Human Taenia Solium Cysticercosis in the District of Angonia, Mozambique: Prevalence Rates and Clinical Aspects

By

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ABSTRACT

Cysticercosis is emerging as a serious public health and agricultural problem in countries of Eastern and Southern Africa (ESA). Caused by a pork tapeworm, this zoonotic disease forms cysts in the tissues of pigs and humans that reduce the value of pigs, makes pork unsafe to eat and can lead to neurological disease including epilepsy and death in humans. It occurs where pigs range freely, sanitation is poor, and meat inspection is absent or inadequate, and thus strongly associated with poverty and smallholder farming. Although theoretically easy to control and declared eradicable cysticercosis remains neglected in ESA due to lack of information and awareness about the extent of the problem, lack of suitable diagnostic and management capacity, and appropriate prevention and control strategies. Mozambique is still lacking epidemiological data on human taeniosis and cysticercosis and it is not possible to draw firm conclusions on its prevalence and geographical distribution. Until now, all the work developed in this area has been exploratory and of a piloting nature.

The objectives of the proposed study were 1) to determine the prevalence of neurocysticercosis (NCC) in humans in the district of Angonia, 2) determine the distribution of epilepsy and 3) explore possible relationships between NCC and epilepsy. The present study was conducted in the district of Angonia, located in Tete province in the central region of Mozambique.

1723 individuals from 16 towns of the two administrative posts, Ulongue and Domue in the Angonia district were included.

The proportion of interviewed people reporting symptoms of epilepsy was 15,6% (268) while 84,4% (1454) reported no symptoms. A total of 249 (14,5%) were ELISA Ag positive for cysticercosis and 1774 (85,5%) were negative. Of those with positive ELISA Ag 118 (47,4%) had a history of epilepsy. CT scans were performed on 107 (90,7%) of the 118 and 44 (33,6%) of the ELISA Ag negative

with symptoms suggestive of epilepsy. Of the ELISA Ag positive group, 77 (72%) showed abnormal scans suggesting NCC, compared to the 8 (18,2%) in the negative group. 151 people were also submitted to EEG exam and 79 presented abnormal results. Considering the type of seizures of the total of 79 individuals, 73,4% (58) were affected by partial seizures and the remaining by generalized seizures.

We concluded that *T. solium* NCC appears to be an important but overlooked cause of epilepsy in Angonia. The main recommendation for reducing the prevalence of human cysticercosis is to provide more effective education campaigns and proper sanitary facilities with improved health care and socioeconomic status of the people in developing countries, aimed at preventing both *T. solium* infection and cysticercosis.

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ABBREVIATIONS AND ACRONYMS

CDC	Centre of Disease Control
CESA	Cysticercosis in Eastern and Southern Africa
CI	Confidence Interval
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CT	Computed Tomography
CWGESA	Cysticercosis Working Group in Eastern and Southern Africa
CWGP	Cysticercosis Working Group in Peru
DANIDA	Danish International Development Agency
EEG	Electroencephalogram
EITB	Enzyme-Linked Immunoelectrotransfer Blot
ELISA	Enzyme-Linked Immunosorbent Assay
ESA	Eastern and Southern Africa
FAO	Food and Agriculture Organization
FAOSTAT	The statistical database of FAO
ILAE	International League Against Epilepsy
ITFDE	International Task Force for Disease Eradication
KAP	Knowledge, Attitude and Practice
MRI	Magnetic Resonance Imaging
NCC	Neurocysticercosis
OR	Crude Odds Ratio
PPS	Probability Proportional to Size
SCG	Solitary Cysticercus Granuloma
UN	United Nations
USA	United States of America
WHO	World Health Organization

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DEDICATION

I dedicate this research to

Mariam, my wife and best friend

Ayman, my son and inspiration

CHAPTER ONE
INTRODUCTION

Pig rearing and pork meat consumption have increased significantly in eastern and southern Africa (ESA) during the past decade (FAO, 2005) especially in rural smallholder communities, primarily due to the lack of grazing land for ruminants and the recognition by farmers of a quicker and more impressive return on their investment from raising pigs. In addition, the increased demand for pork in urban areas in the region has resulted in the transportation of pigs from these rural smallholder communities to large population centers.

