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PORCINE CYSTICERCOSIS : EPIDEMIOLOGY, DIAGNOSIS AND TREATMENT

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INTRODUCTION

Cysticercosis is a common disease in pig raising areas of the third world.[1,2] The life cycle of *Taenia solium* includes the pig as the normal intermediate host, harboring the larval vesicles or cysticerci, and human as the definitive host, harboring the adult form of the tapeworm. Humans can also serve as the intermediate host and develop the cystic form by accidental ingestion of tapeworm eggs.[3] Human cysticercosis causes a variety of neurological symptoms, most commonly seizures due to cysts in the brain (neurocysticercosis).[4,5]

Porcine cysticercosis produces widespread livestock production losses.[6] The rates of porcine infection are variable, but in endemic regions, over 30% of pigs may be infected.[7,8] In an abattoir study in Nigeria, over 20% (483/2,358) of pigs were found infected by ante-mortem examination of the pigs' tongues and post-mortem examination of the carcasses.[9] However, figures obtained from slaughterhouse inspection generally provide lower levels of infection because obviously infected pigs are not brought to the abattoir for slaughter.[10] Geerts[11] found that, although the official figures returned by the meat inspection services show that the number of Belgian cattle infected with cysticercosis decreased during last years from 0.3 to 0.03%, systematic search and careful detection proved that 9.5% of cattle were infected with cysticerci of *Taenia saginata*. This discrepancy with the official figures was due to the

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inappropriate detection techniques used routinely in the slaughtering, and demonstrated that, even in Europe, official data may widely differ from reality.

In this report we will review the existing studies on the epidemiology of porcine cysticercosis, including our initial description of the use of sentinel pigs to monitor environmental contamination, and will summarize our experience in the diagnosis and treatment of porcine cysticercosis, including the introduction of oxfendazole as the first effective, single dose therapeutic regimen.

DIAGNOSTIC TECHNIQUES

Infection by *T. solium* in pigs can be detected by necropsy, by examination of the tongue of the animal, or by serology (using the immunoblot assay to demonstrate antibodies to *T. solium*). Necropsy is only of limited use for epidemiological studies, because in endemic countries most pigs are killed clandestinely. Tongue examination, although specific, is only moderately sensitive, requires highly trained personnel, is time-consuming and entails the risk of being bitten. The latter technique appears to be highly reliable, and it is therefore best suited to field surveys. Pigs can be bled rapidly from the anterior cava vein, a task which requires less training, and involves less danger for the operator than does the examination of the tongue. The enzyme-linked immunoelectrotransfer blot (EITB, Western Blot) assay is highly specific, and is more sensitive than either necropsy or tongue examination for the detection of *T. solium* infection.[7]

Porcine serology does not correlate perfectly with necropsy, and often returns positive results when necropsy is negative. The EITB assay, however, is highly specific since pigs from *T. solium* non-endemic areas are serologically negative. A positive result in the face of a negative necropsy could result from either exposure to *T. solium* infection, a past infection that has cleared, or from an occult lesion (missed on necropsy).[7]

THE MARKETING OF CYSTICERCOTIC PIGS IN THE SIERRA OF PERU

In Peru, consumption of pork supplied from regulated slaughterhouses is primarily restricted to the large cities on the coast. Approximately 65% of the pork consumed in the country is obtained through informal channels that are

not inspected or supervised. The pathways via which pigs are sold were studied by our group in Huancayo, a city in the Peruvian Sierra where cysticercosis is endemic, between 1988 and 1989. Official purchase, slaughter and market records were reviewed. Also, direct surveys and participant observation were carried out at two informal meat markets.[10]

Huancayo (population 500,000) is located 300 Km East of Lima (altitude 3215 m). It is the major agricultural and commercial town in the Peruvian central highlands. Based on estimates by the National Statistics Office, 1988, there were 35,000 pigs in Huancayo. Of this number, 25,000 are butchered per year (ca. 1,220 ton. of meat per annum). Officially, none of the inspected and condemned meat in Huancayo was reported to be cysticercotic. The two official abattoirs butchered only 18 pigs in 1988 and none in 1989.

The meat sold in the official market was graded for its quality and inspected for cysticercosis. No restrictions were placed on the sale of the meat, based on where or how the carcass was obtained. Infected meat was not sold in the official market. At four visits to the market for the purpose of direct observation, 220 pig carcasses were inspected and two were found to be infected. These carcasses were then returned to their owner. Observations were also carried out at two local live pig markets in the area surrounding Huancayo. Official pig inspections were never observed in over ten separate visits to each fair. Instead, tongue examinations were routinely performed by local peasants in an attempt to establish the value of the pigs. Infected pigs were often sought by buyers because of their low price. Buyers mentioned that they also examined the pigs' tongues for scars; sellers would apparently excise cysts from the tongue in order to increase the market value of the pig. Based on findings of the tongue examinations performed by buyers, approximately 15% of the pigs sold in the fair were considered to be infected. Also, a total of 52 pigs were inspected at six informal slaughter houses. Examination of the heads and carcasses of these pigs indicated that seven (14%) had cysticercotic cysts in the muscles or brain. Interviews with the informal butchers revealed that infected meat was sold either to another city, or for use in fried pork (chicharrones). Infected meat was sold to selected individuals known to the seller. Two processed-meat sellers were interviewed, both admitted to selling infected pork; small quantities of infected meat were mixed with non-infected meat, and the mixture was then roasted or fried in fat. This study demonstrated the impressive prevalence of cysticercosis infection in the pork commercialized in this zone of the Peruvian highlands.

