South-East Asian countries. However, with the introduction of molecular methods in epidemiological studies, its far more extensive geographical distribution was laid bare. Hitherto, the species has been found in Korea, Taiwan, the Philippines, China, Thailand, Indonesia, Vietnam, Japan, Lao PDR, Nepal and India (Eom et al., 2020). In Bangladesh, its presence is suspected but it would require molecular confirmation. *T. asiaticus* prevalence can reach up to 21% and is even becoming the dominant human *Taenia* tapeworm in several countries (Eom et al., 2009).

Considering that *T. asiaticus* has cosmopolitan hosts (humans and pigs), it seems strange that globalization has not affected it (Galán-Puchades and Fuentes, 2014). The lack of identifying this parasite outside Asia is probably due to misdiagnosis since eggs as well as gravid proglottids, have the same morphology as *T. saginata*. Therefore, unless molecular techniques are applied in diagnosis, *T. asiaticus* can easily be confounded with *T. saginata* outside Asia as, aforementioned, was the case in Asia for more than 200 years (Eom, 2006).

Taenia asiaticus epidemiology

The human factor

According to the clear hepatic tropism of the cysticercus of *T. asiaticus* in pigs, the main risk factor for humans is the consumption of raw or undercooked infected pork liver or foods containing it. Although the consumption of pork liver is generally less popular than that of pork meat, this liver tropism does not seem to be the reason of its, so far, exclusively Asian distribution, since pork liver is a cheap and ubiquitous food consumed in whatever non-Islamic country and Israel (Fig. 9). The possibility of becoming infected when consuming raw or undercooked pork meat also exists since cysticerci of *T. asiaticus* have also been found in the muscles of naturally infected pigs (Singh et al., 2016).

Fig. 9 Pork liver trays in a Spanish supermarket.

In Asian countries, the transmission of *T. asiaticus* is often related to social, cultural, and religious practices that entail the consumption of raw pork liver. Ale et al. (2014) reviewed the different ethno-geographical foci where *T. asiaticus* has been studied. The consumption patterns could explain the fact that prevalence increases with age and its apparent predominance in males.

For more than 30 years, the passing of motile proglottids from carriers has been reported in 3% of all cases (Eom et al., 2020).

It is still not known whether *T. asiaticus* eggs are able to produce human cysticercosis (Galán-Puchades and Fuentes, 2013a).

The environment

No specific study has been carried out on the survival or dispersal agents of *T. asiaticus* eggs, although the same results obtained with other taeniid eggs could be expected for this species.

Livestock: Pigs

T. asiaticus grows to young cysticercus in the visceral organs of pigs within 1–2 months after the ingestion of the eggs. The metacestodes are mainly found in the liver parenchyma and to a lesser extent on the liver surface. Other viscera, such as lungs, omentum, serosa and mesentery, may also harbor cysts (Eom et al., 2020). *C. viscerotropica*, as already mentioned, has also been found in the muscles of pigs, which increases the likelihood of human infection.

Pork is a staple of the diet in South-East Asia. In fact, it is a common practice in many rural parts to house pigs and other animals under the floor of the house, creating an ideal environment for its transmission. Consumption of pork meat and viscera was far more common than that of beef, yet *T. solium* had a surprisingly low prevalence compared to *T. saginata* in certain Asian countries. This epidemiological paradox led investigators to hypothesize that another *Taenia* parasite might be present, closely resembling the *T. saginata* morphology but the *T. solium* life cycle, and, hence, *T. asiaticus* was subsequently classified (Eom et al., 2020).

In spite of the presence of *T. asiaticus* human taeniasis in 11 Asian countries, according to the literature search carried out by Braae et al. (2018) in certain countries of East and South-East Asia, the presence of *T. asiaticus* porcine cysticercosis was only confirmed in one country (Lao PDR). However, Simanjuntak et al. (1997) found that approximately 23% of pork liver samples in Bali, Indonesia, harbored *T. asiaticus* metacestodes and 1.01% was found in South Korea (Eom et al., 2020).