A high and increasing prevalence of epilepsy in ESA, without a clear etiology, and the appearance and increase in cases of porcine cysticercosis have been noted in this region (Phiri *et al.*, 2003). Caused by a zoonotic pork tapeworm, *Taenia solium*, the disease forms cysts in pigs that reduce the market value of pigs, render pork unsafe to eat and can lead to neurocysticercosis (NCC) with epilepsy and death in humans (Garcia *et al.*, 2003).

According to the International League Against Epilepsy (ILAE), cysticercosis is probably the single most common cause of acquired epilepsy in the developing world, where prevalence rates of active epilepsy are twice those of the developed countries (Del Brutto et al, 2001). It is also a growing problem in industrialized countries because of immigration of tapeworm carriers from areas of endemic disease (Burneo and Garcia, 2001). The majority of the worldwide burden of epilepsy is found in low-income countries, where the prevalence is substantially higher than in high-income countries (Diop et al., 2003; Preux & Druet-Cabanac, 2005).

Globally, NCC is considered to be the most common parasitic disease of the nervous system (Burneo and Garcia, 2001). This infection of the human Central

Nervous System (CNS) by the larvae of *T. solium* is a major cause of epilepsy and mortality in developing countries (WHO, 2002).

An international workshop on taeniosis and cysticercosis, held in South Africa in 1997, provided the first indication of an emerging problem with *T. solium* cysticercosis in the ESA region. The issue was subsequently discussed in 2000 in Lusaka, Zambia, at a meeting on *Human Helminthoses: Future Research Foci* organized by the University of Zambia and DBL- Institute for Health Research and Development (Olsen *et al*., 2001). The issue of parasitic zoonoses was identified as an emerging and neglected problem in the ESA region.

During the Lusaka meeting researchers in the region presented research results that substantiated *T. solium* cysticercosis is present throughout the region and the number of cases is increasing. It is an important constraint for regional agricultural and health development (Phiri *et al*., 2003; Mafojane *et al.,* 2003). Recognizing this problem, the scientists conducting research on cysticercosis in ESA formed the Cysticercosis Working Group in Eastern and Southern Africa (CWGESA) in order to facilitate increased awareness of the problem and help promote a coordinated regional approach for research and control of *T. solium,* while making more effective and efficient use of scarce resources.

In 2001 the CWGESA concluded that evidence concerning the cysticercosis situation in the region urgently needed to be shared with relevant authorities at the regional and international levels to instigate interest, will and support for further baseline studies on the situation in pigs and humans. In addition, it would be mandatory to establish surveillance, prevention and control efforts in ESA. The CWGESA in collaboration with the WHO/FAO Collaborating Centre for Parasitic Zoonoses in Denmark, the DBL- centre for Health Research and Development, and the DANIDA funded Livestock Helminths Research Project in ESA, organized an international action planning workshop on cysticercosis/taeniosis caused by *T. solium* held in August, 2002 in Arusha,

Tanzania, bringing together scientists, government authorities, health and veterinary officials as well as community leaders and delegates from international and regional support agencies.

Risk factors for the development of NCC in humans are older age groups, absence of sanitary facilities, poor formal education and inability to recognise infected pork. Informal interviews with pig owners in Angonia have indicated that rural pork producers are not motivated to pass pork through meat inspection because of the threat of condemnation. Furthermore, local culinary habits facilitate the consumption of raw or partly cooked meat.

These factors could lead to transmission of the cysticercus from the pig to the human being in endemic areas (Carpio, 2002). According to Phiri et al. (2003), the majority of pig keeping in the ESA region is free-range, but if housed, the housing is poorly built and allows pigs to break out at will. This is indeed a problem in the area chosen for this study. In the absence of sanitary infrastructure, people use open areas and fields for defaecation; free ranging pigs thus have access to human faeces. If the inhabitants are carriers of the tapeworm, they will produce thousands of highly contagious eggs in their stool, which perpetuates tansmission of the parasite from the human being to the pig. In areas where meat inspection and control are lacking, infected pigs are often slaughtered informally and the pork is eaten or sold for human consumption, thus completing the life-cycle.