FIELD EPIDEMIOLOGY

Early studies carried out in Mexico and Ecuador,[12-14] demonstrated the endemicity and the immediate impact of mass human chemotherapy on porcine infection. In one study, porcine prevalence was increased one year after a mass human chemotherapy campaign, whereas it was decreased in several others.[14] Also, health education improved the knowledge of the disease among the villagers,[13,15] but did not lead to the corresponding changes in practices.[15] Another consistent finding in field studies is that the risk of seropositivity for persons living in the same household with a *T. solium* tapeworm carrier is markedly increased. High seropositivity rates are significantly associated with tapeworm clusters, as well as with individuals with a clinical history of seizures.[16,17]

The prevalence and risk factors for *T. solium* infection in pigs were studied in a rural community in Michoacan state, Mexico. Visual inspection of the tongues of 216 pigs revealed cysticerci in 14 (6.5%). The prevalence was slightly higher in male than female pigs, and the most important risk factors for infection in pigs were access to human feces, the presence of an indoor latrine, and indiscriminate disposal of human feces around the pig owner's household.[18,19]

The seroepidemiology of human and porcine cysticercosis using an EITB assay was studied in a Peruvian jungle community.[8] Sera and stools were collected from nearly all villagers. Those positive for tapeworm eggs or who were serologically positive were treated with niclosamide. Thirty (8%) of the 371 inhabitants were seropositive. After niclosamide therapy, four *Taenia sp.* worms were identified in the EITB positive group compared to one in the controls ($p=0.06$). Pigs were frequently infected; 32% had a positive tongue examination and 43% were positive by EITB. Seventy-one percent of houses had at least one EITB positive pig. This study demonstrated the usefulness of porcine serology.

T. solium ENVIRONMENTAL CONTAMINATION APPRAISAL

The same epidemiological study[8] showed that it was practically not feasible to demonstrate environmental contamination by *T. solium* eggs using standard techniques. Five samples of river water obtained at different points were pumped through a 0.10 micron nylon filter. Water quantity varied be-

tween 50-100 gallons depending on the amount of sediment present in the water. In addition, five soil samples were taken near the edge of stool pits or latrines and examined for the presence of *Taenia sp.* eggs using sedimentation techniques. None were positive for *T. solium* eggs.[8] Direct detection of eggs in the environment is extremely difficult because *Taenia* eggs are scarce and large amounts of soil must be processed and examined microscopically to find a single egg.[12,13]

SENTINEL PIG TRIALS

Most cysticercosis intervention programmes use stool examination and serodiagnosis to determine disease prevalence (in the human population), but these methods are generally expensive, slow, and difficult to comply with, partly because of cultural problems associated with obtaining human blood and stool samples.[12,14] Since pigs become infected only by ingesting eggs from human feces, pig infection rates must reflect the relative quantity of *T. solium* eggs in the environment. Obtaining blood samples from pigs is acceptable to villagers, and is easily performed; thus, serodiagnosis in pigs provides a valid and practical way to monitor the potential for cysticercosis infection and can be used to evaluate the efficacy of control programmes. A similar use of sentinel hamsters and mice to indicate schistosome contamination of the environment has been previously described.[20] Some details of the design, data analysis and interpretation of a sentinel pig trial performed by the author[21] are discussed below.

Twelve two-month-old seronegative piglets from Lima, Peru (a non-endemic area for the disease) were relocated to Maceda (population 421), an endemic village in the Peruvian jungle.[8] All native two-month-old piglets in Maceda (n=157) were also tested by EITB at the same time. All 12 non-native pigs and 28 surviving native pigs were re-tested at nine months of age.

Infection status was determined using the EITB serological assay, performed according to the method of Tsang *et al.*[22] Reaction to any of the seven diagnostic bands indicates *T. solium* infection in the non-native sentinel pigs and native pigs from seronegative sows. In piglets from infected (EITB +) sows, reactions to bands different from those of the mother were presumed to indicate new infection, since new reactive bands produced by the piglet alone most certainly represent a new antigenic stimulus, and are therefore presumed to be the result of new infection.

All of the non-native piglets survived the duration of the experiment (nine months). Only 28 of the original 157 native piglets surveyed initially at two months of age were surviving at nine months of age. The low survival rate is partially due to the fact that pigs are usually slaughtered before they are a year old. In Peruvian villages, animal vaccination is not routine, and mortality varies greatly, depending on current infectious diseases. In Maceda, a hog cholera outbreak killed a large number of the pigs during our study period.

Of the 12 non-native pigs, four animals (33%) had acquired antibody to EITB bands after nine months, but these bands were rather faint. Of 28 native pigs, 18 (64%) acquired the infection by nine months of age; 75% (9 of 12) of the initially positive native pigs showed new antibody bands and 56.2% (9 of 16) of the initially negative pigs showed new antibody bands. Although not statistically significant (p=0.07), there was a strong trend for higher infection rates in native pigs. Non-native pigs had a trend toward lower infection rates, and their positive reactions are faint. This may be caused by a lower infection burden, secondary to differences in feeding habits, age and/or genetic susceptibility, or possibly humoral immune regulation.[23]

Three years before this experiment, mass niclosamide chemotherapy had been given to 93% of the seropositive persons in the study village of Maceda. At that time, 43% (57 of 153) of all pigs were EITB positive.[8] These results show that there was still environmental contamination with *T. solium* eggs, and that niclosamide, as applied, did not break the cycle of infection and transmission. As pig populations are renewed yearly,[10] EITB prevalence rates in piglets less than one year old would allow assessment of the effect of interventions and intensity of environmental contamination by *T. solium* along time.

