Prevention and control of *Taenia solium* taeniasis/cysticercosis in Peru

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Taenia solium is endemic in most of the world, causing seizures and other neurological symptoms. Transmission is mainly maintained in rural areas by a human to pig cycle. Despite claims on its eradicability, sustainable interruption of transmission has not yet been reported. This manuscript reviews the conceptual basis for control, available diagnostic and control tools, and recent experiences on control in the field performed in Peru along the past decade

Keywords: *Taenia solium*, Taeniasis, Cysticercosis, Neurocysticercosis, Epilepsy, Peru

Introduction

Suffering due to seizures and other neurological symptoms caused by human neurocysticercosis (NCC), economical losses associated with both human disease and depreciation or confiscation of infected pork, and the cost for prevention and control of taeniasis/cysticercosis make this infection a public health priority in endemic areas.¹ Several characteristics of cysticercosis make it reasonable to consider its eradication: a single definitive host and the sole source of infection for intermediate hosts (human tapeworm carrier); domestic animals as main intermediate hosts; no important wild reservoirs; and availability of interventions for control.² In fact, *Taenia solium* was eliminated from most of Europe approximately a century ago following improvements in sanitation, education, and commercial pig production. Thus far, however, attempted interventions in endemic developing countries have only achieved temporary decreases in transmission. This manuscript provides a base conceptual framework and elaborates on control tools and interventions as used in a wide scale elimination program in Peru.

Conceptual Framework for Control

Taeniasis/cysticercosis is a disease of poverty

Peasants raise pigs because of economic reasons. They do not have to feed these free-roaming animals,

and will not immunize or treat their animals also because of costs. As a clear example, in many places peasants do not vaccinate pigs against hog cholera, a disease that can kill ~30% of their herds and for which there is a cheap and available vaccine.³

Taeniasis/cysticercosis has a very high biotic potential

The numbers of infective eggs expelled by an adult tapeworm may easily be over 100 000 in a day,⁴ and apparently can disseminate far away from the infected household, as shown by serological evidence of exposure in endemic regions.^{5,6} It follows that after a control intervention, a few surviving tapeworms would probably reinstate endemicity in a reasonably short period if control pressure abates. As per other parasites, probably after a few years of successful control, one can change the strategy to one of maintenance.

Taeniasis/cysticercosis is a neglected, neglected tropical disease

A group of infectious diseases related to poverty has been selected as ‘neglected tropical diseases’ and given particular attention to leveraging support for their control and prevention. These include filarial infections, Buruli ulcer, Chagas’ disease, African trypanosomiasis, among others, and until very recently it surprisingly ignored cysticercosis and hydatid disease, two larval cestode zoonoses. This is probably due to several factors, which include the requirement for sophisticated equipment for its

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diagnosis and the long time between infection and disease.⁷

From the above reasons, it follows that control of taeniasis/cysticercosis will require economical and political support, at least for a few years, effective control tools, high coverage and compliance from the population — a task that will surely face enormous difficulties. Interrupting transmission requires information on case prevalence and may also require case identification. The following sections will revise the available diagnostic tools (for taeniasis, porcine cysticercosis and human cysticercosis) and treatment options, to continue with an overview of intervention measures.

Potential Diagnostic Tools

Diagnosis of taeniasis

Taeniasis is present in 0.5–2% of the general population of endemic regions.⁸ For practical reasons, this means that an assay with a specificity of 98% will detect at least as many true positives as false positives and potentially 4:1 false to true positives, duplicating treatment efforts or requiring a second diagnostic assay. Available diagnostic tools for taeniasis include the following.

Stool microscopy

The classic and standard diagnostic tool in most settings, microscopic examination of stools after concentration aims to demonstrate *Taenia spp.* eggs. While its specificity is extremely high for the trained eye, its sensitivity is low because of erratic numbers of eggs and the small volume of sample examined.⁹

Stool tapeworm antigen detection

Detection of specific tapeworm antigens in stools using ELISA increases the sensitivity of the diagnosis.^{10,11} Drawbacks of this technique include its costs, the need for an ELISA reader machine and reagents, and trained operators.

Stool PCR

Molecular methods can provide a species-specific diagnosis when proglottid material is recovered from stools, and apparently newer versions can detect *Taenia* eggs in stools above a determined threshold.^{12,13} These tests require particular facilities and equipment and trained personnel, and have not yet been tested in controlled field trials.