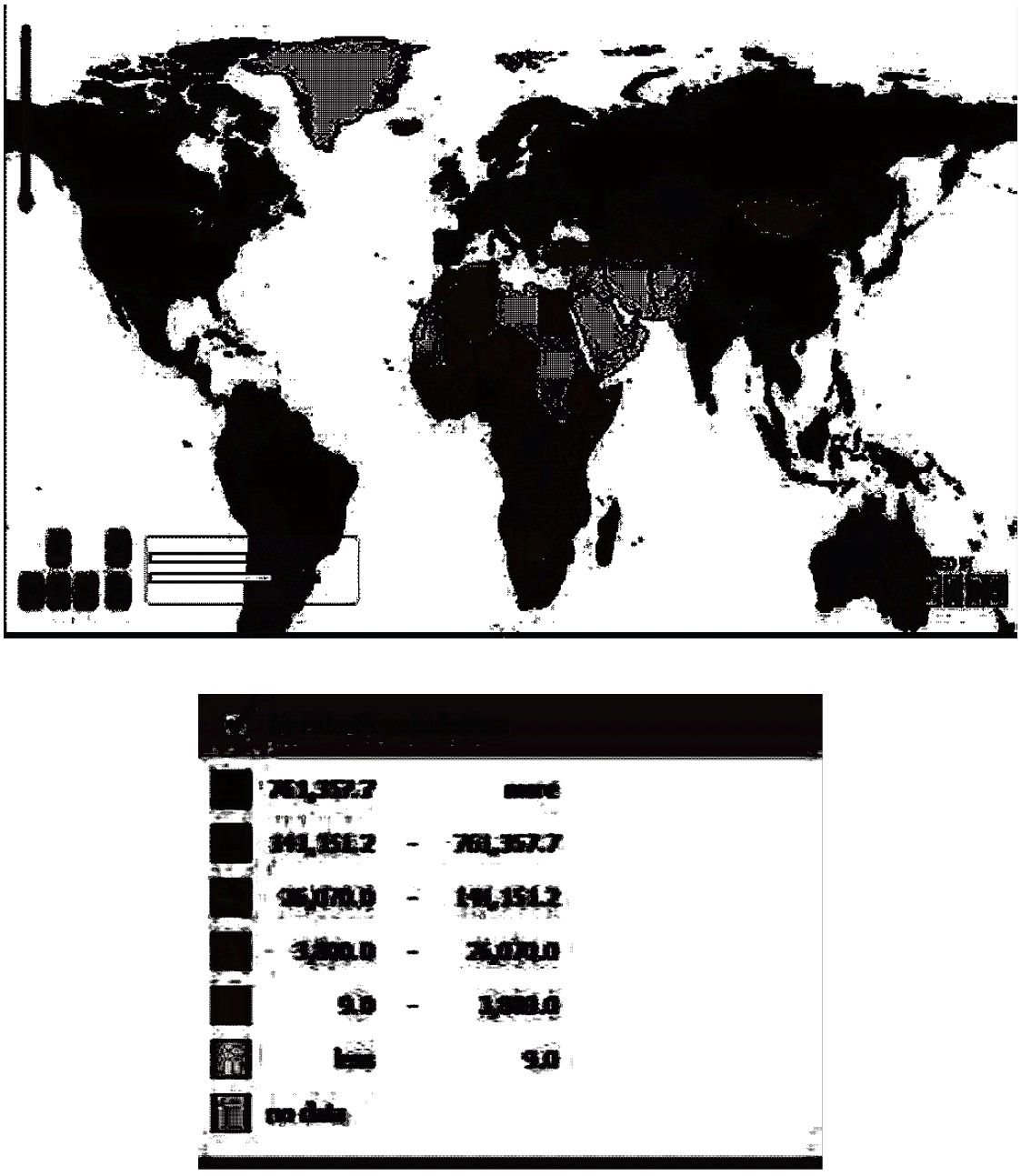
Although theoretically easy to control and declared eradicable (ITFDE, 1993), cysticercosis remains neglected in ESA due to lack of information and awareness about the extent of the problem, suitable diagnostic and management capacity, and appropriate prevention and control stategies.

