

Elimination of *Taenia solium* cysticercosis through vaccination of pigs: a realistic option?

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KEYWORDS. —*Taenia solium*; Cysticercosis; Elimination; Vaccination; Pigs

SUMMARY. — *Taenia solium* cysticercosis is a neglected zoonotic disease which is endemic in many developing countries where traditional pig production systems are prevailing. In endemic countries neurocysticercosis is responsible for about 30 % of the cases of epilepsy. In the past several attempts have been made to control the disease: community mass treatment with taeniocidal drugs, health education, programmes to stimulate the use of latrines, anthelmintic treatment of pigs, improved meat inspection of rural pigs, etc. However, none of these approaches have been very successful. Recently, vaccination of pigs with a recombinant *T. solium* vaccine has been shown to completely eliminate parasite transmission in large field trials in Cameroon and in Peru. The Global Alliance for Livestock Veterinary Medicines (GalvMed) is now financing vaccine production at a large scale so that the vaccine can be made available to the farmers at a reasonable price. The sustainability of such a vaccination programme and whether or not it may lead to the elimination of the parasite will be critically discussed.

TREFWOORDEN.— *Taenia solium*; Cysticercose; Eliminatie, Vaccinatie, Varkens.

SAMENVATTING. — *Eliminatie van Taenia solium cysticercosis door middel van vaccinatie van varkens: een realistische optie?* *Taenia solium* cysticercosis is een verwaarloosde zoönotische aandoening, die endemisch is in veel ontwikkelingslanden waar varkens op een traditionele manier worden gekweekt. In endemische landen is neurocysticercose verantwoordelijk voor ongeveer 30 % van de gevallen van epilepsie. In het verleden werden heel wat pogingen ondernomen om de ziekte onder controle te krijgen: massa behandeling van de bevolking met anthelmintica, gezondheidseducatie, programma's om het gebruik van latrines te stimuleren, ontworming van varkens, verbeterde vleeskeuring in de slachthuizen, enz. Geen enkele van deze aanpakken heeft de verhoopde resultaten opgeleverd. Recent werd echter aangetoond in grootschalige veldtesten in Kameroen en Peru dat vaccinatie van varkens met een recombinant *T. solium* vaccin in staat is de transmissie van de parasiet te elimineren. De 'Global Alliance for Livestock Veterinary Medicines' (GalvMed) financiert momenteel de grootschalige productie van dit vaccin zodat het aan een redelijke prijs ter beschikking kan gesteld worden van de varkensboeren. De duurzaamheid

van zulk een vaccinatieprogramma wordt kritisch geanalyseerd alsook de vraag of dit op termijn al dan niet kan leiden tot de eliminatie van de parasiet.

MOTS-CLES. — *Taenia solium*; Cysticercose; Elimination; Vaccination; Porcs

RESUME. — *L'élimination de la cysticercose à Taenia solium par la vaccination des porcs: une option réaliste?* La cysticercose à *Taenia solium* est une maladie zoonotique négligée, qui est endémique dans plusieurs pays en voie de développement où la production de porcs se fait de manière traditionnelle. Dans les pays endémiques la neurocysticercose est responsable pour environ 30 % des cas d'épilepsie. Dans le passé plusieurs tentatives ont été faites pour contrôler la maladie: traitement de masse avec des médicaments téniacides, éducation sanitaire, programmes de construction de latrines, traitement anthelminthique des porcs, amélioration de l'inspection de viande, etc. Aucune de ces approches n'a été très efficace. Récemment, il a été démontré dans des essais de terrain au Cameroun et au Pérou que la vaccination des porcs avec un vaccin récombinant à base de *T. solium* était capable d'éliminer complètement la transmission du parasite. Actuellement GalvMed (Global Alliance for Livestock Veterinary Medicines) est en train de financer la production du vaccin à large échelle de sorte qu'il puisse être mis à la disposition des éleveurs à un prix raisonnable. La durabilité d'un programme de vaccination pareil est analysée de façon critique ainsi que la question si l'élimination du parasite puisse être atteinte.