The scarcity of data indicates that *T. asiaticus* porcine cysticercosis is vastly underreported, and that more epidemiological survey data are required in order to determine the burden of this parasite within Asia as well as in the rest of the world. Due to the small size of the cysticerci and their location in pigs, routine post-mortem inspection lacks sensitivity, making the disease practically undetectable. In experimental infections, 88.9% of the small cysticerci were located in the hepatic parenchyma. Consequently, unless slices of 2–3 mm were made, cysticerci could not be found in livers, and this procedure is not carried out in any routine inspection. This scenario makes it currently almost impossible to determine if the parasite is present or not on a worldwide scale (Galán-Puchades and Fuentes, 2014).

Clinical aspects and human response to the parasite

Taeniasis

Taeniasis is generally a silent disease. In spite of the size of human *Taenia* spp. and regardless of the species involved, intestinal taeniasis is usually asymptomatic. Only mild and non-specific symptoms are described as associated to intestinal taeniasis. Among those infected with *T. saginata*, the most common sign of the disease is the unpleasant sensation due to the discharge of proglottids, independent of defecation. Abdominal pain, nausea, diarrhea or constipation, changes in appetite, weakness, weight loss, pruritus at the perianal area, and general malaise are other symptoms that a small number of patients experience. On occasions, neuropsychiatric disturbances usually appear after diagnosis, when the patient is aware that a several-meter long parasite inhabits his/her intestine.

Exceptional symptoms gathered from literature include toxic effects due to metabolites of the parasite, Binge Eating Disorder (Fernández-Aranda et al., 2000) and iron deficiency anemia (Shorbagi et al., 2012). Wani et al. (2018) and Karanikas et al. (2007) described, respectively, two cases of bowel obstruction due to *T. saginata* and the latter also reviewed other rare complications such as acute obstruction of the Wirsung duct and pancreatitis, gangrenous cholecystitis, Meckel's diverticulitis, acute abdomen following rupture of a liver abscess caused by the presence of *T. saginata* in the right lobe, acute appendicitis and cholangitis.

There are only few studies on the immune response in patients suffering from taeniasis. By contrast, numerous studies have been made on cysticercosis to determine the mechanisms of immune response directed against the cysticerci of *T. solium*. Recently, Prodjinotho et al. (2020) reviewed the host immune responses during NCC infection. This response to the cyst is remarkably complex and diverse. The immune response to the parasite is of type 2 as observed in the majority of affected individuals with asymptomatic infection, however, it can change during symptomatic diseases. Regarding humoral responses in NCC, several antibody classes are produced during the clinical course of NCC, with the most prominent being IgG in serum and CSF. In extraparenchymal infection, increased levels of Ig G, IgM, and IgE were observed in symptomatic patients (Prodjinotho et al., 2020).

Cellular immune responses during NCC are diverse and distinct with regard to the localization and stages of parasite in the brain and mostly limit the progression of the disease. After months to years in the brain tissue, the cysticerci start to degenerate, either naturally or due to anthelmintic treatment, and lose their ability to regulate the host response. Thus, an inflammatory immune

response characterized by an increase in interleukin 1 beta, tumor necrosis factor alpha, and interferon gamma production is instigated (Prodjinotho et al., 2020).

Regarding the interaction with the host, *T. solium* is the species that deserves more attention considering that its adult stage produces the eggs, i.e., the source of human and pig cysticercosis infection. Due to the scolex fixation by means of the suckers and the hooks, there is local damage and an inflammatory response in the upper small intestine that involves mast cells and goblet cells and varied cell populations including plasma cells, lymphocytes, neutrophils and eosinophils (Willms, 2008). Stage-specific antibody responses have been identified in serum from *T. solium* tapeworm carriers. However, considering that humans can suffer from taeniasis and cysticercosis at the same time, it is difficult to determine whether the antibodies detected could be due to the adult or the larval stage (Correa and Medina, 1999).

Human tapeworm carriers are the main risk factor for acquiring cysticercosis. Since humans are the only definitive hosts, different experimental models of *T. solium* taeniasis have been explored in order to study humoral and cellular immune responses in the intestinal mucosa, mesenteric lymph nodes, spleen, serum, saliva and feces of experimental hosts for immunodiagnosis and vaccine development (Flisser et al., 2010).

