Landscape analysis: control of *Taenia solium*

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1 Summary

This landscape analysis has identified all the current evidence for *T. solium* control available in the literature published in English. We identify eight key intervention components, being: preventative chemotherapy (through mass drug administration, focus-orientated chemotherapy or identification and treatment of taeniasis cases), health education, improved pig husbandry, improved sanitation, anthelmintic treatment of pigs, vaccination of pigs, improved meat inspection and processing of meat products. Empirical data was available for preventative chemotherapy, health education, anthelmintic treatment of pigs and vaccination of pigs and some combinations thereof.

Valid comparison between control strategies is difficult due especially to short and variable durations of follow-up and differing methods of monitoring between studies. Over the short term, however, there is an indication that disruption of transmission has been achieved through mass drug administration to humans using niclosamide or praziquantel with and without the addition of health education or anthelmintic treatment of pigs. Some reduction in transmission has been reported through the use of health education although it has been difficult to attribute this directly to the interventions used. Oxfendazole administration and vaccination of pigs have both shown efficacy in the treatment and prevention of porcine cysticercosis, although the impact of these strategies on the prevalence of human taeniasis and cysticercosis infections has yet to be quantified.

Due to the paucity of data available it is difficult to make definitive recommendations on control strategies to be used for this parasite. Extrapolation from the evidence available along with modelled projections and the various recommendations of experts available in the literature, however indicates that a combined approach utilising the treatment of human taeniasis cases (through mass drug administration or selective chemotherapy) combined with the vaccination and treatment of the porcine host would be the ‘best-bet’ for rapid reduction of infection pressure. These core approaches should be supplemented where possible by longer-term sustainable measures such as health education, focusing on the need for improvements in sanitation, pig husbandry and meat inspection.

2 Objectives

This landscape analysis has been undertaken to identify the empirical data currently available for all suggested control strategies for *Taenia solium*. It is hoped that this document will guide discussion at an upcoming expert consultation to identify a control strategy to be undertaken in several identified pilot countries prior to the expected roll-out of control in 2020 according to the road-map for NTD control. This will supplement a landscape analysis on management of neurocysticercosis with an emphasis on low-and-middle-income countries.
3 Methods

This landscape analysis constituted a desk review of the currently available evidence for control of *Taenia solium*. Documentary evidence was collected as follows;

A literature search was conducted using the search engines; IngentaConnect, PubMed, Library of Congress, British Library, ScienceDirect, African Journals Online and Google Scholar using the search terms listed here; *Taenia solium*, Cysticercosis, Taeniasis, neurocysticercosis, neglected tropical diseases, Helminths, control, integrated, efficacy, praziquantel, niclosamide, albendazole, mass drug administration, TSOL18, vaccination, diagnoses, oxfendazole, education, latrines, sanitation, husbandry and combinations thereof. Duplicates were removed and English language citations were then screened firstly on title, then abstract and finally on full text and were excluded according to the following criteria;

1. studies not relating to humans or pigs
2. Studies not relating to Neglected Tropical Diseases (NTDs)
3. Studies on aspects of NTDs which DO NOT discuss issues relevant to *T. solium* control
4. studies on epilepsy NOT related to NCC
5. Papers relating to clinical symptoms, diagnoses and treatment of NCC including case studies
6. Purely epidemiological studies on *T. solium*
7. Papers on diagnoses of *T. solium* cysticercosis/taeniasis (including diagnostic imaging)
8. Papers on aspects of basic sciences (immunology/molecular biology/ physiology/biochemistry/ basic pharmacology)

Additional resources were identified through solicitation from experts and accessing citations within selected papers which had not appeared in the original search. 12 such documents have so far been forthcoming. A flow diagram illustrating the search and exclusion process can be found in the appendices.

Of the 199 papers included in this analysis 36 are field trials relating to control, 28 studies contain experimental (non-field trials) data or data relating to aspects of other NTD control which were directly relevant to control. The remaining manuscripts comprised of reviews, opinion pieces, meeting reports and national/international guidelines and strategies.

4 Background

As early as 1976 a joint FAO/UNEP/WHO consultation Nairobi, Kenya aimed to formulate practical recommendations which would lead towards planning of successful control of *T. solium* (FAO/UNEP/WHO, 1977). In the intervening 38 years there has been much progress in terms of tool development (diagnostics, treatment) and in the international communities’ recognition of this important issue. In 1993 International Task Force on Disease Eradication (ITFDE) declared that *T. solium* was one of six potentially eradicable diseases, due to; 1) the life cycle requires humans as its definitive host, 2) tapeworm infection in humans is the only source of infection for pigs, the natural intermediate hosts, 3) domestic pigs, the intermediate hosts, can be managed, 4) no significant wildlife reservoir exists, and 5) practical intervention is available in the form of chemotherapy for human taeniosis and porcine cysticercosis with safe and effective drugs (CDC, 1992). In 2003 the ITFDE agreed that *T. solium* was indeed eradicable but that there was need for
a national scale pilot as 'proof of principle' (ITFDE, 2003). This need for evidence was re-iterated in 2013 when the ITFDE also noted the challenges still remaining for eradication, specifically the paucity of routine surveillance and reporting, the need to convince farmers that there is a financial incentive in better husbandry, a fact which in itself need evidence, the on-going need for rapid diagnostic tests and the need for data of how preventative chemotherapy (PC) effects prevalence (Center, 2013).

The World Health Organisation (WHO) has been instrumental in engaging and maintaining international interest in this parasite, with T. solium being highlighted as both a ‘Neglected Zoonotic Disease’ (NZD) (World Health Organization, 2006, World Health Organization, 2007b, World Health Organization, 2010). More recently T. solium was included in the road map to tackle the ‘Neglected Tropical Diseases’ (NTDs), which requires a validated strategy for control to be available by 2015, with interventions scaled up in selected countries by 2020 (World Health Organization, 2012a). The international community pledged their commitment to this goal in the London Declaration (World Health Organization, 2013a) and World Health Assembly Resolution WHA66.12 also requested member states, international partners and the Director General WHO to provide support for the activities outlined in this road map.

WHA66.12 specifically requested that the leadership of the WHO be sustained, with emphasis on the development and updating of evidence-based norms, standard and policies. It is hoped that the current report and expert consultation will assist the achievement of this goal for T. solium (World Health Organization, 2013b).

Despite the agreement that the control of T. solium has been considered ‘tool ready’ for several years, and various strategies have been proposed, no evidence is yet available of wide-scale reduction. As we discuss the evidence regarding the control of this parasite, it is important that we are consistent in our uses of the terms control, eradication and elimination and that agreement is made on what we wish to achieve in both the short and long terms. The ITFDE agreed upon definitions of the following terms (Molyneux et al., 2004);

- Control; Reduction of disease incidence, prevalence, morbidity or mortality to a locally acceptable level as a result of deliberate efforts. Continued intervention measures are required to maintain the reduction
- Elimination; Reduction to zero the incidence of a specified disease in a defined geographical area as a result of deliberate efforts. Continued measures to prevent re-establishment of transmission are required
- Eradication; Permanent reduction to zero of the worldwide incidence of infection caused by a specific agent as a result of deliberate efforts. Intervention measures are no-longer needed
- Extinction; The specific infectious agent no longer exists in nature or the laboratory

The WHO Strategic and Technical Advisory Group for NTDs then agreed in 2012 on the above use of the terms Control, Elimination and Eradication and that the term “elimination as a public-health problem” should be used only for political rather than scientific reasons (World Health Organization, 2012b). For the purposes of this review the term ‘control’ will be used at all times as no evidence is available for elimination or eradication of the parasite.
5 Suggested Interventions with current evidence

Suggested measures for control of *T. solium* have consistently focused on 8 key interventions and combinations thereof. These interventions and current evidence for their use are reviewed here:

5.1 Preventative chemotherapy

Preventative chemotherapy (PC) involves the distribution of anthelmintic drugs to populations at risk at regular intervals and is a cornerstone intervention in the control of several NTDs including lymphatic filariasis, onchocerciasis, schistosomiasis and soil-transmitted helminths (STH) (Gabrielli et al., 2011). Gabrielli *et al* in 2011 suggested criteria by which a helminth infection could be judged eligible for PC, these being: slow or unclear onset of clinical symptoms, slow increase in the likelihood of morbidity or disease transmission, high efficacy, safety, and ease of treatment and low cost of PC intervention (Gabrielli et al., 2011). *T. solium* is eligible for PC on these criteria as Taeniasis is characterised by mild or no symptoms, gravid proglottids are not released until approximately 2 months after infection (García *et al.*, 2003). Praziquantel and Niclosamide are effective and safe drugs available for the treatment of taeniasis (Pearson and Guerrant, 1983, Pearson and Hewlett, 1985) at a cost of $5/person (niclosamide) (Alexander *et al.*, 2011) and $0.05-0.1/person (praziquantel) (Engels *et al.*, 2003).

PC can be implemented in three ways: as Mass drug administration (MDA) when the entire population of a pre-defined area is treated at regular intervals, irrespective of clinical status, targeted chemotherapy where specific risk groups are treated, again irrespective of clinical status and selective chemotherapy, where following screening infected or suspected infected individuals are then treated (Gabrielli *et al.*, 2011). Both MDA and selective chemotherapy have been recommended at different times for the control of *T. solium* and some evidence is available on their relative efficacy and cost-effectiveness.

MDA has been used as a stand-alone strategy for control in Ecuador (Cruz *et al.*, 1989), Guatemala (Allan *et al.*, 1997), Mexico (Diaz *et al.*, 1991, Sarti *et al.*, 2000) and China (Wu *et al.*, 2012) and its effect on transmission modelled (Kyvsgaard *et al.*, 2007).

The use of a single round of praziquantel at 5mg/kg was studied in Ecuador where a population of over 13,000 people was targeted and coverage of over 75% was achieved (all but <6yrs, those with history of epilepsy, currently pregnant or ill were invited to participate). Efficacy of the intervention was monitored through the lingual palpation of pigs, which found a reduction from 11.4% to 2.6% prevalence one year later. The prevalence of taeniasis in the population was 1.6% upon treatment (based upon reported expulsion of tapeworms) and was found to be 0% among a sub-population of 539 people who underwent re-treatment and examination one year later suggesting a low re-infection rate in this population. Two taenia carriers were however detected on microscopy (n=420) during the follow-up period, both of whom had not been treated in the first round, highlighting the potential for untreated individuals or new arrivals to an area to re-establish transmission (Cruz *et al.*, 1989).
A single dose of praziquantel at 5mg/kg was also used in Mexico in 1991 where treatment was offered to all consenting individuals in a community of over 3000 excluding those <4yrs, pregnant or with history of hepatic disease. Treatment coverage of 87% was reported and the prevalence of taeniasis, human and porcine cysticercosis was monitored at 6 and 42 months post treatment to evaluate efficacy. The sero-prevalence of human cysticercosis (as evaluated by antibody ELISA) was 5.7% at treatment, rising to 10.1% at 6mths following treatment before falling to 2.2% at 42 months post treatment (a reduction of 60%). Sero-prevalence of porcine cysticercosis (Ab-ELISA) was found to be 4.8% at initiation of the program, there was a significant reduction in 6 months to 2.2%, but at 42 months post-treatment 3.4% of pigs were positive on Ab-ELISA, which was not significant reduction from initiation. Prevalence of porcine cysticercosis identified by lingual palpation was reduced at 42mths from 1.2% to 0.6%. The prevalence of taeniasis by copro-Ag ELISA in the 304 people who provided 3 stool samples, decreased during the program from 2% to 1% at 6mths and 0.7% at 42mths, a reduction of 67% overall. Late onset epilepsy as identified by a questionnaire also showed a significant reduction in 42mths from 1.5% to 0.4% indicating a possible reduction in NCC cases (Sarti et al., 2000).