Introduction

Taenia solium cysticercosis is a neglected zoonotic disease which is endemic in many low- and middle income countries of sub-Saharan Africa, Latin America and south-east Asia where traditional pig production systems are prevailing. The parasite has a complex life cycle (Fig. 1). Humans are the only definitive host in which the adult tapeworm develops after the ingestion of cysticerci (also called metacestodes) present in raw or undercooked pork. The proglottids and eggs of *T. solium* are eliminated with the faeces. Pigs are the most common intermediate hosts, but dogs and monkeys can also be infected. In the intermediate host the *T. solium* egg develops into a cysticercus in the muscles. In heavy infections the organs and brain can also be involved. Humans may develop cysticercosis after the accidental ingestion of eggs, which are present in the environment (particularly in the vicinity of tapeworm

carriers), in food or water contaminated by faeces of a *T. solium* carrier or by introduction of eggs from faeces into the mouth by contaminated hands (Geerts, 2015). Neurocysticercosis (NCC) is caused by the presence of cysticerci in the human brain. In *T. solium* endemic countries neurocysticercosis is responsible for about 30 % of the cases of epilepsy (Ndimubanzi et al., 2010). A joint FAO/WHO expert group ranked *T. solium* first of a list of food-borne parasites of greatest global concern (FAO/WHO, 2014). The burden of *T. solium* cysticercosis is for 80 to 95 % related to losses due to NCC (hospital, doctor or traditional healer, drugs and wage loss) and for 5 to 20 % to pig cysticercosis (an infected pig loses 30 to 50 % of its value; Zoli et al., 2003) (Carabin et al., 2006; Praet et al., 2009).

Insert Figure 1. Lifecycle of Taenia solium (CDC, 2015)

In this paper a brief overview is given of the possible interventions to control taeniasis-cysticercosis due to *T. solium* with emphasis on the vaccination of pigs. The sustainability of such a vaccination programme and whether or not it may lead to the elimination of the parasite will be critically discussed.

Possible interventions for the control of taeniasis-cysticercosis at the human level

Table 1. Possible interventions for the control of *T. solium* taeniasis-cysticercosis

At the level of the pig	At the human level
<ul style="list-style-type: none"> • Anthelmintic treatment • Improved husbandry • Slaughterhouse control • Vaccination 	<ul style="list-style-type: none"> • Anthelmintic treatment • Cooking or freezing meat • Improved hygiene and sanitary facilities • Health education

Table 1 summarizes the possible interventions for the control of taeniasis-cysticercosis at the human and porcine level. At the level of the definitive host several options are available. Mass treatment using niclosamid or praziquantel has been evaluated by several authors (Cruz et al., 1989; Allan et al., 1997; Diaz-Camacho et al., 1991; Sarti et al., 2000) with varying results ranging from almost no effect (Sarti et al., 2000) to highly effective (Cruz et al., 1989). The equivocal outcomes of mass taeniocide treatment as a stand-alone measure are probably the result of insufficient coverage of the population (in order to be fully effective 100 % of the population should be covered) and/or unsafe disposal of expelled tapeworms (since the currently available taeniocides are not ovicidal, the expelled worms should be destroyed). Furthermore, re-infection of treated persons is possible after consumption of infected pork. Another disadvantage of mass drug administration programmes is the risk of development of anthelmintic resistance (Geerts & Gryseels, 2000). Despite the difficulties related to mass or targeted treatment of tapeworm carriers, the epidemiological basis of removing carriers from the population is undeniable (Thomas, 2015).

A simple measure to avoid human taeniasis is heat or cold treatment of pork. Cysticerci are killed if the meat reaches a core temperature of 80 °C or if it is kept for 10 days at – 10 °C or equivalent (OIE, 2015). In many cysticercosis endemic areas freezers are often not available, but meat is usually well cooked. Unfortunately, pork is often consumed under grilled or fried form (brochettes or ‘porc braisé’), which are not sufficiently heated to kill all cysticerci (Assana et al., 2013). Similarly, at big events such as funerals, where many people come together, it happens that cheap pork is served (i.e. pork containing cysticerci) and that the meat is not cooked long enough (Zoli, 2009, pers. comm.). It is evident that the correct processing of meat requires appropriate health education programmes resulting in effective and sustained behavior change.