Cysticercosis

When humans accidentally ingest *T. solium* eggs, within 2 h of liberation, oncospheres enter submucosal blood and/or lymphatic vessels and migrate to a number of internal organs. *T. solium* cysticercosis can occur in almost any part of the body. In humans, cysticerci are most commonly found in skeletal muscles and in the CNS (NCC), mainly in the brain although they can also be found in the skin, subcutaneous tissue, eye (ophtalmocysticercosis), and heart. Although embryos are distributed to all tissues, they are commonly destroyed by the human immune response, thus surviving, preferentially, in the brain and eye (García et al., 2020).

Cysticerci in humans (and pigs) can be found in different morphological states; some are clearly cystic with intact structures (vesicular) while others seem coagulated and their structures somewhat disassembled (colloidal), or, they may be necrotic and sometimes calcified, partially or totally (calcified) (Sciutto et al., 2000). All these forms of the cysticerci possess the potential of causing functional disturbances due to space occupation and/or local inflammation. Viable cysticerci have been shown to use multiple active mechanisms of immune evasion even covering themselves with host immunoglobulins (García et al., 2020).

When located in the tissues, cysticerci are rarely symptomatic unless they encyst in the eye or in the CNS.

Cysticercosis out of the CNS

Cysticercosis can cause subcutaneous nodules in the skin that, occasionally, become swollen and painful. In muscles or viscera, they do not seem to cause any apparent clinical manifestation beyond detectable masses, although muscular pseudohypertrophy when there is a very high worm burden in skeletal muscles has occasionally also been reported. Cysts in the heart are apparently asymptomatic in most cases and are mostly found in patients with disseminated cysticercal infections (Vaidya et al., 2013). Disseminated cysticercosis, a rare complication of the disease with the involvement of almost any organ of the body, has more frequently been reported in immunocompromised than in immunocompetent patients (Banu and Veena, 2011; Gnanamoorthy and Suthakaran, 2019).

Conversely, ophthalmic cysticercosis is frequently a clinical problem. Ophtalmocysticercosis is the most common intra-orbital parasitic infection. Ocular and orbital cysticercosis has varied clinical manifestations depending upon the site of involvement, stage of the cyst and the host-immune responses. The infection may involve the sub-retinal space, extra-ocular muscles, eyelid and/or lachrymal glands surrounding the eye. The most frequent symptoms are pain in the eyes, blurriness, partial or complete loss of vision and, in extreme cases, complete detachment of the retina. A study, in which 171 patients suffering from orbital cysticercosis were involved, revealed periocular swelling, proptosis, ptosis and diplopia as the main symptoms (Rath et al., 2010).

With the advent of the new imaging techniques, ocular and orbital cysticercosis is now increasingly diagnosed even in non-endemic zones (Dhiman et al., 2017).

Neurocysticercosis

NCC, the infection of the CNS by the metacestode of *T. solium*, is the most common helminthic neurological infection and a major public health problem in most parts of the world, still being a major cause of acquired epilepsy in most low-income countries. In endemic settings, approximately 30% of all epilepsy is due to NCC (WHO, 2016). This causes 50,000 deaths/year, and many of the people affected suffer from active epilepsy, with all the social and economic consequences that this implies (García et al., 2005).

In addition to the cysticerci with the same morphology as those from pigs (cellulose cysticercus), a racemose cysticercus can grow exclusively in the human brain. These peculiar cysticerci show a larger size (10–20 cm), being rounded or lobulated and, importantly, without scolex. These racemose cysticerci usually occur in extraparenchymal sites (e.g., subarachnoid space, meninges). The absence of the scolex is believed to be the result of hydropic degeneration caused by the continuous adsorption of cerebrospinal fluid (Del Brutto, 2002). Between the cellulose and the racemose forms, intermediate forms of cysticerci can also be found in human brains (Rabiela et al., 1989).