Serum antibody tests for taeniasis

Adult *T. solium* tapeworm-specific circulating antibodies have been identified and detected in tapeworm carriers using immunoblot and ELISA. These assays seem to have high sensitivity and specificity. Their usefulness in field conditions will be determined by the survival of circulating antibodies: if they persist for long periods after the tapeworm has died,

the predictive value of the assay will decrease significantly.^{14,15}

Diagnosis of porcine cysticercosis

Over-dispersion has been clearly demonstrated in cysticercosis infected pigs, with a very small number of animals harbouring massive infections, and most of the infected pigs harbouring only a few viable cysts. A sizable proportion of infected animals are found to have only degenerated cysts (killed by the pig's immunity). This situation may, however, vary in hyperendemic conditions. Diagnosing infected pigs is necessary to control the animal reservoir and avoid new cases of taeniasis. Tongue examination of the pigs is widely used by villagers and pig traders in endemic regions.¹⁶ This test is only low or moderately sensitive but highly specific. However, instead of controlling the dissemination of infected pork, this 'screening' leads to the introduction of sizable amounts of infected pork, at reduced prices, into the human food chain. A major drawback for using antibody-detecting immunological assays are the high background seroprevalence levels: there are many times more antibody-positive pigs than pigs harbouring cysts,^{17,18} thus the positive predictive value of these assays to detect animals with viable cysts is very low. Whether a strong reaction can have a better positive predictive value to detect animals with established cysts is a possibility currently under study. Antigen-detection tests, on the other hand, have the potential to determine viable cyst infections in pigs.¹⁹ To date, however, the reported specificities are not yet close to levels required for mass screening of pigs in endemic areas.

Diagnosis of human cysticercosis

The diagnosis of cysticercosis bases on imaging and serology. Imaging determines whether parasitic lesions are present in the examined body area, whereas immunodiagnostic assays may detect circulating antigens or antibodies. In terms of controlling transmission of cysticercosis; however, the diagnosis of human cysticercosis bears no major significance beyond the parallel detection of a minority of patients with NCC who simultaneously carry an intestinal tapeworm and are thus active sources of transmission.

Diagnosis by imaging

NCC is the most clinically relevant manifestation of human cysticercosis and thus useful imaging tools are mainly restricted to computed tomography (CT) or magnetic resonance imaging (MRI). In general both are expensive and poorly available in rural areas of endemic regions. When available, however, CT/MRI diagnosis is the best tool to diagnose NCC. A good CT scanner will detect most cases of NCC with the exception of small lesions, those close to the bone, or

small lesions in the ventricles or basal cisterns. MRI provides better image definition. Its disadvantages are its higher costs, limited availability, and poor imaging of calcified lesions.^{20,21}

Antibody-detecting immunodiagnostic tests

The enzyme-linked immunoelectrotransfer blot assay with purified glycoprotein antigens is the assay of choice for diagnosis. It may detect specific antibodies in up to 98% of patients with cysticercosis without cross-reacting with other pathologies.²² In endemic areas, a sizable proportion of the population may be seropositive because of exposure to the parasite without established infection (or naturally cured infections) and thus the serological results have to be interpreted in context with the clinical manifestations. In patients with neurological symptoms as those seen in hospital laboratories, this assay has an excellent performance, particularly in cases where images are not conclusive. Up to 30–40% of cases with a single cyst (mostly a degenerating parasite) can, however, be seronegative. New assay formats could provide better alternatives for field use.^{23,24}

Antigen-detecting tests

Antigen detection by ELISA was reported as early as 1989.²⁵ Detection of circulating specific antigens marks the presence of live parasites. It seems to have a sensitivity of around 85% in serum.²⁶ At this point, its major potential seems to be to monitor antigen levels after antiparasitic treatment.²⁷

Epilepsy

While not directly related to interruption of transmission, detection of NCC-associated epilepsy cases in cysticercosis areas is key for control. It contributes to awareness and compliance from the population and serves to locate high transmission spots (albeit less accurately than finding infected pigs). NCC is associated to approximately 30–40% of cases of seizures and epilepsy in endemic regions,^{28–31} some of which may improve their prognosis after antiparasitic treatment. Moreover, most cases of epilepsy in developing countries are not treated (the treatment gap) and simple, cheap anti-epileptic drug regimes can strikingly improve life quality, employment possibilities, and family income.