A higher dose of praziquantel (10mg/kg) was utilised in another Mexican study in a village of 559 individuals in which all community members over 5yrs and without history suggestive of NCC were invited to participate (8 suspected NCC cases were treated with 2g niclosamide as were all those with *Taenia spp* identified on initial microscopy). Coverage of 71% was achieved, with 339 people receiving one round of treatment. Seroprevalence measured by Ab-ELISA was found to be 11% at the start of the study and 7.1% 12mths post treatment, including 9 individuals who had been exposed after the drug administration. The reduction in prevalence was only significant in the 30-39yr age group (27% to 7%). Prevalence of porcine cysticercosis ascertained by lingual palpation and taeniasis cases as identified by microscopy were not found to be significantly reduced (Diaz et al., 1991).

In 1994 niclosamide was used for MDA in Guatemala, with all consenting individuals within a population of approximately 2000 offered treatment. The program achieved treatment coverage of 74.9%. Individuals over 6yrs of age were offered a single dose of 2g niclosamide, with those under 6yrs receiving 1g. A magnesium sulphate purgative was given to those who were positive for *Taenia spp* on microscopy. Ten months post treatment the prevalence of human and porcine cysticercosis was monitored by EITB and taeniasis by microscopy. This study found a significant reduction in taeniasis (3.5% to 1%, p<0.0001) and porcine cysticercosis (55% to 7%, p<0.0001).

In the 1970’s a 6yr MDA program in Henan Province, China using Agrimophol, a herb extract from Hairyvein Agrimonia, found a reduction in taeniasis of 90.8% and human cysticercosis of 96.8% (diagnostic techniques were not disclosed in review) (Wu et al., 2012).
Table 1. Mass Drug Administration Programs

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Drug Description</th>
<th>Coverage</th>
<th>Taeniasis</th>
<th>Reduction in Prevalence/Incidence</th>
<th>Follow up</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1978-83</td>
<td>China</td>
<td>Yearly Agrimophol</td>
<td>Not reported</td>
<td>90.8% reduction in incidence</td>
<td>96.8% reduction in incidence</td>
<td>Not reported</td>
<td>6 yrs.</td>
</tr>
<tr>
<td>1986-7</td>
<td>Ecuador</td>
<td>1 round 5mg/kg Praziquantel</td>
<td>75.8%</td>
<td>Prevalence 1.6% to 0%</td>
<td>Not reported</td>
<td>Prevalence 11.4% to 2.6%</td>
<td>1yr</td>
</tr>
<tr>
<td>1988-9</td>
<td>Mexico</td>
<td>1 round 10mg/kg Praziquantel</td>
<td>71%</td>
<td>No infections found (not significant)</td>
<td>Significant reduction in 30-39yr age group (27%-7%)</td>
<td>No infections found (not significant)</td>
<td>1yr</td>
</tr>
<tr>
<td>1994-96</td>
<td>Guatemala</td>
<td>1 round niclosamide (2g &gt;6yrs, 1g &lt;6yrs)</td>
<td>74.9%</td>
<td>Significant reduction (3.3% to 1%, p&lt;0.0001)</td>
<td>Not reported</td>
<td>Significant reduction (55% to 7%, p&lt;0.0001)</td>
<td>10mths</td>
</tr>
<tr>
<td>1991-96</td>
<td>Mexico</td>
<td>1 round Praziquantel (5mg/kg)</td>
<td>87%</td>
<td>67% reduction in 42mths</td>
<td>60% reduction in 42mths (nb rise in first 6mths)</td>
<td>Significant reduction at 6mths. Non-significant reduction at 42mths</td>
<td>42mths</td>
</tr>
</tbody>
</table>

*Review

The data presented here indicates some success in reducing infection pressure in the short term has been achieved, there is, however insufficient evidence to indicate whether MDA alone can provide significant and sustained reductions in *T. solium* prevalence and incidence as no program has provided data over a sufficiently long period. The likely scenario from a single round of human MDA has been modelled and suggests that after an initial drop in prevalence of both human and porcine infections the prevalence would re-establish to pre-treatment levels within approximately 70 months. A more sustained reduction in prevalence was achieved in the model through the combination of human MDA with a porcine vaccination program (Kyvsgaard et al., 2007).

Combined approaches utilising human MDA have been undertaken in field trials. MDA has been combined with porcine anthelmintic treatment (Garcia et al., 2006), health education (Keilbach et al., 1989, Sarti et al., 1998, Pawlowski et al., 2005) and the combination of identification and treatment of taeniasis cases, construction of latrines and health education (Medina et al., 2011).

In Mexico 5mg/kg Praziquantel was offered to all but those under 5yrs old and those with suspected NCC who received niclosamide and a treatment coverage of 60% was achieved. Drug administration was combined with education on the disease and parasite life-cycle, with emphasis on latrine construction. The education campaign consisted of meetings with the adult population and lectures and demonstrations at primary and secondary schools. Lingual palpation of pigs found an increase in prevalence from 6.6% to 11% 1 year after the intervention, knowledge on *T. solium* was found to increase in school children from 0 to 76% providing correct answers, though only increased to 2% in adults but increased knowledge did not appear to correspond to changes in risk behaviours (Keilbach et al., 1989).

A very short report from Mexico indicated that an MDA program, with or without health education using 5mg/kg Praziquantel lead to a 68% reduction in taeniasis cases, with a 56% reduction in taeniasis cases found in the community receiving health education alone. When the use of praziquantel was combined with health education there was a significant increase in knowledge about the parasite and reduction in porcine cysticercosis cases over 3 years of monitoring (Sarti et al., 1998).
A Chinese program, reviewed by Pawlowski in 2005 had success in reducing the prevalence of taeniasis from 1512/100,000 in 1978 to 21/100,000 in 1987 and porcine cysticercosis from 7.7% to 0.27% through bi-annual anthelmintic treatment of the population in combination with health education and confinement of pigs (Pawlowski et al., 2005).

Selective chemotherapy, the identification and subsequent treatment of taeniasis cases or identification and treatment of people at risk, is an alternative or complementary form of PC to the mass administration approach. It has been championed as an integral part of T. solium control (Pawlowski et al., 2005, Pawlowski, 1987, Pawlowski, 1990, Pawlowski, 1991, Pawlowski, 1993, Pawlowski, 2006, Pawlowski, 2008, Montresor and Palmer, 2006, Penrith, 2009) and is a key aspect of the Mexican standard guidelines on T. solium control (MEDICA, 1994) and Guidelines for control in Indonesia (Suroso, 2002). It has been suggested that such selective treatment is a good option where a strong primary health care network, covering >70% of the population is present (Sarti and Rajshekhar, 2003). No evidence is currently available of the effect of identification and treatment as a stand alone strategy on T. solium transmission, although it has been utilised as part of a combined strategy.

Between 1997 and 2005 mass administration of albendazole (3 daily doses of 400mg, followed by a single 400mg dose every 6mths) to school children was combined with selective treatment of taenia carriers and their contacts with 2g niclosamide, construction of latrines and water projects and health education to the public via the media and to pig farmers in Honduras. Latrine coverage increased from 35-51% during the program duration. The prevalence of taeniasis in school children and a sample of the population, as identified by microscopy, were found to have fallen from 2.8% in 2001 to 0.3% in 2005. The prevalence of active epilepsy as determined by a capture-recapture survey of the population, aided by review of medical records and information from key informants followed by neurological evaluation was found not to change significantly between 1999 and 2005. There was however a significant (p=0.02) reduction in NCC as an etiology of epilepsy, being responsible for 36.9% of active epilepsy in 1999 and 13.9% in 2005. It was estimated that 11 cases of NCC were prevented during this program, at a cost/case avoided of $80,000, although much of this cost was attributed to the construction of a maternal health clinic which contributed little towards the control of T. solium (Medina et al., 2011).

The cost-effectiveness of MDA vs selective treatment of taeniasis cases was modelled utilising field data obtained in India in 2008. 653 consenting individuals selected at random were screened for taeniasis using copro-antigen ELISA and positive cases were treated with 2g niclosamide. The cost/case treated was determined and then modelled for populations with differing prevalence and compared to the cost/case treated utilising a MDA approach without pre-screening. The study population was found to have a prevalence of taeniasis of 0.31%. The cost per person screened by stool testing for coproantigens was $ 12, and the cost per case of taeniasis detected was US $ 4051 in comparison to $2791 for cost per case of taeniasis treated. At a prevalence of 9.7% a screening program would cost $54/case treated vs an MDA approach costing $34/case treated. At a prevalence of 18.6% pre-screening with copro-antigen ELISA would cost $31/case treated with MDA costing $18/case treated. The authors concluded that an MDA approach was the most cost-effective strategy for at all levels of prevalence (Alexander et al., 2011).

It may be that selective treatment of Taenia spp. carriers would be more cost-effective if alternative identification processes are used. To this end a self-detection tool consisting of glass bottles containing tapeworm segments fixed in formaldehyde was provided to health workers in the Guanajuato state of Mexico. The use of this tool was supported with training of health
workers, animal health workers, teachers and communication to the public through the media (radio, posters, newspapers and loudspeaker announcements) and informative talks in a variety of settings. Detection of taeniasis cases increased by 6 fold (p<0.001) after the intervention compared to the year prior to the intervention. All cases were treated with 10mg/kg Praziquantel followed by milk of magnesia and faeces were collected for speciation of the tapeworm, 37 of which were *T. saginata* and 4 being *T. solium*. The authors suggest that self-detection of taeniasis has an impact of public health. Due to the availability of ministry of health employees and dedicated time allocated in the national media for public-health messages this intervention was stated to have been implemented at 'no cost' (Flisser et al., 2005). Active lobbying of politicians to increase the implementation of the Mexican national guidelines and education of health providers stressing the obligation to notify taeniasis cases has been suggested to improve control through selective chemotherapy (Fleury et al., 2013).

Detection of areas suitable for ‘focus-orientated’ treatment has been proposed as a cost-effective way of providing selective treatment. It is suggested that the foci could be identified through existing data from medical services regarding taeniasis cases (confirmed or positive), cysticercosis patients and late onset epilepsy patients. Veterinary data could also be used to identify foci based upon a high prevalence of cysticercotic pigs in small localities, or isolated farms who frequently supply cysticercotic pigs. Within these geographical foci treatment should then be offered to all identified or suspected carriers with a potential to also undertake a MDA program within high-risk populations within the foci (e.g. workers within the meat industry) (Pawlowski, 2008).