NCC is highly pleomorphic and there is no possibility to define a pathognomonic clinical syndrome (Del Brutto, 2013). The clinical presentation of NCC is varied and depends on the stage, number, size, form and location of the larval stages within the CNS and the host's immune response to the parasite. Thus, NCC can be classified following different criteria (Mahanty and García, 2010; Ferrer and Gárate, 2014): (i) cysticerci location: *intraparenchymal* (the most common form) and *extraparenchymal* (subarachnoid

space, ventricles, or spinal cord); (ii) viability of the cysticerci: *viable or active* (single, multiple, massive), *transitional or degenerating* (single, multiple, massive), and *calcified or inactive* (single, multiple); (iii) the evolutionary stages of parenchymal lesions as evidenced by neuroimaging techniques: *viable or vesicular form* (small single or multiple lesions), hypodense rounded images, with a hyperdense nodule inside (scolex), lacking surrounding edema. *Colloidal*, lesions surrounded by edema representing the acute encephalitis phase in which the host's immune system reacts against the parasite. *Nodular-granular*, hyperdense lesions surrounded by edema, referred to as "cysticercus granuloma." *Calcified lesions*: small hyperdense nodules without perilesional edema, being the most common finding in NCC.

Therefore, depending on the location, number and type of cysticerci in the CNS, clinical manifestations can vary from completely asymptomatic infection to severe disease and death. Generally, most of patients with parenchymal brain cysticercosis develop seizures as the main or sole manifestation of the disease. Viable cysts are able to survive for years or even decades with intermittent neurological symptoms. Conversely, extra parenchymal NCC has a direr prognosis. Those patients presenting the subarachnoid and ventricular forms of the disease often display focal neurological deficits (paralysis of extraocular muscles, hearing loss, facial nerve palsy or trigeminal neuralgia, and focal neurological symptoms related to brainstem impairment), acute intracranial hypertension secondary to hydrocephalus, ischemic cerebrovascular complications and cognitive decline.

Racemose cysts usually are encountered in the basal cisterns and can cause an intense inflammatory reaction, fibrosis, and progressive thickening of the leptomeninges at the base of the brain; it is also usually an obstruction of the cerebrospinal fluid circulation, resulting in hydrocephalus and intracranial hypertension as a consequence of the unrestricted growth of the racemose parasite. Mortality rates can reach up to 20% in those who do not receive optimum treatment (Ferrer and Gárate, 2014; García et al., 2014). However, NCC prognosis has apparently improved thanks to better diagnostic techniques and improved disease management.

Other presentations of NCC are subdural and spinal. Radicular pain, weakness, and sensory deficits are common in patients with cysticercosis of the spinal cord (García et al., 2014).

NCC might, in fact, present any neurological symptom, but other manifestations more frequently seen are headache, nausea, vomiting, ataxia, confusion, associated stroke, or involuntary movements (Ferrer and Gárate, 2014; García et al., 2014).

Diagnosis

Taeniasis

Specific diagnosis of human taeniasis is mainly required in order to detect *T. solium* carriers, the source of infection of human cysticercosis. Thomas (2015) analyzed the different diagnostic assays for *T. solium* pointing out their benefits as well as their barriers.

Historically, taeniasis has been diagnosed by microscopic examination of human feces with the aim of finding parasite eggs and/or proglottids. Considering the intermittence in eggs/proglottids excretion, this microscopic method lacks sensitivity. In addition, the finding of eggs only reveals the presence of a tapeworm of *Taenia* genus since the morphology of the eggs of the three human species is the same. Concentration methods, particularly those using sedimentation, increase the diagnostic yield; however, the overall sensitivity of serial stool exams using concentration methods is still suboptimal (García et al., 2020). In fact, the reported sensitivity of microscopy ranges from 0% to 59% (Zammarchi et al., 2017).

The study of well-preserved gravid proglottids allows distinguishing between *T. solium* and the complex *T. saginata/asiaticus*. Proglottids can be pressed between glass slides to count the number of lateral branches (7–13 branches for *T. solium* and 14–32 for *T. saginata/asiaticus*) (Table 2) after India ink injection staining through the genital pore or some other clearing method. If the scolex were retrieved, the presence of the rostellar hooks could also enable the differentiation of *T. solium* from *T. saginata/asiaticus*, but the scolex is rarely available. There are some other morphological differences in mature proglottids to distinguish *T. solium* but the morphological identification of mature proglottids requires laboratory facilities and trained personnel.