Table 1. EITB assay conversion rates at nine months of age in non-native pigs compared with native animals.

Population (type of piglets)	Baseline EITB	Infected Month 9
Sentinel (non native)	Negative (n=12)	4 (33%) - EITB +
Native	Negative (n=16)	9 (56%) - EITB +
	Positive (n=12)	9 (75%) - New bands on EITB.

These preliminary data demonstrates that, using relatively small numbers of randomly selected pigs, it was possible to demonstrate that high rates of environmental contamination were still present in the village. Another advantage of using pigs as an indicator is that large numbers of new susceptible pigs are available for examination by serology and tongue examination, and in a subgroup of these animals infection can be assessed by necropsy.

ECONOMIC AND SOCIAL BURDEN

Economic losses resulting from food-borne parasitic zoonoses are difficult to assess. Estimations of the global economic impact of these diseases are handicapped by inadequate information on the prevalence and public health importance of parasitic zoonoses for most countries. However, the economic losses caused by certain zoonoses have been estimated for some countries and in these instances the costs are significant. *T. solium* not only produces a severe zoonotic disease,[24] but also causes severe economic losses to the pig industry.[25] In Mexico, for example, porcine cysticercosis is responsible for a loss of more than one-half of the national investment in swine production and for more than US$ 20 million annually in hospitalization and treatment costs for humans with cysticercosis.[6] Flisser[26] estimates that neurocysticercosis costs Mexico about US$ 15 million per year just for the hospitalization of newly diagnosed cases.

CONTROL PROGRAMMES FOR CYSTICERCOSIS

Control of porcine cysticercosis is currently based primarily on inspection and condemnation of infected pig carcasses.[27] Less than 10% of Peruvian pigs, however, are registered, and 55% are illegally slaughtered.[28] This makes control measures to prevent human consumption impractical and currently inadequate in endemic areas. In slaughterhouses where control and confiscation are not carried out, rates or infection among pigs may be as high as 30%.[29] A series of specific control measures, in addition to abattoir inspection, must be considered to avoid human and swine infection with cysticercosis.

Other proposed strategies for control emphasize eliminating egg dissemination in the environment by using community health education[30] and by means of mass human chemotherapy.[14,16,31,32] However, sustainable control has not yet been achieved. This strategy is based on the assumption that if egg dispersion is stopped, then the disease cycle will be broken. These measures

were successfully used with other animal cestodes such as *Echinococcus granulosus*. Consequently, this approach was proposed and used as a model for controlling *T. solium* cysticercosis.[14,27] However, as pointed out by Lawson and Gemmell,[33] field trials and control programmes demonstrate that ovine echinococcosis (*E. granulosus*) and the cysticercosis (*Taenia hydatigena* and *T. ovis*) have different stability and do not respond in the same way to control. In the endemic state, *T. hydatigena* is readily transformed by dog-dosing programmes to an extinction status. In contrast, *T. solium* cysticercosis, which is usually in the hyperendemic state, may only be transformed to the endemic state.

Furthermore, other crucial aspects were neglected in this mass treatment strategy. Human taeniasis is not easy to treat.[34] There is also a theoretical risk of a temporary increase in human cysticercosis infection during taeniasis treatment campaigns if disposal of stools is not carefully controlled; a study performed in a community in Mexico found that swine cysticercosis prevalence increased from 6.6% to 11% one year after mass human chemotherapy.[13]

There is a great economic incentive for farmers to allow access to their pigs for testing and treatment. Furthermore, virtually all pigs are replaced through slaughter every year, thus eliminating concerns about persistence of antibody. Effective treatment of infected pigs is the next logical step for controlling this disease, and should therefore, be considered an important, cost-effective addition to control programmes. As humans can only become infected with the adult stages of this parasite when they eat contaminated pork, treatment of pigs prior to slaughter may block a key step in the transmission cycle of cysticercosis.

SWINE CYSTICERCOSIS TREATMENT

Several drugs have been tested for the treatment of porcine cysticercosis. Early efforts with flubendazole[35] were followed by testing different dosages of praziquantel in therapies lasting 15 days, with variable efficacy.[36] A single dose of praziquantel was later reported to kill all cysts in 10 out of 17 pigs (59%).[37] We initially demonstrated that albendazole therapy is effective for porcine cysticercosis when given as a three-day scheme, and later introduced oxfendazole as the first effective, cheap, single-dose treatment for swine cysticercosis. Details of four treatment trials with albendazole, praziquantel, and oxfendazole are summarized below.

Treatment of porcine cysticercosis with albendazole

In this randomized, controlled study the efficacy and safety of two different schemes of albendazole therapy for treatment of porcine cysticercosis were tested.[38] Seventeen naturally-infected pigs were purchased from Huancayo, a city in the Peruvian Sierra, and brought to the veterinary facilities in Lima for the duration of the study. All pigs had palpable lingual nodules, implying heavy cysticercosis infection.[7] Each pig was weighed and hog cholera vaccine was given immediately after purchase. The pigs were fed freely, and no other medication was given.