Drugs for Treating Taeniasis

Taeniasis is treated with niclosamide or praziquantel. Both have problems in availability in many countries. Between them, niclosamide is regarded as the treatment of choice because it is not absorbed from the intestinal tract and thus there is no chance of provoking neurological symptoms, if latent NCC is present in the same individual.^{32–34} While mass praziquantel chemotherapy has been administered for schistosomiasis in wide areas of Africa, no

controlled safety data on its use in cysticercosis-endemic regions is yet available. Post-treatment coproantigen monitoring could prove helpful to detect treatment failures.³⁵

Drugs for Treating Porcine Cysticercosis

Oxfendazole

Oxfendazole when given as a single dose at 30 mg/kg kills all cysts in the pig's muscles. Some cysts may survive in the brain of the animal, although this should have minimal impact in transmission.^{36–39} A major drawback of using oxfendazole as a control measure includes the delay between drug therapy and complete disappearance of cyst remnants (it takes three months for the pork to look completely clean).⁴⁰

Other drugs

Flubendazole, albendazole, and praziquantel have been used for treating porcine cysticercosis but they require multiple doses and do not kill all parasites.^{41–44}

Potential Intervention Measures

Slaughterhouse control

Slaughterhouse control is suggested as a key control component by some agencies. However, this control measure is mostly ineffective, particularly if we take into account that most infected pigs in the field harbour a few cysts that will be easily missed by routine carcass examination. Even worse, the local detection of infected animals in rural endemic villages by examination of the tongue of the pig⁴⁵ leads to the development and establishment of illegal markets for infected pork. To avoid confiscation, peasants will not take their tongue-positive animals to the formal slaughterhouse.⁴⁶

Pig corralling

Intuitively, the simplest way to eliminate transmission would be to corral pigs to prevent their contact with human stools. However, one of the reasons why rural villagers in developing countries raise pigs is precisely that by allowing pigs to roam free, the owner does not need to invest in feeding them. This practice is crucial in subsistence economies where the pigs frequently represent a key cash income and are bought or sold according to the economical situation of the owners.

Targeted treatment of humans

To decrease the source of infection, finding and treating tapeworm-infected individuals would be the intervention of choice. Once a *Taenia* carrier is identified, then careful treatment and follow-up can ensure the cure of the patient and thus close the foci of transmission. Drawbacks of this intervention include coverage in sample collection (villagers in many places may be reluctant to collect stool samples

due to hygienic reasons or cultural beliefs, or dislike blood collection for serology). Even if a sample is collected, the delay between sample collection and diagnosis will cause that some individuals with taeniasis will not come back for their results thus requiring increased efforts to find and treat them.^{3,47}

Mass treatment of humans (mass drug administration, mass chemotherapy)

In order to decrease logistic costs and increase feasibility, treating the whole village has been proposed as it is done routinely for geohelminths. Advantages of this intervention include the requirement for less field visits with the subsequent decrease in costs. However, concerns have been raised about environmental contamination with *Taenia* eggs. Other issues include low availability of niclosamide and praziquantel and the infrequent possibility of triggering seizures by giving praziquantel to individuals with asymptomatic viable brain cysts. Mass human chemotherapy has been tested in several countries.^{48–51} In general, the result was a decrease in prevalence of porcine cysticercosis and human taeniasis. The scarce data available in regards to the sustainability of its effect suggests that transmission will very quickly recover after chemotherapy is stopped.^{52,53}

Health education

Health education of the target population should be included in the design of control/elimination programs for several reasons, including increased sustainability of the program along time. Health education alone was tested in a Mexican study comparing health education, human mass chemotherapy, and both. The study showed decreased transmission in the village allocated to education, but the effect in the village receiving health education plus praziquantel was smaller.⁵⁴ Whether this resulted from particular characteristics in one of the study villages can not be ruled out.

Targeted/mass treatment of pigs

In low prevalence areas, it may be possible to use a serological test to focalize porcine treatment with oxfendazole. In many endemic areas, however, seroprevalence in pigs exceeds 30% of the population and thus mass treatment of pigs would be more appropriate in terms of cost/benefit.

Meat radiation

The use of gamma-radiation has also been proposed.⁵⁵ Feasibility of these interventions at the rural level, however, is minimal because of the dependence on expensive and sophisticated equipment.