Specific techniques to differentiate *Taenia* species include enzyme electrophoresis (glucose phosphate isomerase zymogrammes), molecular methods [different types of polymerase chain reaction (PCR) (Yamasaki et al., 2004; Mayta et al., 2008; Ng-Nguyen et al., 2017), loop mediated amplification method (LAMP) (Nkouawa et al., 2010), LAMP in combination with dot enzyme linked immunosorbent assay (dot-ELISA) (Nkouawa et al., 2016)] and coproantigen ELISA (CoAg-ELISA). A *T. solium* species-specific CoAg-ELISA (Guezala et al., 2009) showed high sensitivity and specificity. Unfortunately, it is experimental, and rarely available except to those working in this field. Similarly, neither enzyme electrophoresis nor molecular methods are available in most laboratories.

Summarizing, the following tools are recommended for the diagnosis of *T. solium* taeniasis (Zammarchi et al., 2017): (i) investigating the history of proglottid expulsion within the past year, with the support of visual materials to help the subject identify the proglottids; (ii) microscopic and macroscopic examination of stool samples collected on three different days; (iii) *Taenia* species identification should always be performed, especially in subjects exposed to *T. solium* in highly endemic countries (Latin America, Asia and Africa).

Cysticercosis

Cysticercosis out of the CNS

Palpable subcutaneous nodules can sometimes be felt and diagnosis is confirmed by biopsy. X-rays will only detect old cysts that have calcified. Ultrasonography may enable the visualization of the echogenic scolex in viable cysts (Satya et al., 2016).

Imaging studies are the most helpful in establishing the diagnosis of ophtalmocysticercosis. High resolution ultrasonography (USG), computed tomography (CT) and magnetic resonance imaging (MRI) help in the detection of the orbital cyst. The clinical diagnosis of live intraocular cysticercosis is based on the morphology of the parasite as visualized with the ophthalmoscope or slit-lamp biomicroscope (Dhiman et al., 2017).

Neurocysticercosis

Currently, a combination of neuroimaging tools and immunodiagnosis is used to identify cysticerci in the SNC. CT and MRI are safe and precise techniques (providing data on the number, localization, stage of the lesions and inflammation status). However, as they are also expensive ways of diagnosing NCC, they are usually scarce in many impoverished endemic areas of the world. Routine hematological tests are of poor use and, to date, molecular tests are not sensitive enough to be directly applied for routine case assessment (García et al., 2020).

When neuroimaging is inconclusive, the diagnosis can be confirmed with serology. Antibody detection is more frequently used given its higher sensitivity. The assay of choice for antibody detection is the enzyme-linked immunoelectrotransfer blot (EITB) assay, using lentil lectin purified parasite glycoprotein antigens (LLGP), which is available through the CDC Parasitic Disease Reference Laboratory (García et al., 2018). EITB sensitivity is around 98% for patients with two or more live parasites in the nervous system. However, the sensitivity is low (50–60%) in patients with only one intracranial cysticercus. The sensitivity is, in turn, higher in serum than in CSF (100% vs. 90%) (García et al., 2014). EITB specificity seems to be 100%, although pigs infected with *T. asiaticus* showed positive bands when tested with the EITB assay (Pilcher et al., 1991). The antibody detection in CSF by ELISAs in patients with more than one viable cysticercus is 89% sensitive and 93% specific. ELISAs are used when EITB is not available (García et al., 2014).

The detection of parasite antigens confirms the presence of viable parasites. Circulating antigens are only present as long as the infection is active. That is why the detection of antigens by ELISA with monoclonal antibodies in serum (the duration of antigens in CSF is unknown) is used to monitor the effectiveness of treatment or surgery (García et al., 2014).