In Mozambique, abattoir records indicate that porcine cysticercosis is present in all provinces of the country. A sero-prevalence study on rural Tete Province

demonstrated that 15% of 387 pigs were seropositive (Phiri *et al.,* 2003). In 1960 Ferreira de Abreu reported that in some regions in the south of Save River more than 80% of pigs had cysticercosis and in 1968, Limpo Serra noted that infestation of pigs by cysticercosis was found in almost all slaughter houses of the country. Human infestation by *T. solium* was also recorded by the same author (Vilhena, *et al.,* 1995). Seroepidemiological studies undertaken in the 1990s recorded prevalence of seropositivity from 14-18% among humans in different regions of Mozambique where pigs are farmed (Vilhena, *et al.,* 1994, 1995, 1999). A study in Maputo revealed the existence of a relationship between cysticercosis, epilepsy and psychiatric conditions. The most critical factor for the high prevalence of cysticercosis verified by this study was water contaminated by faecal materials that was in turn used for watering production plots of which the products are consumed in the markets of Maputo City and suburbs (Noormahomed, 2005). No neuroepidemiological studies have been undertaken in Mozambique to date.

Pork is the most popular type of meat consumed in the world today and 44% of world meat protein consumption is derived from pork and pork products (FAO, 2001). As presented in the Figure 1 below, the world pig population is estimated to be 923 million, of which 552 million are found in Asia, 72 million in North America, 194 million in Europe, 81 million in South and Central America, and 18 million in Africa (FAO-STAT, 2002).

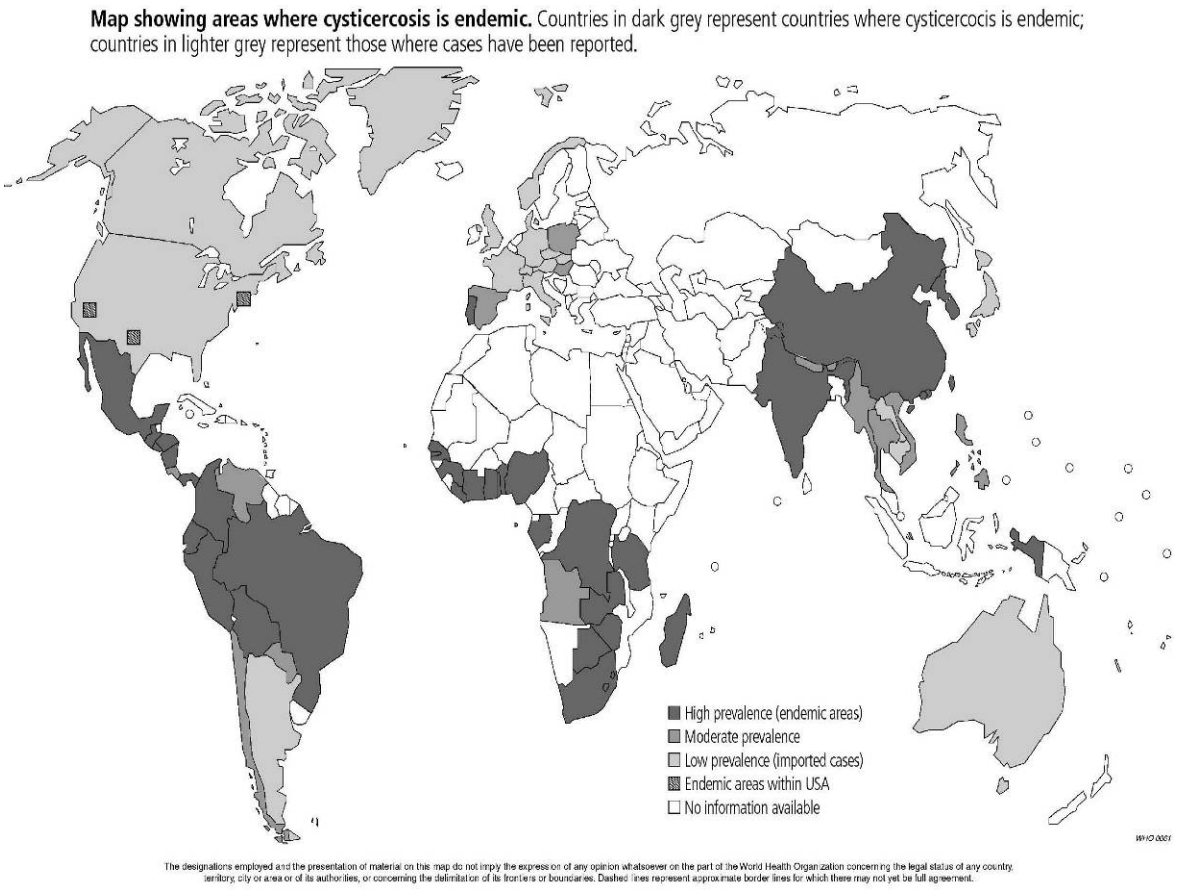
Figure 1 – Pig Population Distribution in the World



Source: FAO – Statistics Database 2009

The world map of the prevalence of the *T. solium* taeniosis/cysticercosis has been updated considerably during the last decade (see Figure 2). Infection with *T. solium* is widely prevalent in humans and pigs in many developing countries of Latin America, Africa, and Asia (Sarti et al., 1992; WHO, 2002; Zoli et al., 2003; Phiri et al., 2003; Rajshekhar, 2003).

