Taenia solium taeniasis/cysticercosis: From parasite biology and immunology to diagnosis and control

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Contents

1. Introduction 4

2. *Taenia solium* Biology and Epidemiology 5

2.1. Human taeniasis: pre-adult and adult tapeworm parasitology and immunology 6

2.2. Human taeniasis: epidemiology and risk factors 7

2.3. Eggs in the environment: biological characteristics 13

2.4. Porcine cysticercosis: oncosphere, post-oncosphere and cysticercus parasitology and immunology 14

2.5. Porcine cysticercosis: epidemiology and risk factors 18

2.6. Human cysticercosis: parasitology, immunology and clinical pathogenesis 28

2.7. Human cysticercosis: epidemiology and risk factors 30

3. Morbidity and Economic Impact Associated with *Taenia solium* 40

4. Interventions to Control and Eliminate *Taenia solium* 44
4.1. *Taenia solium* diagnostics. 44
4.2. Chemotherapy in humans 49
4.2.1 Mass Drug Administration in humans alone 47
4.2.2 Mass Drug Administration in humans combined with health education 47
4.2.3 Treatment of school-age children or selected treatment of taeniasis carriers/those at risk 52
4.3. Health education 56
4.4. Improved pig husbandry 57
4.5. Improved sanitation 58
4.6. Improved meat inspection 58
4.7. Porcine cysticercosis treatment 59
4.8. Porcine cysticercosis vaccination 60
4.8.1 TSOL18 vaccine 62
4.8.2 S3Pvac vaccine 65
4.9. Combined interventions 67
5. Conclusions and Future Directions 71
List of Abbreviations 74
References 78

Abstract

Infection with the pork tapeworm (*Taenia solium*) is responsible for a substantial global burden of disease, not only restricted to its impact on human health, but also resulting in a considerable economic burden to smallholder pig farmers due to pig cysticercosis infection. The life-cycle, parasitology and immunology of *T. solium* are complex, involving pigs (the intermediate host, harbouring the larval metacestode stage), humans (the definitive host, harbouring the adult tapeworm, in addition to acting as accidental intermediate hosts) and the environment (the source of infection with eggs/proglottids). We review the parasitology, immunology, and epidemiology of the infection associated with each of the *T. solium* life-cycle stages, including the pre-adult/adult tapeworm responsible for human taeniasis; post-oncosphere and cysticercus associated with porcine and human cysticercosis, and the biological characteristics of eggs in the environment. We discuss the burden associated, in endemic settings, with neurocysticercosis (NCC) in humans, and the broader cross-sectoral economic impact associated both with NCC and porcine cysticercosis, the latter impacting food-value chains. Existing tools for diagnostics and control interventions that target different stages of the *T. solium* transmission cycle are reviewed and their limitations discussed. Currently, no national *T. solium* control programmes have been established in

endemic areas, with further work required to identify optimal strategies according to epidemiological setting. There is increasing evidence suggesting that cross-sectoral interventions which target the parasite in both the human and pig host provide the most effective approaches for achieving control and ultimately elimination. We discuss future avenues for research on *T. solium* to support the attainement of the goals proposed in the revised World Health Organization neglected tropical diseases roadmap for 2021–2030 adopted at the 73rd World Health Assembly in November 2020.

Key-words: *Taenia solium*, human taeniasis, human cysticercosis, neurocysticercosis, porcine cysticercosis, risk factors, diagnosis, praziquantel, oxfendazole, vaccination

1. INTRODUCTION

Taenia solium, also known as the pork tapeworm, is a species of parasitic tapeworm belonging to the Taeniidae family (Phylum: Platyhelminthes, Class: Cestoda, Subclass: Eucestoda, Order: Cyclophyllidea) (CAB International, 2020). Approximately 20 species are included in the *Taenia* genus along with *T. solium*, including *T. sagniata* (beef tapeworm), *T. hydatigena* (canine tapeworm), *T. crassiceps* (rodent tapeworm), *T. ovis* (canine tapeworm or sheep measles), *T. pisiformis* (canine tapeworm) (Pawlowski, 2002) and the more recently characterised *T. asiatica* (pork tapeworm exhibiting a *T. saginata*-like morphology and geographically restricted to Asia) (Galán-Puchades and Fuentes, 2013). All *Taenia* species involve multi-host systems; however only *T. solium*, *T. saginata* and *T. asiatica* are zoonotic, involving human hosts as a component of their life-cycle (Galán-Puchades and Fuentes, 2013; Eom *et al*., 2020).

Taenia solium is widely endemic across Meso and South America, sub-Saharan Africa, and Central and East Asia, based on country-level classification for strong evidence indicating presence of the full transmission cycle (Fig. 1) (Donadeu *et al.*, 2016). Regionally, the most recent literature-based mapping work has identified that *T. solium* is present in 31 of 54 countries in Africa (Braae *et al.*, 2015b), 16 of 41 countries in Central America and the Caribbean Basin (with reports of porcine cysticercosis in 11 departments across Colombia, Guatemala, Honduras, Mexico, Nicaragua and Venezuela (Braae *et al.*, 2017a)), and eight of 16 countries for *T. solium* porcine cysticercosis across East and Southeast Asia (Cambodia, China, East Timor, Indonesia, Lao People's Democratic Republic (Lao PDR), Mongolia, Myanmar and Vietnam) (Braae *et al.*, 2018a). There is substantial geographical overlap with other *Taenia* species, for example with *T. saginata*, which is present across the Americas

(Braae *et al.*, 2018b), Africa (Dermauw *et al.*, 2018a; Hendrick *et al.*, 2019; Saratsis *et al.*, 2019) and parts of Asia (Torgerson *et al.*, 2019).

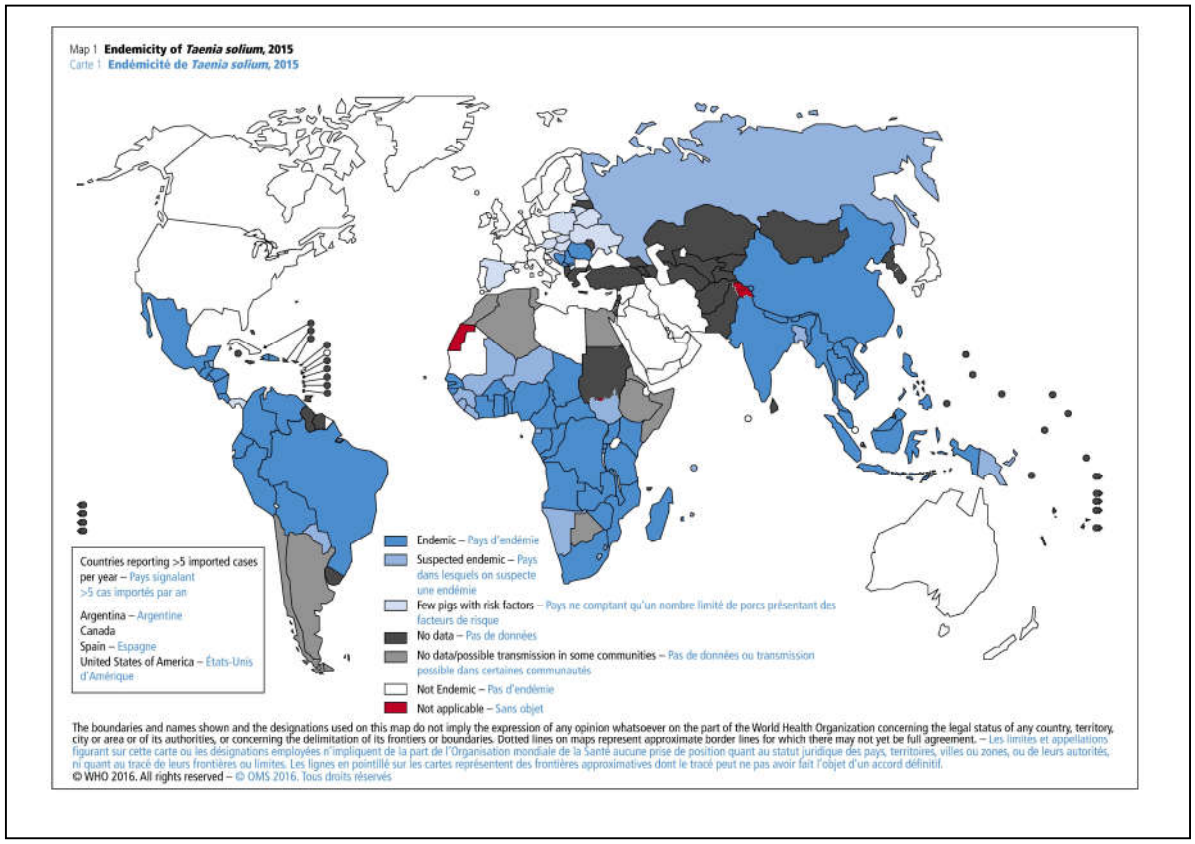

Figure 1. Endemicity map of *Taenia solium* for 2015 based on evidence for porcine cysticercosis, information obtained from peer-reviewed publications, and evidence of imported cases of porcine cysticercosis. Reproduced from Donadeu *et al.* (2016). Available: https://apps.who.int/iris/bitstream/handle/10665/251908/WER9149_50.pdf?sequence=1.

2. *TAENIA SOLIUM* BIOLOGY AND EPIDEMIOLOGY

A number of stages are involved in the development of *T. solium*, including pre-adult tapeworm and reproductive adult tapeworm stages in the definitive human host, an egg stage in the environment, and the cysticercus stage in the intermediate porcine host (Pawlowski, 2002). Fig. 2 illustrates the life-cycle of *T. solium*.

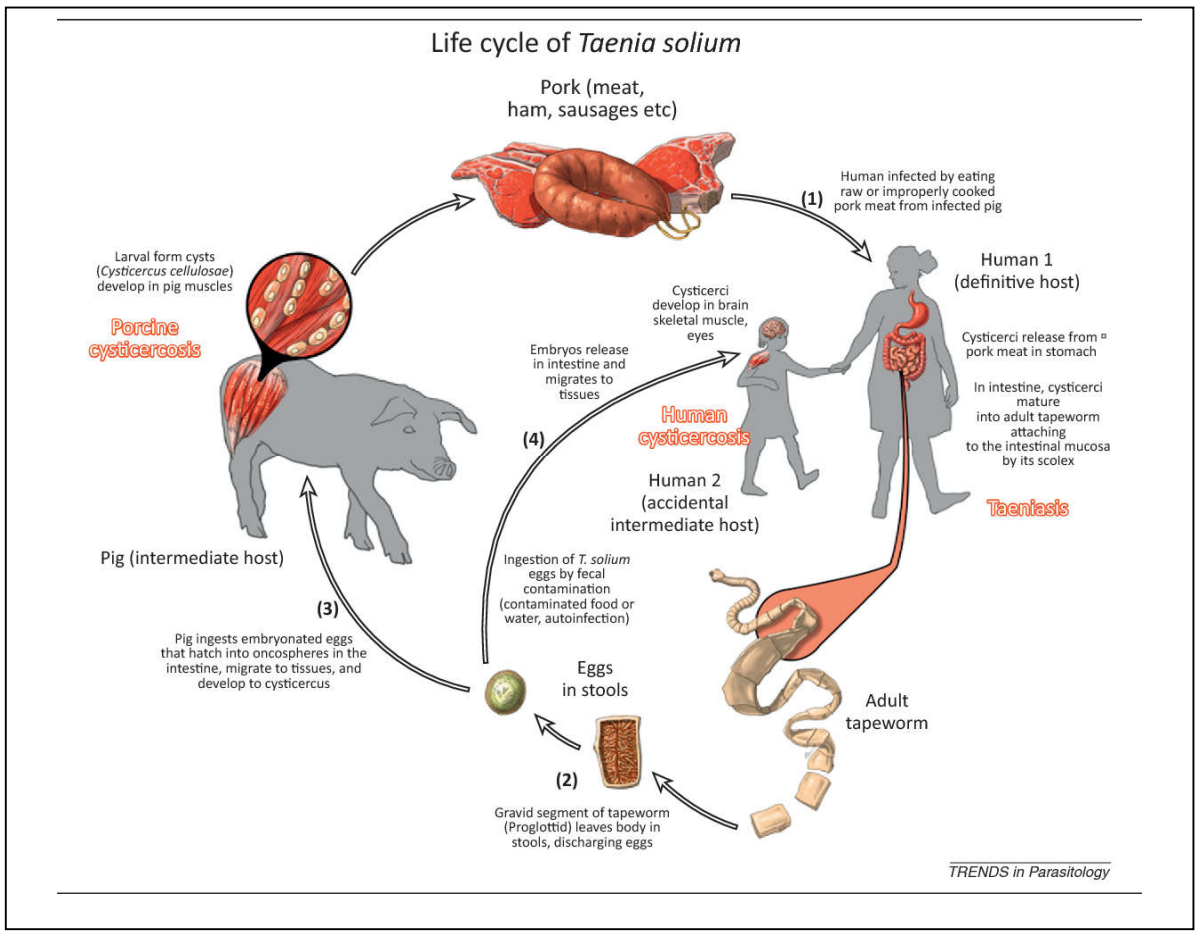

Figure 2. Life-cycle of *Taenia solium* showing the main stages in the human, pig host and environment. Reproduced from Rasamoelina-Andriamanivo *et al.* (2013).

2.1. Human taeniasis: pre-adult and adult tapeworm parasitology and immunology

Consumption of undercooked or raw pork meat, infected with cysticerci, leads to adult tapeworm infection in the definitive human host. Within the human intestine, the cysticercus loses its bladder wall and the scolex evaginates, enabling attachment to the intestinal mucosa by the hooks and suckers located on the scolex (Rabiela *et al.*, 2000). The duration of the process of development from successful invasion and evagination of the cysticercus to a fully mature and reproductively competent adult (the pre-adult tapeworm stage) is 2–4 months (Pawlowski, 2002; Flisser, 2013). A crucial *T. solium*-derived protein called *Taenia solium* calreticulin, expressed in the suckers and rostellum, may be involved in the modulation of the

host immune system during definitive-host infection (Flisser *et al.*, 2010). An adult tapeworm measures approximately 1.5–4 m in length (Flisser, 2013; Garcia *et al.*, 2014), with the scolex and neck preceding the elongated, ribbon-shaped strobila (or the main body segments) which consists of 700–1,000 proglottid segments (Pawlowski, 2002; Flisser, 2013). These segments will be of different shape, size and stage of development, with small immature proglottids located nearest to the scolex, followed by the mature proglottids which contain both testes and ovary lobes, hence making the organism hermaphroditic. Finally, the gravid segments, containing approximately 50,000–60,000 eggs each (Pawlowski, 2002; Flisser, 2013), are located furthest from the scolex, at the end of the strobila.

A number of animal models are currently available to study host immunity and variability in susceptibly to *T. solium* intestinal taeniasis, including the hamster (*Mesocricetus auratus*) and mongrel gerbils (*Meriones unguiculatus*) (Ávila *et al.*, 2006, 2008). However, the chinchilla (*Chinchilla lanigera*) is the only animal model in which adult tapeworms become gravid and produce viable eggs capable of onward infectivity (Maravilla *et al.*, 2011). These models have demonstrated an initial host immune response in the intestinal mucosa involving both subsets of T-helper cells (Th1/Th2), followed by a shift towards a Th2 immune response as adult worm expulsion begins from the host (Ávila *et al.*, 2008). While it is generally considered that the majority of human taeniasis infections involve a single tapeworm (Pawlowski, 2002), multiple infections have been reported. A study in China, for example, identified that of 42 *T. solium* taeniasis cases in school-age children, 12 harboured multiple tapeworms, with one individual hosting 11 adult tapeworms (Li *et al.*, 2019).

Eggs are released into the environment via the faeces freely or within the detached gravid proglottids by apolysis, approximately 2–3 times per week (Pawlowski, 2002; Flisser, Craig and Ito, 2011), with each adult worm capable of shedding up to 300,000 eggs per day (Pawlowski, 2002). Specific tapeworm proteins of interest are the copro-antigens, which are

genus-specific parasite products associated with metabolism, and are found in the faeces of infected hosts independent of the presence of eggs and proglottids (Allan *et al.*, 2003; Mwape and Gabriël, 2014). These antigens (Ag) form the target for the widely used enzyme-linked immunosorbent assay (copro-Ag-ELISA) (Allan *et al.*, 1990), specifically the assay developed from hyperimmunized rabbit-derived polyclonal antibodies with either adult worm excretion-secretion (ES) or somatic products (Allan *et al.*, 1990, 1992; Deplazes *et al.*, 1991; Mwape and Gabriël, 2014). *Taenia* infection using the copro-Ag-ELISA can be detected as early as 2 weeks post-infection, i.e. before proglottid patency (Tembo and Craig, 2015), which occurs 86 days post-infection as reported by Tembo and Craig (2015). This highlights the ability of the copro-Ag-ELISA test to detect immature tapeworms and explains why this assay reports approximately 2.5 times more cases than other methods which detect reproductive stages, such as coprology/microscopy to detect eggs (Mwape and Gabriël, 2014). Other ES products expressed by the adult tapeworm (Wilkins *et al.*, 1999), for example ES33 and ES38 (Levine *et al.*, 2004, 2007), have been used as targets for antibody-based diagnostics including an immunoblot assay.

Evidence suggests that adult tapeworms live for less than five years (Garcia *et al.*, 2014). This estimate is based on observations following the return of British soldiers from a military tour of India whereby significant numbers of soldiers or their immediate relatives developed neurological disease due to neurocysticercosis (NCC) approximately 2–5 years later, but only very few tapeworm carriers were identified after five years amongst this cohort (Mac Arthur, 1934; Dixon and Hargreaves, 1944; Dixon and Lipscomb, 1962).