Considering that tuberculosis and NCC show similar clinical and radiological features, a panel of diagnostic criteria for NCC was elaborated by Del Brutto et al. (2001), which has recently been updated by García et al. (2020). These diagnostic criteria are organized into absolute, neuroimaging, and clinical/exposure criteria. Likewise, proper interpretation of these criteria allows two degrees of diagnostic certainty, definitive and probable. These criteria have been widely used for the diagnosis of NCC in both hospital and field settings and have proven useful in areas of endemicity and non-endemicity.

Treatment

Taeniasis

Two drugs are the most effective against the three species of human *Taenia*, niclosamide and praziquantel. Niclosamide has little absorption, and therefore, no effect on NCC. However, praziquantel is well absorbed after oral administration and it is active not only against the adult stages of *Taenia* spp. but also against the larval stages. In the case of human taeniasis caused by *T. solium*, the patient could probably be infected by the adult stage as well as by the cysticercus. Therefore, to avoid that possible previously silent brain cysts can trigger seizures or other neurological symptoms as a consequence of the treatment with praziquantel (Flisser et al., 1993), niclosamide is recommended in *T. solium* taeniasis cases.

According to the systematic review conducted by Haby et al. (2020), the treatment with niclosamide 2 g for adults, praziquantel also in a single oral dose of 10 mg and triple-dose albendazole 400 mg, seem to be effective as taenicides in mass chemotherapy for *T. solium* taeniasis. However, White et al. (2020) are critical of the systematic review elaborated by Haby et al. (2020), since with respect to the analysis of efficacy, the authors did not account for differences in the methods used to ascertain the outcomes in the studies analyzed.

Neurological side effects in *T. solium* carriers are a potential danger in albendazole treatment that, like praziquantel, also crosses the blood-brain barrier (Sotelo and Jung, 1998).

Cysticercosis

Cysticercosis outside of the central nervous system and the eye is usually asymptomatic and does not require therapy. Untreated intraocular cysticercosis incites severe ocular inflammation, more so when the cyst dies. Anthelminthic therapy can lead, in turn, to severe inflammation in the event of a live cyst degenerating, hence, surgery is the treatment of choice.

In NCC cases, a single therapeutic approach does not exist. Depending on the viability, size and location of the cysts as well as the severity of the host immune response, a rational treatment has to be planned (García and Del Brutto, 2000). The treatment of NCC involves (Nash, 2003; Quintana, 2013): (i) prevention and health monitoring; (ii) anthelmintic drugs, which induce the death of

the larva and tapeworm; (iii) corticosteroids and other agents, which reduce or prevent the inflammatory phenomena related to the involution of the cyst, either spontaneous or induced; (iv) antiepileptic drugs, which reduce the frequency of or suppress seizures; (v) osmotic diuretics to treat increased intracranial pressure; and (vi) surgical procedures to treat increased intracranial pressure, hydrocephalus, and the mass effect of some lesions.

Related to the use of anthelmintic treatment in NCC, unfortunately, the efficacy of the two available cysticidal drugs, albendazole and praziquantel, is suboptimal, with cure rates between 40% and 50% at the doses usually recommended (Nash et al., 2013). The main point of the debate on the treatment of NCC is centered on whether the destruction of parasites by the antiparasitic drugs has clinical benefits to patients. There are arguments in favor (disappearance of the cysts, better clinical evolution of the treated patients, less severe cases), as well as against (antiparasitic treatment can cause severe and unnecessary brain inflammation or stroke which can be fatal, NCC becomes symptomatic only when the parasite naturally dies years after) (García et al., 2017). In 2002, a relative consensus was adopted among the specialists involved in the disease, and guidelines for the use of antiparasitic treatment in NCC were published (García et al., 2002).

Surgery is reserved for selected patients with NCC and plays a minor role in the management of the disease. The commonest indication is for the excision of intraventricular cysts, with endoscopy surgery being the procedure of choice as it is minimally invasive (Rajshekhar, 2010).

Control

Transmission of taeniasis has been largely eliminated in industrialized countries by improving sanitation and meat inspection. The intervention measures in the three *Taenia* species to interrupt the life cycle can be targeted at human level (tapeworm carriers as the infective source of infection of human, porcine and cattle cysticercosis), and at pig and cattle level (infected pigs and cattle as reservoirs of human taeniasis). Most of the control interventions target *T. solium* in order to prevent human NCC.