The pigs were divided into three groups based on weight and burden of infection (grossly assessed by tongue examination), and were randomly assigned to treatment *per os* with albendazole (50 mg/kg, single dose; 6 pigs), albendazole (30 mg/kg/day for three days; 6 pigs) or a placebo (4 pigs) respectively. All treatments were mixed with food. All personnel involved in the study were blinded to the therapeutic schedule. Pigs were sacrificed 12 weeks after treatment. Normal necropsy was performed on each carcass, during which the psoas and anconeal muscles, the tongue, the heart, and the brain of each pig were dissected. All cysts present in the left psoas and anconeal muscles, and in the left half of the tongue, heart and brain, were removed and tested for viability using evagination.[39] Up to 200 cysts from other muscle samples or the right half of the tongue, heart and brain were included for testing in pigs from the control group. Cyst excision and evagination techniques were performed at different laboratories.

All animals treated with a single dose of 50 mg/kg of albendazole had side effects (extreme prostration, complete anorexia and reluctance to move), and one of the pigs died three days post-therapy. Those treated for three days (30 mg/kg/day) also had side effects (lethargy and anorexia). No side effects were noted in the placebo group. Three-day albendazole therapy killed all but one cyst. The meat, however, remained measly with dead and degenerating cysts. Single dose albendazole therapy left some viable cysts remaining in the meat. The proportion of cysts which evaginated (therefore presumed to be viable and infective) from each tissue are depicted in Table 2. Significant differences between groups were found for each tissue. Interestingly, a proportion of the cysts from one of the control pigs were non-viable. We had observed this phenomenon in previous studies (A. E. Gonzalez, unpublished data). Since there was no chance of albendazole ingestion in the controls, this must reflect natural variability in the evolution of porcine cysticercosis.

Three days of albendazole therapy was shown to be effective in this study, but the need for multiple doses makes this regimen impractical for use in field control programmes. Furthermore, although the cysts were not viable, the meat was measly and unattractive as a food product.

Table 2. Summary of evagination percentages for different albendazole treatments mean and standard deviation

TISSUE	50 mg/kg single dose	30 mg/kg/day 3 days	Placebo	p*
Muscle*	10.9 (11.8)	0 (0)	81.9 (27.4)	0.001
Tongue*	11.8 (20.9)	0 (0)	88.4 (11.2)	0.0014
Heart*	0 (0)	0 (0)	68.0 (40.1)	0.0276
Brain*	6.7 (9.8)	0.8 (2.0)	46.4 (30.7)	0.0031

* $p<0.05$, Non parametric one way ANOVA (Kruskall-Wallis)

Treatment of porcine cysticercosis with oxfendazole

Oxfendazole (OFZ, methyl[5-(phenylsulphinyl)-1Hbenzimidazole- 2-yl] carbamate, Synanthic™) was first identified as having anthelmintic properties against larval and adult forms of gastrointestinal cestodes and nematodes in various animal species in the laboratories of Syntex Research, Palo Alto, California. The structure of oxfendazole consists of the benzimidazole carbamate, characteristic of this group of drugs, with a phenylsulphinyl substituent in position 5.[40] In this randomized, placebo-controlled study, we compared the efficacy of single dose schemes using oxfendazole, praziquantel and oxfendazole plus praziquantel, for the treatment of porcine cysticercosis.

Sixteen privately reared, naturally infected pigs were purchased and managed as described in the albendazole experiment. The pigs were divided into four similar groups of four pigs each, based on weight and infection burden (grossly assessed by tongue examination). These groups were randomly assigned to treatment with praziquantel, praziquantel plus oxfendazole, oxfendazole, or placebo. All pigs were coded, labeled, and each group was housed in the same pen. The treatment drug (50 mg/kg of praziquantel and/or 30 mg/kg of oxfendazole) was given orally, mixed with the food. All personnel who conducted necropsies and/or evagination tests were blinded to the

therapeutic schedule. Necropsy, evagination and data analysis procedures were also carried out as above described.

No detectable side effects were seen in any of the groups. Viability of praziquantel-treated cysts was preserved, but their total number appeared to be lower than in the control group. Whether this represents a bias in the selection of pigs, a random variation in infection burden, or a true therapeutic effect can not be determined because of the lack of an estimate of severity of infection pre-treatment, and the increased number of tested cysts in the control animals. Both oxfendazole and oxfendazole plus praziquantel killed all the parasites, and left only microcalcifications in the meat. The proportions of cysts that evaginated (and were therefore presumed to be viable and infective) from each tissue are shown in Table 3. Cysts appeared clearly visible in the carcasses of pigs of groups 1 (control) and 2 (praziquantel). In contrast, the meat appeared clean and only minuscule scars were observed in all treated pigs of groups 3 (oxfendazole) and 4 (oxfendazole + praziquantel). The appearance of this meat was suitable for marketing, and no apparent differences in taste were found compared to pork sold in Lima markets, as tested by organoleptic trials in an expert panel.

This study demonstrated the safety and efficacy of a single dose (30 mg/kg) of oxfendazole in the treatment of porcine cysticercosis, providing for the first time a suitable therapy for porcine cysticercosis. All other regimens are either ineffective, need multiple dosing, have marked side effects or leave meat unsuitable for sale.[35-38]

A series of specific control measures, other than just abattoir inspection, have been advocated to avoid human and swine cysticercosis, including community health education,[30] and mass human chemotherapy,[31] but no sustainable control has yet been achieved. An effective therapy for porcine cysticercosis will interrupt the life cycle of *Taenia solium* and improve control programmes for cysticercosis. Humans can only become infected with the adult stage of this parasite when they ingest contaminated pork. Treatment of pigs prior to slaughter may block a key step in the transmission cycle of cysticercosis. Better market prices for treated pork and access to the formal marketing system will be strong incentives for farmers to treat their pigs, and community co-operation will be ensured. Until a vaccine for porcine cysticercosis is available, treatment of infected pigs is a logical approach for controlling this disease, and should therefore be considered an important, cost-effective addition to the control of cysticercosis.