To increase the efficacy of utilising existing health systems to identify foci of infection a proposal has been made to make neurocysticercosis a reportable disease. Giving clinicians the responsibility to report cases to their respective ministry of health could enable investigations to be undertaken to identify the source of infection (*T. solium* carriers) (Román et al., 2000, Fleury et al., 2013). It is important, however, that health and reporting systems are robust to enable this to occur. Due to the national standard in Mexico *T. solium* has been a reportable disease since 1994 (MEDICA, 1994) and there is some evidence that NCC cases have been falling in Mexico (Flisser et al., 2007) although a discrepancy between NCC national statistics and other epidemiological data has been noted which indicates that under-reporting is still a problem in this country (Fleury et al., 2012). Under-reporting can occur due to lack of access of the population to health care, misdiagnoses of etiologic factors or poorly established data reporting systems; all of these factors are likely to be present in the majority of *T. solium* endemic countries (World Health Organization, 2006) and indeed poor surveillance and reporting was highlighted by the ITFDE (Center, 2013) as a challenge to this strategy for control.

**Despite inconclusive evidence on the efficacy and cost-effectiveness of identification and treatment of taeniasis as a control strategy, the epidemiological basis of removing carriers from the population is undeniable. We would strongly recommend that all in-contacts of NCC cases are treated (2g niclosamide for safety) as standard.** (Lian F. Thomas & Andrea Winkler)
Table 2. Combined approaches utilising Mass Drug Administration

<table>
<thead>
<tr>
<th>Country</th>
<th>Drug</th>
<th>Ancillary strategy</th>
<th>Coverage</th>
<th>Change from baseline</th>
<th>Follow up</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Knowledge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mexico</td>
<td>Praziquantel 5mg/kg</td>
<td>Health education</td>
<td>60%</td>
<td>School children increased 0-76%</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adults increased 0-2%</td>
<td>Not reported</td>
<td>Increased 6.6-11%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Change from baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mexico</td>
<td>Praziquantel 5mg/kg</td>
<td>Health Education</td>
<td>Not reported</td>
<td>Significant changes in KAP</td>
<td>Not reported</td>
<td>50-100% reduction</td>
</tr>
<tr>
<td>China</td>
<td>2 yearly MDA (praziquantel)</td>
<td>Health Education &amp; restraint of pigs</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Reduced from 1512/100,000 (1978) to 21/100,000</td>
<td>Not reported</td>
</tr>
<tr>
<td>Peru</td>
<td>Praziquantel 5mg/kg</td>
<td>Porcine tx Oxfendazole 30mg/kg (2 rounds)</td>
<td>75% human 90% porcine</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Intervention protective (OR 0.51, p&lt;0.001)</td>
</tr>
</tbody>
</table>

*review

5.1.1 Challenges for Preventative Chemotherapy

Preventative chemotherapy, either in the form of mass administration to whole populations, or in a focus-orientated approach has several challenges for its successful implementation

- Achieving coverage

The success of mass drug administration programmes relies on achieving adequate coverage, with a target of 75% being considered the norm in current NTD programs (Allen and Parker, 2011). Ensuring correct compliance (i.e. drugs distributed actually being taken as instructed) is also vital (Utzinger et al., 2012). Several rounds of drug administration over a period of several years (e.g. twice a year for 5 years) is likely to be required to have a sustainable effect on *T. solium* prevalence (Sarti and Rajshekhar, 2003). Maintaining coverage levels over repeated rounds of treatment is a challenge in itself as there is evidence from Tanzania that participation in MDA programmes fell year on year between 2004-7 (Allen and Parker, 2011) as has also been documented in Uganda (Parker et al., 2008).

Achieving good treatment coverage relies on appropriate sensitisation of the community and is vitally important, especially when people may feel well and see no immediate need to take drugs. The effect of poor sensitisation on the uptake of treatment in a community was clearly documented through the experience in Tanzania where riots took place in protest of an MDA program within a local school (Hastings and Parker, 2013). Resistance to MDA in both Tanzania and Uganda appears to arise due to a combination of misunderstanding of the rational for treatment and fears, for instance of the side-effects of the drugs, or that drugs are part of a sterilisation campaign (Parker et al., 2008, Hastings and Parker, 2013).

Treatment coverage of 75.8% has been achieved in a *T. solium* control program in Ecuador through the use of extensive and appropriate sensitisation and good buy-in from the government. Sensitisation was achieved through a 3 month preparatory phase with messages disseminated through radio, posters and educational leaflets followed by house-to-house visits for data collection including information on safe collection of faecal samples and hygiene (Cruz et al.,
Careful thought should be given to ensuring that both genders have access to treatment through use of appropriate distribution channels (Rilkoff et al., 2013). Techniques to improve community acceptance of programs, such as participatory processes are important for all control programs, but especially for PC (Gazzinelli et al., 2012, Garcia et al., 2003, Enander et al., 2010).

Monitoring coverage accurately is very important for all MDA programs, with routine coverage surveys having been recommended as an integral part of monitoring and evaluation (M&E) (Worrell and Mathieu, 2012). Experience from other on-going NTD programs such as the Schistosomiasis Control Initiative (SCI) should be utilised to ensure best practise in MDA for any proposed *T. solium* control program.

- **Agreement on which anthelmintic to use as routine**
  
  Although several anthelmintics have shown efficacy in the treatment of taeniasis, including Tribendimidine (Steinmann et al., 2008) Albendazole (Steinmann et al., 2011) and Agrimophol (Wu et al., 2012), Praziquantel or Niclosamide are the anthelmintic compounds of choice for taeniasis. There is some debate as to whether Praziquantel or Niclosamide is the best anthelmintic for routine use in preventative chemotherapy. Agreement on standard treatment protocols would allow for easier comparison of trials. There are advantages and disadvantages of the two drugs as discussed briefly here:

  - **Niclosamide – 2mg/kg**
    - Good efficacy reported at 2mg single dose (Pearson and Hewlett, 1985)
    - Little systemic absorption therefore no effect on NCC (Pawlowski, 2006)
    - More expensive than Praziquantel (Pawlowski, 2006)
    - Potential reduction in efficacy in some generic formulations and after storage (Pawlowski, 2006)

  - **Praziquantel**
    - Is routinely used in MDA programs targeting schistosomiasis and therefore opens an opportunity to tackle two NTDs within the same treatment protocol
    - Safe to use in pregnant and lactating women (Savioli et al., 2003)
    - Is systemically absorbed and can cross the blood-brain-barrier resulting in activity against cerebral cysticercosis. Differing opinion of extent of this problem in NCC endemic areas (Flisser et al., 2003).
    - Although a good cure-rate has been reported at 3.4-7.5mg/kg  .(Pawłowski, 1990) reduced efficacy has been reported at 5mg/kg (Sarti et al., 2000) and it is recommended that it should be used at 10mg/kg or more (Flisser et al., 2003). Nb. Dose for schistosomiasis 40mg/kg(Hotez, 2009).

**Conclusion; Making a recommendation on which drug to use in PC strategies is very difficult, due to the potential safety issues which have yet to be studied in depth. Results from a study in Malawi investigating the effects of mass praziquantel administration for schistosomiasis in NCC endemic areas are currently being analysed and will assist in decision making in co-endemic areas (Personal communication, Andrea Winkler).**
• Ensuring safe disposal of faeces
The increase in porcine exposure to infection during the 6mths prior to treatment identified in Mexico may be attributed to an 'egg storm', where the mass treatment of the community lead to increased environmental contamination with eggs (Sarti et al., 2000). All participants in such programs must be clearly instructed in the safe disposal of potentially infective faecal material where it cannot be accessed by pigs or contaminate food or water sources for humans.

• Anthelmintic resistance
The increasing anthelmintic resistance observed in livestock systems has raised fears of the development of resistance to the drugs utilised in PC programs. Thus far none has been reported but it has been recommended that a clear definition of drug resistance is needed, with evidence-based thresholds to be stated as part of standard operating protocols (SOPs) for monitoring of all MDA programs. There should also be international agreement on a plan of action in the case of resistance being developed (Rasamoelina-Andriamanivo et al., 2013, Vercruysse et al., 2012, Vercruysse et al., 2011, Utzinger et al., 2012).

Key Points; MDA
- Some evidence to indicate efficacy in the short term
- Longer-term trials needed
- Model data suggests success will require combined approach
- Does not address underlying causal factors
- Community sensitisation/participatory approach very important to achieve coverage
- Larger NTD community can provide valuable experience
- Potential to integrate with other NTD programs
- Standardised guidelines on drug administration needed

5.2 Health Education

Health education is an integral part of the sensitisation aspect of a PC program as discussed above, but has also been proposed as a stand-alone activity for T. solium control. Health education campaigns can focus on the biology of the disease, improvements in meat preparation and hygiene, need for adequate sanitation or on improved pig husbandry and can be targeted at the general population, health workers or pig farmers and meat workers.

A health education program aimed at the control of T. solium was implemented between 2002-5 in Tanzania utilising a PRECEDE-PROCEED approach and was evaluated as a randomised control trial (Ngowi et al., 2009, Ngowi et al., 2007b, Ngowi et al., 2008). Forty-two villages were selected to participate on the following eligibility criteria; village keeps pigs, village had not been ‘overly’ studied for cysti, >20 pig keeping houses per village, agreement of local leader to participate and that village is virtually independent from other villages (although it is not indicated what this means). A random sample of 827 pig-owning homesteads were selected for baseline monitoring from those eligible on the basis of having at least one pig 2-12mths and the willingness of the
owner to participate. The base-line monitoring survey consisted of a Knowledge & Practises (KAP) study and collection of prevalence data for porcine cysticercosis, with one pig selected at random from each homestead for blood testing. All farmers from control and intervention villages were offered a sentinel pig (cysticercosis free as determined by lingual palpation), however of the farmers selected to raise sentinel pigs 434 (52%) refused the sentinel pig due to feed scarcity.

Participation in the educational intervention was then offered to 409 selected pig farmers (within intervention villages), of which 253 (62%) attended at least 1 session and those not attending were provided with educational pamphlets. Farmers from control villages received no educational intervention. Training of farmers was preceded by a training-of-trainers program. Follow up KAP studies and monitoring of sentinel pigs were carried out at 4 months post intervention and 10-12 months post intervention.

The educational programs was found to reduce incidence of porcine cysticercosis (as detected by Ag-ELISA) in the intervention villages by 43% compared to the control group, with an incidence rate of 25/100 pig-years in the control group and 12/100 pig-years in the intervention group 10-12 months post-intervention. A significant improvement in knowledge on the transmission and control of cysticercosis was observed 10-12 months post intervention; however it could not be attributed to the intervention as similar improvement was observed in both control and intervention groups. The intervention did correspond to a reduction in the consumption of infected pork in the intervention group, but this was offset by an increase in the sale of infected pigs and increased consumption of infected pork by the control group.