At human level

Ignorance is a major obstacle for the effective control of whatever disease. Even small changes in the behavior of people living in endemic areas by means of public education can affect parasite transmissions. In this sense, Johansen et al. (2014) developed an inexpensive, locally-adaptable, and implementable computer-based education tool, "The Vicious Worm," to improve the knowledge concerning *T. solium*.

By not eating raw or poorly cooked pork (*T. solium*, *T. asiaticus*) or beef (*T. saginata*), the likelihood that a person becomes infected is considerably reduced. Meat should be cooked at a temperature of between 60 °C and 65 °C, or until it loses its pink color, to ensure that cysts are killed (Okello and Thomas, 2017).

Improvements in personal sanitation (personal hygiene, washing hands after defecation) and safe disposal of feces (avoiding open defecation) could prevent human and porcine/bovine cysticercosis.

A limiting factor of the widespread application of health education is, on one hand, the high cost of such programs (Pawlowski et al., 2005), which also impacts the sustainability of this measure of this control measure. On the other hand, in cases in which health education has been included together with other intervention measures against *T. solium*, education appears to have had a limited impact (Lightowlers, 2013; Thomas, 2015).

Preventive chemotherapy is defined as the use of anthelminthic drugs, either alone or in combination, as a public health tool against helminth infections (WHO, 2006). Treatment of *Taenia* spp. carriers can be implemented in three ways (Gabrielli et al., 2011): mass drug administration (MDA) (the whole population is treated), targeted chemotherapy (only specific risk groups are treated), and selective chemotherapy (only patients, according to clinical status, are treated). Both, MDA and selective chemotherapy have been recommended for the control of *T. solium* and some evidence is available on their relative efficacy and cost-effectiveness.

The multiple control initiatives implemented in Ecuador, Guatemala, Mexico, and China were reviewed by Thomas (2015), concluding that (sic.) "Despite inconclusive evidence on the efficacy and cost-effectiveness of identification and treatment of taeniasis as a control strategy, the epidemiological basis of removing carriers from the population is undeniable. We would strongly recommend that all in-contacts of NCC cases are treated (2 g niclosamide for safety) as standard (Lian F. Thomas and Andrea Winkler)".

At porcine/bovine level

A key point in the propagation of the *Taenia* spp. lifecycle is the contact between pigs/cattle and human fecal material containing infective eggs. Hygiene measures such as best practices in animal husbandry and a correct management of sewage sludge and wastewater contribute to the prevention of the intermediate host becoming infected.

To prevent infection, chemoprophylaxis in pigs has been widely suggested as a control strategy. Besides, several vaccines against *T. solium* pig cysticercosis have been developed, of which two have progressed a great deal and have shown a high degree of potential for use in control strategies, namely SP3Vac and TSOL18 (Cysvax® produced by India Immunological Limited). Vaccination of

cattle against *T. saginata* with the TSA9/TSA18 vaccine has been attempted with some success. However, it does not seem that this vaccine is going to be commercialized any time soon (Thomas, 2015).

Once infected, porcine cysticercosis can be treated with a series of anthelmintics (Lightowlers, 2013; Thomas, 2015) of which oxfendazole (one single dose of 30 mg/kg) has demonstrated the best efficacy with a rapid reduction in cyst viability with 50% of cysts found to be nonviable at 1 week post-treatment and after 12 weeks all muscle cysts appear to be nonviable. Bovine cysticercosis also responds to anthelmintic treatment with praziquantel, and protection against reinfection appears to last for at least 12 weeks. Despite its efficacy, praziquantel has not yet been formulated for cattle and is, therefore, not commercially available as a control measure for *T. saginata* (Okello and Thomas, 2017).

Once dead, post-mortem detection of cysticerci in pigs and cattle by means of visual inspection of the carcasses is fundamental to prevent human taeniasis. However, meat inspection lacks sensitivity, especially in cases of low cost burden. In addition, in many *T. solium* endemic low income countries infected pigs are diagnosed ante-mortem (tongue inspection) and sold in clandestine markets, thus escaping the condemnation of carcasses (Murrell, 2005).