Oxfendazole may be applicable to human disease. Albendazole is currently the drug of choice, given for at least 8 to 15 days.[41-43] If its safety is demonstrated in Phase I studies, oxfendazole may provide an effective and cheap single-dose therapy for human neurocysticercosis. Also, oxfendazole therapy caused fewer secondary reactions than albendazole when used to treat porcine cysticercosis.[38]

Table 3. Summary of evagination percentages (mean +/- standard deviation).

TISSUE	Group 1 Placebo	Group 2 Praziquantel	Group 3 PZQ + OFZ	Group 4 Oxfendazole
Muscle*	99.88 +/- 0.25	100 +/- 0	0 +/- 0	0 +/- 0
Tongue*	98.50 +/- 1.73	99.60 +/- 0.69	0 +/- 0	0 +/- 0
Heart*	96.75 +/- 5.25	97.73 +/- 4.55	0 +/- 0	0 +/- 0
Brain*	72.38 +/- 23.83	97.62 +/- 4.76	0 +/- 0	0 +/- 0

* $p<0.05$, Non parametric one way ANOVA (Kruskall-Wallis)

A dose-response trial of oxfendazole treatment of swine cysticercosis.

As seen above, oxfendazole, administered as a single dose of 30 mg/kg body weight, is highly effective for the treatment of porcine cysticercosis.[44] However, this dose calculation was based upon previous experiences with albendazole and may over-estimate the amount of drug needed for cysticercosis treatment. This experiment was designed to determine the minimal effective single dose of oxfendazole required to kill all cysticercotic cysts in pigs.[45]

Twenty-four privately reared pigs sold for slaughter were purchased at Huancayo, a city in the Peruvian Sierra and brought to veterinary facilities in Lima for the duration of the study. The pigs were divided into four similar groups of six pigs, based on live weight and estimated infection burden (grossly assessed by tongue examination). These groups were randomly assigned to treatment with oxfendazole at either 10, 20, or 30 mg/kg body weight, or no treatment (controls). The 30 mg/kg group was later reduced to 5 animals because one of the pigs assigned to this group died before therapy commenced. All pigs were coded, labeled, and each group was housed in the same pen. Oxfendazole was given orally, mixed with the food. The therapeutic

schedule was not disclosed to personnel who conducted necropsies and/or evagination tests.

Following treatment, all animals had normal feeding habits, activities and behavior. No visible side effects were noted. More than 75% of cysts in pigs from the control group were viable, irrespective of their anatomical location. There were viable parasites in samples from four pigs from the 10 mg/kg group, present in muscle (three pigs), tongue (two pigs), and brain (two pigs). There were viable cysts also in four animals from the 20 mg/kg group, although only present in muscle (one pig) and brain (three pigs). The number of viable cysts in animals from these treated groups was very low: 18 out of 216 (8%) at 10 mg/kg, and 11 out of 198 (6%) at 20 mg/kg. No viable cysts were recovered from animals belonging to the 30 mg/kg group. The proportion of cysts that evaginated (hence presumed to be viable and infective) from each tissue is shown in Table 4. Most of the cysts recovered showed marked signs of degeneration or remained as minuscule scars. Carcasses of pigs treated with 30 mg/kg had a normal appearance, looking suitable for human consumption.

Table 4. Mean cysticercus evagination rates for each tissue in oxfendazole treated and untreated control pigs, according to dose.

Dose (mg/kg)	Muscle (%)	Heart (%)	Tongue (%)	Brain (%)
0 *	90.7	99.2	100	75.2
10 *	10.0	0	4.0	4.5
20 *	5.0	0	0	12.3
30 *	0	0	0	0

* $p<0.05$, Non parametric one way ANOVA (Kruskall-Wallis)

Time-Response curve of Oxfendazole

Survival of cysticerci in host tissues involves active immune evasion mechanisms.[46,47] Previous studies using praziquantel[36] and flubendazole[35] have shown that cyst death is not immediate after treatment. It is hypothesized that although anthelminthic drugs affect parasite metabolism and damage the cyst, the death of the parasite occurs later as a result of direct attack on the dam-

aged cyst by the immune system of the host.[48] In the context of control programs, the time between therapy and cyst death is extremely important. If death is delayed beyond a few days, then OFZ treatment of infected pigs would not be a useful strategy for slaughterhouse control. Conversely, if the process is prolonged, both the time before slaughtering when the treatment must be administered and the potential for reinfection must be addressed. This controlled study determined the time period between pig treatment with a single dose of OFZ and the death of *T. solium* cysticerci in order to define its applicability as pre-slaughter treatment or as a field control measure.[48]

Twenty naturally infected pigs were bought and managed as in the above described trials. Four infected animals that received no treatment were defined as non treatment infected controls. The other 16 animals received a single dose of 30 mg/kg of OFZ and were randomly assigned into groups of four to be killed at one, two, four and 12 weeks after treatment. This schedule was based on our previous study that showed that 12 weeks after OFZ treatment all cysts were dead and only visible as minuscule scars.[45] The four untreated controls were killed at the end of the experiment (week 12).

Pigs were anaesthetized and humanely killed. In addition to standard necropsy procedures, the heart, tongue, brain, psoas and anconeal muscles were removed. The left psoas and anconeal muscles and left half of the brain, tongue and heart were weighed and carefully dissected to evaluate parasitic burden. The number of cysts for each tissue sample was recorded and used to calculate the number of cysts and/or scars per 100 grams. Efficacy of therapy was measured by cyst evagination.