The financial efficacy of this approach was evaluated in terms of the costs incurred by the farmer and their expected revenue. It was found that a net benefit would be incurred by the farmer over 5yrs of $515, with the control groups (no education) incurring a loss of $296 under the assumption that infected pigs are condemned. The net present value (NPV) of intervention was calculated to be $3507, with an internal rate of return (IRR) of 370%. IRR was best if infected pigs are condemned and healthy pigs are sold at average prices, although a cost benefit was remained over the various price strategies modelled including both healthy and infected pigs being sold at average prices of $45 and $21 respectively (Ngowi et al., 2007a). The condemnation of infected pork assumes an efficient and enforced meat inspectorate and lack of black market, barriers which were highlighted by the authors (Ngowi et al., 2007b) and are common in many endemic areas including Indonesia (Suroso et al., 2006), Kenya (Kagira et al., 2010) and Uganda (Nsadha et al., 2010).

Other barriers to the success of this intervention were noted, these being: A difficulty in changing farmer behaviour due to the perception of benefits of free-ranging pigs, insufficiencies in public health provision due to poor staffing and poor infrastructure (Ngowi et al., 2007b). The careful planning of this intervention using the PRECEDE approach enabled it to be relevant to the setting (Ngowi et al., 2007b).
Health education was used as a stand-alone intervention in India and a KAP study undertaken pre-intervention and at 6 months post intervention showed an increase in the composite knowledge score from 5.35 to 7.8, self-reported hand washing increased by 4.8 times and latrine use increased by 3.6 times. The content of the intervention was based upon the international cysticercosis co-ordination centre (ICCC) poster ‘Lets break the tapeworm cycle’ (www.slideshare.net/ILRI/lets-break-the-pork-tapeworm-cycle) with messages disseminated through street plays, songs, discussions, posters, banners and leaflets. Pig farmers were targeted in separate group education sessions and school children were also targeted in separate meetings (Alexander et al., 2012).

In Nepal, the PRECEDE-PROCEED approach was used to implement a health-education intervention which identified priority activities to be a training program on hygienic meat production and marketing and for the Nepal Veterinary Council (NVC) to initiate and enforce meat inspection systems. Eighty-two meat sellers/producers were given training and a private modern slaughterhouse opened with the technical support of the research team (Jimba and Joshi, 2001, Jimba et al., 2003, Joshi et al., 2001). No data on the efficacy of this approach has been published to date.

A ‘training of trainers’ approach was used in Western Kenya between 2006-8 using a combination of workshops and one-to-one interviews and training of 282 small-holder farmers. Farmers were randomly selected for training in proportion to the number of farmers in the village (targeting approximately 65% of all farms in a village) Approximately 50% of farmers selected for training attended the meetings, with a small decrease in the number of farmers participating in the one-to-one interviews over the 3 rounds. During the follow-up period the number of farmers tethering their pigs 100% of the time increased from 32% to 51% at visit 2 (0<0.001) and 62% (p<0.001) at visit 3, although this increase was not associated with workshop or training attendance. Knowledge about T. solium transmission and epilepsy increased between the 2nd and 3rd visit and was more likely to have increased if farmers had attended the workshop than in farmers who did not attend (Wohlgemut et al., 2010).

In China a health education program in Henan Province from 1994-6 was found to reduce the prevalence of taeniasis from 0.045% to 0.002% and a program in Shangong Province from 1996-8 saw a reduction in human cysticercosis from 1.73% to 0.59%. These programs utilised the mass media, personal communication and workshops for doctors who then spread the messages through broadcasts, interviews, focus group discussions etc. (Wu et al., 2012)

A Mexican health education intervention resulted in a reduction in the prevalence of porcine cysticercosis (Ag ELISA) of 5.2% to 1.2% (p<0.05) and a non-significant reduction in taeniasis cases one year after the intervention. The authors found that there was a significant improvement in knowledge 6mths after intervention, with some reduction at 1yr post intervention, but that knowledge was still generally above that found at baseline. Behaviour change was less pronounced than improvements in knowledge which was potentially due to limited resources. The number of pigs running loose did, however, reduce by 50% which may have been responsible for the decrease in porcine cysticercosis (Sarti et al., 1997).
Table 3. Health Education Programs

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Population &amp; Coverage</th>
<th>Human Cysticercosis</th>
<th>Porcine Cysticercosis</th>
<th>Taeniasis</th>
<th>Knowledge</th>
<th>Good Practise</th>
<th>Follow-up period</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanzania</td>
<td>2002-5</td>
<td>Farmers 62%</td>
<td></td>
<td></td>
<td></td>
<td>Significant in control and intervention group</td>
<td>Reduction in consumption of infective pork</td>
<td>12 months</td>
<td>(Ngowi et al., 2009, Ngowi et al., 2007b, Ngowi et al., 2008)</td>
</tr>
<tr>
<td>India</td>
<td>2008-10</td>
<td>School children, farmers &amp; community members</td>
<td>Not reported</td>
<td></td>
<td></td>
<td>Increased 46%</td>
<td>Hand washing (x4.8) latrine use (x3.6)</td>
<td>6 months</td>
<td>(Alexander et al., 2012)</td>
</tr>
<tr>
<td>Nepal</td>
<td>2000-?</td>
<td>Meat sellers/producers</td>
<td>Not reported</td>
<td></td>
<td></td>
<td>Not reported</td>
<td>N/A</td>
<td>N/A</td>
<td>(Jimba and Joshi, 2001, Jimba et al., 2003, Joshi et al., 2001)</td>
</tr>
<tr>
<td>Kenya</td>
<td>2006-8</td>
<td>Pig farmers 46% (Busia) 37% (Kakamega)</td>
<td>Not reported</td>
<td></td>
<td></td>
<td>Increased more in those attending workshop</td>
<td>Significant increase in tethering</td>
<td>24 months</td>
<td>(Wohlgemut et al., 2010)</td>
</tr>
<tr>
<td>China</td>
<td>1994-6/6-8</td>
<td>Not reported</td>
<td></td>
<td>95%</td>
<td></td>
<td>Not reported</td>
<td>N/A</td>
<td>2 yrs.</td>
<td>Reviewed by (Wu et al., 2012)</td>
</tr>
<tr>
<td>Mexico</td>
<td>1992-3</td>
<td>Teachers, health personnel, students, community members</td>
<td>Not reported</td>
<td>77% Significant (p&lt;0.05)</td>
<td></td>
<td>Non-significant n(1yr) 56% reduction (3yrs)</td>
<td>Significant increase</td>
<td>1yr &amp; 3yrs</td>
<td>(Sarti et al., 1997)</td>
</tr>
</tbody>
</table>

The program was implemented in three stages: firstly interviews with key informants, followed by a KAP study and then a two stage education program the first stage of which concentrated on improving knowledge and the second on modification of risk behaviour. Each educational aspect consisted of: educating teachers, health personnel and junior high students, house-house visits by students to sensitize the community and the establishment of a group of facilitators to lead an open assembly to show educational videos followed by reinforcement visits (Sarti et al., 1997). The success of this program has been attributed to careful preparation and the use of materials relevant to the community and indeed development of culturally relevant health education materials has been highlighted by various researchers, including production of video material and electronic resources for the education of educators (Rimm, 2003, Sanchez and Fairfield, 2003). An intense program of in-depth scientific talks for members of community has also been developed in Mexico (Vargas-Parada et al., 2006) although no information is available on the efficacy of this approach and funding has been withdrawn from the project at this moment (Personal communication, Vargas-Parada).

In summary, in agreement with Lightowlers (2013), evidence for efficacy and cost-benefit of health education as a control strategy for *T. solium* are lacking and therefore no recommendation can be made for it’s use as a stand-alone strategy. The use of appropriate health education, should be recommended both as part of a sensitisation campaign for other strategies and for long-term control of the parasite.

An open access advocacy tool has been developed as part of the ICONZ project (http://www.iconzafrica.org/) and is available to all interested parties here: http://www.theviciousworm.org/
Suggestion; A single repository for all developed materials – could be hosted by PIGTrop? Or WHO?

<table>
<thead>
<tr>
<th>Key Points</th>
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<tbody>
<tr>
<td>• Education agreed by the majority of experts to be an important aspect of control</td>
</tr>
<tr>
<td>• Differing methodologies makes comparison difficult</td>
</tr>
<tr>
<td>• No evidence of sustained control</td>
</tr>
<tr>
<td>• No good evidence of cost-effectiveness without infrastructure development (e.g., enforcement of meat inspection)</td>
</tr>
<tr>
<td>• Need for single open repository for educational materials</td>
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</tbody>
</table>

5.3 Improving Pig Husbandry

Encouraging farmers to adopt better husbandry practises, specifically the confinement of pigs so that they can not access human faecal material is consistently included in recommendations for *T. solium* control (Penrith, 2009, European Commission, 2000, Fleury et al., 2013). In areas where pig confinement is the norm cysticercosis has not been found (Flisser et al., 2003) and the increase in pig confinement was thought to be responsible for some of the reduction in porcine cysticercosis found in a Mexican study (Sarti et al., 1997). Confinement of pigs in piggeries and the prevention of piggeries being used as latrines are part of the official standard for *T. solium* in Mexico (MEDICA, 1994).

There is, however, no quantitative evidence available on the use of pig restraint as a stand alone strategy and there have been several barriers described to its implementation. Key barriers for confinement of pigs include: the need for development of feed strategies for low income communities based on cheap locally available feedstuffs, simple, relevantly designed houses and availability of money to pay for their construction and institutional support to industry to ensure proper control programs (Lekule and Kyvsgaard, 2003, Murrell et al., 2005). It is felt that the perception of risk (for *T. solium*) is low and is outweighed by the perceived benefits of low-cost production to the farmer (Gonzalez et al., 2003) and adoption of confined pig production would require national economic development (Lightowers, 1999). These economic barriers are thought to make pig confinement an unrealistic strategy, at least in the short term (Mahanty and Garcia, 2010, Gilman et al., 2012, Garcia et al., 2003, García et al., 2007), though it should still remain part of long-term control strategies (Murrell et al., 2005, Enander et al., 2010).

5.3.1 Improved sanitation

To prevent contact between pigs and infective faecal material pigs can either be prevented from scavenging or people can be prevented from openly defecating. Providing adequate and appropriate sanitation and ensuring that facilities are utilised by the community has advantages far beyond that of *T. solium* and should be highly recommended as part of any long-term control strategy. There are, however, currently no published studies providing data on the efficacy of improved sanitation for *T. solium* control. It is proposed that the reduction in NCC cases observed in both an urban and a rural location in Ecuador between 1990-2009 may be related to increased sanitation provision during this time (Del Brutto and Del Brutto, 2012, Suástegui et al., 2009). We as a community are currently awaiting results from a community lead total sanitation program in Zambia which aims to control *T. solium* and was presented at the 2010 NZD3 meeting in Geneva (World Health Organization, 2010).
5.3.2 Anthelmintic treatment of pigs

The treatment of porcine cysticercosis in pigs has been attempted using several anthelmintics (including Albendazole (Gonzalez et al., 1995), Albenza Sulphate (Peniche-Cardeña et al., 2002), Praziquantel (Gonzales et al., 1996), Flubendazole (Telléz-Girón et al., 1981)) of which a single dose of Oxfendazole at 30mg/kg has been the most promising (Mkupasi et al., 2013b). Oxfendazole has not shown 100% efficacy against cerebral cysts (Gonzalez et al., 1998, Sikasunge et al., 2008), although it is thought that there is little cultural precedent of eating pork brains in most endemic areas (Gonzalez et al., 1998).