2.2. Human taeniasis: epidemiology and risk factors

Prevalence surveys indicate that human taeniasis prevalence due to *T. solium* is substantially lower than the prevalence of infection by the other parasite stages (i.e., porcine and human

cysticercosis). As measured by antigen detection in stool with the copro-Ag-ELISA, prevalence ranges from 1.5% to 23.4% across settings (Rodriguez-Canul *et al.*, 1999; Garcia *et al.*, 2003b; Raghava *et al.*, 2010; Mwape *et al.*, 2012, 2015; O'Neal *et al.*, 2012; Mohan *et al.*, 2014; Madinga *et al.*, 2017). However, the majority of studies (6/9) shows a prevalence of approximately 3% or less (Rodriguez-Canul *et al.*, 1999; Garcia *et al.*, 2003b; Raghava *et al.*, 2010; Mwape *et al.*, 2012; O'Neal *et al.*, 2012; Mohan *et al.*, 2014). Seroprevalence based on antibodies against *T. solium* tapeworm ranges from 2.3% to 2.9% (Holt *et al.*, 2016). Stool examination-based surveys have reported 9.7% prevalence (Vora *et al.*, 2008), and an egg positive/self-reported survey reported 8.4% prevalence (Conlan *et al.*, 2012).

Exploring risk factors for *T. solium* taeniasis in humans is challenging given the low prevalence of infection in most settings. The low number of positives therefore requires a substantial sample size to explore associations with potential risk factors (Rodriguez-Canul *et al.*, 1999; Mohan *et al.*, 2014). Identified risk factors (Table 1) statistically significantly associated with human *T. solium* taeniasis by antigen positivity (copro-Ag-ELISA) include: i) household overcrowding (of more than six people), identified through a classification and regression tree (CART) analysis of risk variables in Zambia (Mwape *et al.*, 2015); ii) individuals frequently consuming pork tongue in Vietnam (Odds Ratio (OR) = 4.62, 95% CI = 1.49–14.3) (Ng-Nguyen *et al.*, 2018c), and iii) consumption of undercooked pork in India (OR = 2.65, 95% CI = 1.19–5.94), with positivity measured by stool examination and multiplex polymerase chain reaction (PCR) (Prasad *et al.*, 2007). Copro-Ag-ELISA positivity was also significantly associated with iv) individuals belonging to households containing an infected pig (lingual palpation and serology confirmed) in Mexico (chi-squared = 17.81, p-value = 0.005) (Rodriguez-Canul *et al.*, 1999); v) history of passing tapeworm segments in stool (OR = 3.31, 95% CI= 2.31–4.76) in India (Prasad *et al.*, 2007), and vi) family members with NCC (OR = 17.12, 95% CI= 1.51–194.21), also in India (Mohan *et al.*, 2014).

Age-related associations and trends in human taeniasis have been identified across geographical settings (Garcia *et al.*, 2003b; Prasad *et al.*, 2007; Vora *et al.*, 2008; Madinga *et al.*, 2017). Age-infection peaks in younger individuals have been observed, with copro-Ag-ELISA prevalence statistically significantly associated with age (p-value < 0.05) in the Democratic Republic of the Congo (DRC) (Madinga *et al.*, 2017). Evidence for this association includes the observation of: a) highest prevalence and age peaks in those less than 10 years of age in the DRC (Madinga *et al.*, 2017); b) individuals being < 55 years identified as an important determinant in the CART analysis in one of two districts analysed in Zambia (Mwape *et al.*, 2015), and c) a significant copro-Ag-ELISA positivity peak in those less than 10 years of age compared to other age groups (p-value = 0.042) in Peru (Garcia *et al.*, 2003b). In Guatemala, prevalence initially increases with age, followed by a sharp decrease after 30 years of age (Allan *et al.*, 1996). By contrast, a few studies have identified age-infection peaks in older age groups, with stool examination prevalence peaking in 45–55 year olds in India (Vora *et al.*, 2008), and the odds of being stool examination/multiplex PCR-positive being higher in those over 15 years of age (OR = 1.47, 95% CI= 1.01–2.13) also in India (Prasad *et al.*, 2007).

Sex is also associated with risk of infection in Asia, with the male sex being statistically significantly and positively associated (OR = 2.20, 95% CI= 1.34–3.63) in Lao PDR (Conlan *et al.*, 2012). However, this was based on egg-positivity and self-reporting, which can introduce substantial measurement bias. Males also had significantly higher odds of being *Taenia* species-positive based on microscopy/multiplex PCR (OR = 2.77, 95% CI = 1.00–7.68) in Vietnam (Ng-Nguyen *et al.*, 2018c). A number of studies, especially those conducted in Asia, where other *Taenia* species are highly prevalent, have either used diagnostics which are unable to differentiate between *Taenia* species (e.g. microscopy, self-reporting), or only report associations with all aggregated *Taenia* species identified, rather

than with individual species, even when adopting molecular methods of detection (Prasad *et al.*, 2007; Ng-Nguyen *et al.*, 2018c; Li *et al.*, 2019).

A further feature of human taeniasis infection epidemiology is spatial clustering of infection. A large cluster of copro-Ag-ELISA positive cases was identified in Zambia using a risk-adjusted nearest neighbour hierarchical spatial clustering method (Mwape *et al.*, 2012). In the DRC two statistically significant clusters (total sample $n = 276$ and $n = 9$, respectively, p-value < 0.001) were identified by Madinga *et al.* (2017) using (Ripley's) K functions. (Ripley's K functions (Ripley, 1981) are used to quantify significant spatial clustering of infection indicators over and above what would be expected due to natural environmental heterogeneity.) In Peru. residents were more likely to be copro-antigen positive if living within 100 m of a tongue-positive pig (p-value = 0.02) (O'Neal *et al.*, 2012). Significant hotspots, based on stool examination/copro-Ag-ELISA were identified in India (using the spatial scan statistics software SaTScan™), with Relative Risk (RR) = 36.67 (p-value = 0.02) (Raghava *et al.*, 2010). (SaTScan™ (SaTScan, 2018) is a free software that analyses spatial, temporal and space-time data using spatial, temporal, or space-time scan statistics.)

Table 1 Risk factors for *Taenia solium* taeniasis in humans

Region	Eating infected pork/under-cooked pork	Belonging to a household with an infected pig	Household size (number of residents > 6)	Sex	Age	Geographical hetero-geneity	Spatial clustering	Ethnicity	History of past or current infection
Africa			Mwape *et al.*, 2015**		Mwape *et al.*, 2015** Madinga *et al.*, 2017**		Mwape *et al.*, 2012** Madinga *et al.*, 2017**		
Central/ South America	Rodriguez-Canul *et al.*, 1999**	Rodriguez-Canul *et al.*, 1999**			Garcia *et al.*, 2003b**		O'Neal *et al.*, 2012**		
Asia	Ng-Nguyen *et al.*, 2018c^** Prasad *et al.*, 2007**			Conlan *et al.*, 2012^** Ng-Nguyen *et al.*, 2018c^**	Prasad *et al.*, 2007** Vora *et al.*, 2008**	Li *et al.*, 2019	Raghava *et al.*, 2010**	Conlan *et al.*, 2012	Prasad *et al.*, 2007** Mohan *et al.*, 2014** Li *et al.*, 2019

** Statistically significant association identified in formal statistical analysis used to test associations of risk factors or in spatial statistics analysis.

^ *Taenia* spp, not just *T. solium.*

2.3. Eggs in the environment: biological characteristics

Taenia solium eggs (from which the oncospheres will hatch, Singh *et al.*, 2020), are spherical or radial in appearance and found individually or within gravid proglottids. While eggs can be identified through traditional stool examination, it is impossible to discriminate *T. solium* eggs morphologically from those of *T. saginata* and other *Taenia* species (Jeri *et al.*, 2004). The oncosphere is surrounded by a protective embryophore, measuring approximately 26–43 μm in diameter (Yoshino, 1933c; Flisser, 2013) to protect against external factors in the environment. This stage is known as the hexacanth embryo, as six embryonic hooklets are located on the oncosphere. Eggs released from the human gut will be at a range of developmental stages: i) some still developing (although the capability of further maturation of immature eggs in the environment is debated (Alvarez Rojas *et al.*, 2018)); ii) those which are readily infective to the intermediate host; and iii) non-infective or senile eggs, which are hypothesised to serve as immunizing factors if consumed by the intermediate host (Pawlowski, 2002).

Most of the research to assess extrinsic factors affecting survival and viability of taeniid eggs has been conducted in other species. Essential extrinsic factors, mainly examined in *T. saginata* (Murrell, 2005), include: whether oncospheres are located in the proglottids or isolated (tested under lab conditions) (Suvorov, 1965); humidity (Silverman and Maneely, 1955); temperature, and seasonal factors (Rukhova, 1963; Bucur *et al.*, 2019). Studies of longevity of *T. saginata* eggs have shown that a small proportion of them remains infective for approximately six months in natural soil conditions, in Denmark (Ilsoe *et al.*, 1990). Under different climatic conditions they can, approximately, survive for: i) 10 months in damp temperate climates (Shekhovstov, 1975); ii) up to five months in winter and spring;

iii) up to nine months in warm climates in summer/autumn (Rukhova, 1963), and iv) up to 130 days in water (Shekhovstov, 1975).

Mechanisms of dispersal for *T. solium* eggs have also been explored, implicating dung beetles as a key dispersal vector in Peru (Arriola *et al*., 2014; Gomez-Puerta *et al*., 2014; Gomez-Puerta *et al*., 2018; Vargas-Calla *et al*., 2018). Studies have documented that pigs infected with two nematode species (*Ascarops strongylina* and *Physocephalus sexalatus*), which require dung beetles (*Ammophorus rubripes*) as an intermediate host, were statistically significantly associated with presence of cysticercus-antibody positivity in pigs (OR = 4.30, 95% CI = 1.83–10.09 and OR = 2.21, 95% CI = 1.50–3.28, respectively) (Arriola *et al.*, 2014). Gomez-Puerta *et al*. (2014) established that *T. solium* viable eggs could be carried in the digestive system of *Am. rubripes* dung beetles for up to 39 days with approximately 40% viability at 24 days post-infection. *Ammophorus rubripes* harbouring *T. solium* eggs have been captured from villages in Piura, Northern Peru (Vargas-Calla *et al.*, 2018), while cysticercosis has developed in pigs orally challenged with *Am. rubripes* harbouring *T. solium* eggs (Gomez-Puerta *et al*., 2018).

2.4. Porcine cysticercosis: oncosphere, post-oncosphere and cysticercus parasitology and immunology

Consumption of infective material (released mature individual eggs and gravid proglottids) by the porcine intermediate host results in development of porcine cysticercosis. Once ingested, oncospheres hatch and are exposed to bile and enzymes which disaggregate the embryophoric structure, permitting dissolution of the oncospheral membrane and activation of mature oncospheres in the porcine gut (Pawlowski, 2002; Flisser, 2013). Oncosphere-derived enzymes and hooks located on the surface enable crossing through the intestinal mucosa, whereby activated oncospheres are able to enter sub-mucosal blood and/or lymphatic

vessels for further dissemination (Pawlowski, 2002; Flisser, 2013). Migration occurs to predilection sites including the skeletal and cardiac muscles, brain and sub-cutaneous tissue, where the oncospheral stage initiates the process of metacestode (or larval-stage) development into mature vesicular (viable) cysticerci. Pawlowski (2002) described a post-oncospheral stage. However, Rodríguez *et al.* (2006) did not find evidence for a post-oncospheral stage, defined as an intermediate embryonic latent stage capable of dividing and migrating to further host muscles and tissues. Yoshino was the first to examine post-embryonal metacestode development in the porcine host (Yoshino, 1933a,b,c), with the process of maturation taking 2–3 months (Yoshino, 1933b; Verastegui *et al.*, 2000). Structures suggestive of metacestodes are evident in tissues very early (2–6 days post-infection) in these original studies (Yoshino, 1933b). More recent work suggests, however, that cysticerci are first detectable macroscopically at 14 days post-infection (Garrido *et al.*, 2007). Endogenous production of testosterone has been hypothesised to be important in cysticercal growth and development, as demonstrated for *T. crassiceps* (Romano *et al.*, 2003).

When maturation is achieved, the cysticerci develop into small (0.5–1.5cm), spherical or oval vesicles containing an invaginated scolex within an inner chamber and an outer chamber comprising the vesicular fluid, which is enclosed by a translucent bladder wall (Pawlowski, 2002; Flisser, 2013). This stage is infective, and in the porcine host is morphologically characterised as a cellulose-type cysticercus (Flisser, 2013) (which gives rise to the name *Cysticercus cellulosae*). Direct observation of (viable) cysticerci in pigs can either by undertaken by the simplest method of tongue inspection (lingual palpation), although this is likely to miss animals with low infection burdens (Sciutto *et al.*, 1998), or by the more-intensive necropsy-based approach, with subsequent inspection of carcass tissues (Lightowlers *et al.*, 2016a).

A number of host-derived proteins have been implicated in cysticercal growth, survival and permanence. These include *in vitro* identification of transforming growth factor-β (TGF-β) (Adalid-Peralta *et al.*, 2017), and the localisation of intermediate-host haptoglobin and haemoglobin in cysticercal vesicular fluid, with the ability to bind to cysticercal receptors (Navarrete-Perea *et al.*, 2014, 2016). Victor *et al.* (2012) further characterised the proteome of ES proteins produced by *T. solium* cysticerci, reporting 76 proteins including 27 *T. solium*-derived proteins and a further 32 likely to be of *T. solium* origin, with the majority likely involved in parasite survival (the remaining 17 were of host origin). ES proteins are also important parasite targets for porcine cysticercosis serological diagnostics, including the monoclonal antibodies selected against these proteins in the antigen-ELISA (Ag-ELISA) assays (Harrison *et al.*, 1989; Dorny *et al.*, 2000). Antibody-based diagnostics, such as the widely used immunoblot format (Tsang *et al.*, 1989), also target extracellular secreted proteins in the 8-kDa glycoprotein family located in the vesicular fluid, alongside other anchor-membrane proteins and integral membrane proteins (Hancock *et al.*, 2004, 2006; Garcia *et al.*, 2018).

Other immune evasion and mitigation strategies employed by the metacestode stage may also involve host lymphocyte apoptosis induced by parasite-expressed cysteine proteases in the inflammatory reaction surrounding both pig musculature and brain metacestodes (Solano *et al.*, 2006; Sikasunge *et al.*, 2008a). Porcine cysticercosis can also manifest as NCC, with localisation of the cysticerci in the central nervous system (CNS). Work in Tanzania has demonstrated that naturally-infected pigs with NCC develop clinical signs and seizures comparable to human NCC, with older pigs more likely to have degenerating cysts and suffer seizures (Trevisan *et al.*, 2016), alongside alterations of behaviours in infected sows including less time spent feeding and increased social isolation (Trevisan, *et al.*, 2017a). This contradicts earlier work by Mkupasi *et al.* (2015), who found mainly viable cysts with

mostly mild/moderate inflammation in older pigs. The authors suggested, based on these findings, that pigs are more adapted to larval-stage infection (as they are the natural intermediate host), although the authors did not control for the time of exposure.

The efficiency of establishment of *T. solium* eggs in the porcine host (proportion of eggs establishing and developing to metacestode infection) ranges from 0.94% to 5% of all ingested eggs using an 8,400–15,000 egg input (Flisser *et al.*, 1979; Molinari *et al.*, 1983; Kumar *et al.*, 1987; Pathak and Gaur, 1990; Nascimento *et al.*, 1995). Tsang *et al.* (1991) identified a 0.28% infection efficiency using 10–20,000 eggs with 20% viability. A low-intensity porcine cysticercosis infection model (median of 2–40 cysts per pig) has also been developed with susceptible pigs ingesting *Ammophorus rubripes* beetles harbouring 12–52 eggs (beetles all exposed to a single proglottid) (Gomez-Puerta *et al.*, 2018). Santamaria *et al.* (2002). These studies suggest that egg viability before challenge should be determined, not always the case in historical studies, in order to calculate reliably the efficiency of establishment (and determining whether this would be positively or negatively density dependent). Santamaria *et al.* (2002) estimated that after challenge with eggs of 80% viability, the percentage of pigs infected at approximately 2–4 months (determined by necropsy) was approximately 87%. In addition, pigs receiving small doses (10 or 100 eggs) harboured caseous (inactive) cysticerci, indicating that the host immune system had killed the metacestode in a relatively short period, compared to mainly vesicular, infective cysticerci, also found in the brain, in those pigs receiving higher doses (1,000 eggs or more) (Santamaria *et al.*, 2002). Antibodies were also detected in 40–75% of pigs in the lower-dose group, whereas 100% of pigs developed an antibody response in the higher-dose group, suggesting humoral immunity is related to the developmental stage of the metacestode and the severity (intensity) of the infection input. A correlation between circulating Ag titre and number of viable cysts has also been confirmed (Deckers *et al.*, 2008).

Conlan *et al*. (2009) suggested that acquired immunity to *T. solium* can be elicited following ingestion of eggs (de Aluja *et al.*, 1996, 1999; Santamaria *et al*., 2002; Lightowlers *et al.*, 2003; Deckers *et al.*, 2008), as either pre- or post-encystment immunity was demonstrated for other *Taenia* species (Lightowlers and Rickard, 1993). Equally, a role of age at primary egg exposure has been suggested in relation to the robustness of the innate immune response (Conlan *et al.*, 2009). This was motivated by the study of Deckers *et al.* (2008), who found, in naïve pigs (and at 3 months post-infection), the presence of 98% viable cysts when the pigs were infected at 1 month of age, 45% viable cysts when pigs were infected at 3 months of age, but mostly degenerated cysts (1.5% viable) when pigs were infected at 5 months of age.