After OFZ therapy, no visible adverse reactions were noted. The pigs all fed normally and demonstrated no signs of illness. A clear decrease in viability and number of cysts was noted after the first week after therapy (Table 5), but even at week 4 some live cysticerci were found in all tissues. Twelve weeks after OFZ treatment, the meat was clean and only minuscule scars were observed, except in one animal that had viable cysts in the brain. The predicted time to total viability decay depended on the organ. The time for zero viability in muscle and heart was 3.94 and 3.47 weeks, respectively. Interestingly, the time for the tongue, another voluntary muscle, was 4.7 weeks. Due to higher viability at week 4 than at week 2, and to the presence of live cysts in one sample, it is not possible to evaluate the time for total decay in brain cysts evagination, although three of four animals did not have viable brain cysts at week 12.

Table 5. Cyst evagination rates after oxfendazole treatment, for each animal and anatomic location

Week	Pig	Muscle		Tongue		Heart		Brain	
		Total	Viable (%)	Total	Viable (%)	Total	Viable (%)	Total	Viable (%)
0	717	100	72 (72)	100	62 (62)	100	49 (49)	100	49 (49)
0	840	100	46 (46)	100	65 (65)	100	35 (35)	22	11 (50)
0	834	25	25 (100)	92	82 (89)	2	1 (50)	86	40 (47)
0	722	100	80 (80)	100	70 (70)	100	70 (70)	70	60 (86)
1	849	100	10 (10)	100	10 (10)	100	27 (27)	100	35 (35)
1	751	100	20 (20)	67	30 (45)	20	4 (20)	6	3 (50)
1	841	100	6 (6)	100	34 (34)	100	13 (13)	95	22 (23)
1	831	100	58 (58)	82	31 (38)	85	14 (170	43	29 (67)
2	845	42	20 (47)	40	10 (25)	53	2 (4)	12	10 (83)
2	835	100	0 (0)	100	5 (5)	100	1 (1)	100	21 (21)
2	719	30	1 (2)	38	2 (5)	16	1 (6)	2	0 (0)
2	827	100	4 (4)	27	5 (19)	10	1 (10)	13	0 (0)
4	720	100	21 (21)	100	26 (26)	2	0 (0)	8	6 (75)
4	826	100	6 (6)	100	12 (12)	100	3 (3)	42	19 (45)
4	850	26	1 (4)	12	3 (25)	3	0 (0)	3	1 (33)
4	718	89	9 (10)	62	10 (16)	48	2 (4)	26	18 (69)
12	828	4	0 (0)	2	0 (0)	1	0 (0)	0	0 (0)
12	847	4	0 (0)	10	0 (0)	10	0 (0)	3	0 (0)
12	848	100	0 (0)	100	0 (0)	44	0 (0)	3	0 (0)
12	846	100	0 (0)	25	0 (0)	4	0 (0)	100	20 (20)

The treatment of *T. solium*-infected pigs with OFZ as part of a control program for cysticercosis has the advantage of being relatively inexpensive, sustainable, and culturally acceptable.[34] Oxfendazole is superior to other agents for this purpose because it is nearly 100% effective and safe when given as a single dose. This study demonstrates, however, that cyst death is not immediate but rather requires a period of at least one month after treatment before cyst viability is reduced to levels that will effectively control the

T. solium life cycle, and thus pre-slaughter treatment of pigs with OFZ will not be a useful strategy to control cysticercosis.

Our pigs actually had less viable cysts at two compared with four weeks after therapy. We have no explanation for this except that it may be due to the variability that occurs with the small number of animals used per group. In a previous study, we have demonstrated that doses less than 30 mg/kg were not 100% effective in killing all cysts.[45] In this study, we demonstrated again that all cysts except for some in one brain sample were killed by 12 weeks when OFZ was given as a single 30 mg/kg of OFZ. Survival of cysts in brain tissue may be explained by lower concentrations of the drug or reduced immune efficacies in the central nervous system because of the blood-brain barrier.[49] Pig brain is not commonly eaten raw; thus, it is highly improbable that cysts that survive only in the brain will be ingested and perpetuate the cycle.

Treatment with OFZ should be used eight or more weeks before a pig is brought to slaughter because killed cysts are still visible, thus making it difficult to market the meat.[45] The use of OFZ as a control measure in the village is, however, highly promising. Most control programs to date are limited to the treatment of humans alone, leaving the huge pig reservoir of cysticercosis untouched and available to infect and complete the cycle in humans. Adding a pig treatment arm to mass human chemotherapy campaigns will interrupt the cycle at the two potential points of *T. solium* transmission, pig and human. This dual interruption of the *T. solium* cycle should be also allow re-treatment campaign cycles to be spaced farther apart. Pigs, once treated with OFZ, probably will not become reinfected. In *T. saginata* cysticercosis, successfully treated cows remain immune to reinfection for at least six months.[10] Although direct evidence is lacking, pigs may also be immune to reinfection for a time period after treatment. Also, some evidence suggests that infection occurs rarely in older pigs.[50] Pigs are normally slaughtered in the villages around nine months of age, and may not live long enough to develop new infections.