Treatment with Oxfendazole appears to reduce cyst viability quickly, with 50% of cysts found to be non-viable at 1 week post treatment (Sikasunge et al., 2008) and at 12 weeks post treatment all muscle cysts appear to be non-viable (Gonzalez et al., 1998). The time for resolution of all cysts and the meat to regain a ‘normal’ appearance may be variable, with miniscule scarring being reported at 10-12 weeks (Gonzales et al., 1996), normal appearance reported at 12 weeks post treatment (Gonzalez et al., 1997) and with 4/5 carcasses having meat fit for human consumption at 26 weeks post treatment (Sikasunge et al., 2008). A withdrawal time of 17 days has been established for meat to be fit for human consumption, therefore treatment at least 12 weeks before anticipated slaughter to allow for destruction of cysts will ensure the meat is safe in terms of anthelmintic residues (Moreno et al., 2012).

A randomised control trial in Mozambique carried out between 2008-9 allocated 216 pigs from 54 litters into three treatment groups. Group one received a single oral dose of Oxfendazole (30mg/kg) at 4 months (n=54), group 2 received the same treatment at 9 months (n=54) and 108 pigs were allocated to a non-treated control group. At 12 months of age 30 pigs were selected at random for purchase and necropsy. At baseline no significant difference was found between treatment and control groups. At 9 and 12 months the control group had a significantly higher prevalence (p<0.001) than the treatment groups, between which there was no significant difference (Pondja et al., 2012).

To increase the buy-in of farmers to oxfendazole treatment a combination of oxfendazole and ivermectin for joint treatment of endo and ecto parasites has been proposed (Mkupasi et al., 2013a). Some degree of protection has been demonstrated for 3 months after oxfendazole treatment, although most probably due to animals own immunity to prior infections (Pondja et al., 2012). In order to provide immunity to all pigs, those uninfected and infected at time of treatment, vaccines to porcine cysticercosis have been developed and shown to be successful.
5.3.3 Vaccination of pigs

Chemoprophylaxis in pigs has been widely suggested as a control strategy (Sciutto et al., 2007b, Sciutto et al., 2007c, Rosales-Mendoza et al., 2012, Lightowers, 1999, Lightowers, 2010, Lightowlers, 2013, Center, 2013, CGWESA, 2011, de Aluja, 2008, Kock et al., 2012, Fleury et al., 2013, Flisser et al., 2003, Flisser et al., 2006, García et al., 2007, Garcia et al., 2003, Giri and Parija, 2012, Hotez et al., 2008, Montresor and Palmer, 2006, Assana et al., 2013). Several vaccines have been developed, of which two have progressed the furthest and have shown a high degree of potential for use in control strategies.
**SP3Vac**: has been used in several trials, all thus far conducted in Mexico. Experimental challenge in 10 pigs, matched with unvaccinated controls 30 days after immunisation was found to lead to a significant (p<0.05) reduction in viable cyst numbers at necropsy 80 days post challenge (Huerta et al., 2000). A trial of efficacy against natural exposure was conducted with 120 vaccinated pigs (born from vaccinated sows) and 120 control pigs (born from unvaccinated sows) distributed to farms as matched case-control pairs. Necropsy at 10-12 months post vaccination demonstrated a 52.6% efficacy of the vaccine (prevalence control 15.8%, vaccinated 7.5%) and a 97.9% reduction in parasite load (Huerta et al., 2002).

In 2001-3 a trial was conducted with 381 pigs allocated to 3 groups; the first received one dose of SP3Vac, the second group received 2 doses a month apart and the third group comprised of un-vaccinated controls all kept under the same conditions. A further random selection of pigs in the community was made at 3 time points during the trial to act as sentinels. Only 44% of trial pigs were recovered for follow up at 7-12 months post vaccination. Based on lingual palpation the control group were found to have a prevalence of 10%, single vaccination group 4.2% and two dose vaccination group 3.1%. Sentinel pigs were examined prior to vaccination (prevalence 13.8%), at 15mths (12%) and at 29mths post vaccination (16%). A significant reduction in prevalence was found between the (pooled) vaccination groups and the sentinel pigs. The lack of change observed in sentinel pigs indicated that a one-off vaccination intervention was insufficient to effect transmission of the parasite at the community level (Sciutto et al., 2007a).

Improvements have since been made in the vaccination with the peptides now expressed in filamentous phage (SP3Vac-phage). 1047 lingual negative pigs were included in a trial between 2004-6 with half of each litter allocated to a vaccination group which received 2 doses of SP3Vac-phage 1 month apart and half to the control group which received an injection of saline as a placebo. Farmers were blinded to the allocation of pigs to groups and were instructed to keep the pigs as normal. Necropsy performed upon 331 pigs at 5-27 months of age showed a significant (61.7%, p = 0.006) reduction in cysticercosis in the vaccination group. The mean individual parasite load was also reduced by 67.4% with an 88.89% reduction in the global number of cysticeri. There was also an increased proportion of intermediate and high inflammatory response around cysts p<0.01 indicating potential anti-cysticidal properties of the vaccine (Morales et al., 2008, Morales et al., 2011).

A three dose vaccination schedule (3mths between doses) with SP3Vac-phage has been combined with health education in improved husbandry, hygiene, latrine use and the need to treat taeniasis from 2012 onwards. The intervention has been well received due to good sensitisation; through the authors indicate problems identifying pigs, leading to worries about vaccination coverage. No results have thus far been published from this study (de Aluja et al., 2012)

**TSOL18**: has been demonstrated to provide a high degree of protection both in experimental challenges and natural exposure in the field. TSOL18 given as two doses 4 weeks apart provided 99.9% protection to 8 pigs exposed to experimental challenge in Peru (Gonzalez et al., 2005). Experimental challenge after vaccination with TSOL18 expressed in *Salmonella* and provided as an oral vaccine also demonstrated high efficacy, with mean and total number of viable cysts being significantly lower than in controls (P<0.05) (Silva, 2010)
TSOL18 has been combined with TSOL16 for a field trial in Peru where it was provided to 274 matched pairs of pigs, with the control pig in each pair being given classical swine fever vaccine only. A two dose protocol was used with 4 weeks between doses and 220 pairs of pigs were followed to necropsy 7mths post vaccination (4mths spent in an endemic area and 3mths in a cysticercosis free unit). There was a 99.7% (p<0.01) reduction in viable cysts in the vaccination group compared to the controls (Jayashi et al., 2012). It was noted in this study that pigs may have been infected prior to distribution.

To address the issue of early exposure prior to vaccination, several strategies have been suggested, either; early vaccination of piglets, which is thought to be impractical and may encounter problems with immature immune systems, sow vaccination, which may have problems handling pregnant sows, or chemotherapy (oxfendazole) combined with vaccination (European Commission, 2000).

The success of this option has been demonstrated by a field trial in Cameroon that combined TSOL18 vaccination with oxfendazole treatment. 200ug of TSOL18 vaccine was administered at 2-3 months, with a booster and 30mg/kg oxfendazole provided 4wks later and a third immunisation 3 months after the booster. 240 pigs were distributed as matched pairs to 114 farms with one of each pair being provided with vaccine and the control pig receiving only oxfendazole treatment. Pigs were examined by necropsy at 12-14 months post vaccination with 19.6% of controls found to be infected and with none of the vaccinated pigs found to be infected (p<0.0001) (Assana et al., 2010b). The use of this strategy has been recommended as a short-term vertical control program followed by a long-term sustainable horizontal program with the potential for eradication in 2 seasons (Assana et al., 2013).

**Table 5. Vaccination of pigs**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Challenge</th>
<th>Protocol</th>
<th>No. Pigs</th>
<th>Follow-up</th>
<th>Protection</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSOL18</td>
<td>Experimental</td>
<td>Oral</td>
<td>8</td>
<td>3mths</td>
<td>Significant reduction in viable cysts (p&lt;0.05)</td>
<td>(Silva, 2010)</td>
</tr>
<tr>
<td>TSOL18</td>
<td>Experimental</td>
<td>2 doses 4wks apart</td>
<td>8</td>
<td>12 wks.</td>
<td>99.9%</td>
<td>(Gonzalez et al., 2005)</td>
</tr>
<tr>
<td>TSOL18</td>
<td>Natural</td>
<td>3 doses (4wks/16wks) + oxfendazole</td>
<td>120</td>
<td>12-14mths</td>
<td>100%</td>
<td>(Assana et al., 2010b)</td>
</tr>
<tr>
<td>TSOL18 + 16</td>
<td>Natural</td>
<td>2 doses 4wks between</td>
<td>220 (followed to necropsy)</td>
<td>7mths</td>
<td>99.7% reduction in viable cysts (p&lt;0.01)</td>
<td>(Jayashi et al., 2012)</td>
</tr>
<tr>
<td>SP3Vac-phage</td>
<td>Natural</td>
<td>2 doses 4 weeks apart</td>
<td>331 followed to necropsy</td>
<td>5-27mths</td>
<td>61.7% reduction in prevalence (p&lt;0.05), 88.9% reduction in number of cysticerci</td>
<td>(Morales et al., 2011, Morales et al., 2008)</td>
</tr>
</tbody>
</table>
5.3.4 Improved meat inspection

Preventing people from consuming infected pork is another option for breaking the lifecycle of *T. solium* and is partly responsible for the control of the parasite within Europe (Gemmell, 1987), where pork is processed through official channels and where the laws on meat inspection are strongly enforced, including confiscation and destruction of infected carcasses. This can certainly provide an important degree of protection as indicated by the Reed-Frost model by Kyvsgaard et al. (2007).

There is however, no evidence that this will be effective in developing countries (Gonzalez et al., 2003), the technique itself is known to be insensitive, especially in low cyst burdens (García et al., 2007, Gilman et al., 2012, Dorny et al., 2004), the presence of black markets in many endemic countries and poor staffing levels within the meat inspectorate also present barriers to effective implementation (García et al., 2007, Ngowi et al., 2007b, O’Neal et al., 2011).

Improving meat inspection would also assist with control of other food-borne diseases and as is the case for improved sanitation and husbandry, should be encouraged as part of any long-term strategy. Reviewing and strengthening the meat inspectorate in Southern and Eastern Africa is part of the regional action plan for *T. solium* formulated by CWGES (Boa et al., 2003), has been recommended in Nepal (Joshi et al., 2003) and is part of the Mexican official standard for control of *T. solium* (MEDICA, 1994).

5.3.5 Processing of meat

Freezing, gamma-radiation, cooking and salt pickling have been shown to successfully reduce the viability of *T. solium* cysticerci, thereby breaking the life-cycle at the pig to human transmission (Rodriguez-Canul et al., 2002, García et al., 2007). Ensuring correct processing of meat requires, however, successful health education programs resulting in effective and sustained behaviour change, which are difficult to implement as reviewed above.
6 Combination strategies

There have been several trials utilising a combination of strategies to combat *T. solium*. Combining health education with the detection and treatment of *Taenia* spp. carriers (Flisser et al., 2005) or mass drug administration to the community (Keilbach et al., 1989, Medina et al., 2011, Sarti et al., 1998, Pawlowski et al., 2005) have been discussed above, as has the combination of vaccination and anthelmintic treatment of pigs (Assana et al., 2010).