Maternal protection from antibodies passed from sow to offspring via colostrum has been documented. In studies conducted in Peru, maternally-derived IgG antibodies were detected at 7 months (28 weeks) of age (against synthetic peptides) (Handali *et al.*, 2004), and even at 35 weeks (27 weeks after weaning) (Gonzalez *et al.*, 1999). A study in Zambia, however, only found maternally-derived antibodies up to 2 months of age (Sikasunge *et al.*, 2010). Both in Peru and Zambia, it was documented that the majority of IgG antibodies began waning from 8 to 14 weeks of age (Gonzalez *et al.*, 1999; Sikasunge *et al.*, 2010).

2.5. Porcine cysticercosis: epidemiology and risk factors

Estimates of porcine cysticercosis (sero)prevalence vary significantly given location and type of diagnostic used.

Prevalence by antibody-based measurement is generally higher than other prevalence indicators, as this diagnostic measures exposure rather than active infection, with seroprevalence estimates ranging from 3.2% to 76% (Rodriguez-Canul *et al.*, 1998; Garcia *et al.*, 1999, 2003a; Widdowson *et al.*, 2000; Sakai *et al.*, 2001; Moro *et al.*, 2003; Lescano *et*

al., 2007, 2019; Jayashi *et al.*, 2012b; Mohan *et al.*, 2013; Pray *et al.*, 2017; Morales *et al.*, 2018; Ng-Nguyen *et al.*, 2018a,b; Rojas *et al.*, 2019).

Measurement of antigen is more closely associated with being a marker of active infection, ranging from 4.7% to 59% seroprevalence (Carrique-Mas *et al.*, 2001; Sikasunge *et al.*, 2008c; Assana *et al.*, 2010a; Pondja *et al.*, 2010; Ganaba *et al.*, 2011; Krecek *et al.*, 2012; Komba *et al.*, 2013; Mohan *et al.*, 2013; Braae *et al.*, 2014; Wardrop *et al.*, 2015; Kungu *et al.*, 2017b; Madinga *et al.*, 2017; Adenuga *et al.*, 2018; Maganira *et al.*, 2019; Rojas *et al.*, 2019).

Prevalence estimated from direct observation of cysts, through lingual palpation, ranges from 5.85% to 33% (Rodriguez-Canul *et al.*, 1999; Morales *et al.*, 2002, 2006, 2008a; Ngowi *et al.*, 2004, 2010; Sikasunge *et al.*, 2007, 2008; Gweba *et al.*, 2010; Komba *et al.*, 2013; Mushonga *et al.*, 2018).

Prevalence at necropsy or meat inspection (including retrospective review of records) ranges from 3.94% to 29.10% (Porphyre *et al.*, 2015, 2016; Pray *et al.*, 2017; Mushonga *et al.*, 2018; Adesokan and Adeoye, 2019; Lescano *et al.*, 2019; Poudel *et al.*, 2019).

Many studies have been conducted to assess risk factors associated with *T. solium* porcine cysticercosis infection (Table 2). Across sub-Saharan Africa, Meso and South America, and Asia, studies show that the type of husbandry system, with predominantly free-range systems, was significantly associated with porcine cysticercosis exposure/infection indicated by antibody, antigen, lingual palpation and meat-inspection-based (sero)positivity (ORs ranging from 1.68 to 42 across studies, p-value(s) < 0.05) (Sikasunge *et al.*, 2007; Pondja *et al.*, 2010; Mohan *et al.*, 2013; Shonyela *et al.*, 2017; Morales *et al.*, 2018; Mushonga *et al.*, 2018). Antigen seropositivity was also significantly associated with absence of pig pens (OR = 0.446, 95% CI = 0.231–0.860) (Assana *et al.*, 2010a), and lingual

palpation/antigen (sero)positivity was significantly associated with the periods when farmers enable free-roaming behaviour (OR = 2.1, 95% CI = 1.3–3.6) (Komba *et al.*, 2013). In addition, factors related to the type of material used for, and structure of pig pens are significantly associated with positivity. Antigen seropositivity has been found to be positively and significantly associated with: a) presence of slatted, raised floors (OR = 8.4, 95% CI = 1.0–70.0) (Komba *et al.*, 2013); b) pigs kept in raised pens (OR = 5.33, 95% CI = 1.08–32.27), and c) dirt floors compared to cement floors (OR = 9.87, 95%CI = 1.29–114.55) (Braae *et al.*, 2015a), in Tanzania. Besides, type of feedstuff has also been reported as a significant risk factor (e.g., feeding potato peels conjectured to be contaminated with eggs; OR = 3.45, 95% CI = 1.43–8.79), also in Tanzania (Braae *et al.*, 2015a).

Availability/usage of latrines and poor sanitation have also been identified as significant risk factors. Antigen seropositivity was significantly associated with (non) usage of latrines in Tanzania (OR = 2.04, 95% Bayesian credible interval (95% BCI) = 1.25–3.45) in one study (Ngowi *et al.*, 2004) and another study (OR = 5.98, 95% CI = 1.33–43.02) (Braae *et al.*, 2015a), while open defecation practices were also significantly associated in Tanzania (p-value = 0.0001) (Shonyela *et al.*, 2017). Equally, antigen positivity was significantly associated with (non) latrine use in South Africa (p-value = 0.006) (Krecek *et al.*, 2012), and Uganda (able to use latrines; OR = 0.576, 95% CI = 0.389–0.853) (Kungu *et al.*, 2017a). In Mexico, absence of latrines was significantly associated with lingual palpation positivity (two studies; OR = 2.37, p-value = 0.005 (Widdowson *et al.*, 2000), and OR = 2.4, p-value < 0.001 (Morales *et al.*, 2008a)). In Peru, presence of latrines in households decreased the odds of antibody seropositivity (OR = 0.51, 95%CI = 0.39–0.67) (Jayashi *et al.*, 2012b) (summarised in Table 2). Finally, the odds of antigen seropositivity significantly decreased with improved sanitation and hygiene practices in Tanzania (OR = 0.19, 95%CI = 0.04–0.34) (Maganira *et al.*, 2019).

Water-source provision was also identified as a significant risk factor; for example, lingual palpation/antigen (sero)positivity was statistically significantly associated with sourcing of water in Tanzania (OR = 3.1, 95% CI = 1.6–6.3) (Komba *et al.*, 2013). Antigen seropositivity was significantly and negatively associated with provision of protected water sources (acting as a protective factor) in Uganda (OR = 0.525, p-value = 0.350–0.787) (Kungu *et al.*, 2017a). Other significant factors associated with antigen positivity included knowledge of the transmission cycle, which acts as a protective factor in smallholder pig production systems in Uganda (OR = 0.476, 95% CI= 0.291–0.779) (Kungu *et al.*, 2017a) and Cameroon (OR = 0.360, 95% CI = 0.130–0.940) (Assana *et al.*, 2010a). Household overcrowding with more than six people (OR = 1.75, p-value = 0.034) (Widdowson *et al.*, 2000) and socioeconomic marginalisation (Morales *et al.*, 2018) (OR = 1.95, p-value = 0.001) were significantly associated with porcine cysticercosis antibody seropositivity in Mexico.

Table 2 Risk factors for *Taenia solium* cysticercosis in pigs

Region	Pig husbandry (husbandry system, free-roaming behaviour, material, structure, feedstuffs)	Sanitation and latrine use	Food-chain factors (meat inspection; food preparation; consumption; selling of meat; knowledge)	Other socio-economic factors (household overcrowding, marginalization)	Age- and/or sex-, and related factors	Breed	Geographical factors (including land-use and production system heterogeneity)	Spatial clustering	Seasonal variation
Africa	Sikasunge *et al.*, 2007** Assana *et al.*, 2010a** Pondja *et al.*, 2010** Komba *et al.*, 2013** Braae *et al.*, 2015a** Mushonga *et al.*, 2018** Shonyela *et al.*, 2017** Maganira *et al.*, 2019*	Ngowi *et al.*, 2004** Krecek *et al.*, 2012** Komba *et al.*, 2013** Braae *et al.*, 2015a** Kungu *et al.*, 2017a** Shonyela *et al.*, 2017** Maganira *et al.*, 2019**	Sikasunge *et al.*, 2007** Assana *et al.*, 2010a** Kungu *et al.*, 2017a** Shonyela *et al.*, 2017** Mushonga *et al.*, 2018		Pouedet *et al.*, 2002** Pondja *et al.*, 2010** Gweba *et al.*, 2010** Komba *et al.*, 2013** Wardrop *et al.*, 2015 Shonyela *et al.*, 2017**	Sikasunge *et al.*, 2008c** Porphyre *et al.*, 2015** Kungu *et al.*, 2017a**	Praet *et al.*, 2010c** Kungu *et al.*, 2017a** Wardrop *et al.*, 2015**	Ngowi *et al.*, 2010** Madinga *et al.*, 2017**	Braae *et al.*, 2014** Porphyre *et al.*, 2015** Maganira *et al.*, 2019**
Central/ South America	Rodriguez-Canul *et al.*, 1999** Widdowson *et al.*, 2000**	Widdowson *et al.*, 2000** Sakai *et al.*, 2001	Sakai *et al.*, 2001	Widdowson *et al.*, 2000* Morales *et al.*, 2018*	Carrique-Mas *et al.*, 2001* Morales *et al.*, 2002*	Morales *et al.*, 2006, 2018*	Garcia *et al.*, 1999** Jayashi *et al.*, 2012b	Sarti-Gutierrez *et al.*, 1988** Sarti *et al.*, 1992	

	Morales *et al.*, 2008a**, 2018** Rojas *et al.*, 2019	Morales *et al.*, 2006, 2008a** Jayashi *et al.*, 2012b** Rojas *et al.*, 2019	Garcia *et al.*, 2003a Morales *et al.*, 2006** Jayashi *et al.*, 2012b**		Widdowson *et al.*, 2000 García *et al.*, 2003a** Lescano *et al.*, 2007** Pray *et al.*, 2017**
Asia	Mohan *et al.*, 2013** Holt *et al.*, 2016			Adenuga *et al.*, 2018*	Adenuga *et al.*, 2018** Ng-Nguyen *et al.*, 2018a**

** Statistically significant association identified in formal statistical analysis used to test associations of risk factors or in spatial statistics.

* Borderline but not statistically significant.

Geographical Positioning System (GPS) studies looking at roaming behaviours: in West Kenya (Thomas *et al.*, 2013); in Northern Peru (Pray *et al.*, 2017, 2019).

The age of the pig host was identified as a risk factor in Sub-Saharan Africa for antigen seropositivity, with increasing age in Mozambique (OR = 1.63; 95% CI = 1.13–2.37) (Pondja *et al.*, 2010) and Tanzania (OR = 1.9; 95% CI = 1.2–3.0) (Komba *et al.*, 2013). In Cameroon, a significantly higher seroprevalence was associated with pigs over 1 year of age (Pouedet *et al.*, 2002). In Bolivia, pigs over two years of age were significantly associated with antigen seropositivity compared to those aged 2–7 months (OR = 3.83; 95% CI = 1.01–16.31) (Carrique-Mas *et al.*, 2001). In Peru, the risk of being antibody seropositive significantly increased by 7% for every additional month of pig age (OR = 1.07; 95% CI = 1.05–1.09) (Jayashi *et al.*, 2012b). In a separate study, also in Peru, antibody seroprevalence increased monotonically with age (similarly for both sexes), although this was not statistically tested (Garcia *et al.*, 2003b). Lingual palpation positivity was also significantly associated with increasing age in Nigeria (p-value < 0.05) (Gweba *et al.*, 2010) and in Mexico (p-value < 0.05) (Sarti *et al.*, 1992). Necropsy data are also supportive of this trend. In Peru, significantly increasing odds of necropsy positivity were significantly associated with pig age for any infection, with the following ORs per additional month of age: low-infection intensity (>1 cyst; OR = 1.08, 95% CI = 1.04–1.12), moderate-heavy infection (>10 cysts; OR = 1.08, 95% CI = 1.03–1.13), and heavy infection (>100 cysts; OR = 1.08, 95% CI = 1.01–1.14) (Pray *et al.*, 2017).

On the other hand, studies in Honduras (Sakai *et al.*, 2001) and Mexico (Widdowson *et al.*, 2000) did not find an association between pig age and antibody seroprevalence, while one study in Mexico (Rodriguez-Canul *et al.*, 1999) showed that antibody seroprevalence decreased statistically significantly with age (chi squared-test for trend = 7.803; p-value = 0.006), with the highest exposure in the youngest age group. Other necropsy datasets, such as those from Nepal (Sah *et al.*, 2017; Poudel *et al.*, 2019) suggest prevalence does not increase

with age. As these age-profiles are restricted to animals of slaughter age, it is difficult to infer trends across the full age-range.

The sex of the pig is also a significant risk factor in some settings, with female pigs generally being at higher risk of infection. Such evidence includes: a) higher antigen seroprevalence in females in Tanzania (p-value = 0.01); b) higher odds in breeding sows in Kenya (OR = 10.35, p-value = 0.01) (Wardrop *et al.*, 2015); c) borderline significant odds of antigen positivity in female pigs in Tanzania (OR = 1.51, 95%CI = 0.99–2.33) (Braae *et al.*, 2014), and d) a higher prevalence in female pigs compared to male pigs in Nigeria (Gweba *et al.*, 2010), although statistical significance was not tested in the latter. Keeping female pigs for longer for breeding purposes as suggested by Khaing *et al.*, 2015 in Myanmar, and as shown to significantly increase lingual palpation prevalence in Mexico from 28 to 59% (p-value < 0.001) (Morales *et al.*, 2002), could therefore provide a mechanism to explain this. Interestingly, in one Mexican study, castration of males significantly increased prevalence from 23 to 50% (p-value < 0.001) (Morales *et al.*, 2002).

A number of studies, however, have failed to identify an association between the sex of the pigs and the prevalence of antibodies (Rodriguez-Canul *et al.*, 1998, in Mexico; Garcia *et al.*, 1999, 2003a; 2003b, in Peru), or between sex and active infection (Sarti *et al.*, 1992; Morales *et al.*, 2008a, also in Mexico). Exposure heterogeneity to infective material based on age and sex has also been proposed following the observation of social dynamics within pig population hierarchy structures (Copado *et al.*, 2004).

Breed of pig has also been considered as a risk factor in Sub-Saharan Africa, showing that cross-bred pigs are 72% less likely to have been antigen seropositive than local Zambian dwarf breeds (OR = 0.72, 95% CI = 0.63–0.81) (Sikasunge *et al.*, 2008c), and in Uganda, where cross-bred pigs (OR = 3.221, 95% CI = 1.60–6.49) and exotic pigs (OR = 3.11,

95% CI = 1.73–5.58) were at higher antigen-positivity risk compared to local pigs (Kungu *et al.*, 2017a). These findings differ from those in Madagascar, which suggested indigenous pigs are 8.5 times more likely (95% CI = 6.7–10.7) to be infected compared to exotic improved pigs based on abattoir data (Porphyre *et al.*, 2015). In Meso America, porcine antibody seropositivity was also associated with the Mexican rustic phenotype (OR = 1.46, 95% CI = 1.01–2.11) compared to genetically-improved pigs (Morales *et al.*, 2018).

Another important feature of pig cysticercosis epidemiology is the observation of spatial clustering reported across a variety of settings. The use of (Ripley's) K functions (a spatial analysis method used to determine if the phenomenon of interest appears to be clustered or randomly distributed (Ripley, 1981)) revealed general clustering of porcine cysticercosis incidence for distances between 600 m and 5 km (from a randomly chosen household case) based on antigen data, and between the 0.5–6 km and 7.5–10 km ranges for lingual palpation incidence data in high-risk areas of Tanzania. Spatial scan statistics found one large significant cluster of porcine cysticercosis prevalence by lingual palpation (p-value = 0.0036, n = 370) in the same study area of Tanzania (Ngowi *et al.*, 2010). K-function spatial analysis also identified a cluster of porcine cysticercosis antigen seropositivity in the DRC (p-value < 0.001, n = 24), although the analysis did not find any spatial dependence between clusters of human taeniasis and porcine cysticercosis (Madinga *et al.*, 2017).

Geographical correlation between porcine cysticercosis antibody seropositivity and human tapeworm carriers has also been identified in Peru, as the odds of finding a pig with one cyst significantly increased (OR = 4.6, 95% CI = 1.36–15.4) within 50 m of a tapeworm carrier (Pray *et al.*, 2017). Furthermore, research from the same area in Northern Peru demonstrated that pigs spend most of their time roaming and interacting with open defecation areas within 100 m of their homes (Pray *et al.*, 2016). Spatial dynamics also fluctuated by location and season in the study area, with home-range size and contact with open defecation

sites significantly varying between local villages and home ranges identified as significantly larger in the rainy season compared to the dry season (61%, 95% CI = 41–73%) (Pray *et al.*, 2019). These observations are supported by earlier work in Peru, where Lescano *et al.* (2007) demonstrated a porcine cysticercosis antibody seroincidence gradient near tapeworm carriers and general positive correlation between porcine cysticercosis seroprevalence and human taeniasis coproantigen (Spearman's rank correlation coefficient = 0.866, p-value = 0.005). Earlier work in Mexico first identified clustering of lingual palpation cases in the same or adjacent houses (Sarti-Gutierrez *et al.*, 1988), also using antibody seropositivity (Widdowson *et al.*, 2000). However, Morales *et al.* (2008a) found that while all pigs were clustered in households, there was no significant difference between clustering of non-infected and infected (measured by lingual palpation) pigs. Studies in Asia have further highlighted spatial clustering within Cambodian smallholder farming units for antibody seropositive pigs (intraclass correlation coefficient = 0.20, 95% CI = 0.03–0.34) (Adenuga *et al.*, 2018). Clustering was also demonstrated in Vietnam, with antibody seropositive pigs clustered around a 1,500 m radius in one village, possibly suggesting that roaming ranges are larger for pigs in this village compared to other settings (Ng-Nguyen *et al.*, 2018a).