Another major advantage of adding an OFZ-porcine treatment arm to control programs is that it uses economic pressure to drive the control program. Unlike human disease, porcine cysticercosis is felt by villagers as an important problem: *T. solium*-infected pigs if sold in the formal market may be confiscated and in the informal market will get much lower prices than uninfected animals. This economic pressure may serve as an incentive for locally administered porcine treatment programs, providing both community support and long term sustainability. In summary, single dose OFZ treatment of pigs should be included in mass cysticercosis control programs as a simple

but effective method of decreasing the porcine reservoir of cysticercosis in disease-endemic countries.

IMMUNOTHERAPY FOR PORCINE CYSTICERCOSIS

Improvements in public health and animal husbandry have led to the virtual eradication of human and porcine cysticercosis in developed countries, but such measures are too expensive for immediate implementation in less developed areas.[27] Vaccination of healthy pigs with cysticercal antigens caused partial protection against porcine cysticercosis,[51,52] but a vaccine is not available and may be difficult to implement in endemic regions. In contrast to preventive measures, an inexpensive *treatment* for porcine cysticercosis may be sought after and used by owners of infected pigs if it improved animal health, meat yield, and especially if it caused the degeneration of cysticerci in infected meat, thus increasing its value.

Cysticerci survive within host tissues by evading and modulating host immunity.[48,53] The rationale for immunotherapy is the observation that immunological intervention may alter this host-parasite interaction, causing destruction of cysticerci. For example, pigs infected with two successive doses of *T. solium* eggs paradoxically developed significantly fewer cysticerci than pigs that had been infected with a single dose, implying that re-infection accelerated cysticercus degeneration and absorption.[54] Similarly, re-infection of cows infected with *T. saginata*[54,55] and of sheep infected with *T. hydatigena*[56] caused degeneration of established cysticerci. Furthermore, laboratory[57] and field[58] studies have reported that immunotherapy with cysticercal antigens caused the partial resolution of porcine cysticercosis. These encouraging results led us to investigate further the effects of immunotherapy on porcine cysticercosis in a blinded, randomized and controlled study.

Twenty-eight privately reared, naturally parasitized pigs that were bought and managed as referred in the previous experiments. The animals were randomly allocated to one of four treatment groups: a) membrane-enriched antigens (MA), 5 pigs; b) saline control, 7 pigs; c) aqueous crude antigens (AA) in adjuvant, 9 pigs; and d) adjuvant alone, 7 pigs. Details on antigen preparation and injection schedules are published elsewhere.[47] Pigs were anaesthetized and humanely killed 10-12 weeks after the first vaccination. Sections through the right psoas muscle, the heart and the right half of the brain were fixed in 10% buffered formalin (0.15M, pH 7.2), dehydrated, set in paraffin and stained with hematoxylin and eosin. At least 3 cysticerci from

each of these 3 tissues were examined for every pig. Predetermined criteria were used by a histopathologist blind to treatment group to assess the host inflammatory response (cell density, predominant cell type, granulomatous reaction and degree of fibrosis) and the degree of inflammation of the cyst membrane, spiral canal and scolex (none, oedema, mild to severe inflammation, presence of host cells and degeneration or necrosis). The cell type was identified by morphology. Parasite viability was evaluated by cyst evagination.

There were no serious adverse reactions to antigenic challenge. EITB with lentil-lectin-purified glycoprotein and AA confirmed that all pigs were antibody positive at the start of the study and repeat lentil-lectin-purified-EITB testing at the end of the study did not reveal any changes. Using AA-EITB, some pigs developed new antibody bands during the study (12-13, 19 and 24 kD). Nine of 14 (64%) pigs given immunotherapy developed new bands in contrast to only 7% (1/14) control pigs ($p<0.01$). The presence or development of one or more of these bands was not significantly related to white cell count, eosinophilia or cysticercal viability. Necropsy confirmed that all pigs were heavily parasitized with *T. solium* cysticercosis. Overall, the mean number of cysticerci/kg varied considerably between pigs and was highest for the saline control group, but there were no significant differences between treatment groups. Some inflammation was present around all of the cysticerci examined but this was so variable, even between adjacent cysticerci, that it was not possible to correlate inflammatory changes with treatment group or cysticercal viability.

The macroscopic appearance of cysticerci revealed only 6 clearly degenerated cysticerci, all of which were found in 2 pigs that had been given AA in adjuvant. The percentage of cysticerci that failed to evaginate and were presumably not infective was calculated for each tissue from each pig. Adjuvant alone had no significant effect upon viability compared with saline. The effect of MA was not significant when compared with adjuvant, saline, or combined control groups. Immunotherapy (AA and MA groups combined) was associated with a 50% increase in the percentage of non-viable cysticerci when compared with the combined control groups ($p<0.04$). Immunotherapy was associated with a 3-fold increase in the proportion of non-viable cysticerci in tongue tissue ($p<0.03$) and muscle ($p<0.06$), but no effect was detected in the brain ($p<0.9$) There were relatively few cysticerci in brain tissue and these were of low viability for all treatment groups. Overall, 35% of cysts dissected from pigs given immunotherapy were non-viable, compared with 10% of those from all of the control animals ($p<0.05$). In spite of these effects, at

least a quarter of cysticerci were viable in every pig and more than half were viable in 11 of the 14 pigs given immunotherapy.

This randomized, controlled and blinded study confirmed that administration of cysticercal antigens to pigs naturally infected with *T. solium* cysticercosis caused a significant reduction in the viability of cysticerci for causing human tapeworm infection. In a previous immunotherapy study, 2 cysticercotic pigs inoculated with MA developed marked eosinophilia. Furthermore, necropsy 4 and 8 weeks later revealed histological findings suggestive of cyst degeneration.[58] However, the viability of cysticerci was not assessed in this study and the histopathological findings may have been biased by the small number of pigs and cysticerci studied, particularly in view of the highly variable inflammation we observed after administering the same dose of MA.