As a zoonotic disease, there are great opportunities to tackle *T. solium* control through strategies which target both the human and porcine hosts (Prichard et al., 2012, Center, 2013, CGWESA, 2011, Fleury et al., 2013, Flisser et al., 2006, Garcia and Del Brutto, 2005, Garcia et al., 2003, Giri and Parija, 2012, Murrell et al., 2005, Sarti and Rajshekhar, 2003). To this end two strategies have been attempted, the combination of human and porcine mass drug administration (Garcia et al., 2006) and the combination of porcine vaccination with health education (de Aluja et al., 2012). The combination of porcine vaccination with human mass drug administration has also been modelled (Kyvsgaard et al., 2007).

A Peruvian case-control study carried out between 1996-7 involved a single round of MDA in humans with two rounds of porcine treatment. Individuals within treatment villages received 5mg/kg praziquantel and pigs received 30mg/kg oxfendazole in combination with hog cholera vaccine. The control village residents were offered pyrantel pamoate (11mg/kg) with pigs being vaccinated against hog cholera without anthelmintic treatment. 75% coverage of the human population and approximately 90% coverage of the porcine population were achieved. Pigs were monitored over a 18mth period using EITB and being in a treatment village after the intervention was shown to be a protective factor against porcine cysticercosis compared to being in a control village (OR 0.51, p<0.001) (Garcia et al., 2006). A Mexican study combining porcine vaccination with SP3Vac-phage (3 x at 3mth intervals) with health education started in 2012 and is currently on-going. The health education program focuses on improving porcine husbandry, hygiene and latrine use by the community and educating people on the need to have taeniasis cases treated, which is offered free of charge at government health centres (de Aluja et al., 2012). We eagerly await results from this trial.

Modelling of a single round of MDA in humans combined with annual vaccination of pigs indicates that prevalence of taeniasis and porcine cysticercosis would reduce rapidly and that low prevalence levels would be sustained over the 120 months modelled. 24% and 15% of replications of the model resulted in 0% prevalence in humans and pigs respectively (Kyvsgaard et al., 2007). In comparison to the rapid return to baseline prevalence after human MDA alone this indicates the benefit of a ‘two-pronged’ strategy targeting both human and animal host.

Combining human and porcine MDA with porcine vaccination has been recommended as a control strategy by the Cysticercosis Working Group for East and Southern Africa. This recommendation requires the following activities;
• Year 1
  o Vaccination of pigs (twice, 1 month apart) with Oxfendazole treatment at time of second vaccine administration
  o MDA with Niclosamide
  o 3rd vaccination 6 months later and commencement of vaccination regime for all new pigs

• Year 2
  o Single vaccine administration to all previously vaccinated pigs
  o Vaccination of all new pigs (twice, 1 month apart).
  o MDA with Niclosamide

• Years 3&4
  o Single vaccine administration to all previously vaccinated pigs
  o Vaccination of all new pigs (twice, 1 month apart)

(CGWESA, 2011).

A similar regime is being utilised by a Gates foundation funded control program currently underway in Peru. This intervention has been scaled up to target 100,000 people and results are eagerly awaited (Mahanty and Garcia, 2010). This strategy has also been suggested as a short term control measure to be followed up by longer term improvements in sanitation, husbandry and health education (Enander et al., 2010).

Combined strategies including health education, incorporation of taeniasis into deworming programs (using niclosamide), improving slaughter facilities and meat inspection and facilitating community lead total sanitation campaigns have been suggested in a policy brief produced for the Tanzanian government, although it is unclear if these recommendations have yet been adopted (Lekule and Ngowi, 2010).

7 Integration


The efficacy of Praziquantel against taeniasis and schistosomiasis opens up an ideal opportunity for integration of control strategies for these two diseases (Budke et al., 2009). Barriers to this possible integration include: requirement to map co-endemicity of the two parasites (World Health Organization, 2011a) and the safety of Praziquantel administration (at 40mg/kg) for schistosomiasis in NCC endemic areas (Engels et al., 2003, Sarti et al., 2000). Work is on-going through the Schistosomiasis Control Initiative (SCI) to evaluate the safety of Praziquantel in NCC endemic areas but coverage was difficult to achieve in this study and data analysis is still on-going (AW/WH). The potential adverse effects of albendazole treatment on NCC must also be investigated if integrated packages of anthelmintics are being considered (Loyo-Varela et al.,
Obviously the integration of NTD programs is not applicable in geographical areas without co-endemicity and the integration of programs can increase the bureaucratic burden and workload for communities (Kolaczinski et al., 2007).

Suitable tools and guidelines for mapping, monitoring and post-elimination surveillance are required for the integration of all NTD programs (Baker et al., 2010) and as these are being developed *T. solium* should be considered for inclusion. A multiplex diagnostic platform has been suggested for a variety of NTDs and there is surely potential for *T. solium* to be included within this (Solomon et al., 2012). Meetings between the NTD and the Water and Sanitation sector (WASH) should also include discussion of *T. solium* (Freeman et al., 2013). Several papers review the requirements and challenges for rolling out integrated programs, which between them lay out a reasonably comprehensive framework to be followed. Issues to consider include the need to ensure government commitment, performing a situation analysis including leveraging synergy between different programmes (both vertical and horizontal), defining monitoring and evaluation strategies including the need to monitor drug resistance and define the end-point for intervention (Bockarie et al., 2013, Hanson et al., 2012, Allotey et al., 2010, Amazigo et al., 2012).

### Integration

- Integration of complimentary vertical programs and integration of vertical programs with PHC should be long-term aims
- Efficiency gains through integration with other NTD programs in co-endemic areas
- Capacity strengthening through integration with PHC
- Requirements for joint mapping/monitoring tools
- Safety concerns for co-administration of drugs or administration of drugs in certain risk groups
- Requirement for political will

### 8 Monitoring & Evaluation

Any control strategy requires stringent M&E in order that progress can be measured and compared across programs. USAID have a standardised M&E strategy for NTD programs ([http://www.ntdenvision.org/technical_areas/monitoring_and_evaluation_for_ntds](http://www.ntdenvision.org/technical_areas/monitoring_and_evaluation_for_ntds)) and any *T. solium* program should incorporate similar standardised guidelines.

Before strategies are implemented it will be important to decide upon which disease prevalence will be measured (porcine or human cysticercosis or human taeniasis), which diagnostic tools will be used to measure disease prevalence, an ‘endpoint’ for intervention, length of follow-up etcetera. There are many pros and cons for the different diagnostic techniques which could be used to measure disease prevalence and these are summarised briefly below. A decision should be reached by the scientific community on which diagnostic technique to use so that programs can be more easily compared and contrasted.
8.1 Diagnostic Techniques

In both the human and porcine host serological assays have been used extensively in the epidemiological setting and are based around the detection of antibodies raised towards the parasite or of specific parasite antigens. Two techniques dominate the literature, being the Enzyme linked immunosorbent assay (ELISA) and the Enzyme linked immune electrotransfer blot (EITB). The EITB assay combines sodium dodecyl sulfate- polyacrylamide gel electrophoresis (SDS-PAGE) and ELISA techniques to detect circulating antibodies in sera or cerebrospinal fluid (CSF). Lectin bound glycoproteins extracted from homogenised T. solium cysts provide seven glycoprotein bands to which anticysticerci antibodies in sera or CSF will bind. A signal from any one of these bands being considered to indicate exposure to T. solium (Tsang et al., 1989b).

High sensitivity (se) and specificity (sp), of 98%/100%, has been reported in human samples (Tsang et al., 1989b) and 100%/100% in pigs (Tsang et al., 1991). In NCC cases with multiple active cysts, the EITB has been shown to perform with very high sensitivity (Blocher et al., 2011). However, it has been shown to have a low sensitivity for detection of NCC in patients with a single calcified lesion (Blocher et al., 2011). If EITB is to be used to detect human cysticercosis and taeniasis the sample size required to detect various prevalence levels of infection have been modelled with a suggestion that if disease freedom was to be declared a minimum sample size of 5000 would be required (Handali and Pawitan, 2012). The assay has performed well when compared to antibody and antigen ELISAs (Diaz et al., 1992a) but the relative technical difficulties in protein purification and standardizing the polyacrylamide gel system (Handali et al., 2010) combined with relatively higher costs makes ELISA a favoured choice in a developing nation or field setting (Dorny et al., 2003, Rodriguez et al., 2012).

ELISA techniques have been developed for the detection of circulating antibodies in sera and CSF using either a variety of antigens, crude cysticeri extracts, extracts from vesicular fluid or partially purified surface antigens. These assays have been found to have se/sp ranging between 80-100% in sera and CSF in NCC cases (Espinoza et al., 1986), and for the detection of cysticercosis in endemic and non-endemic regions (Larralde et al., 1986). Both the EITB and Antibody-capture ELISA techniques detect circulating antibodies (Ab), which indicates exposure to the parasite, but not necessarily an active infection (Rodriguez et al., 2012). This makes these assays useful for understanding the presence of the parasite in a population, but cannot identify those who are currently harbouring the infection or in a clinical setting for the diagnosis of cases and is likely to lead to over-estimation of infections (Rodriguez et al., 2012).

Active infections can be determined through detection of T. solium antigens (Ag) and serological detection of circulating antigen has been achieved using monoclonal antibodies (MAb), including HP10 (Harrison et al., 1989) and B158/B60 (Dorny et al., 2000) and various oncospheral peptides (Ferrer et al., 2005). The HP10 and B158/B60 Ag-ELISAs have been used routinely for detection of T. solium infections in humans and pigs, with varying sensitivity and specificity reported, as summarized in Table 6 below. In human NCC the sensitivity of both HP10 and B158/B60 Antigen ELISAs depends on the location of lesions, with extra-parenchymal lesions more easily detected than intra-parenchymal lesions (Fleury et al., 2007, Rodriguez et al., 2009). The B158/B60 Antigen ELISA has very recently been commercialized (ApDia n.v., Belgium) and the manufacturers report a sensitivity of 94% in human NCC cases (n=100), of 100% in experimentally infected pigs (n=31) and specificity of 99.3% in humans (n=300) and 99.6% in pigs (n=300).
The requirement for obtaining blood samples raises ethical issues in both animals and humans. Genuine fears about having blood samples taken have been encountered by medical researchers in several countries in sub-Saharan Africa, seemingly stemming from colonial times and rumours of “Kachinja” (blood stealer) (Geissler, 2005, Geissler and Pool, 2006).

Despite the benefits of immunological diagnostics, in terms of relative sensitivity and specificity, analysis of samples requires basic consumables for sample collection, equipment such as refrigerators, centrifuges, access to utilities such as water and electricity and technical expertise, all of which may be lacking in the developing country settings in which *T. solium* is prevalent (Petti et al., 2005). These limitations have lead to the call for a more user-friendly, cheap and rapid diagnostic tools for use in field conditions. The good performance of the HP10 Antigen ELISA for the detection of neurocysticercosis cases and in porcine cysticercosis has led to the suggestion that this MAb be incorporated into a lateral flow format assay which could fulfil this role (Fleury et al., 2007). A prototype of such a lateral flow assay (LFA) is currently under development at the International Livestock Research Institute (ILRI).