Community-led total sanitation (CLTS) is an innovative community-based sanitation programme pioneered in 1999 by Kamal Kar (Kar & Pasteur, 2005) which aims at reducing open-air defecation in rural communities through the construction of pit latrines. In order to test whether CLTS would be able to control *T. solium* cysticercosis a preliminary trial was carried out in a hyperendemic region in Zambia (Bulaya et al, 2015). Pre- and post-intervention (8 months later) assessments in 9 villages showed that there was no difference in the prevalence of porcine cysticercosis. A significant increase in the number of latrines in the study villages was observed, but many newly constructed latrines were not used. Anthropological surveys showed that men expressed reluctance to abandon open-air defecation mainly because of toilet-associated taboos with in-laws and grown-up children of the opposite gender (Thys et al., 2015).

A few research teams (Ngowi et al., 2008; Ngowi et al., 2009; Sarti et al., 1997) have assessed the value of health education interventions to control *T. solium* taeniasis-cysticercosis. As shown in table 2 some changes in behavior could be obtained, but as a stand-alone measure health education will not be able to fully control the parasite. Recently, a promising computer-based *T. solium* education tool “The vicious worm” has been developed to provide evidence-based knowledge about prevention and control of *T. solium* cysticercosis for different target groups (Johansen et al., 2014). The vicious worm programme can be downloaded for free at www.theviciousworm.org and is currently being assessed for its efficacy in knowledge uptake, cultural acceptability, and compliance in different test groups.

Table 2. Results of a health education intervention^o to control *T. solium* taeniasis-cysticercosis in a rural Mexican village (Sarti et al., 1997)

Changes in behaviour (%)	Before	Immediately after	6 months later

• Defecation outdoors	49.3	43.3	39
• Pigs allowed to roam freely	22	ND	11*
• Consumption of infected pork within past 6 months	5.5	ND	0.7*

*: significant decrease; ND: not done

°: Intervention (posters, videos) during 6 months: training of teachers, house-to-house visits, meeting with target groups (housewives, farmers)

Possible interventions for the control of *T. solium* cysticercosis at the level of the pig

Porcine cysticercosis can be controlled by improving husbandry practices and slaughterhouse control, by anthelmintic treatment or by vaccination. A very effective method to control cysticercosis is to confine the pigs instead of letting them free roaming in the environment. Confined pigs run also less risk of other disease such as African swine fever. Unfortunately, in many cysticercosis endemic areas pig raising is a zero- or low-input activity and pig owners usually don't have the financial means to construct pigsties and to buy pig feed (Assana et al., 2013). These economic barriers make pig confinement an unrealistic strategy at short term, although it should still remain part of long-term control strategies (Thomas, 2015).

In many developing countries porcine cysticercosis control is carried out by tongue inspection on markets or at slaughter. However, it is well known that tongue inspection detects only the heavily infected pigs (Dorny et al., 2004). Similarly, meat inspection has a sensitivity of only 22.1 % (Dorny et al., 2004). Furthermore, in a lot of cysticercosis endemic areas a high percentage of pigs are slaughtered outside the abattoir without any veterinary supervision. Although its efficacy in the control of porcine cysticercosis is limited, improved meat inspection of slaughtered pigs will assist with the control of other food-borne diseases and should be encouraged.

A single dose of oxfendazole (OFZ, 30 mg/kg) is highly effective against porcine cysticercosis and kills all cysticerci in the muscles (Gonzalez et al., 1997). Infected and treated pigs are resistant against re-infection for at least 4 months. The drug is now registered as Paranthic[®] (produced by M.C.I. Santé Animale in Morocco) for use in pigs. The cost for treating a pig of 30 kg is about 0.5 USD, which makes it an interesting tool for the small-scale pig owner. Pondja et al. (2012) have used OFZ to control porcine cysticercosis in a highly endemic area of Mozambique. At the end of the study when the pigs were 12 month old, 66.7% of the controls were found seropositive by an antigen detection ELISA, whereas 21.4% of the pigs treated at 4 months old and 9.1% of the pigs treated at an age of 9 months were seropositive, respectively. Although this is a promising result, the strategic use of OFZ cannot be used as a stand-alone approach because in highly endemic areas a certain number of animals will inevitably get infected after the last treatment and before slaughter (Pondja et al., 2012).