Geographical and production system variation in porcine cysticercosis seroprevalence is also apparent at zone level (Garcia *et al.*, 1999) and aggregate village level (Jayashi *et al.*, 2012b) in Peru; at village level in the DRC (Praet *et al.*, 2010c); between pig production systems in Uganda (Kungu *et al.*, 2017b); by type of pig sector unit in Cambodia (Adenuga *et al.*, 2018), and based on land type and use in Kenya, with flooded agricultural land and grassland associated with higher antigen seropositivity (Wardrop *et al.*, 2015).

Seasonal variation in porcine cysticercosis infection is further recognised in studies, linking to the findings of Pray *et al.* (2019) regarding seasonal roaming differences. For example, Braae *et al.* (2014) showed seasonal variation in antigen seroprevalence, possibly

linked to seasonally-dependent local crop production practices, whereas Porphyre *et al.* (2015) reported less infected pig carcasses in dry seasons (e.g. cold dry season in June and August; OR = 0.53, p-value = 0.32–0.88) compared to the rainy season in Madagascar, which supports the finding of higher antigen seroprevalence in the rainy season compared to the dry season in Tanzania (p-value = 0.019) (Maganira *et al.*, 2019).

2.6. Human cysticercosis: parasitology, immunology and clinical pathogenesis

Humans can act as accidental intermediate hosts, whereby they are exposed to and consume eggs via the faecal-oral transmission route and, therefore, develop human cysticercosis. Exposure to eggs in *T. solium* endemic areas is assumed to be high, between 10 and 25% of all villages demonstrating anti-*T. solium* antibody responses (Tsang and Wilson, 1995; Schantz, 2002; Garcia *et al.*, 2014). However, this is likely to be a substantial underestimation of the total population exposed (Garcia *et al.*, 2001; Meza-Lucas *et al.*, 2003; Mwape *et al.*, 2013). Upon consumption of *T. solium* eggs and activation (hatching) in the human gut, oncospheres cross the mucosa and migrate to sites in the central nervous system (CNS), eye, striated/heart muscles and sub-cutaneous tissues of the human host (Pawlowski, 2002), where cysticerci establish as the vesicular (viable) stage. In the case of porcine cysticercosis, only the morphologically distinct cellulose form of the cysticerci develop. In human cysticercosis both the cellulose and racemose types of cysticerci can develop (Rabiela *et al.*, 1989; Flisser, 2013). While the cellulose type cysticerci are small vesicles as previously described for porcine cysticercosis, the racemose cysticerci, found primarily in certain areas of the CNS, can measure 10–20 cm, with the potential to contain up to 60 ml of fluid and appear as a large, round or lobulated bladder which is bounded by a delicate wall (Flisser, 2013). Localisation of cysticerci in the human CNS produces NCC, the stage almost

entirely responsible for the human disease burden. Detection in humans is based on cysticercosis antigen and antibody serological tests, which are the same tools as for porcine cysticercosis detection against cysticerci-derived glycoproteins. The cysticercosis serological tests were originally developed for human cysticercosis, and while they can be considered highly specific in humans, reduced specificity in porcine cysticercosis diagnosis is due to the wider spectrum of taeniid species that pigs are exposed to and infected with (Lightowlers *et al.*, 2016a). A combination of imaging and serology is used, where resources permit, for diagnosis of human NCC in clinical settings (Garcia *et al.*, 2012; Lightowlers *et al.*, 2016a).

A successful host immunological response to CNS-located cysticerci results in a process of degeneration from a colloidal stage to a non-viable granular stage, and finally transformation to a mineralized nodule known as the calcified stage (Del Brutto, 2012). Cysticerci may also remain viable for decades in humans. When the colloidal stage is reached, a mononuclear inflammatory reaction results in damage to surrounding brain parenchyma, oedema, gliosis, fibrosis, necrosis and wider neuronal degenerative changes (White, 2000; Carpio, 2002). In the final granular and calcified stages, local oedema subsides but the subsequent formation of multinucleated giant cells (brain granulomas) and gliosis may persist (White, 2000). Several factors determine the clinical manifestations of symptomatic human NCC, depending on location and number of cysts. Degeneration of cysticerci located in the parenchymal area of the brain (intraparenchymal NCC) manifests clinically as seizures, while location of cysticerci in the subarachnoid space, basal cisterns and within vesicles (extra-parenchymal NCC) follows a different clinical course, with the racemose cysticercal morphology being more common (Garcia *et al.*, 2014). Extra-parenchymal NCC is a progressive disease, associated with clinical morbidity due to hydrocephalus from blockage of the cerebrospinal fluid circulation following racemose cysticerci growth (Garcia *et al.*, 2014; Mahale, Mehta and Rangasetty, 2015). High mortality

rates (~50%) are also associated with cysticerci meningitis stemming from racemose extra-parenchymal NCC (Takayanagui and Odashima, 2006; Mahale *et al*., 2015).

As previously discussed, NCC also occurs in pigs, with the predominance of parenchyma-located vesicular cysticerci in porcine NCC, compared to a more pleiomorphic disease in human NCC (Sáenz *et al.*, 2008). The pleiomorphic nature of disease in human NCC has also been hypothesised to be a result of genetic factors influencing susceptibility and individual-level pathogenesis, given the diverse clinical manifestations occurring in infected individuals of the same age, sex and from similar study populations (Fleury *et al.*, 2004; Gripper and Welburn, 2017). For example, genetic polymorphisms related to the expression of the matrix metallopeptidase (MMP)-9 enzyme, which alters permeability of the blood-brain barrier and influx of immune cells to stimulate NCC cysticerci degeneration (Gupta *et al.*, 2012), and variations in susceptibility due to the toll-like receptor (TLR)-4 gene, are possible candidates underpinning genetic variation between human hosts in NCC clinical manifestations (Verma *et al.*, 2010).

2.7. Human cysticercosis: epidemiology and risk factors

Human cysticercosis seroprevalence ranges from: a) 1.6% to 45.3% based on antibody detection (Diaz *et al.*, 1992; Sarti *et al.*, 1992; Garcia-Noval *et al.*, 1996; Sánchez, Medina and Ljungström, 1998; Garcia *et al.*, 1998, 1999, 2003b; Gomes *et al.*, 2002; Agudelo-Florez and Palacio, 2003; Moro *et al.*, 2003; Montano *et al.*, 2005; Lescano *et al.*, 2009; Praet *et al.*, 2010a; Jayaraman *et al.*, 2011; Mwanjali *et al.*, 2013; Edia-Asuke *et al.*, 2015); b) 0.4% to 16.7% based on antigen seroprevalence (Nguekam *et al.*, 2003; Praet *et al.*, 2010a; Jayaraman *et al.*, 2011; Kanobana *et al.*, 2011; Mwape *et al.*, 2012, 2013; Mwanjali *et al.*, 2013; Wardrop *et al.*, 2015), and c) 0.7% to 11.9% based on combined antigen/antibody or adjusted seroprevalence (Secka *et al.*, 2011; Coral-Almeida *et al.*, 2014). A systematic review

conducted by Coral-Almeida *et al.* (2015) has previously analysed risk factors for human cysticercosis seropositivity globally. Reported associations between risk factors and human cysticercosis seropositivity, based on the review by Coral-Almeida *et al.*, 2015, are included in the following section, with this paper providing an updated literature review to the end of 2019 (Table 3).

Sanitation practices, including latrine availability and usage, have been clearly documented as risk factors. Latrine availability and usage were positively and statistically significantly associated with antigen seropositivity in Senegal (p-value < 0.001) (Secka *et al.*, 2011); antibody seropositivity in Honduras (OR = 2.92, 95% CI = 1.35–6.05) (Sánchez *et al.*, 1998); with defecating outdoors in Vietnam (OR = 11.1, 95% CI = 2.97–42.0) (Ng-Nguyen *et al.*, 2018c), and in Chinese schoolchildren coming from households lacking a toilet (OR = 1.84, 95% CI = 1.38–2.46) (Openshaw *et al.*, 2018). Antigen seropositivity was also positively and significantly associated with the use of well-derived water in Kenya (OR = 2.76, p-value = 0.02) (Wardrop *et al.*, 2015), and with washing hands by 'dipping method' in Tanzania (OR = 3.8, 95% CI = 2.5–5.9) (Mwanjali *et al.*, 2013). Antibody seropositivity was significantly associated with lack of potable water in Honduras (OR = 3.66, 95% CI = 1.25–9.94) (Sánchez *et al.*, 1998); presence of a sewage installation in the household in Peru (OR = 2.45, 95% CI = 1.3–4.68) (Montano *et al.*, 2005), and 'poor' personal (OR = 3.4, 95% CI = 1.87–6.4) and household hygiene (OR = 2.64, 95% CI = 1.28–5.44) in Mexico (Sarti *et al.* 1992).

Owning and raising pigs are significantly associated with seropositivity. In Burkina Faso, the percentage of households owning pigs (at village level) was associated with higher 18-month antigen seroconversion rate (cumulative incidence ratio (CIR) = 1.03, 95% CI = 1.01–1.05) (Dermauw *et al.*, 2018b); antibody seropositivity was associated with pig ownership in Honduras (OR = 5.39, 95% CI = 1.42–19.50) (Sánchez *et al.*, 1998), and with

owning infected pigs in Peru (OR = 1.33, 95% CI = 1.06–1.66) (Garcia *et al.*, 2003b). In India, there was a significant association between those living in pig-rearing areas and antigen seropositivity (p-value = 0.006), but not antibody seropositivity (Jayaraman *et al.*, 2011). In Chinese schoolchildren, antibody seropositivity was associated with pig-owning households (OR = 1.81, 95% CI = 1.08–3.03); those households allowing pigs to roam freely (OR = 2.26, 95% CI = 1.72–2.98), and those reporting feeding human faeces to pigs (OR = 1.49, 95% CI = 1.03–2.16) (Openshaw *et al.*, 2018).

Across a range of settings, pork consumption and related factors have also been significantly associated with risk of human cysticercosis. For example, antigen seropositivity was significantly associated with eating pork or a history of eating pork (OR = 1.99, 95% CI = 1.27–3.57) (Carabin *et al.*, 2015), and with a higher individual-level 18-month antigen seroconversion rate (CIR = 2.75, 95% CI = 1.28–5.89) in Burkina Faso (Dermauw *et al.*, 2018b). Antibody seropositivity was also significantly associated with consumption of undercooked pork in Venezuela (OR = 18, 95% CI = 5.78–55.9) (Toquero *et al.*, 2017), and frequent consumption of pork in Mexico (OR = 1.6, 95% CI = 1.18–2.37) (Sarti *et al.*, 1992). In addition, the location where pork is eaten has been demonstrated as a risk factor. In Burkina Faso, antigen seropositivity was significantly associated with eating pork at home (OR = 2.76, 95% CI = 1.42–5.31) as well as eating pork at the village market (OR = 4.10, 95% CI = 2.07–8.11) compared to never eating pork (Carabin *et al.*, 2015), and also significantly associated with the individual-level 18-month antigen seroconversion rate for eating pork at home (CIR = 2.5, 95% CI = 1.11–5.63), at the local village market (CIR = 3.71, 95% CI = 1.56–8.84) or any village market (CIR = 4.5, 95% CI = 1.48–13.71) (Dermauw *et al.*, 2018b). In addition, antibody seropositivity was significantly associated with eating pork at home in Cameroon (p-value < 0.001) (Nkouawa *et al.*, 2017). Consuming

raw vegetables regularly in Vietnam (Ng-Nguyen *et al.*, 2018c) has also been significantly associated with antibody seropositivity (OR = 9.98, 95% CI = 2.89–34.4).

Table 3 Risk factors for *Taenia solium* cysticercosis in humans

Region	Sanitation, hygiene and latrine use	Pig ownership, husbandry system & practices	Pork consumption and location of consumption	Consumption of raw vegetables	Socioeconomic factors (occupation, marginalization, wealth, education)	Climate and land-use	Age- and/or sex-related factors	Current or history of *T. solium* taeniasis	Spatial clustering	Geographical heterogeneity
Africa	Secka *et al.*, 2011** Mwanjali *et al.*, 2013** Edia-Asuke *et al.*, 2015 Wardrop *et al.*, 2015**	Edia-Asuke *et al.*, 2015 Dermauw *et al.*, 2018b**	Edia-Asuke *et al.*, 2015 Carabin *et al.*, 2015** Nkouawa *et al.*, 2017** Dermauw *et al.*, 2018b**		Edia-Asuke *et al.*, 2015 Carabin *et al.*, 2015** Wardrop *et al.*, 2015*	Wardrop *et al.*, 2015** Dermauw *et al.*, 2018b**	Nguekam *et al.*, 2003** Kanobana *et al.*, 2011** Secka *et al.*, 2011** Mwape *et al.*, 2012**, 2013 Mwanjali *et al.*, 2013** Carabin *et al.*, 2015** Wardrop *et al.*, 2015**	Mwape *et al.*, 2012** Mwanjali *et al.*, 2013**	Mwape *et al.*, 2013**	Nguekam *et al.*, 2003** Kanobana *et al.*, 2011 Carabin *et al.*, 2015** Dermauw *et al.*, 2018b
Central/ South America	Sarti *et al.*, 1992** Sánchez, Medina and Ljungström, 1998** Agudelo-Florez and Palacio, 2003*	Sánchez *et al.*, 1998** Garcia *et al.*, 2003b**	Sarti *et al.*, 1992 Toquero, Morocoima and Ferrer, 2017**		Sánchez *et al.*, 1998** Moro *et al.*, 2003** Morales *et al.*, 2018**		Diaz *et al.*, 1992** Sarti *et al.*, 1992** Garcia-Noval *et al.*, 1996** Garcia *et al.*, 1998** Moro *et al.*, 2003**	Sarti *et al.*, 1992** Garcia-Noval *et al.*, 1996** Gomes *et al.*, 2002** Lescano *et al.*, 2009**	Sarti *et al.*, 1992** García *et al.*, 2003a** Lescano *et al.*, 2009**	Garcia-Noval *et al.*, 1996** Morales *et al.*, 2018**

	Montano *et al.*, 2005**			Montano *et al.*, 2005 Praet *et al.*, 2010a** Coral-Almeida *et al.*, 2014 Toquero *et al.*, 2017			
Asia	Ng-Nguyen *et al.*, 2018c** Openshaw *et al.*, 2018**	Openshaw *et al.*, 2018** Jayaraman* *et al.*, 2011*	Ng-Nguyen *et al.*, 2018c**		Openshaw *et al.*, 2018** Li *et al.*, 2019**	Ng-Nguyen *et al.*, 2018a** Raghava *et al.*, 2010**	Jayaraman *et al.*, 2011**

** Statistically significant association identified in formal statistical analysis used to test associations of risk factors or in spatial statistics.

* Borderline but not statistically significant.

Further socio-economic factors are also implicated, including being in a higher wealth quintile at the individual level significantly and negatively associated with antigen seropositvity in Burkina Faso (OR = 0.64, 95% CI = 0.42–0.95) (Carabin *et al.*, 2015), social marginalization being associated with an increased antibody seroprevalence in Mexico (p-value = 0.01) (Morales *et al.*, 2018), and low education levels being associated with increased antibody seropositivity in Honduras (OR = 2.5, 95% CI = 1.33–4.69) (Sánchez, Medina and Ljungström, 1998) and Peru (OR = 2.69, 95% CI = 1.09–6.65) (Moro *et al.*, 2003). In addition, antigen seropositivity was significantly and positively associated with lack of knowledge of the transmission cycle in Burkina Faso (OR = 3.02, 95% CI = 1.86–4.90) (Carabin *et al.*, 2015), and antibody seropositivity with lack of knowledge in Honduras (OR = 2.39, 95% CI = 1.26–4.49) (Sánchez *et al.*, 1998).

Individuals with a history of or having current *T. solium* taeniasis have been widely reported to be at an increased risk, highlighting the role of auto-infection. *Taenia solium* taeniasis positivity by copro-Ag-ELISA was statistically significantly and positively associated with human cysticercosis antigen seropositivity (OR = 2.6, 95% CI = 1.3–5.2) and antibody seropositivity (OR = 2.6, 95% CI = 1.3–5.2) in Tanzania (Mwanjali *et al.*, 2013); antigen seropositivity in Zambia (OR = 2.9, p-value = 0.029); antibody seropositivity with passing proglottids in Mexico (OR = 2.26, 95% CI = 1.2–4.4) (Sarti *et al.*, 1992), and with human taeniasis carrier households measured by copro-Ag-ELISA (OR = 2.21, 95% CI = 1.43–3.42) in Guatemala (Garcia-Noval *et al.*, 1996) and Brazil (p-value = 0.017) (Gomes *et al.*, 2002). In China, school-children with taeniasis (by stool microscopy) were statistically significantly more likely to have cysticercosis antibody seropositivity (chi-squared = 69.293, p-value < 0.001), while at the school level, those with higher taeniasis prevalence were associated with significantly higher cysticercosis seroprevalence (Spearman's rank correlation coefficient = 0.925, p-value < 0.05) (Li *et al.*, 2019). Another study of *T. solium*

infection in Chinese school-children also found an association of cysticercosis antibody seropositivity with "self-reporting of worms in faeces" (OR = 1.85, 95% CI = 1.18–2.91) through a mixed-effect logistic regression model controlling for school-level clustering (Openshaw *et al.*, 2018). Outcome measurement through self-reporting, however, is open to substantial limitations including recall bias, alongside the inability to identify the tapeworm species.