Figure 2 – Distribution of Cysticercosis in the World



Source: WHO Zoonotic Diseases Website

CHAPTER TWO

THE CURRENT STATUS OF HUMAN CYSTICERCOSIS IN THE WORLD

T. solium infestation is a major public health problem in most areas of Latin America, Africa and Asia. Geographically, it is generally considered that Latin America and the Far East are the most affected regions, but there is increasing evidence that also on the Indian subcontinent and in ESA the prevalence is increasing.

Conservative figures mention that 50 million people are infected with the parasite and some 50 000 die due to cysticercosis annually (Aubry et al., 1995).

T. solium is probably responsible for over 10% of acute care admissions to neurological wards of countries where it is endemic (Garcia and Del Brutto, 2000). It is calculated that in developing countries 30 to 50% of epilepsy cases are associated with NCC (ILAE, 1994). Approximately 75% of patients with NCC are in their productive age and once the symptoms are established they frequently become incapable of work (Flisser, 1988).

The prevalence of porcine cysticercosis found in the ESA countries rank among the highest in the world and the disease is emerging as an important constraint for the nutritional and economic well being of resource-poor smallholder farmer communities (Phiri et al., 2003; Mafojane et al., 2003).

In both rural areas and urban centres in this region, findings suggest widespread presence of human tapeworm carriers and thus a high risk of human cysticercosis. Additional research and study are required to estimate the extent of public health and economic impact of *T. solium* infection. This is critical to identify

whether prevention and control efforts are needed in ESA region (Phiri et al, 2003) and if so what those constituted.

In South Africa, several studies indicated that 28% to 50% of epileptic patients were positive for cysticercosis (Mafojane et al., 2003; van As and Joubert, 1991; Campbell and Farrel, 1987; Naidoo et al., 1987; Thomson et al., 1984).

Human cysticercosis appears to be most prevalent in Eastern Cape Province particularly in rural areas of Ciskei and Transkei, where pigs are allowed to roam freely and sanitation facilities are inadequate or nonexistent. Community-based epidemiological studies conducted in these areas have involved children where surveys have indicated that 2,5-5,5% were serologically positive for cysticercosis (Shasha and Pammenter, 1991).

In addition to the surveys of rural inhabitants, a small hospital survey of urban black South Africans indicated a prevalence of 7,4% suggesting that urban dwellers are also at risk of infection with cysticercosis (Sacks and Berkowitz, 1990).

In Zambia, studies have indicated that epilepsy is responsible for a significant burden of disease in rural areas. Some evidence suggests that epilepsy is under reported, under recognised, and under treated in this population (Birbeck, 2000).

In Zimbabwe, Mason et al. (1992) reported a prevalence of anticysticercal antibodies of 12% in patients with signs and symptoms compatible with NCC. A study in Bulawayo reported calcified cysticerci in 11% patients presenting with seizures (Rashman, 1970).

With high porcine cysticercosis prevalence rates in areas of Kenya, Tanzania and Uganda, it may be anticipated that the prevalence rates of human cysticercosis are also high in the region.

Despite the fact that reliable and updated official data is unavailable, in countries from the Western and Central Africa regions it has been reported that the necessary conditions for the transmission of the parasite from pigs to human and vice versa exist: open air defecation or deliberate defecation in pig sites, clandestine slaughtering of pigs, lack of trained and qualified meat inspectors, lack of detection and treatment of *T. solium* carriers and consumption of raw or not well cooked pork meat (Preux et al., 1996; Zoli et al., 1998; Geerts et al., 2002).

Several surveys have been conducted in many of the countries from the Western and Central Africa regions; in Benin, Togo and Cameroon more comprehensive studies were performed looking at the taeniosis-cysticercosis complex. Except for Muslim countries, it was observed and reported that *T. solium* affects all countries in the region (Zoli et al., 2003).