More details about the pros and the cons of the various intervention tools discussed above can be found in the reviews by Lightowlers et al.(2013) and Thomas (2015).

Vaccination against porcine cysticercosis

Although several immunogens have been tested as vaccines against *T. solium* cysticercosis in pigs (for a review see Lightowlers et al., 2003; Sciutto et al., 2008), the most effective one today is the recombinant oncosphere antigen of *T. solium* designated TSOL18. Controlled experimental vaccine trials using TSOL18 have been undertaken in 3 different countries (Cameroon, Mexico, Peru) achieving a protection level of 99.5 to 100 % (Flisser et al., 2004; Gonzalez et al., 2005). Two large scale field trials have confirmed these excellent results. In a first field trial in Cameroon 240 piglets were distributed in matched pairs (one vaccinated and one control) in 114 selected pig farms. Table 3 shows the vaccination schedule

and the results of the Cameroonian trial. Simultaneously with the second vaccine oxfendazole was administered to the pigs because the vaccine is only effective against new infections and does not kill cysticerci which are already present in the pig. None of the vaccinated pigs harboured any cysticerci while 19.6 % of the control pigs were infected (Assana et al., 2010).

Table 3. Field trial using TSOL18 recombinant antigen in Cameroon (Assana et al., 2010)

	Vaccinated pigs (n=120)	Control pigs (n=120)
• First vaccine (at age of 2-3 months)	+	-
• Second vaccine + OFZ (4 weeks later)	+	+
• Third vaccine (3 months later)	+	-
• Autopsy (10 months after 1 st vaccine)	0 % infected	19.6 % infected

*OFZ: oxfendazole 30 mg/kg

A second field trial in Peru confirmed these results. In this experiment the recombinant vaccine contained a mixture of TSOL18 and TSOL16. The piglets were vaccinated twice with one month interval and without OFZ treatment. At the autopsy 7 months after the first vaccination the vaccinated pigs showed a reduction of 99.9 % of the number of viable cysts as compared to the control group (Jayashi et al., 2012). Lightowlers (2013) compared three potential intervention scenarios for the control of cysticercosis in pigs, using either oxfendazole or vaccination. A control scenario involving vaccination plus oxfendazole treatment delivered at 4 monthly intervals was predicted to achieve the best outcome, with no pigs slaughtered at 12 months of age having viable *T. solium* cysticerci.

Currently, the TSOL18 vaccine is produced at a large scale by Indian Immunologicals Limited with sponsoring of the Global Alliance for Livestock Veterinary Medicines, a private public partnership (GalvMed; www.galvmed.org) so that the vaccine can be made available to farmers at a reasonable price. The price of one dose of the vaccine is estimated at 0.1 USD (The Pigsite, 2015.). Two doses of the vaccine in combination with an OFZ treatment (0.5 USD) will cost 0.7 USD in total.

Some critical issues concerning vaccination as a tool for the elimination of *T. solium* cysticercosis

The TSOL18 vaccine

Before the vaccine can be used, it should be officially registered. GALVmed is currently continuing together with Indian Immunologicals Limited towards registration of the vaccine in India. After the country or manufacture registration, it will be much simpler to get registration in other countries. Another problem which has to be solved is the number of vaccine doses needed and the duration of the immunity induced by the vaccine. Based on the available data two doses of the vaccine given with one month interval protect the pigs at least 5 months (Jayashi et al., 2012). Ideally one vaccine dose should protect the pigs during their whole life (in many traditional pig breeding areas where pigs are free roaming the life of a slaughter pig is about 12 months). This might be possible by using delayed- or pulse-release vaccine formulations or by using live recombinant vaccine vectors such as *Salmonella* (Lightowlers, 2010).

Sustainability of a vaccination program

An important question concerning the sustainability of a vaccination programme is: who will pay for the vaccine? The pig owner or the government? The answer to this question depends on the fact whether or not the vaccine is considered as a public or a private good

where the benefits go to the society or to the individual farmer, respectively. In the case of the TSOL18 vaccine the benefits go to both. The pig owner benefits because he/she avoids economic losses due to the decreased value of a pig carcass infected with cysticercosis (30 to 50% of its value). The benefits to the society are the decrease and eventually the disappearance of *T. solium* tapeworm carriers and in the long term the disappearance of neurocysticercosis. As mentioned earlier the disease burden of *T. solium* is related for 80 to 95 % to NCC and only 5 to 20 % to porcine cysticercosis. This is a sufficient justification for a government to fund a vaccination campaign against *T. solium* cysticercosis.