Increasing age is strongly associated with human cysticercosis exposure and infection. In Senegal, older age groups were statistically significantly associated with combined antigen and antibody seropositivity (p-value = 0.001) (Secka *et al.*, 2011); with antigen seropositivity in Tanzania (higher in 35–45 year olds (OR = 2.5, 95% CI = 1.20–5.00) and in 46–60 year olds (OR = 2.6, 95% CI = 1.30–5.30) than in those aged 15–25 years) (Mwanjali *et al.*, 2013), and with being over 30 years of age in Zambia (p-value = 0.001) (Mwape *et al.*, 2012). In Cameroon, age had a significant effect on the odds of infection (OR = 1.05, p-value < 0.001) (Nguekam *et al.*, 2003), and this increase was also documented in two of three provinces in Burkina Faso (OR = 2.43, 95% CI = 1.53–3.88) (Carabin *et al.*, 2015). In Meso and South America, significantly increased antibody seropositivity with age was observed in Mexico (p = 0.05 for those aged 46–55 years compared to those in the 4–9-year age group) (Sarti *et al.*, 1992). In Peru, seropositivity in those aged 6–15 years was significantly lower compared to older age groups (p-value < 0.05) (Diaz *et al.*, 1992), and to pork vendors over the age of 30 years (p-value = 0.001), also in Peru (Garcia *et al.*, 1998). A change point analysis (which identifies abrupt changes in positivity frequencies as a function of age) and logistic regression in Ecuador (Praet *et al.*, 2010a), identified that the proportion of antibody-seropositive increased significantly up to 40 years of age (p-value < 0.001) before plateauing, in contrast to antigen seropositivity, which remained at a constant level until 60 years of age before significantly increasing thereafter (p-value < 0.001). By contrast, Moro *et al.* (2003)

identified that antibody seropositivity was significantly higher in younger age groups (below 30 years; OR = 2.53, 95% CI = 1.39–4.60) in Peru.

Being of the male sex has been statistically significantly associated with increased odds of exposure as measured by antibody seropositivity in Tanzania (OR = 1.6, 95% CI = 1.1–2.1) (Mwanjali *et al.*, 2013), with prevalence of active infection by antigen seropositivity in the DRC (26.4%, 95% CI = 21.8–31.1% in males compared to 17.5%, 95% CI = 13.8–21.2% in females) (Kanobana *et al.*, 2011), and with antigen seropositivity in Burkina Faso (OR = 1.53, 95% CI = 1.74–3.69) (Carabin *et al.*, 2015). However, being male was protective for antigen seropositivity in Kenya (OR = 0.58, 95% CI = 0.37–0.91) (Wardrop *et al.*, 2015). In Meso and South America, females had a significantly higher antibody seroprevalence across two Guatemalan villages (OR = 1.85, 95% CI = 1.3–2.5) (Garcia-Noval *et al.*, 1996), and antibody seroprevalence was significantly and positively associated with being a female pork vendor (p-value = 0.001), but being male was positively and significantly associated with antibody seroprevalence in the general population in Peru (p-value = 0.04) (Garcia *et al.*, 1998).

Spatial clustering of human cysticercosis cases is a feature of transmission, particularly in Meso and South America. In Mexico, household clustering of antibody seropositive cases was evident (chi-squared test = 22.1, degrees of freedom = 6, p-value < 0.005, indicating that the rate of seropositivity varies significantly by household) (Sarti *et al.*, 1992). In Peru, Garcia *et al.* (2003b) identified that cluster-level effects explained most of variance per case (p-value < 0.001), and also showed that household contacts of taeniasis carriers had a 3.4 times increased odds of being seropositive (p-value < 0.001). Lescano *et al.* (2009), also in Peru, further reported the operation of a statistically significant gradient of antibody seroprevalence with distance from a microscopy-positive taeniasis household as follows: being located at 1–50 m from a carrier household was associated with 64%

seroprevalence; 2–50 m with 32%, and > 50 m with 21%; prevalence ratio (PR) (PR = 1.98, 95% CI = 1.25–3.14 for < 50 m and PR = 1.52, 95% CI = 1.01–2.29 for > 50 m). In India, and using the spatial scan statistic software SaTScan™, significant clusters of human cysticercosis antigen seropositivity (i.e. most significant; RR = 14.2, p-value = 0.002) and of antibody seropositivity (i.e. most significant; RR = 4.28, p-value = 0.007) were identified (Raghava *et al.*, 2010). In Vietnam, antibody-positive household clusters were found to cluster, using K functions, within distances of 200–300 m (Ng-Nguyen *et al.*, 2018a), although the authors noted that it was not possible to test whether a spatial dependence existed between human taeniasis and cysticercosis cases due to the low numbers of taeniasis cases in the study area. One study in Africa also documented multiple clusters of human cysticercosis antigen seropositivity in Zambia, with one larger cluster related to an identified taeniasis cluster (Mwape *et al.*, 2012). Therefore, in certain settings, there is a clear spatial relationship between human cysticercosis and taeniasis cases.

Geographical heterogeneity in human cysticercosis seroprevalence also clearly exists as demonstrated for antigen seropositivity (p-value < 0.001) between communities in Cameroon (Nguekam *et al.*, 2003), and through univariate analysis for one province (Boulkiemdé; OR = 2.43, 95% CI = 1.53–3.88) compared to the reference province in Burkina Faso (Carabin *et al.*, 2015). Antibody seroprevalence was also significantly different between two communities in Guatemala (OR = 1.85, 95% CI= 1.3–2.5) (Garcia-Noval *et al.*, 1996), between regions in Morelos state in Mexico (p-value = 0.01) (Morales *et al.*, 2018), and between rural and urban populations for both antigen and antibody seroprevalence in India (p-value < 0.006) (Jayaraman *et al.*, 2011).

Other environmental factors of interest include the association of land-use type, including the proportion of either flooded agricultural land (OR = 1.09, p-value= 0.03) or grassland (OR = 0.998, p-value = 0.03) within a 1 km buffer, and precipitation (OR = 0.998,

p-value = 0.02) with antigen seropositivity in Kenya (Wardrop *et al.*, 2015). In Burkina Faso, and at village level, the percentage of sand in the soil (CIR = 1.02, 95% CI = 1.0–1.04) was significantly associated with antigen seroconversion rates over 18 months, but not the pH level, or the percentage of silt or clay in the soil (Dermauw *et al.*, 2018b).

3. MORBIDITY AND ECONOMIC IMPACT ASSOCIATED WITH *TAENIA SOLIUM*

The burden of human disease associated with *T. solium* infection results from the development of cysts in the CNS including brain tissue, leading to NCC as previously described. Epileptic seizures have been identified as the most commonly reported presenting symptom of NCC (Winkler and Richter, 2015; Singh *et al*., 2020), but a range of other neurological and psychiatric symptoms have been identified (White, 2000; Widdowson *et al.*, 2000; Murray *et al.*, 2012). Furthermore, there is a broader psychological and social burden associated with chronic epilepsy in affected communities, with increased stigmatization experienced by those with epilepsy, especially in rural, marginalised settings and those communities where traditional belief systems predominate (Baskind and Birkbek, 2005; Winkler *et al*., 2010; O'Neill *et al*. 2019).

In 2015, the World Health Organization (WHO) Foodborne Disease Burden Epidemiology Reference Group (FERG) (WHO, 2015) estimated the global burden of disease by assuming that 29% of the burden of epilepsy would be attributable to NCC in *T. solium*-endemic populations, as identified in a meta-analysis by Ndimubanzi *et al.* (2010) to total populations estimated to be at risk. Estimation of Disability-Adjusted Life Years (DALYs) due to NCC-associated epilepsy, therefore, used prevalence-based estimates of Years Lived with Disability (YLDs) as an approximation for incidence-based YLDs, as data did not

suggest presence of a strong temporal trend in incidence (Torgerson *et al.*, 2015). The analysis calculated that NCC-associated epilepsy was responsible for a median of 2,788,426 (95% uncertainty interval (UI) = 2,137,613–3,606,82) DALYS globally in 2010 (Torgerson *et al.*, 2015). Gripper and Welburn (2017) more recently conducted a systematic review to quantify the relationship between epilepsy and NCC through a meta-analysis of case-control studies, showing that an individual with NCC has a 2.76 times increased risk (common odds) of developing epilepsy (95% CI = 2.19–3.48) compared to an uninfected individual. In addition, Gripper and Welburn (2017) also estimated a common proportion of 31.54% of epilepsy cases (95% CI = 26.86%–36.41%) associated with NCC, suggesting that earlier attributable proportions of epilepsy to NCC were reasonable. The study also suggested that geographical heterogeneity may exist in the proportion of epilepsy cases attributable to NCC between continents, although the authors noted that there is a wide degree of heterogeneity in the studies that were incorporated in the meta-analysis. The Global Burden of Disease (GBD) 2017 Study estimated the number of DALYs due to cysticercosis at 1,610,000 (95% UI = 1,050,000–2,230,000), an 8% increase since 2007 (GBD 2017 DALYs and HALE Collaborators, 2018), and the GBD 2019 Study at 1,370,000 (95% UI = 874,000–1,960,000) through modelling the prevalence of NCC with epilepsy (GBD 2019 Cause and Risk Summaries, 2020).

The WHO FERG calculation for cysticercosis YLDs, as previously performed for the Global Burden of Disease Study iterations, is likely still to be an underestimation of the total burden given that, due to the paucity of data, the estimate is yet to include the role of other neurological sequelae (Hotez *et al.*, 2014). Other zoonotic and vector-borne parasites are also considered important risk factors for epilepsy (Ngugi *et al.*, 2013; Singh *et al.*, 2020). For example, onchocerciasis, caused by the filarial nematode *Onchocerca volvulus*, is also associated with epilepsy, currently in sub-Saharan Africa (but see also Jilek-Aall, 2004), with

the observation of increasing epilepsy prevalence in proximity to rivers where the blackfly vector breeds (Colebunders *et al.*, 2019; Lakwo *et al.*, 2020; Singh *et al.*, 2020). Understanding the geographical distribution and overlap between epilepsy caused by different infectious agents, especially in sub-Saharan African settings (Katabarwa *et al.*, 2008), is therefore an important research gap. There may also be some burden associated with taeniasis in humans, particularly in childhood, as infection with *T. solium* can be associated with blood loss and anaemia in a small number of cases (Yoshino, 1933b; Shekhovstov, 1975; Vuylsteke *et al.*, 2004). However, it is considered that infection with the adult tapeworm is, by and large, asymptomatic (Garcia *et al.*, 2014).

The cross-sectoral nature of the *Taenia solium* disease system means that there are economic costs associated with both human NCC-related morbidity, and the impact of cysticercosis infection in the pig population. A WHO landscaping review on this subject area (Winkler and Richter, 2015) identified a number of studies demonstrating the significant cost to patients with NCC-associated morbidity. In Peru, the total costs from a patient perspective were USD 996 per person over a period of two years (Rajkotia *et al.*, 2007), while Bhattarai *et al.* (2012) identified the total annual costs to patients in two Mexican referral hospitals as 212% of the annual minimum wage salary if the individual had received prior medical attention. In India, the costs accrued in the period between presentation of new onset seizures to resolution of the NCC lesion were on average 50.9% of the per capita Gross Domestic Product (GDP) (Murthy and Rajshekar, 2007). A study in the Eastern Cape Province of South Africa estimated the monetary burden per capita to be between USD 2.6–4.8 in the context of the annual health expenditure set at USD 41.3 per capita in the region, relating to an overall monetary burden of USD 18.6–34.2 million in an area with an estimated 34,662 people living with NCC-associated epilepsy (Carabin *et al.*, 2006).

Several studies have attempted to evaluate the cross-sectoral economic burden, also termed the 'total societal burden' by considering both the human NCC morbidity cost and the economic losses to pig production in *T. solium*-endemic regions. In Western Cameroon, 95.3% of the burden was attributed to human NCC direct and indirect costs, while 4.7% was attributed to pig production losses (Praet *et al.*, 2009). Parameters used to calculate pig production losses were the average value of an adult pig and a set reduction of 30% in value after diagnosis with cysticercosis, applying these to Food and Agriculture Organization (FAO, 2007) estimates for pig population numbers and the porcine cysticercosis prevalence defined by tongue inspection (Pouedet *et al.*, 2002; Shey-Njila *et al.*, 2003). A similar approach to costing, applied to the Eastern Cape Province of South Africa study, found that pig production losses contributed to 20% of the total economic burden (Carabin *et al.*, 2006). Trevisan *et al*. (2017b) estimated that pig production losses accounted for closer to a third of the total societal economic burden in Tanzania. The authors suggested that the greater contribution of pig production losses in Tanzania compared to both the Eastern Cape Province and Cameroon studies resulted from the significantly higher pig population numbers, higher tongue-based porcine cysticercosis prevalence and the higher assumed price reduction of infected pigs (50% in Tanzania study compared to 30% in Cameroon). It is clear that parameter assumptions can markedly vary the estimates associated with the human health and pig production sectors. Authors across the studies suggest that limitations exist in the availability of context-specific estimates, especially for NCC-associated burden of disease parameters to assess accurately the true burden and cost (Carabin *et al.*, 2005; Praet *et al.*, 2009; Haagsma *et al.*, 2014; Jordan *et al.*, 2016; Trevisan *et al.*, 2017b; Trevisan *et al*., 2018). Broader, regional estimates such as those calculated for sub-Saharan Africa or expert opinion are often used in place of specific estimates.

Data limitations are also likely to exist for pig-production loss parameters. For example, estimation of porcine cysticercosis prevalence across the entire at-risk population using prevalence data measured by tongue inspection will likely be a significant underestimation, as this diagnostic has low sensitivity for light infections (Dorny *et al.*, 2004; Phiri *et al.*, 2006). It is, therefore, critical that economic burden calculations are appropriately parameterised for specific settings. For Meso and South America, recent estimates have been calculated that consider the broader societal economic burden. Bhattarai *et al.* (2019) estimated that the burden in Mexico was USD 215.7 million (95% BCI = USD 109.3–361.9 million) due to NCC clinical morbidity, and USD 19.5 million (95%BCI = USD 5.7–35.9 million) due to porcine cysticercosis.

Torgerson *et al.* (2018) has recently proposed a zoonotic, zDALY metric, which incorporates an additional component to the traditional DALY estimate – the animal loss equivalents (ALEs), through estimation of the local *per capita* income and monetary value of livestock losses (divided by the gross national per capita income). This methodology has been applied to *T. solium* in Cameroon by assuming a 30% reduction in price of infected pigs, calculating that only 1% on the total societal burden was associated with ALEs (the remaining 99% attributed to DALYs) in Cameroon, compared to 90% attributed to ALEs for brucellosis in Kyrgyzstan, and 31% attributed to ALEs for Q fever in the Netherlands (Torgerson *et al.*, 2018). The cross-sectoral burden, impacting human health and agricultural sectors, implicates *T. solium* as a One Health problem, defined as a "collaborative effort of multiple disciplines—working locally, nationally, and globally—to attain optimal health for people, animals and our environment" (American Veterinary Medical Association (AVMA), 2008).

4. INTERVENTIONS TO CONTROL AND ELIMINATE *TAENIA SOLIUM*

Extensive reviews have been conducted to assess the impact of interventions over the last 5 years, including a critical appraisal of intervention study designs by Carabin and Traoré (2014), a WHO landscaping review in 2015 (Thomas, 2015), and the most recent systematic review of interventions between the period 1st January 2014 till 1st May 2017 undertaken by de Coster *et al*. (2018). The following analysis leans heavily on the WHO landscaping review of Thomas (2015) and Carabin and Traoré (2014), but has been conducted independently of the de Coster *et al*. (2018) review, and includes cross-checking of studies for the sake of completeness. Fig. 3 highlights the available intervention tools for the control of *T. solium* taeniasis/cysticercosis, indicates the components of the life-cycle which contribute to the main health burden and economic impact of the disease, and illustrates the intersection between human health, veterinary health and the environment to emphasize the need for a One Health approach to curb taeniasis/cysticercosis.