Cheaper and more widely accessible than other diagnostics available, is the diagnosis of cysticercosis in pigs by lingual palpation. This is a well established technique that is routinely used by farmers in Peru to screen their own pigs before being sent to slaughter (Gonzalez et al., 1990). The cheap technique, although requiring no special equipment, does require technical skill to identify the parasite, has a very low sensitivity and is only likely to detect heavily infected animals (Dorny et al., 2004). This technique has been suggested as useful for the rapid assessment of areas for the presence of the parasite (Gonzalez et al., 1990) and has been used to monitor prevalence in several intervention trials (Diaz et al., 1991, Keilbach et al., 1989, Molinari et al., 1993, Vargas-Parada et al., 2006, Wohlgemut et al., 2010, Ngowi et al., 2008, Morales et al., 2008, Sarti et al., 1997, de Aluja et al., 2012, Sciutto et al., 2007a, Peniche-Cardeña et al., 2002).

Meat inspection is used the world over, to a greater or lesser extent, for the condemnation of meat which is unfit for human consumption for various reasons, such as for;

- the detection of zoonotic parasitic infections including; trichinosis, echinococcosis and cysticercosis
- the detection of signs indicative of systemic disease such as septicaemia and jaundice
- the detection of notifiable diseases
- to ensure the correct and hygienic handling of meat for the prevention of food borne bacterial contamination

Provision is made within official meat hygiene regulations laid down by the majority of governments for specific procedures to be undertaken for the detection of cysticercosis. These include parallel incisions into the external and internal masseter muscles, a longitudinal incision along the length of the tongue, incision into the heart septum and three incisions into the triceps muscle (Boa et al., 2002).

The specificity of meat inspection is high, but the sensitivity has been reported to be low, 38.7% (95% C.I. 0.22-0.58) as practiced in Zambia (Dorny et al., 2004), especially when there are few cysts present in the pigs (Dorny et al., 2004, Boa et al., 2002, Gonzalez et al., 1990). Enforcement of meat inspection has been suggested as part of *T. solium* control as discussed above and where enforced and where robust reporting structures are in place meat inspection could play an integral part of post-control surveillance.
Traditional diagnoses of adult *Taenia* carriers rely on direct microscopy of expelled eggs in faeces. The sensitivity of microscopy is, however, estimated to be approximately 39% (Allan et al., 1996) to 52.5% (Praet et al., 2013), due to the intermittent nature of egg shedding. The specificity of microscopy is high at the species level, but as the as the eggs of *Taenia spp.* appear identical under the light microscope there is a requirement for observation of expelled proglottids for speciation (Allan and Craig, 2006, Wilkins et al., 1999). In order to improve the detection of taeniasis cases; immunodiagnostic assays, on faecal or sera samples, have been developed with a great improvement in sensitivity and specificity.

Copro-antigen diagnostics, based upon the detection of parasite specific secretory antigens, was first reported in the 1960’s although did not gain widespread scientific attention until the 1980’s (Allan et al., 2003). Specific secretory antigens are produced independently from reproductive material and are therefore not reliant on active shedding of eggs or proglottids. Copro-antigen ELISA has now been used in a variety of situations to detect *Taenia spp.* carriers. A field trial in Mexico, achieved a Se/Sp of 98%/99.2% with copro-antigen ELISA in comparison to a 38% sensitivity achieved with microscopy (Allan et al., 1996). The copro-Ag ELISA currently available are not species specific, detecting both *T. solium* and *T. saginata* (Allan et al., 1990) and cross-reactions have been reported with a variety of other gastro-intestinal parasites, including; *Ascaris lumbricoides*, *Trichuris triichiuria*, *Hymenolepis nana* and parasitic protozoa (Rodriguez-Hidalgo et al., 2003). To obtain a species specific diagnosis of *T. solium* work has been done on DNA based diagnostics. A rapid nested Polymerase chain reaction (PCR) assay using primers based on the published gene sequence of the oncospheral protein Tso31 achieved a 100% specificity, even under field conditions, whilst achieving a sensitivity of 97%-100% (Mayta et al., 2008).

The problems associated with diagnostic assays on faecal material regarding biohazards and cultural acceptability, have indicated a place for serological diagnoses of adult *Taenia spp.* carriers. This has been achieved with an immunoblot assay for the detection of antibodies towards *T. solium* excretory secretory (TSES) antigens. The assay achieved a Se/Sp of 95%/100% when used to analyse sera of known infection status, including sera from *T. saginata* carriers and Echinococcosis infections (Wilkins et al., 1999). The use of native proteins, however, was a limitation on the utility of this test in the field and recombinant proteins have now been expressed in a baculovirus system for use in diagnostic assays (Levine et al., 2004). These protein antigens (rES33 & rES38) are currently being used in an EITB format in the Peruvian cysticercosis elimination program, both having shown high sensitivity (97%/98%) and specificity (100% /91% respectively) in field trials (Levine et al., 2007).

Diagnosis of NCC is discussed in detail in the accompanying landscape analysis “*Management of neurocysticercosis with an emphasis on low-and-middle-income countries*”. Clinical signs of NCC are equivocal and serological diagnostics can indicate the presence of (Ag-ELISA) or exposure to (EITB/Ab-ELISA) a parasite but will not definitively indicate this as the etiological agent (Hawk et al., 2005). Diagnostic criteria have been recommended from which one may make a definitive or probable diagnosis (Del Brutto, 2012). Neuro-imaging technologies such as Computed Tomography(CT) and magnetic resonance imaging (MRI) are a vital tool in accurate diagnoses of NCC, but the availability and cost of such modalities are, however, prohibitive to their use in many of the endemic areas and in the majority of epidemiological studies and surveillance programs (Foyaca-Sibat et al., 2009, Gilman et al., 2012).
<table>
<thead>
<tr>
<th>Diagnostic Assay</th>
<th>Species &amp; Stage</th>
<th>technique</th>
<th>Se</th>
<th>Sp</th>
<th>Benefits</th>
<th>Barriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ag-ELISA</td>
<td>Human cysticercosis</td>
<td>HP10 (Harrison et al., 1989)</td>
<td>84.8 (74.4-95.2) (Fleury et al., 2007)</td>
<td>94 (90.2-97.8) (Fleury et al., 2007)</td>
<td>-identifies active infections &lt;br&gt;-indicates human to pig transmission (porcine cysticercosis) or human-human transmission (human cysticercosis)</td>
<td>-laboratory capacity required &lt;br&gt;-requirement for blood sampling &lt;br&gt;-expense &lt;br&gt;-remains positive for 18wks post treatment (pigs) (Sikasunge et al., 2008)</td>
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<td></td>
<td></td>
<td>ApDia Ref 650501</td>
<td>94 (87.4-97.8) (kit insert)</td>
<td>99.3 (97.6-99.9) (kit insert)</td>
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<td></td>
<td></td>
<td>B60/158 (Dorny et al., 2000)</td>
<td>100% (Gabriël et al., 2012)</td>
<td>84% (Gabriël et al., 2012)</td>
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<tr>
<td>Porcine cysticercosis</td>
<td></td>
<td>HP10 (Harrison et al., 1989)</td>
<td>70.4 (52.7-84.7) (Krecek et al., 2011a)</td>
<td>66.1 (44.6-85.1) (Krecek et al., 2011b)</td>
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<td></td>
<td></td>
<td>ApDia Ref 650501</td>
<td>100 (83.8-100) (Kit insert)</td>
<td>99.7 (98.2-99.9) (kit insert)</td>
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<td></td>
<td>B60/158 (Dorny et al., 2000)</td>
<td>89.5 (80.4-99.4) (Assana et al., 2010)</td>
<td>0.947 (0.902–0.997) (Assana et al., 2010a)</td>
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<tr>
<td>Ab-ELISA</td>
<td>Human cysticercosis</td>
<td>Crude antigen extract (Diaz et al., 1992b)</td>
<td>65% (Diaz et al., 1992b)</td>
<td>63% (Diaz et al., 1992b)</td>
<td>- identifies exposure to parasite &lt;br&gt;--indicates human to pig transmission (porcine cysticercosis) or human-human transmission (human cysticercosis)</td>
<td>-laboratory capacity required &lt;br&gt;-requirement for blood sampling &lt;br&gt;-expense</td>
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<td></td>
<td></td>
<td>F3 Antigen (Assana et al., 2007)</td>
<td>0.585 (0.425–0.787) (Assana et al., 2010a)</td>
<td>0.754 (0.689–0.818) (Assana et al., 2010a)</td>
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<td>T crassiceps (Dorny et al., 2004)</td>
<td>45.2 (27-64) (Dorny et al., 2004)</td>
<td>88.2 (73-97) (Dorny et al., 2004)</td>
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<tr>
<td>EITB</td>
<td>Human cysticercosis</td>
<td>(Tsang et al., 1989b)</td>
<td>100 (Tsang et al., 1989b) &lt;br&gt;94 (Diaz et al., 1992b)</td>
<td>98 (Tsang et al., 1989b)</td>
<td>- identifies exposure to parasite &lt;br&gt;-indicates human to pig transmission (porcine cysticercosis) or human-human transmission (human cysticercosis)</td>
<td>-laboratory capacity required &lt;br&gt;-higher technical capacity required than ELISA &lt;br&gt;-requirement for blood sampling &lt;br&gt;-expense</td>
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<td></td>
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<td>Porcine cysticercosis</td>
<td>100 (90.4-100) (Tsang et al., 1991)</td>
<td>100 (90.4-100) (Tsang et al., 1991)</td>
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<tr>
<td>Method</td>
<td>Diagnosis</td>
<td>Sensitivity (Lower - Upper)</td>
<td>Specificity (Lower - Upper)</td>
<td>Advantages</td>
<td>Disadvantages</td>
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<tr>
<td>Lingual Palpation</td>
<td>Porcine cysticercosis</td>
<td>16.1 (5-34) (Dorny et al., 2004)</td>
<td>100 (90-100) (Dorny et al., 2004)</td>
<td>-Cheap&lt;br&gt;-Relative technical ease&lt;br&gt;-Rapid&lt;br&gt;-No requirement for invasive sampling&lt;br&gt;-No laboratory capacity needed&lt;br&gt;-Indicates human-pig transmission</td>
<td>-Poor sensitivity, particularly for light infections&lt;br&gt;-No indication of pig-human transmission&lt;br&gt;-Requires capture and ID of pigs</td>
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<tr>
<td>Meat inspection</td>
<td>Porcine cysticercosis</td>
<td>38.7 (22-58) (Dorny et al., 2004)</td>
<td>100 (90-100) (Dorny et al., 2004)</td>
<td>-Statutory regulations in place in majority of counties&lt;br&gt;-Well enforced assists in control&lt;br&gt;-Excellent for ongoing surveillance&lt;br&gt;-Indication of human-pig transmission</td>
<td>-Regulations poorly enforced&lt;br&gt;-Low se for light infections&lt;br&gt;-Requirement for good reporting structure</td>
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<tr>
<td>Neuroimaging</td>
<td>Human NCC</td>
<td></td>
<td></td>
<td>-Key diagnostic for NCC&lt;br&gt;-Important for case ID and Tx&lt;br&gt;-Indication of human-human transmission</td>
<td>-Expensive&lt;br&gt;-High technical capacity required (equipment and skills)</td>
<td></td>
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<tr>
<td>Microscopy</td>
<td>Human taeniasis</td>
<td>52.5 (11.1-96.5) (Praet et al., 2013)</td>
<td>99.9 (99.5-100) (Praet et al., 2013)</td>
<td>-Low cost&lt;br&gt;-Low technology requirement&lt;br&gt;-Indication of pig-human transmission</td>
<td>-Good technical skills needed&lt;br&gt;-Poor sensitivity&lt;br&gt;-Need to collect and handle human faecal material</td>
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<tr>
<td>Copro-antigen ELISA</td>
<td>Human taeniasis</td>
<td>98 (89.3-99.6) (Allan et al., 1990)</td>
<td>99.1 (98.4-99.4) (Allan et al., 1996)</td>
<td>-Improved se over microscopy&lt;br&gt;-Indication of pig-human transmission</td>
<td>-Laboratory capacity required&lt;br&gt;-Need to collect and handle human faecal material&lt;br&gt;-Expense</td>
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</table>
Currently a wide variety of diagnostic techniques have been used to monitor the intervention trials conducted thus far as can be seen in Table 7. The lack of consistency in diagnoses makes it difficult to make direct comparisons between trials and a decision should be made on standardised monitoring techniques to address this issue.