In some countries, however, pig owners might be prepared to pay for the TSOL18 vaccine in combination with OFZ if the price is affordable as was shown by face-to-face interviews with pig owners in Cameroon (Assana, 2011, pers. comm.), although other researchers reported that people were not prepared to pay for the vaccine even in an area which was hyperendemic for *T. solium* taeniasis-cysticercosis (Bardosh et al., 2014). Reports indicate that a retail price of around 1 USD per dose is an acceptable limit for smallholder farmers to be able to purchase the vaccine (Pedersen et al., 2000). The current estimation of the price of the TSOL18-OFZ combination is lower than this.

Is elimination of T. solium possible using vaccination of pigs?

Although taeniasis-cysticercosis by *T. solium* has been considered as an eradicable disease (Schantz et al., 1993), there are serious doubts whether eradication, i.e. the permanent reduction to zero of the worldwide incidence of an infection, is possible (Pawlowski et al., 2005). However, elimination, i.e. the reduction to zero of the incidence of a disease in a defined geographical area (Molyneux et al., 2004) might be possible. Using a combination of the TSOL18 vaccine and OFZ it should be theoretically possible to get rid of *T. solium*. The

time needed to achieve elimination will depend on the longevity of the adult worm of *T. solium* which is estimated at 1 to 3 years (Lightowlers, 2010). New cases of taeniasis will not develop because there are no infected pigs anymore. The impact of this approach on the incidence of neurocysticercosis will be slow and depends on the survival of *T. solium* eggs in the environment which is not well known.

Elimination of *T. solium* taeniasis-cysticercosis will be reached faster if vaccination+OFZ treatment of pigs is combined with the treatment of tapeworm carriers (mass or targeted treatment). The success of this approach will depend on the coverage of the mass treatment (should be near to 100 %) or the efficacy to detect all tapeworm carriers in case of a targeted treatment. Furthermore, the expelled tapeworms should be destroyed because none of the available anthelmintics is ovicidal, which means that *T. solium* eggs remain viable and infective after expulsion. In order to keep the region free of *T. solium*, it will be necessary 1. to control and eventually treat any newcomers to the region, which might be tapeworm carriers and 2. to avoid that people living in the region visit neighboring regions where transmission of *T. solium* is still ongoing and infect themselves by eating pork with cysticerci. From the foregoing it can be concluded that elimination of *T. solium* is theoretically possible, but that it will be not easy to achieve.

One Health approach

T. solium taeniasis-cysticercosis is a typical example of a parasitic zoonosis for which the control and eventual elimination will absolutely benefit from a “one health” approach, i.e. multiple interventions in the field of human, animal and ecosystem health implemented simultaneously across sectors and supported by appropriate health education tools (Johansen et al., 2014; WHO, 2015a). Based on a *T. solium* transmission model (Kyvsgaard et al., 2007) and on available evidence in the literature the WHO recommends that a combined approach

utilising the treatment of human taeniasis cases (through mass drug administration or selective chemotherapy) combined with the vaccination (TSOL18) and treatment of the porcine host (oxfendazole 30mg/kg) is currently the ‘best-bet’ option for rapid reduction of infection pressure. This core approach should be supplemented by supporting measures such as health education and followed by measures requiring fundamental social changes including improved meat inspection, improved husbandry and improved sanitation (WHO, 2015b). Intensive sensitisation campaigns aiming to get full community commitment will be essential in order to achieve successful and sustainable control of this complex and socially determined zoonotic disease (Bardosh et al., 2014).

The WHO is strongly committed to battle cysticercosis. A pilot control programme using the abovementioned approach will be evaluated in 6 countries. WHO in close collaboration with FAO and OIE will assist these 6 endemic countries (Madagascar, Ivory Coast, Brazil, China, Peru and Vietnam) to “bring the disease to its knees” (Maurice, 2014).

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