Dumas et al. (1989) reported 2,4% and 29,5% seropositives for cysticercosis in the adult population and in epileptics of northern Togo, respectively. A prevalence of 10,8% was reported in hospitalized epileptic patients in the capital Lome (Grunitzky et al., 1995).

A nation-wide survey in Benin revealed that the overall seroprevalence of cysticercosis in the general population was 1,3% and the prevalence rate of epilepsy was 15,2 per thousand (Houinato et al., 1998; Avode et al., 1996).

Tsang and Wilson (1995) reported a prevalence rate of 21% of seropositives for cysticercosis among epileptics in Rwanda. In Burundi, Newell et al. (1997) reported a seroprevalence of 2,8% in general population and 11,7% in epileptics. In the West Province of Cameroon the prevalence of human cysticercosis has been reported to range between 0,7 and 2,4% (Zoli et al., 1987; Nguekam et al., 2003).

Based on epidemiological studies and autopsy findings, cysticercosis is also considered a priority health problem in Latin American countries, namely Brazil, Colombia, Mexico and Peru. The problem is also expanding to more countries in the region, such as Guatemala and USA (Chimelli et al., 1998; Schenone et al., 1982; Flisser, 2002 a,b; Allan et al., 1996).

USA and other developed countries are also beginning to realize that NCC is an emerging disease. In Los Angeles, 138 cases have been reported between 1988 and 1999. More than 80% of cases appeared in foreign-born immigrants, 7% in individuals who travelled to endemic countries and 8% acquired the disease locally (Schantz et al., 1999).

Several reports of patients with cysticercosis from Asia indicate that T. *solium* is widely distributed in Asian countries (Rajshekhar et al., 2003). While in some countries such as Japan and Singapore increasing economic prosperity and accompanying infrastructure have made the disease almost non-existent, in others, such as the Islamic countries of the Middle East and West Asia, religious prohibition of the consumption of pork has had a similar result. Thus, NCC did not receive a great deal of attention in Asia as a relevant cause for neurological morbidity and economic loss. Unlike in Latin America, in Asia the disease was previously ignored and only recently has it started to become of interest to this group of countries. As a natural consequence, data on the epidemiological aspects of the disease are poor or of questionable reliability (Rajshekhar et al., 2003).

In Europe the disease has been assumed eradicated and only occasional cases are reported in Portugal, Spain, Italy, Germany and France (Crimmins et al., 1990; Pedro et al 1991; Monteiro, 1993; Wiegand et al., 1999; Font Puig et al., 1999; Rousseau et al., 1999; Gemmell et al., 1976; Vilhena et al., 1997).

The final decline of the disease is a consequence of economic development and the improvements in personal hygiene, basic sanitation, changes in the type of pork production and meat inspection institutions.

However, due to emigrations and increases in the level of travelling between countries, *T. solium* cysticercosis has recently also started to be an emerging disease in Europe. Evidence showed that the infection was locally acquired and recent surveys revealed that out of a total of 45 cases of NCC diagnosed between 1996 and 2000, 11 were autochthonous (Overbosh et al., 2002).

CHAPTER THREE
TAENIA SOLIUM / CYSTICERCOSIS / NEUROCYSTICERCOSIS

3.1. *Taenia solium* and Cysticercus Cellulosae

Reports of *Taenia* parasites have been known for centuries and have been referred to by ancient civilizations such as Egyptian 2000 years before Christ (Hoeppli, 1956). Aristotle in the “Histoire des Animaux” refers to it as the pork disease, easily found on the inferior side of the tongue.

The name *T. solium* was recorded for the first time in 1300 in a publication by Arnauld de Villeneuve (Hoeppli, 1956) and human NCC was described for the first time by Gessner and Rumler in 1558 who found cysticercus in the dura mater of an epileptic patient (Nieto, 1982).

Cysticercosis was identified by Mapighi as a parasitic infection in 1686 (Nieto, 1982). Goeze classified it for the first time as an helminth in 1784 and only in 1854 did van Beneden clarify part of its lifecycle by feeding pork with proglottids of *T. solium* and subsequently finding several cysticerci at necropsy (Smith, 1994).

In 1855 Kuchenmeister supplied pork meat with cysticercus to death sentenced prisoners and found 10 adult parasites in the intestine by the time he was performing the necropsies, therefore completing the knowledge about the parasite lifecycle (Webbe, 1994).