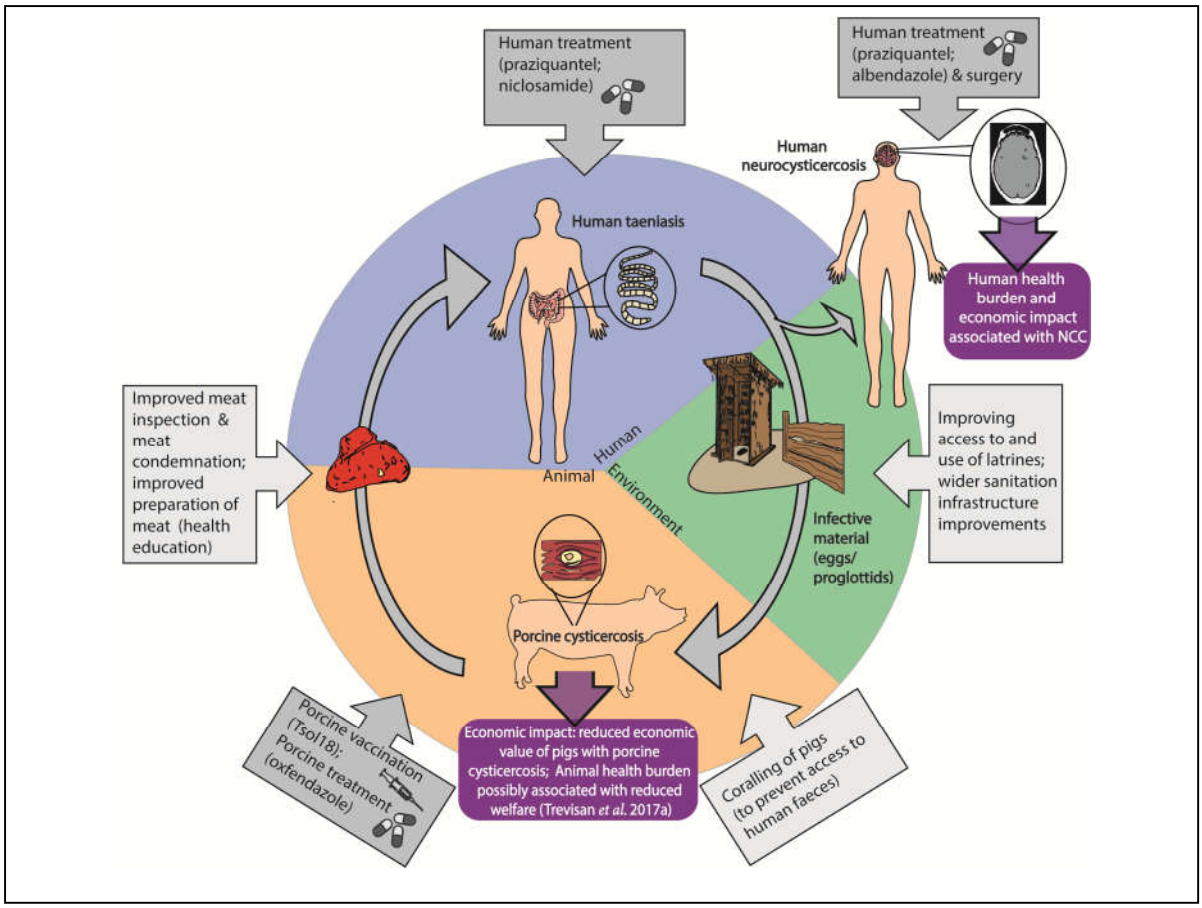

Figure 3. Schematic representation of the transmission cycle of *Taenia solium*, epitomising a One Health approach. The human (blue), animal (orange), and environment (green) components are represented by interlocking sections that intersect and form a whole entity whose parts cannot be tackled in isolation. The purple boxes indicate the parasite stages responsible for the main human health burden (associated with neurocysticercosis) and economic impact (due to both neurocysticercosis and porcine cysticercosis) of the disease. The grey boxes highlight the points in the parasite's life-cycle upon which currently available intervention strategies operate: dark grey boxes indicate biomedical approaches (treatment, vaccination); light grey boxes indicate behaviour- and environment-focussed interventions. Modified from Dixon *et al.* (2019).

4.1. *Taenia solium* diagnostics

The ability to monitor the impact of interventions on transmission using diagnostic tools is central to research and programmatic efforts for the neglected (and other) infectious diseases (Ghani *et al.*, 2015). Given the multi-host system characteristic of *T. solium*, several diagnostics are available for the different life-cycle stages (an overview is provided in Table 4).

Table 4 Overview of the main diagnostic approaches and diagnostic performance of assays used in prevalence/incidence surveys and intervention studies of *Taenia solium* taeniasis/cysticercosis

Infection status	Life-stage targeted	Diagnostic test	Sensitivity (Se) in % Specificity (Sp) in % (95% CIs or 95% BCI*)	Reference
Human taeniasis	Direct observation of eggs in stool	Coprology	Se = 52.5 (11.1 – 96.5) Sp = 99.9 (99.5 – 100.0)	Praet *et al.*, 2013*
	Antigen in stool	Copro-Ag-ELISA	Se = 84.5 (61.9 – 98.0) Sp = 92.0 (90.0 – 93.8)	Praet *et al.*, 2013*
	Antibody	Immunoblot	Se = 97.6 (93.9 – 99.3) Sp = 99.0 (97.2 – 99.7)	Levine *et al.*, 2007
	Molecular detection	Copro-PCR	Se = 82.7 (57.0 – 97.6) Sp = 92.0 (90.0 – 93.8)	Praet *et al.*, 2013*
Porcine cysticercosis	Direction observation of cysts	Lingual palpation; necropsy	Se = 7.3 (0.8 – 15.1) Sp = 80.8 (71.0 – 90.4)	Krecek *et al.*, 2011* (LP)
	Antibody serology	EITB	Se = 88.8 (65.3 – 98.6) Sp = 48.3 (37.6 – 59.2)	Jayashi *et al.*, 2014
	Antigen serology	HP10 Ag-ELISA	Se = 70.4 (52.7 – 84.7) Sp = 66.1 (44.6 – 85.1)	Krecek *et al.*, 2011*
		B158/B60 Ag-ELISA	Se = 63.3 (46.8 – 81.6) Sp = 87.0 (78.2 – 94.9)	Krecek *et al.*, 2011*
Human (neuro)cysticercosis	Antibody serology	EITB	Se = 93.0 (82.0 – 99.0) Sp = 76.0 (72.0 – 79)	Praet *et al.*, 2010b*
	Antigen serology	HP10 Ag-ELISA	Se = 84.8 (74.4 – 95.2) Sp = 94.0 (90.2 – 97.8)	Fleury *et al.*, 2007
		B158/60 Ag-ELISA	Se = 90.0 (80.0 – 99.0) Sp = 98.0 (97.0 – 99.0)	Praet *et al.*, 2010b*
	Imaging	MRI	Not available	

Ag: antigen; ELISA: enzyme-linked immunosorbent assay; EITB: enzyme-linked immunoelectrotransfer blot; HP: horseradish peroxidase; LP: Lingual palpation; PCR: polymerase chain reaction; MRI: magnetic resonance imaging.

*Bayesian estimation and 95% Bayesian credible intervals (95% BCIs) presented by Praet *et al.*, 2013; Krecek *et al.*, 2011 (see also Krecek *et al.*, 2008), and Praet *et al.*, 2010b; otherwise 95% confidence intervals (95% CI).

4.2. Chemotherapy in humans

Directly treating human tapeworm carriers influences transmission by eliminating the source of infection for pigs and humans. The two main approaches for implementing treatment programmes focus on mass drug administration (MDA) or more targeted treatment of tapeworm carriers by using discriminatory diagnostics to identify these individuals followed by treatment (Table 5). At present, the main anthelmintics used in these programmes are either praziquantel (PZQ) or niclosamide (NCZ), with the efficacy of 5mg/kg PZQ estimated to range between 67% and 94% cure rates (Pawlowski, 1990, 1991). A recent meta-analysis by Haby *et al.* (2020a) has indicated cure rates of 99.5% (95%CI = 98%–100%) for PZQ at 10mg/kg, and of 77.9% (95%CI = 66.7%–86.2%) for NCZ across studies (Bustos *et al.*, 2012; Carabin and Traoré, 2014). However, Clinton White et al. (2020) have raised concerns about the analyses presented by Haby *et al.* (2020a), on the grounds that between-study differences in the methods used to assess efficacy were not taken into account. Concerns were also raised regarding the safety analyses, as only a handful of the included studies had implemented carefully designed surveillance protocols aimed to detect epileptic seizures and other neurological side-effects that have been noted after mass PZQ or albendazole (ABZ) therapy, due to the killing of viable brain cysts (Clinton White *et al.*, 2020). PZQ has the limitation of possible adverse neurological outcomes in those individuals with NCC and it can cross the blood-brain barrier, leading to rupture of cysts, especially at higher doses (Pawlowski, 2006). Results from a prospective study on neurological side-effects after praziquantel MDA (for schistosomiasis) identified neurological side-effects likely due to occult cysticercosis (Flisser *et al.*, 1993).

4.2.1 Mass Drug Administration in humans alone

A number of earlier studies have been conducted primarily in Meso and South American settings (Cruz *et al.*, 1989; Keilbach *et al.*, 1989; Diaz Camacho *et al.*, 1991; Allan *et al.*, 1997; Sarti *et al.*, 1998; Sarti *et al.*, 2000), and there is one review of a Chinese MDA programme (Pawlowski *et al.*, 2005). Some of these studies suffer from substantial study design limitations, such as the use of unreliable outcome measures (e.g. self-reported parasite expulsion (Carabin and Traoré, 2014)), or very limited information provided to assess the quality of the studies. More detailed studies have identified a short-term significant reduction in prevalence, given the short follow-up period, of human taeniasis (measured by copro-Ag-ELISA) and porcine cysticercosis antibody seroprevalence after one round of human MDA with PZQ in Mexico at six months post-treatment (Sarti *et al.*, 2000), and after one round of human MDA with NCZ in Guatemala (Allan *et al.*, 1997). In Lao PDR, two MDA rounds using ABZ, also to target other soil-transmitted helminthiases, demonstrated a 100% reduction in human taeniasis carriers (by microscopy and molecular detection) at the end of the study (Ash *et al.*, 2017). However, a case report of NCC following self-medication with a single 400 mg dose of ABZ has been documented in Peru (Garcia *et al.*, 2007). As described above, the quality of available data to assess efficacy and safety of ABZ and PZQ for taeniasis MDA has been questioned (Clinton White *et al.*, 2020) (but also see Haby *et al.*, 2020b). Table 5 summarises the results of intervention studies using treatment of human taeniasis carriers.

4.2.2 Mass Drug Administration in humans combined with health education

Reductions in the prevalence of human taeniasis (diagnosed by the Kato-Katz method) and porcine cysticercosis (by meat inspection) were identified following a human-focussed intervention in Ecuador with one MDA round with PZQ and health education (HE) after one

year (Cruz *et al.*, 1989), as well as in China, using biannual PZQ treatment (Pawlowski *et al.*, 2005). As stated in the previous section, substantial limitations apply to these studies, including the lack of comparison groups; in most cases the comparator was the baseline prevalence value (Table 5). The sections above also discussed the potential risks and concerns posed by MDA for human taeniasis.

Table 5 Intervention studies for *Taenia solium* control focussing on treatment of humans or treatment plus health education (HE)

Country Intervention	Follow-up period	Pig cysticercosis change	Human taeniasis change	Human cysticercosis change	Main features and limitations	Reference
Ecuador 1 MDA round 5mg/kg PZQ	12 mo.	Prevalence: 11.4% to 2.6% (77% decrease)	Prevalence: 1.6% to 0% (100% decrease)	Not measured	No randomisation or control group; comparator is baseline prevalence	Cruz *et al.*, 1989*
Mexico 1 MDA round 5mg/kg PZQ & HE	24 mo.	Prevalence (LP): 6.6 to 11% (67% increase)	Not measured	Not measured	No randomisation or control group; comparator is baseline prevalence LP only; may have missed light infections Low PZQ coverage (60%) Unable to determine relative impact of HE vs. MDA	Keilbach *et al.*, 1989*
Mexico 1 MDA round 10mg/kg PZQ	12 mo.	No infections (LP) found at the end of the study (results not statistically significant)	No infections found at the end of the study (results not statistically significant)	Prevalence in the 30–39yr age group: 27% to 7% (74% decrease)	No randomisation or control group; comparator is baseline prevalence LP only; may have missed light infections ABZ treatment also implemented in study area	Diaz *et al.*, 1991*
Guatemala 1 MDA round 1g NCZ (<6yr olds), 2g NCZ (≥6yr olds)	10 mo.	Prevalence: 55% to 7% (87% decrease; p-value < 0.0001)	Prevalence: 3.5% to 1% (71% decrease; p-value < 0.0001)	Not measured	No randomisation or control group; comparator is baseline prevalence	Allan *et al.*, 1997*

Mexico 1 MDA round 5mg/kg PZQ	36 mo.	Not measured	68% decrease (baseline and final values not given)	50–100% decrease (baseline and final values not given)	Limited information from reference Not able to determine if reductions are significant	Sarti *et al.*, 1998*
Mexico 1 MDA round 5mg/kg PZQ	42 mo.	Significant reduction at 6 months post-treatment. Non-significant reduction at end of the study	60% reduction in 42 months (but an increase at 6 months post-treatment)	67% reduction in 42 months	No randomisation or control group; comparator is baseline prevalence	Sarti *et al.*, 2000*
China Biannual Test & treat with PZQ (from 1983) & HE; restraint of pigs	9-yr programme, 1978–1987	Prevalence: 7.7% to 0.27% (96% decrease)	Incidence: 1512/100,000 (1978) to 21/100,000 (1986) (99% decrease)	Not measured	Limited information (government literature sourced data) Not able to differentiate relative impact of different interventions	Pawlowski *et al.*, 2005*
Honduras Biannual MDA with ABZ to school-age children, HE & training of pig farmers	8-yr programme, 1998–2005	Not measured	2.8% in 2001; 2.6% in 2002; 1.1% in 2003; 0.6% in 2004; 0.3% in 2005 (89% decrease overall)	NCC-associated epilepsy significantly reduced ($p = 0.02$). Incidence & prevalence of active epilepsy reduced (non-significant)	No randomisation or control group; comparator is baseline prevalence Immigration of new onset seizures difficult to control for (Carabin and Traoré, 2014)	Medina *et al.*, 2011*
Peru 4 rounds of Test & treat† with NCZ using ring screening (100m ring defined around a tongue-positive pig to detect	16 mo. sero-incidence calculations and human mass screening of	IRR = 0.59 in intervention (95%CI 0.41–0.87) vs. IRR = 1.1 (95%CI = 0.7–1.47) in control villages at 13–16 months (EITB serology)	Adjusted prevalence ratio = 0.28 (95%CI = 0.08–0.91) in intervention vs. control villages for confirmed taeniasis at 20 mo.	Not measured	No randomisation, allocation bias Small sample size = 2 villages Systematic differences between villages Serology measures exposure only	O'Neal *et al.*, 2014§

taeniasis carriers as in Lescano *et al.*, 2009)	taeniasis at 20 mo.					
Tanzania MDA with PZQ to school-age children for schistosomiasis; Test & treat† for human taeniasis; 2 districts (Mbeye and Mbozi)	36-mo. total follow-up (7–8 mo. after com-pletion)	Not measured	Significant decrease in odds of taeniasis in adults (p-value = 0.031, OR = 0.40) at 36 mo. & prevalence reduction (Copro-Ag) from 2.3% to 0.1% in Mbozi (96% decrease)	Not measured	Low coverage of taeniasis cases compared to wider district No randomisation or control group; comparator is baseline prevalence	Braae *et al.* 2016a; 2017b§
Lao PDR 2 6-monthly MDA rounds with triple 400 mg ABZ. Also measured impact on soil-transmitted helminthiases	Round 1 = 1 & 5 mo. post-MDA Round 2 = 1 mo. post-MDA	Not measured	Prevalence: 79.4% decrease after Round 1 100% decrease after Round 2	Not measured	Large ineligibility/refusal (36.2% in Round 1; 36.9 % in Round 2) No randomisation or control group; comparator is baseline prevalence Varying proportion of unidentified faecal samples per round	Ash *et al.*, 2017§

ABZ: albendazole; Ag: antigen; CI: confidence interval; EITB: enzyme-linked immunoelectrotransfer blot; HE: health education; IRR: incidence rate ratio, LP: lingual palpation; MDA: mass drug administration; mo.: months; NCC: neurocysticercosis; NCZ: niclosamide; OR: odds ratio; Lao PDR: Lao People's Democratic Republic; PZQ: praziquantel.

* Studies identified and appraised in the landscaping review by Thomas *et al.* (2015); § studies identified in this work; † studies examining targeted treatment using a test & treat approach (using diagnostics such as Copro-Ag to first detect taeniasis cases before treatment).

4.2.3 Treatment of school-age children or selected treatment of taeniasis carriers/those at risk

A multifaceted control programme, including treatment with albendazole (ABZ) to school-age children in Honduran schools (in addition to HE and training of pig farmers), resulted in a non-significant reduction of taeniasis prevalence (measured by Kato-Katz) over a four-year period, but a significant reduction in NCC as an aetiology of epilepsy over a six-year period (Medina *et al.*, 2011) (Table 5).

A targeted approach, involving identifying taeniasis carriers within a 100-meter ring around a tongue-positive pig (ring-screening/treatment intervention) was implemented in Peru (O'Neal *et al.*, 2014) (Table 5). O'Neal *et al.* (2014) suggest that the increased participation in a ring-targeted approach (approximately 90%) relative to mass screening/treatment at completion (less than 75%) highlights the potential benefit of this type of approach on community adherence and effective coverage. The ring-screening approach has been tested on a larger scale with parallel study arms including a targeted strategy and MDA, across approximately 10,000 individuals and 6,000 pigs over a longer follow up in Peru (O'Neal *et al.*, 2017).

In Tanzania, a national school-age treatment programme (with 40mg/kg PZQ for schistosomiasis) was augmented with an additional taeniasis test and treat (track-and-treat) strategy and demonstrated a significant decrease in taeniasis prevalence (Braae *et al.*, 2017b). Braae *et al.* (2017b) suggest that while the Tanzanian study shows promise for integration of *T. solium* control within a schistosomiasis control programme, a major barrier might be the risk of possible adverse neurological symptoms in those with NCC (Flisser *et al.*, 1993, 2003).

4.3. Health education

Health education and promotion approaches have been viewed as an effective approach in modifying pig-rearing practices (Sarti *et al.*, 1997; Wohlgemut *et al.*, 2010) and increasing self-reporting by tapeworm carriers. Health education can also help to decrease food preparation practice-associated risk of infection, including consumption of undercooked pork meat through ineffective cooking methods (Djurkovic-Djakovic *et al.*, 2013), or consumption of raw pork (Silva-Vergara *et al.*, 1998; Djurkovic-Djakovic *et al.*, 2013). The most robust evidence for the impact of health education, based on studies with a rigorous study design (i.e., randomisation and control groups), has been demonstrated across settings in Sub-Saharan Africa (Table 6). In Tanzania, an approach using Consolidated Standards of Reporting Trials (CONSORT) guidelines to plan the intervention in smallholder pig farmers demonstrated a reduction (statistical significance not tested) in porcine cysticercosis antigen seroincidence in the intervention group post-intervention, although knowledge improved in both control and intervention villages (Ngowi *et al.*, 2009).