Cold treatment has been proven to kill the cysticerci of *T. solium* and *T. saginata*, within 6–10 days at temperatures below −10 °C and at −24 °C in just 24 h (Sotelo et al., 1986; Hilwig et al., 1978). In addition to freezing, gamma-radiation, cooking and salt pickling have been shown to successfully reduce the viability of cysticerci.

Combining methods in the one health approach

Available data suggests that choosing a single approach to control human *Taenia* is not sufficient. The three *Taenia* species cause zoonotic diseases, in which not only humans but also animals are involved. Therefore, to tackle the problem, strategies that target both, the human and animal hosts, should be adopted (Okello and Thomas, 2017).

In this sense, WHO is promoting prevention and control of *T. solium* infection through animals with the One Health approach (https://www.who.int/activities/promoting-prevention-and-control-of-taenia-solium-infection-through-animals-with-the-one-health-approach). Specific control measures in the pig population include the vaccination of pigs with the TSOL18 vaccine and the treatment with oxfendazole.

Multiple control initiatives can be found in the literature with different results. One successful example is Peru: a large integrated program combining human and porcine mass chemotherapy, pig vaccination, and coproantigen detection-based case confirmation over a one-year period has proven effective in achieving focal elimination of *T. solium* transmission in a large area on the northern coast of the country (García et al., 2016). Likewise, more recently, the integrated interventions in humans and pigs carried out in a 2-year study in Zambia (Africa) (CYSTSTOP), eliminated viable infection in pigs and significantly reduced the prevalence of taeniasis caused by *T. solium* in the intervened villages (Gabriel et al., 2020).

Future perspectives

Taenia solium: The 2012 WHO roadmap for *T. solium* control and elimination by 2015 or 2020, depending on the countries, has not been met, although notable progress has been made (De Coster et al., 2018). *T. solium* has been included in the consultation process for the new 2030 goals proposed for priority NTDs (CystiTeam Group for Epidemiology and Modelling of Taenia solium Taeniasis/Cysticercosis, 2019). According to Dixon et al. (2020), the 2030 target is technically feasible with the current intervention options and tools with the implementation of computational transmission models such as cystiSim (Braae et al., 2016) and EPICYST (Winskill et al., 2017). However, current tools, like diagnostic methods or necropsy of pigs to measure the infection, present many limitations to effectively achieve the target. Existing *T. solium* models can be improved through collaboration between modeling groups, field epidemiologists, program stakeholders and policymakers, and used jointly to support the design, implementation and assessment of interventions in endemic countries (Dixon et al., 2020).

Taenia saginata: Since the eggs of *T. saginata* do not infect humans, NCC is not related to this species, and therefore, the human burden of disease related to this species is assessed as low, although no precise studies have been undertaken. In this sense, the FERG (WHO Foodborne Disease Burden Epidemiology Reference Group) report excluded *T. saginata* from their priority list (FERG, 2015). *T. saginata*, therefore, is mainly of economic interest in the cattle industry due to carcass condemnation. In this sense, *T. saginata* has recently been included in a risk-based surveillance for meat-borne parasites by means of a design tool called SURVTOOLS (Alban et al., 2020).

Taenia asiaticus: An international forum called *Taenia asiatica* Research Group was created in 2011 (TaRG international, targint.net) to raise awareness of the existence of this third *Taenia* species, *T. asiaticus*, among veterinarians, health workers and researchers. TaRG is made up of scientists from countries of different continents with the aim of cooperating in the molecular identification of human and pig material (adult and larval stages) around the world. This cooperation is essential to definitely elucidate whether *T. asiaticus* is an exclusively Asian parasite or if it tends to be misdiagnosed around the world. Another gap in the pathogenicity of this species is to ascertain whether *T. asiaticus* is able to cause human cysticercosis (Galán-Puchades and Fuentes, 2004, 2013a,b). Currently, only molecular methods are able to identify *T. asiaticus* in humans and pigs, since morphology and immunology are useless, but unfortunately, although largely used in research, those methods are not employed in routine diagnosis.

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