Laenec named the metacestode of *T. solium* “cysticercus”, which is an agglutination of two words of Greek origin: “kistic” meaning vesicle and “kercos”

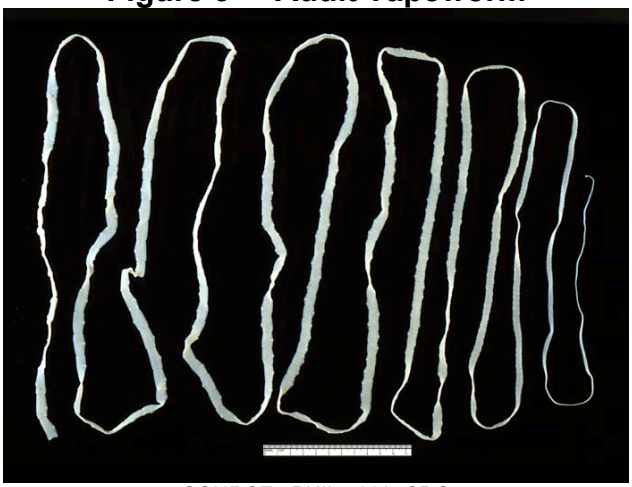
meaning tail (Webbe, 1994). The name *C. Cellulosae* is still being used and was given by Rudolphi in 1909 as a result of its great affinity for connective tissues (Webbe, 1994).

Yoshino in 1933 infected himself with cysticerci from pigs and managed to collect eggs with which he infected pigs, studying the histological structure of eggs of the adult parasite and the metacestode in detail. In his work cited by A. Flisser in 1998, Yoshino also refers to the fact that he expelled 1 to 5 proglottids daily during two years (Nieto, 1982).

3.1.1. Morphology of *T. solium*

The cestodes are platyhelminthes, flattened dorsoventrally in the adult stage and contained in a vesicle (cysticercus) in the larvae phase (metacestode). The parasite is classified as belonging to the Cestode Class, Eucestode Subclass, Cyclophillidea Order, and Taenenidae Family. *T. solium* belongs to the gender *Taenia* (Flisser, 1998). The term *solium* derivates form the fact that the rostellum is similar to the sun (Gerhard, 1989).

Figure 3 – Adult Tapeworm



SOURCE: PHIL 5260, CDC

The adult parasite of *T. solium* (see Figure 3) has a head (scolex), measuring one millimetre in diameter, and is fitted with a short pigmented rostellum armed with two rows of mobile hooks (20 to 36) with which it attaches itself to the human

intestine, in the jejunum area. Some proglottids may even reach the ileum (Webbe, 1994; Schantz et al., 1998) and the length of the adult parasite varies between 2 to 8 meters (Webbe, 1994; Flisser, 1998; Schantz et al., 1998; Gerhard, 1989).

Based on the differences in the number of hooks, Heinz suggests the existence of genetically different populations of *T. solium* (Heinz et al., 1966). The adult parasite possesses four circular hooks, slightly salient, located in the peripheral part of the scolex and measuring approximately 0,5 millimetres in diameter (Gerhard, 1989).

Under the scolex, the neck is made of a mass of cells that constantly multiply throughout the life of the parasite. The estrobil is situated under the neck and is formed by segments of proglottids (800 to 1.000) in different stages of development. When the proglottids are sexually mature they measure approximately 12 x 6 millimetres and are expelled in the faeces (Webbe, 1995).

Generally, the definitive host is only parasitized with one cestode (Fan et al., 1990; Allan et al., 1996), however, an infection with 24 cestodes in one single host has been reported (Fan et al., 1990).

Some authors report that the average life-span of *T. solium* varies from 3 to 7 years, but there are reports of survivals of more than 25 years (Nieto, 1982; Smith, 1994; Barry et al., 1993; Dumas et al., 1989; Flisser et al., 1990). Cysticerci are usually killed at temperatures of > 60 ºc (Knight et al., 2003).

3.1.2. Reproduction of *T. solium*

Each proglottid (see Figure 4 and 5) contains a male and a female sexual organ, and the fertilization occurs in the same segment. The uterus is located in the middle of the proglottid and consists of 7 to 13 diverticulae; each segment can

contain 30.000 to 60.000 eggs (Barry et al., 1993; Schantz et al., 1998; Webbe, 1995; Gerhard, 1989; Baily, 1998).