Meat freezing

Cysts die if meat is stored at 4°C for more than 1 month, or –20°C for 1–3 days.⁵⁶ In most rural areas,

again, facilities for freezing of pig carcasses will not be available and also villagers may be reluctant to wait for a long time before consumption.

Pig immunotherapy

In 1993, Molinari *et al.*^{57,58} proposed to inject pigs with cysticercus antigens to boost their immune response to the parasite and eliminate established cysts, unlike vaccines which are given prior to infection. Data showing a positive, albeit partial effect were obtained by two field studies. More recently, a vaccine made with synthetic peptides derived from another parasite (*Taenia crassiceps*) has been claimed to have a similar effect on already established cysts.⁵⁹

Current More Promising Options

Combined human and porcine treatment.

The simultaneous use of pig and human chemotherapy boosts the effect by targeting both the tapeworm and the cyst populations. It should result in higher efficacy and decreased time for elimination.^{52,60,61}

Pig vaccination

Lightowers *et al.* have obtained close to 100% protection when using a vaccine against *Taenia solium* in pigs, TSOL18, directed towards oncospherical antigens.^{62,63} Currently, the vaccine requires at least two doses to be effective, and has been tested in addition to oxfendazole with promising results.^{64–67} Other vaccine candidates include a *Taenia crassiceps* vaccine⁶⁸ and DNA immunization.⁶⁹

Other Advances

GPS/GIS data and mathematical modelling have provided additional powerful analytical tools to further elucidate the dynamics of this disease complex.^{5,6} Villagers do not always stay in their towns. According to season, harvest time, or routine activities (school, work, etc.) there is continuous migration between villages, mostly towards larger towns. Pigs are also commonly bought and transported to different towns. Spatial analysis should contribute to understand and control for clustering of cases, and migration into the same area, or immigration from neighbouring endemic areas.^{5,6}

Markers for Monitoring Effectiveness

Once a control/elimination intervention is installed, its effects would need to be monitored for a period of several years. From the list of available markers (human taeniasis, porcine serology, slaughterhouse surveillance, human seizure and epilepsy rates), serological surveys of defined subsets of the porcine population seems as the most attractive option based on the fast renewal of the porcine population and higher rates of infection when compared to humans. For this purpose, the only applicable serum assay is

the enzyme-linked immunoelectrotransfer blot, because antigen-detection ELISA crosses with the very common *Taenia hydatigena* which parasites goats, sheep, and pigs. Taeniasis would be difficult to detect due to its typically low prevalence, slaughterhouse surveillance is very limited and affected by clandestine marketing circuits, and seizures are a very late marker and would only present in a small proportion of infected humans.

Management of Clinical Cases as Part of Control Programs

The impact of community-based management of epilepsy cases is of particular help to gain the support of the population for a given intervention program. This carries even more importance since several control interventions would require very high compliance/coverage to ensure their efficacy. Beyond community-wide interventions, medical services should provide appropriate case management for NCC (for all epilepsies), as well as detection and treatment of tapeworm carriers.

The Program in Northern Peru

Presently, a large scale elimination effort on the Northern coast of Peru is in progress, funded by the Bill and Melinda Gates Foundation. The Program initially explored selected combinations of the above described control measures to control or eliminate the disease. A second comparison round applied during 2007 provided data on efficacy, cost and acceptability of two pre-selected combinations of interventions, including the use of a pig vaccine in field conditions. The control activities are already been scaled to a population of approximately 80 000 inhabitants in a final, preferred scheme which included three rounds of mass niclosamide chemotherapy in humans, five rounds of oxfendazole chemotherapy of pigs, and a porcine vaccine (TSOL18). Preliminary results suggest that focal elimination was obtained and persisted for over a year in most villages.

While our Peruvian experience is unique, it does not fully reflect the global situation. Different stages of development, geographical and climatic variations, different pig rearing systems, and people's attitudes towards medical and veterinary interventions may significantly affect the feasibility and outcome of control interventions.^{70–74} Other factors to be taken into account include social determinants in each different reality, whether focal interventions can take advantage of geographic clustering of porcine cysticercosis,^{5,6} and the need for a close interaction between medical and veterinary services involved in control activities.⁷⁵

Controlled data on the efficacy and acceptability of the different interventions is urgently needed to provide a base-line schematic for intervention.⁶⁷ Further steps should later focus on making the elimination tools more affordable and available to

different endemic regions, as well as on adapting the elimination program to each particular endemic scenario.

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