In a field trial in Mexico,[58] 1,076 doses of MA that was almost identical to the preparation we used were administered repeatedly to 447 pigs, although it was not clear how many doses each pig received. The prevalence of cysticercosis, as assessed by tongue palpation, fell significantly in the villages studied, but there was no control group, limiting interpretation of these results. Furthermore, their reliance on tongue palpation alone to assess response to immunotherapy may have been misleading since we found the effect of immunotherapy to be greater in tongue than other tissues. In this Mexican field trial, 7 cysticercotic pigs given immunotherapy were studied in more detail and 73% of cysts excised from treated pigs failed to evaginate compared with 5% in 7 untreated cysticercotic pigs. The ineffectiveness of MA in our study contrasts with these results and might be explained by the smaller number of vaccinations we gave, which may have induced a weaker immune response.

The effect of immunotherapy on *T. solium* viability illustrates the dynamic nature of the host-parasite interaction and the potential for manipulating this relationship to control parasitic infection. Genetically engineered, recombinant vaccines cause greater immunity against other tapeworm species[59,60] and identification and synthesis of the appropriate antigens for porcine cysticercosis may allow more effective immunotherapy. However, the statistically significant effect of immunotherapy on cysticercal viability in our study had limited biological significance: all of the pigs remained macroscopically heavily infected with predominantly viable cysticerci. Immunotherapy alone is, therefore, unlikely to adequately prevent human taeniasis.

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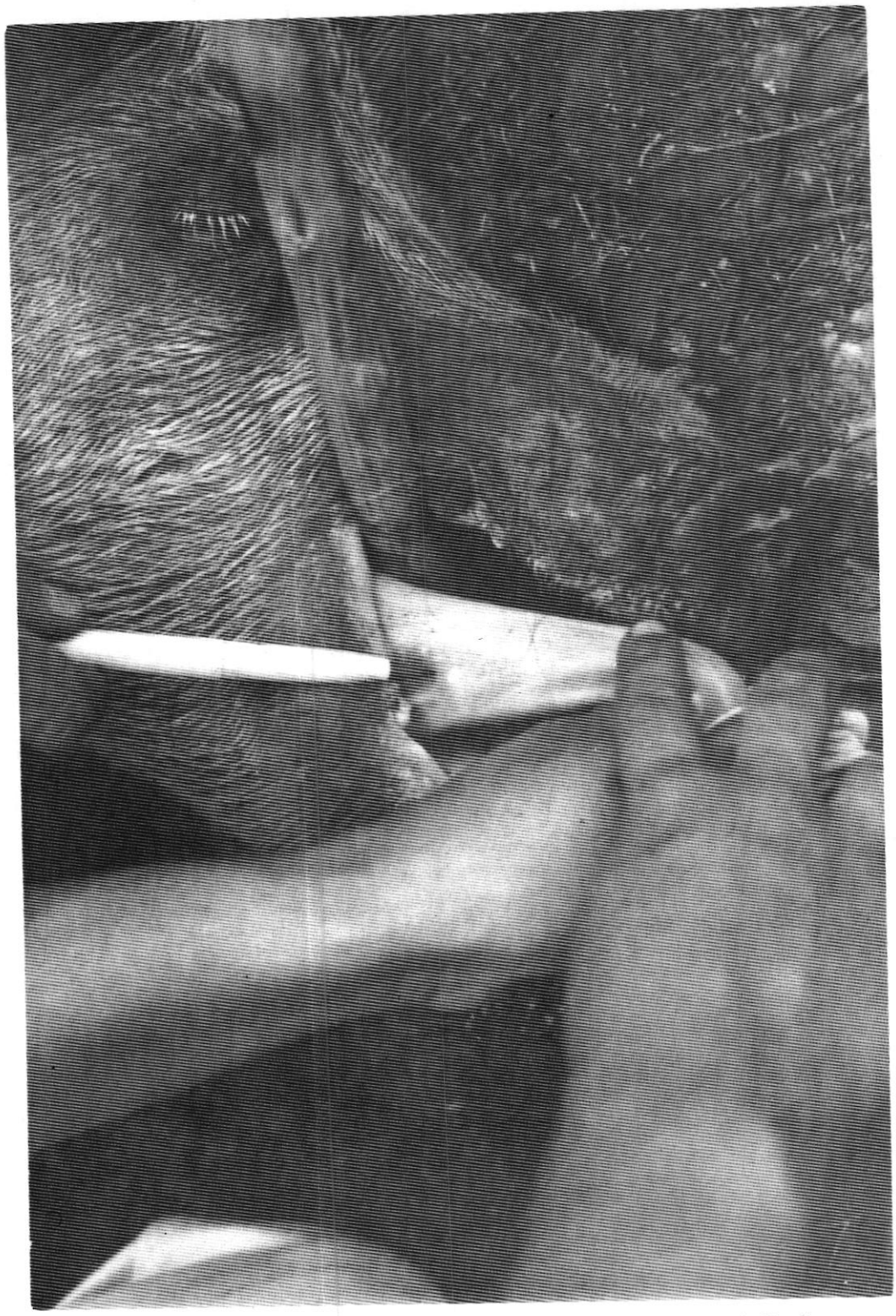

Tongue examination of a pig (Photo: Cysticercosis Working Group in Perú).