A cluster randomised control trial (RCT) testing a health education intervention in Tanzanian school-children, demonstrated significant improvement in knowledge and attitudes at 6 months compared to baseline; however, an increase of knowledge/attitudes scores in both control and intervention groups suggested that possible contamination occurred between groups (Mwidunda *et al.*, 2015). Another cluster RCT, testing a community-based health education intervention in Burkina Faso, demonstrated a cumulative decrease in human cysticercosis antigen incidence and a reduced risk (adjusted CIR) in those exposed to the health education programme, although there were no significant reductions of associated risks (Carabin *et al.*, 2018).

A computer-based health education tool, 'The Vicious Worm' (Vang Johansen *et al.*, 2014), has been evaluated in multiple contexts, demonstrating short- and long-term significant improvements in knowledge and attitudes in health and agricultural professionals in Tanzania (Ertel *et al.*, 2017; Lauridsen *et al.*, 2019) and in primary-school children in Zambia (Hobbs *et al.*, 2018b, 2019), although impact on transmission has not yet been determined. In the context of Zambia, use of 'The Vicious Worm' forms part of a wider prospective, large-scale community-based *T. solium* CYSTISTOP intervention study (Hobbs *et al.*, 2018a, 2019), which may make it difficult to disentangle the impact of the health education component from that of the other intervention components. Table 6 summarises the studies that have implemented health education interventions.

Table 6 Intervention studies for *Taenia solium* control focussing on health education

Country Target groups	Follow-up period	Impact of intervention	Main features and limitations	Reference
Mexico Teachers, health-care professionals, students, wider community	12 mo. & 36 mo.	77% reduction in pig cysticercosis (p-value < 0.05), 56% reduction in human taeniasis after 36 mo. (non-significant). Significant increase in knowledge and 50% reduction in free-ranging pigs	No randomisation or control group; comparator is baseline prevalence Broader health promotion impact (in relation to cholera epidemic)	Sarti *et al.*, 1997*
Tanzania Farmers	12 mo.	43% reduction in porcine cysticercosis. Significant improvement in control and intervention group & reduction in consumption of infective pork	Information bias due to self-reporting questionnaire (Carabin and Traoré, 2014)	Ngowi *et al.*, 2009*
Kenya Pig farmers	24 mo.	Infection indicators not measured. Increase knowledge in those attending workshop and significant increase in pig tethering	No randomisation or control group Information bias due to self-reporting questionnaire (Carabin and Traoré, 2014)	Wohlgemut *et al.*, 2010*
India School-children, farmers, wider community	6 mo.	Infection indicators not measured. Knowledge increased by 46%; hand washing increased by 4.8 times; latrine use increased by 3.6 times	No randomisation or control group Information bias due to self-reporting of taeniasis	Alexander *et al.*, 2012*
Tanzania Cluster RCT testing HE intervention in school-children	6 & 12 mo. post-intervention	Overall scores improved by approximately 10% in all schools at six mo. Knowledge score improvements were greatest for human cysticercosis (adjusted PPR = 1.54, 95%BCI = 1.29–1.84) at 12 months vs. baseline in intervention group	Potential contamination between intervention & control groups	Mwidunda *et al.*, 2015§
Tanzania Ccomputer-based education tool 'The Vicious Worm' (n = 79)	Immediate/ two weeks post-intervention	77% of individuals (95%CI = 67.7%–86.3%) improvement of knowledge (immediately post-intervention) & 70% scores maintained (two weeks after intervention)	Small sample size Very short follow-up No randomisation or control group	Ertel *et al.*, 2017§

Zambia Education workshops in primary schools with 'The Vicious worm' (n = 99)	Questionnaire administered before & after workshop	Participants knowledge significantly increased from initial questionnaire: 11.5% knowledge uptake, p-value < 0.001; revised questionnaire 20.5% knowledge uptake, p-value < 0.0001	Different questionnaires used between study sites Small sample size No randomisation or control group	Hobbs *et al.*, 2018b§
Burkina Faso Community-wide educational programme (based on an augmented PRECEDE-PROCEED approach developed by Ngowi *et al.* (2017)), tested in a cluster RCT trial (n = 58 villages)	Baseline:18 mo. pre-intervention. 36 mo. post-intervention	Cumulative active (serological) human cysticercosis incidence (at village-level) decreased from baseline to 36 mo. post-intervention (adjusted cumulative incidence ratio = 0.65, 95%BCI = 0.39–1.05; & adjusted PPR = 0.84, 95%BCI = 0.59–1.18). Incidence ratio < 1 for 2 of 3 provinces	Authors note baseline active cysticercosis prevalence imbalance between control and intervention villages Significant loss to follow up during 3 years (due to discovery of gold in the area), therefore replaced lost participants with another household member	Carabin *et al.*, 2018§
Zambia 1 year follow up after the Hobbs *et al.* (2018b) study (n = 86)	12 mo.	Knowledge of *T. solium* significantly higher than before questionnaire (knowledge increase change = 14.0%, p-value < 0.001)	Part of the CYSTISTOP trial study area, possible cross-contamination with other project activities HE activities were conducted more frequently in elimination arm of the CYSTISTOP trial 13.14% loss to follow-up since original study	Hobbs *et al.*, 2019§
Tanzania 'The Vicious worm' HE tool provided to health and agricultural professionals (n = 79)	12 mo. follow-up after 1st two questionnaires from Ertel *et al.* (2017) study	Baseline test scores were 74% across all professionals, increasing to 83% at 1st follow-up, 82% at 2nd follow-up and 80% at 3rd follow up (12 mo. later). Significant improvement at 3rd follow up (confidence intervals non-overlapping)	Small sample size No randomisation or control group	Lauridsen *et al.*, 2019§

BCI: Bayesian credible interval; CI: confidence interval; HE: health education; mo.: months; PPR: prevalence proportion ratio; RCT: randomised control trial. * Studies identified and appraised in the landscaping review by Thomas *et al.* (2015); § studies identified in this work.

4.4. Improved pig husbandry

Improved pig husbandry interventions mainly focus on the use of confinement strategies, e.g. use of corrals. In terms of transmission, this prevents pig exposure to *T. solium* infective material in the environment, especially when foraging in areas of a community where individuals defecate openly. However, in cysticercosis-endemic communities, enabling pigs to roam freely provides an investment-free approach to pig rearing (Gilman *et al.*, 2012). Transitioning to larger-scale farming systems with high biosecurity in endemic settings requires regional and national economic development (Lightowlers, 1999) and is unlikely to be a shorter-term viable option for endemic countries. The multifaceted control programme in Honduras discussed in the human chemotherapy section (Medina *et al.*, 2011), contained a training component aimed at pig farmers towards changing husbandry practices; however, it was impossible to disentangle the impact of this component within the entire programme. Braae *et al.* (2014) determined, through a longitudinal analysis, that pigs raised under semi-confined conditions had significantly reduced odds of porcine cysticercosis antigen seropositivity. However, the non-interventional design of the study by Braae *et al.* (2014) makes it difficult to draw firm conclusions (Table 7).

Table 7. Intervention study for *Taenia solium* control focussing on improved pig husbandry

Country Intervention	Follow-up period	Impact of intervention	Main features and limitations	Reference
Tanzania Longitudinal observational study; surveys to compare confined vs. non-confined pigs	14 mo.	Semi-confined pigs showed significantly reduced odds of *T. solium* infection vs. confined pigs measured by Ag-ELISA (OR = 0.35, 95%CI = 0.14–0.78)	Non-experimental design	Braae *et al.*, 2014

Ag: antigen; CI: confidence interval; ELISA: enzyme-linked immunosorbent assay; NA: not applicable; OR: odds ratio.

4.5. Improved sanitation

Preventing environmental contamination with infected material through construction and utilisation of latrines, is another point in the transmission cycle that can be targeted. Improved personal and household hygiene (e.g. washing hands after defecation) can help reduce exposure of humans to *T. solium* eggs and development of human cysticercosis (Mwape *et al.*, 2012). Improvements in household and community sanitation infrastructure alongside personal hygiene have numerous positive externalities associated with risk reduction for other soil-transmitted helminthiases and diarrhoeal pathogens (Clasen *et al.*, 2012; Ziegelbauer *et al.*, 2012). The role of the environment in *T. solium* transmission further re-enforces the need for a One Health approach (AVMA, 2008; Braae *et al.*, 2019) to tackle *T. solium* control and elimination sustainably. The study by Bulaya *et al.* (2015) in Zambia, focussed on a Community-Led Total Sanitation (CLTS)-based intervention, reported on an interim analysis based on a subset of intervention villages (Table 8). This analysis recorded an increase in porcine cysticercosis Ag seroprevalence in intervention villages at the 8-month follow-up compared to baseline, but firm conclusions cannot be drawn as final analysis is not available.

4.6. Improved meat inspection

Implementing improved hygienic conditions for slaughtering of animals in endemic settings and enforcing meat inspection are additional intervention tools to reduce the number of *T. solium* cysts entering the food chain via infected meat. Routine detection is often conducted at the point of sale in rural villages or in slaughter houses, using either tongue or pig carcass inspection, which both have poor sensitivity (Dorny *et al.*, 2004). There are no studies comparing the relative impact on transmission of differing inspections methods, or improved meat inspection techniques.

Table 8 Intervention studies for *Taenia solium* focussing on improved sanitation

Country Intervention	Follow-up period	Impact of intervention	Main features and limitations	Reference
Zambia CLTS intervention (RCT). Interim analysis of a subset of intervention villages	8 mo. post initiation of CTLS	Porcine cysticercosis: 2.9% increase in prevalence from baseline (measured by Ag-ELISA)	Interim findings Low rates of participation leading to small sample sizes Response rates differ between men and women in pre- and post-CTLS surveys	Bulaya *et al*., 2015

Ag: antigen; CLTS: Community-Led Total Sanitation; ELISA: enzyme-linked immunosorbent assay; RCT: randomised control trial.

4.7. Porcine cysticercosis treatment

Anthelmintic treatment of pigs is based on cysticidal agents (Mkupasi *et al*., 2013), which act to reduce rapidly the infectious reservoir pool in pigs thereby preventing human exposure to infected meat. This approach is generally implemented as mass treatment of animals, known as metaphylaxis in food animals (Baptiste and Kyvsgaard, 2017). A range of anthelmintics including flubendazole (Telléz-Girón *et al*., 1981); albendazole (ABZ) (Gonzalez *et al*., 1995); albendazole sulphate (Peniche-Cardena *et al*., 2002) and praziquantel (PZQ) (Gonzalez *et al*., 1996) have been explored for porcine cysticercosis treatment; however, oxfendazole (OFZ) is used as the treatment option of choice. OFZ, a safe and inexpensive benzimidazole, has been established in laboratory experimental studies as a highly efficacious anthelmintic at rapidly reducing the viability and presence of cysts (Gonzalez *et al*., 1996, 1998). OFZ is more effective in eliminating active cysts compared to other antehelmintics such as triclabendazole (TCBZ) (Vargas-Calla *et al*., 2016) (Table 9). Sikasunge *et al*.

(2008b) showed that treated meat takes 10–26 weeks to re-gain 'normal' appearance after infection and that a minimum 21-day withholding period is required before human consumption (Moreno *et al.*, 2012). A randomized control field study with matched non-treated controls in Mozambique (Pondja *et al.*, 2012) also demonstrated that non-viable cysts were seen in the muscles of pigs in the treated group, with a statistically significant reduction in the odds and incidence of porcine cysticercosis by antigen detection in intervention pigs after treatment at 4 and 9 months. The potential use of OFZ for human cysticercosis is also being explored, and the first in-humans study examining the pharmacokinetics, safety and tolerability of OFZ has been recently published (An *et al.*, 2019).

4.8. Porcine cysticercosis vaccination

Prophylactic vaccines to protect pigs from cysticercosis have received major attention as potential control and elimination intervention tools (Lightowlers *et al.*, 2000; Sciutto *et al.*, 2008). The TSOL18 recombinant-antigen vaccine is the leading option, providing a high level of protection against *T. solium* exposure in vaccinated animals (Gonzalez *et al.*, 2005; Jayashi *et al.*, 2012a), and has been licenced in 2016 by Indian Immunologicals Limited (GALVmed, 2017). Two other vaccine candidates – the TSOL45 and a tripeptide vaccine (S3Pvac) – confer high levels of protection in laboratory animals (Martinez-Ocaña *et al.*, 2011). An oral delivery platform for the S3Pvac vaccine has been developed as an alternative oral administration route (Sciutto *et al.*, 2007b).

Table 9 Intervention studies for *Taenia solium* evaluating oxfendazole (OFZ) treatment for porcine cysticercosis

Country Intervention	Follow-up period	Pig cysticercosis change	Main features and limitations (only field trials)	Reference
Peru Experimental: OFZ 30mg/kg single oral dose (treated vs. untreated controls)	2.5, 3 mo.	Miniscule scars observed	NA	Gonzalez *et al.*, 1996*
Peru Experimental: OFZ 30mg/kg single oral dose (treated vs. untreated controls)	0.25, 0.5, 1, 3 mo.	Non-viable cysts still visible at end of study	NA	Gonzalez *et al.*, 1998*
Zambia Experimental: OFZ 30mg/kg single oral dose (treated vs. untreated controls)	0.25, 1, 2, 6.5 mo.	Non-viable cysts visible at 1 mo. No cysts visible at 6.5 mo.	NA	Sikasunge *et al.*, 2008b*
Mozambique Randomized controlled field trial with OFZ 30mg/kg single oral dose	3, 8 mo.	No viable cysts seen in muscles at 8 mo. Significant reduction in porcine cysticercosis risk in treated group for pigs aged 4 mo. (OR = 0.14, 95%CI = 0.05–0.36) or 9 mo. (OR = 0.05, 95%CI = 0.02–0.16)	Strong overall study design (randomisation, control group, use of necropsy and serology)	Pondja *et al.*, 2012*
Peru Experimental: OFZ 30mg/kg single oral dose vs TCBZ 30mg/kg single oral dose vs. placebo control	4.25 mo.	Only degenerated muscular cysts in OFZ-treated pigs, 1,414 viable cysts in TCBZ and 1,658 viable cysts in control	NA	Vargas-Calla *et al.*, 2016§

CI: confidence interval; mo.: months; NA: not applicable; OFZ: oxfendazole; OR: odds ratio; TCBZ: triclabendazole.

* Studies identified and appraised by Thomas *et al.* (2015); § Studies identified in this work.

4.8.1 TSOL18 vaccine

The TSOL18 vaccine has demonstrated clear efficacy in laboratory settings (Gonzalez *et al.*, 2005; Silva *et al.*, 2010). In field settings, TSOL18 has also demonstrated substantial effectiveness. A small-scale study in Cameroon reported a cysticercal prevalence of 0% (0/97; 95%CI = 0%–3.8%) in vaccinated pigs compared to 19.6% (19/97; 95%CI = 12.9%–28.6%) in control pigs (by necropsy at 12–13 months of age). Vaccinated animals received 3 doses (first dose administered at 2–3 months of age; second dose given one month later (3–4 months of age); third dose given at 6 months of age) (Assana *et al.*, 2010b). The TSOL antigens are expressed solely in the oncosphere (Gauci *et al.*, 1998; Martinez-Ocaña *et al.*, 2011) and, therefore, vaccination with these antigens is not expected to affect established cysticerci. However, the study by Jayashi *et al.* (2012a), in Peru, found a statistically significant 99.7% reduction in the number of viable cysticerci in animals vaccinated with 2 doses of TSOL16–TSOL18, indicating that further research is needed to elucidate a potential cysticidal effect.

Lightowlers *et al.* (2016b) investigated the effect of changing the duration between the first and second TSOL18 doses from 4 to 20 weeks. The authors reported that piglets which received the second immunisation 12 weeks after the first one had a 3.1 times greater antibody response than those with a gap between the first and second dose of four weeks (p-value of borderline significance = 0.046). There was no decrease in antibody responses in animals receiving their second injection after 20 weeks, the longest interval investigated. Lightowlers *et al.* (2016b) suggested that this could provide greater flexibility for control programmes as a second vaccine dose could be implemented several months later. Currently, questions around implementation include the need for a cold chain and the feasibility of achieving high coverage where a multiple-dose vaccination schedule is required. Table 10

summarises studies investigating the efficacy of TSOL18 in experimental and natural settings.

Table 10 Studies evaluating the impact of the TSOL18 porcine cysticercosis vaccine on *Taenia solium*

Country Intervention	Follow-up period	Pig cysticercosis change	Main features and limitations (only field trials)	Reference
Peru Experimental: 2 doses 1 mo. apart, delivered intramuscularly	3 mo.	Median no. cysts/pig in control pigs = 1,429; median no. cysts/pig in vaccinated pigs = 0.5 (not viable), 99.9% reduction (p-value = 0.002)	NA	Gonzalez *et al.*, 2005*
Peru Experimental: oral delivery, 1 dose, challenge 1 mo. later Recombinant attenuated salmonella vaccine system expressing TSOL18	3 mo.	Significant reduction in the number of viable cysts (p-value < 0.05)	NA	Silva, 2010*
Cameroon Field trial of paired pigs (vaccinated vs. control), 3 doses (2nd dose 1 mo. after 1st together with 30 mg/kg OFZ to vaccinated and control pigs, 3rd dose at 3 mo. after 2nd)	10 mo.	19.6% cysticercal prevalence in control pigs; no cysticerci found in any of vaccinated pigs (p-value < 0.0001)	Small sample size, initially 120 pig pairs, 97 pairs at necropsy	Assana *et al.*, 2010*
Peru Field trial of paired pigs (vaccinated vs. control), 2 doses 1 mo. apart; TSOL16–TSOL18 vaccine delivered intramuscularly; no OFZ treatment	7 mo.	99.7% reduction in the no. of viable cysts (p-value < 0.01) 16.8% cysticercal prevalence in control pigs; 6.2% prevalence in vaccinated pigs (p-value = 0.0132)	Small sample size, 113 pigs in vaccinated group, 107 in control group Pigs may have acquired infection before trial, making it difficult to interpret vaccine failures	Jayashi *et al.*, 2012a*
Experimental Interval between primary and secondary immunization: 1, 2, 3, 4 or 5 mo.	0.5 mo. after 2nd dose	Booster 3 mo. after 1st dose induced greater Ab responses than booster 1 mo. after 1st dose (p-value = 0.046)	NA	Lightowlers *et al.*, 2016b§

Ab: antibody; CI: confidence interval; mo.: months; OFZ: oxfendazole; NA: not applicable. * Studies identified and appraised in Thomas *et al.* (2015); § Studies identified in this work. N.B. no other *T. solium* indicators (human taeniasis or human cysticercosis) measured.