Table 7.

<table>
<thead>
<tr>
<th>Study</th>
<th>Porcine cysticercosis</th>
<th>Human cysticercosis</th>
<th>Human Taeniasis</th>
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<tbody>
<tr>
<td>(Sarti et al., 2000)</td>
<td>Ab ELISA (Tsang et al., 1989a)</td>
<td>Ab ELISA (Tsang et al., 1989a)</td>
<td>Copro-Ag ELISA &amp; microscopy</td>
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<td>(Allan et al., 1997)</td>
<td>EITB</td>
<td>EITB</td>
<td>microscopy</td>
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<td>(Diaz et al., 1991)</td>
<td>Lingual Palpation</td>
<td>Ab-ELISA (Larralde et al., 1986)</td>
<td>microscopy</td>
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<td>(Keilbach et al., 1989)</td>
<td>Lingual Palpation</td>
<td>Ab ELISA</td>
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<td>(Sarti et al., 1997)</td>
<td>Lingual Palpation</td>
<td>Ab ELISA</td>
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<td>(Medina et al., 2011)</td>
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<td>(Alexander et al., 2012)</td>
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<td>Ag-ELISA</td>
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<td>(Cruz et al., 1989)</td>
<td>Meat inspection</td>
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<td>(de Aluja et al., 2012, Molinari et al., 1997, Molinari et al., 1993, Vargas-Parada et al., 2006, Wohlgemut et al., 2010)</td>
<td>Lingual Palpation</td>
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<tr>
<td>(Gonzalez et al., 2001)</td>
<td>EITB &amp; necropsy</td>
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<tr>
<td>(Huerta et al., 2002, Iburg et al., 2012, Jayashi et al., 2012, Morales et al., 2011)</td>
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<td>Necropsy</td>
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<tr>
<td>(Morales et al., 2008, Sciuotto et al., 2007a)</td>
<td>Lingual palpation &amp; necropsy</td>
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<td>(Ngowi et al., 2009, Ngowi et al., 2008)</td>
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<td>Ag-ELISA &amp; lingual palpation</td>
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All studies conducted so far appear too have utilised the porcine host for monitoring. This should be recommended as identifying infection in the porcine host enables us to gauge environmental contamination with *T. solium* eggs and illustrates on-going potential for human infection with taeniasis. The capture and sampling of pigs also has fewer ethical issues than that of human sampling. Lingual palpation has been widely utilised for monitoring, potentially due to the low cost of the technique. Due to the poor sensitivity of this procedure, however it should not be recommended for monitoring purposes. CGWESA recommends monitoring using Ag-ELISA of pigs
and necropsy in sub-population of pigs, both of which provide good sensitivity and specificity for identification of viable infections. They also recommend hospital monitoring and reporting of newly diagnosed NCC cases and potentially Copro-Ag ELISA or EITB monitoring of taeniasis in pilot villages (CGWESA, 2011). The addition of monitoring for taeniasis cases enables the rapid treatment of these cases, with the immediate removal of a point source of infection. The acceptability of blood or faecal sampling from a human population should be gauged on a case-to-case basis and may not always be appropriate.

9 International collaboration

Knowledge transfer and co-operative working is key to successful interventions. Many regional alliances between researchers now exist and should continue to be supported for continued networking and dissemination of lessons learnt and open communication between networks and international authorities should be encouraged (Fleury et al., 2013). Examples of such networks include: The Cysticercosis working group for East and Southern Africa (CWGES) (Krecek, 2005, Krecek, 2003, CGWESA, 2011, Mukaratiirwa et al., 2003, Mukaratiirwa and Lekule, 2006, Penrith, 2009, Boa et al., 2003), The EU COST funded network of European researchers CystiNet, The regional network for Asian Schistosomiasis and other Zoonotic Helminths (RNAS+) (Zhou et al., 2008a, Zhou et al., 2008b, Schantz, 2006), the Peruvian Working group (Schantz, 2006) and the Global campaign for combating cysticercosis (Flisser et al., 2006, Eddi et al., 2006, Willingham III and Aaen, 2006, Flisser, 2006). A national working group in Indonesia was also established in 1996 and has produced guidelines for control in the country (Suroso, 2002). A limited budget, limited power for decision making and limited number of skilled personal, however renders the group ineffectual and political commitment is required to ensure its’ success (Suroso et al., 2006)

10 Conclusions

In 2007 and again in 2011 the WHO pronounced that we were ‘tool ready’ for the control of Taenia solium (World Health Organization, 2007a, World Health Organization, 2011b). The validity of this claim was questioned somewhat in 2011 when the need for commercial porcine formulations of oxfendazole, a field vaccine for pigs and refinement of diagnostic tools were highlighted (World Health Organization, 2011a). Significant movement has been made to address these gaps, with a commercial formulation of oxfendazole for pigs now available in Africa and TSOL18 currently undergoing registration in India (Donadeu and Lightowlers, 2014), the commercialisation of the B60/158 Ag-ELISA by ApDia and work on-going at ILRI to produce a rapid pen-side diagnostic assay based upon the HP10 Ag-ELISA.

An expert consultation in Laos PDR, 2009, laid out a ‘best bet’ option for T. solium control, the core intervention being the treatment of taeniasis cases combined with mass treatment and vaccination of pigs as is being undertaken in Peru and has been recommended elsewhere (World Health Organization, 2011b, CGWESA, 2011, Mahanty and Garcia, 2010, Enander et al., 2010). The expert consultation suggested that this core approach be supplemented by supporting measures such as

- Which stage to be monitored
- Which technique to be used
- Time scale for monitoring
health education and followed by those measures requiring fundamental social changes including improved meat inspection, improved husbandry and improved sanitation. Until data is released from the Peruvian study there is no evidence of the success of this intervention, though the reported success of sustained mass drug administration in China (Wu et al., 2012, Pawlowski et al., 2005) combined with the high efficacy demonstrated by the TSOL18 vaccine in combination with oxfendazole (Assana et al., 2010b) would indicate that this is indeed a ‘best-bet’ strategy and should result in sustained reduction in transmission according to modellers (Kyvsgaard et al., 2007).
11 References


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Appendix 1. Summary of Literature search

Records identified through database searching (IngentaConnect, PubMed, AJOL, ScienceDirect, Nat.Lib. Science, Lib. of Congress, GoogleScholar) n = 37874

Records screened on title n = 22124

Abstracts assessed for eligibility n = 6184

Full-text articles assessed for eligibility n = 304

Studies included in landscape analysis n = 199

Additional records identified through other sources (solicitation from experts & citations within selected papers) n = 12
Appendix 2. Update on commercialization activities for Oxfendazole against porcine cysticercosis

Working with a network of partners GALVmed has supported the target animal safety, residues and bioequivalence studies at GCP standards, as well as the development of Oxfendazole for the treatment of porcine cysticercosis. For more information please refer to the publication below:

* A high oxfendazole dose to control porcine cysticercosis: Pharmacokinetics and tissue residue profiles (2012). Food and Chemical Toxicology, 50, 3819-3825.

Our commercial partners, Moroccan veterinary pharmaceutical company, M.C.I. Santé Animale, launched Paranthic 10% in November 2012, which is now produced at GMP standards in Africa. It is the first Oxfendazole specifically registered for use in pigs for the treatment of porcine cysticercosis at a single dose of 30 mg/kg. **Oxfendazole for the treatment of cysticercosis in pigs is now commercially available in Africa.**

GALVmed and the Facultad de Veterinaria, Tandil (Argentina) worked on the expansion of label claims of a single dose of Oxfendazole at 30 mg/kg, to support its efficacy against other common parasites of pigs, and make it more attractive for backyard farmers. A single dose of Oxfendazole has proved efficacious against *Ascaris suum, Oesophagostomum spp, Metastrongylus spp* and *Trichuris suis* (see publication below) and *Fasciola* (paper accepted for publication).


**GALVmed & M.C.I. Santé Animale**
1st April 2014
Appendix 3. Update on commercialization activities for the TSOL18 vaccine against porcine cysticercosis

Commercialization of the TSOL18 vaccine is being led by the Global Alliance for Livestock Veterinary Medicines (GALVmed) based in Edinburgh through agreements with Indian Immunologicals Limited (IIL) in Hyderabad, India and the University of Melbourne, Australia.

IIL has developed a scalable and economically viable manufacturing process for production of the vaccine at pilot scale using the Pichia expression system. A series of pig vaccination trials complying with international regulatory standards and Good Clinical Practice procedures have been completed using vaccine from IIL. These include trials to determine the immunogenicity, vaccine target animal safety, as well as efficacy against an experimental challenge infection with *Taenia solium*. The vaccine has proven to be safe and to be highly effective in protecting pigs against cysticercosis, having similar efficacy to the original experimental vaccine developed at the University of Melbourne which had used antigen expressed in *Escherichia coli*.

IIL has initiated the activities and regulatory approvals necessary for the registration of the product in India. Availability of GMP compliant vaccine is anticipated during the second half of 2014 and regulatory approval for commercial manufacture of the vaccine is expected to be available by the first quarter of 2016. Having obtained registration in the country of manufacture, registrations will subsequently be sought in other endemic countries. Use of the vaccine in regional programs, together with Oxfendazole treatment of pigs, will reduce transmission of *Taenia solium* leading to a reduction in the burden of human cysticercosis.

M. Lightowlers, on behalf of:
Indian Immunologicals Limited
& GALVmed

University of Melbourne
3 April 2014