4.8.2 S3Pvac vaccine

Vaccination with S3Pvac vaccine (a *Taenia crassiceps*-based synthetic peptide vaccine) against *T. solium* porcine cysticercosis, found that cysticerci were susceptible to the immune responses induced by the vaccine (de Aluja *et al*., 1999). This vaccine has demonstrated efficacy in relatively small field trials conducted in Mexico, showing a 52.6% cysticercal prevalence reduction, 97.9% reduction in the number of cysticerci between vaccinated and control groups, and a significantly lower relative risk in vaccinated animals (Huerta *et al.*, 2001). In another study, there was no change in sentinel-pig prevalence, indicating limited impact of the vaccine at the population level (Sciutto *et al.*, 2007a).

The S3Pvac vaccine has alternatively been developed with recombinant phage technology (S3Pvac-phage) to reduce production costs (Manoutcharian *et al.*, 2004). Within this format, the S3Pvac-phage vaccine has significantly reduced the prevalence of porcine cysticercosis (by necropsy) in vaccinated animals when tested in larger Mexican field trials (Morales *et al.*, 2008b, 2011). A study using a three-dose S3Pvac-phage regime, in conjunction with a health education programme in Guerrero State, Mexico (de Aluja *et al.*, 2014) documented a statistically significant reduction in two out of three porcine cysticercosis prevalence measures (lingual palpation and ultrasound, but a non-significant reduction in antibody seroprevalence) over a three-year period, although there was substantial variation at village level in prevalence changes over time. Table 11 summarises the studies evaluating the S3Pvac vaccine against porcine cysticercosis.

Table 11 Studies evaluating the impact of the S3Pvac porcine cysticercosis vaccine on *Taenia solium*

Country Intervention	Follow-up period	Pig cysticercosis change	Main features and limitations (only field trials)	Reference
Mexico Field trial with matched (single S3Pvac dose) vaccinated/unvaccinated controls distributed to households	10–12 mo.	Total number of cysticerci (by necropsy) reduced by 98.7%; prevalence reduced by 52.6% Relative risk of being infected significantly lower in vaccinated pigs than in controls (p-value < 0.05)	Small sample Non-randomised	Huerta *et al.*, 2001*
Mexico Field trial with 1- or 2-dose porcine S3Pvac regime and adjuvant only (monitoring of sentinel/non-vaccinated pigs)	4–8 mo. in vaccinated and adjuvant-only groups 8 & 22 mo. in sentinel group	Baseline cysticercal prevalence (by LP) = 13.8% in sentinel/non-vaccinated pigs 4.2% (1-dose); 3.1% (2-dose); 10% (adjuvant-only) (p-value = 0.2) No change in sentinel pigs during the study (12%–16%)	LP may have missed light infections; some necropsy in sentinel pigs Non-randomised Sample size variation between groups/vaccine rounds	Sciutto *et al.*, 2007a*
Mexico Randomized field trial testing porcine S3Pvac-phage vaccine (n = 16 villages; 1,047 pigs)	3–5 mo. for LP 5–27 mo. of age for necropsy	Cysticercal prevalence = 13% in controls; 3.9% in vaccinated pigs (70% reduction) 54% reduction in muscle-cysticercosis and 87% reduction in no. of cysticerci (by necropsy)	High loss to follow up at 3–5 months (49.4%) and 5–27 months (68.4%) but not different between vaccinated and control arms	Morales *et al.*, 2008b*
Mexico Immunogenicity sub-study based on trial described above; same sample size	5–27 mo. of age for necropsy	Cysticercal prevalence (only necropsy) = 19.6% in controls; 7.5% in vaccinated pigs 61.7% prevalence reduction (p-value < 0.05), 88.9% reduction in no. of cysticerci	See above for the 5–27 mo. follow-up	Morales *et al.*, 2011*
Mexico Field study testing porcine S3Pvac-phage vaccine and HE in Guerrero state	36 mo. (pre- and post-trial surveys)	Reduction from 7% to 0.5% (93%; p-value = 0.05) by LP Reduction from 17.7% to 13.3% (25%; p-value = 0.15) by Ab-ELISA	Incomplete follow-up in one village Large inter-village variation in prevalence changes	de Aluja *et al.*, 2014§

Ab-ELISA: antibody enzyme-linked immunosorbent assay; HE: health education; LP: lingual palpation. * Studies identified and appraised in Thomas *et al.*, 2015; § Studies identified in this work. N.B. No other *T. solium* indicators (human taeniasis or human cysticercosis) were measured.

4.9. Combined interventions

Garcia *et al*. (2006) provided the first evidence for the impact of a combined intervention targeting human and pig hosts in Peru, reporting that one round of human MDA with 5mg/kg PZQ plus two rounds of pig MDA with 30mg/kg OFZ significantly impacted transmission and decreased prevalence and seroincidence over 18 months. Carabin and Traoré (2014) highlighted that the Garcia *et al*. (2006) study may have overestimated intervention effectiveness (due to the randomisation approach used) and underestimated contamination within larger villages (due to the 'split' design of the study).

More recently, a regional proof-of-principle elimination strategy was trialled in Peru (Garcia *et al*., 2016), consisting of three rounds of 4-monthly human MDA with NCZ, six rounds of 2-monthly pig treatment with OFZ, and two rounds of 6-monthly TSOL18 pig vaccination. This strategy achieved elimination over a large geographical area as only degenerated, non-viable, cysts were found (Garcia *et al*., 2016). However, this trial required intensive resources over a short (1-year) 'attack phase', potentially limiting the feasibility of deploying similar approaches in poorly-resourced settings and programmatic situations outside of well-resourced research conditions. Also, there was no long-term follow up to examine whether elimination was sustained. A smaller-scale intervention study, aimed at one specific village in Lao PDR (Okello *et al.*, 2016) used a similar combination of interventions as the regional elimination study in Peru, but with larger intervals between intervention rounds to demonstrate interruption of transmission (defined by demonstrating statistically significant reductions in human taeniasis prevalence). Both studies contribute to strengthen the argument for a One Health approach that targets the entire multi-host system (Braae *et al.*, 2019; Thomas *et al.*, 2019).

Elimination has also been demonstrated in a combined intervention focussing on the pig host in Nepal (Poudel *et al.*, 2019), which used four rounds of both 3-monthly pig treatment with OFZ and TSOL18 vaccination, and resulted in the absence of cysts in slaughter-weight animals as determined by necropsy in the intervention area, 9–10 months after the first intervention round (and therefore within the year of the study). Poudel *et al.* (2019) suggested that the interventions tested in Nepal could provide a relatively simple and feasible intervention strategy that could be applied in poorly-resourced settings, and that applying such strategy over a period of years may ultimately reduce the number of tapeworm carriers and the incidence of NCC. Studies using combinations of interventions are presented in Table 12.

Table 12. Studies evaluating the impact of combined interventions on *Taenia solium*

Country Intervention	Follow-up period	Pig cysticercosis change	Human taeniasis change	Human cysticercosis change	Main features and limitations	Reference
Peru Human MDA (PZQ 5mg/kg) plus 2 rounds of pig treatment (OFZ 30 mg/kg) (*n* = 12 villages, 5,658 people &)	18 mo.	Reduction in seroprevalence (OR = 0.51, p-value < 0.001) Reduction in seroincidence (OR = 0.39, p-value = 0.013) EITB	Not measured	Not measured	Problems with randomisation (imbalance in baseline prevalence) (Carabin and Traoré, 2014) Significant loss to follow up (only 16.3% sampled more than twice)	Garcia *et al.*, 2006*
Peru Proof-of principle elimination study (*n* = 107 villages, 81,170 people & 55,638 pigs). Final strategy: Human MDA (NCZ, every 4 mo.) & pig MDA (OFZ, every 2 mo.) plus vaccination (TSOL18, every 6 mo.) during 1 year	12 mo. from baseline	3 pigs with live, non-degenerated cysts (necropsy) found in two villages (out of 107)	Not measured	Not measured	Short follow-up Low efficacy of NCZ (approximately 63.2%) Difficult to determine impact of pig movement	Garcia *et al.*, 2016§
Lao PDR Human MDA (3-day ABZ 400 mg, 2 rounds) plus pig treatment (OFZ 30 mg/kg) and TSOL18 vaccination (6 rounds) during 2 years	6 mo. after final intervention round (study Jan 2013–Jan 2015)	Not measured	Reduction from 29.5% (95%CI = 19.7%–40.9%) to 0% (95%CI = 0%–5.1%) by Copro-Ag ELISA	Not measured	Generalisability, small village of~300 people and ~400 pigs, specific cultural setting No control arm	Okello *et al.*, 2016§

Nepal Randomised, community-level, prospective intervention; pig treatment (OFZ 30 mg/kg) plus TSOL18 vaccination every 3 mo. during 1 year	12 mo. (pre- and post-intervention) Random sample of slaughter-weight animals necropsied	From 34.5% to no cysts detected in animals in the intervention area (p-value = 0.004) 23.6% in control area (no significant prevalence change)	Not measured	Not measured	Pig mortality due to classical swine fever Small sample (intervention area: 115 pig-rearing households (279 pigs); control area: 118 households (218 pigs)	Poudel *et al.*, 2019[§]

Ag: antigen; CI: confidence interval; ELISA: enzyme-linked immunosorbent assay; EITB: enzyme-linked immunoelectrotransfer blot; MDA: mass drug administration; mo.: months; NCZ: niclosamide; OFZ: oxfendazole; OR: odds ratio.

* Studies identified and appraised in Thomas *et al*. (2015); [§] Studies identified in this work.

5. CONCLUSIONS AND FUTURE DIRECTIONS

Great strides have been made towards unravelling the biology and epidemiology of *T. solium* taeniasis/cysticercosis, and towards understanding the effectiveness of interventions targeted to the various stages of the parasite's life-cycle, as documented in this work. Although progress has been impressive, fundamental questions focussing on the biology and epidemiology of *T. solium* remain important areas for future research. Some of the biggest unknowns relate to biological factors including the average lifespan (and distribution of lifespans) of the *T. solium* adult mature tapeworm; processes regulating parasite establishment and survival in humans and pigs; egg production and death rates (and whether abiotic factors influence egg dynamics), and egg dispersal mechanisms (Dixon *et al.*, 2019). Exploring whether density-dependent processes also operate on the different life-cycle stages of *T. solium*, for example on parasite establishment and immunity processes, will be important to better understand epidemiological patterns (Dixon *et al.*, 2020). Determining rates of transmission using, for instance, age-(sero)prevalence (human and pig) data to estimate the Force-of-Infection (per-capita rate at which susceptible hosts become infected) can also help characterise how incidence patterns vary across geographies and ecological / epidemiological settings, and contribute to identify locale-appropriate suites of intervention strategies.

Linked to this, geospatial mapping to define endemic areas and populations at risk, alongside mapping co-endemic areas with other helminth infections tackled with common treatments, such as schistosomiasis, is needed to provide a more comprehensive regional and global picture of prospects for *T. solium* control (Dixon *et al.*, 2020). At regional and smaller spatial scales, spatially-resolved infection datasets including pig movement between communities / households, along food value-chains, in conjunction with human migration

patterns will help to elucidate spatial dynamics and address questions about risks of re-emergence in near-elimination settings.

A crucial area for further research is the development of diagnostics with improved performance and accuracy, and the potential for these methods to become suitable for large-scale use in field epidemiological surveys, monitoring and evaluation of interventions, and post-intervention surveillance (CystiTeam Group for Epidemiology and Modelling of *Taenia solium* Taeniasis/Cysticercosis, 2019). Ideally, the use of such diagnostics would be integrated into other existing disease control programmes to increase cost-effectiveness and improve understanding of important co-endemicities (Katabarwa *et al.*, 2008). There are important limitations with the existing serological diagnostics, especially for porcine cysticercosis where cross-reactions occur with other *Taenia* species (Muro *et al.*, 2017; Cortez *et al.*, 2018) or light infections are missed (Sciutto *et al.*, 1998), with necropsy being considered the gold standard. Use of necropsy, however, poses significant challenges to large-scale implementation and particularly to longitudinal study designs. Finding serological diagnostic markers which represent true infection status, such as efforts towards validation in Zambia of the B158/B60 Ag-ELISA with necropsied animals (Chembensofu *et al.*, 2017), represents the type of research required to improve the applicability of existing diagnostics. For human taeniasis or cysticercosis, a lateral-flow point-of-care (POC) version of the rESS33-immunblot for human taeniasis (Levine *et al.*, 2004), and the rTH24-immunblot for human cysticercosis (Hancock *et al.*, 2004, 2006) are currently undergoing validation studies at the community and primary health facility levels in Tanzania and Zambia (SOLID Workgroup, 2020). Should such a POC diagnostic prove effective, more extensive mapping will be feasible.

The WHO neglected tropical diseases (NTD) roadmap of 2012 (WHO, 2012) called for a validated strategy for *T. solium* control to enable scaling-up of interventions in selected

countries by 2020; however, it is clear that these targets have not been met. A revised WHO NTD roadmap, covering the period of 2021–2030 identified a target of achieving, for 17 endemic countries, intensified control in hyperendemic areas by 2030 (WHO, 2020). The evidence-base for understanding the impact of interventions applied solely or in combination has been expanding, as presented in this work, but it is apparent that there are still priority areas of research to address, such as considering the longer-term sustainability of interventions, the dynamics of resurgence and/or re-introduction of infection when interventions cease, and conducting economic analyses of the different intervention packages to ensure cost-effectivesness across both the human and animal health sectors. For example, the cost-effectiveness of *T. solium* interventions was assessed within integrated NTD programmes in Lao PDR (Okello *et al.*, 2018), with similar studies still needed in different endemic settings. The recently devised metric to capture broader costs associated with zoonotic diseases, including animal costs alongside human costs, through a zoonotic DALY framework (zDALY) (Torgerson *et al.*, 2018) would facilitate such cross-sectoral assessments.

The further development and application of transmission dynamics modelling can also support the design and assessment of interventions, especially by simulating their epidemiological impact on temporal infection trends (e.g. for interventions implemented over longer timeframes), fitting to data obtained in intervention trials, and investigating infection dynamics after cessation of intervention programmes, ideally under a modelling comparison umbrella (such as conducted for other NTDs by the NTD Modelling Consortium; see Walker *et al.*, 2017 for onchocerciasis). A key step in this process is the calibration, comparison and validation of existing *T. solium* transmission dynamics models (e.g., the population-based, deterministic EPICYST model (Winskill *et al.*, 2017), the individual-based, stochastic cystiSim model (Braae *et al.*, 2016b), and others (José *et al.*, 2018)) with longitudinal

intervention datasets (Dixon *et al.*, 2019), such that crucial assumptions can be tested and model outcomes compared. Importantly, transmission dynamics models can be used to link infection dynamics with burden of disease assessments to help understand and quantify the relationship between infection and morbi-mortality, and the effectiveness of interventions in reducing disease burden, a key step for cost-effectiveness analysis (CystiTeam Group for Epidemiology and Modelling of *Taenia solium* Taeniasis/Cysticercosis, 2019). The development of spatially-explicit, individual-based models is also an important avenue of further research that would allow inclusion of behavioural parameters such as pig roaming, open human defecation, and human movement within a spatial framework, as recently shown by Pray *et al.* (2020), who have developed the CystiAgent model. Individual-based models would permit investigation of the influence of heterogeneity in individual host exposure (and immune-mediated susceptibility) within a stochastic framework that would facilitate exploration of elimination probabilities resulting from interventions and resurgence dynamics following their cessation (Hamley *et al.*, 2019; Hamley *et al.*, 2020).

List of Abbreviations

ABZ	Albendazole
Ag	Antigen
ALE	Animan loss equivalents
AVMA	American Veterinary Medical Association
BCI	Bayesian credible interval
CART	Classification and regression tree analysis
CI	Confidence interval
CLTS	Community-led total sanitation
CNS	Central nervous system
CONSORT	Consolidated standards for reporting trials
CIR	Cumulative incidence ratio
DALY	Disability adjusted life year
DRC	Democratic Respublic of the Congo
EITB	Enzyme-linked immunoelectrotransfer blot
ELISA	Enzyme-linked immunosorbent assay
ES	Excretion-secretion products

FAO	Food and Agriculture Organization of the United Nations
FERG	Foodborne Diseases Burden Epidemiology Reference Group
GDP	Gross domestic product
IRR	Incidence rate ratio
Lao PDR	Lao People's Democratic Republic
MDA	Mass drug administration
MRI	Magnetic resonance imaging
NCC	Neurocysticercosis
NCZ	Niclosamide
NTD	Neglected tropical disease
OR	Odds ratio
PCR	Polymerase chain reaction
POC	Point-of-care
PR	Prevalence ratio
PZQ	Praziquantel
RCT	Randomised control trial
RR	Relative risk
TLR	Toll-like receptor
USD	US dollar
WHO	World Health Organization
YLD	Years lived with disability
zDALY	Zoonotic DALY

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