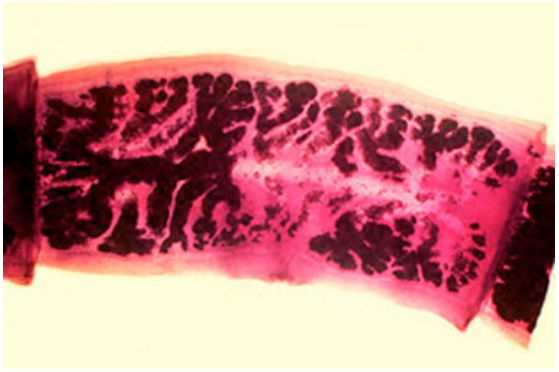


Figure 4 – Mature proglottid of *T. solium*, stained with carmine.

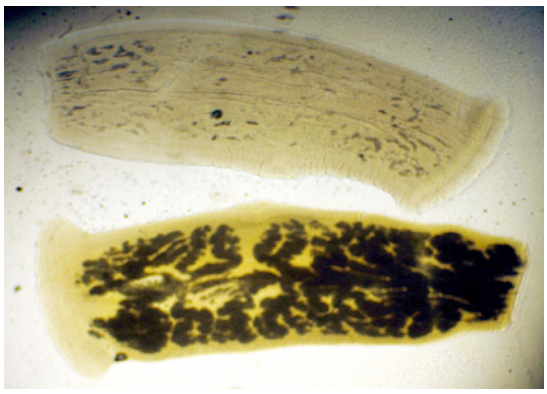


Figure 5 – Mature proglottid of *T. solium*, stained with India ink.

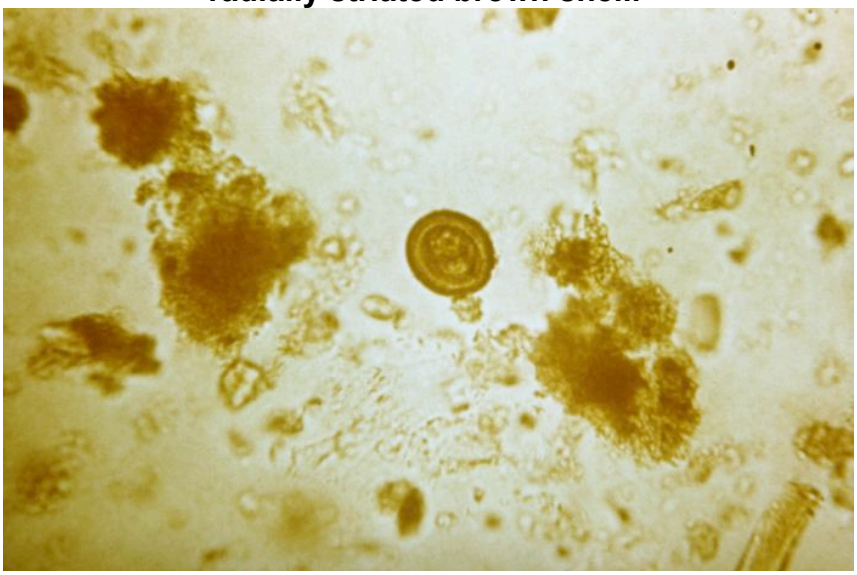
SOURCE: CDC

The pregnant proglottids of *T. solium* are usually expelled with the faeces, in groups of one to five, representing an average of 150.000 to 300.000 eggs daily; 50% of these may be viable and may mature outside the body (Fan et al., 1990; Michel et al., 1993; Gerhard, 1989).

Twelve weeks after the ingestion of meat with viable cestodes, the host starts to release pregnant proglottids (Flisser et al., 1990).

Eggs are oval (see Figure 6) and contain an embryo inside (oncosphere). This is protected by the embryophor that is made of continuous blocks of queratine, giving it a typical radial appearance under a microscope (Webbe, 1994). The embryophor is very resistant to adverse conditions in the external environment, allowing its dispersion and survival (Webbe, 1994).

Figure 6 – Eggs *of Taenia solium*: rounded or subspherical, with a thick radially striated brown shell.



SOURCE: PHIL 4832, CDC

3.1.3. Intermediate host

When the eggs are ingested by an appropriate intermediate host, usually a pig, but may be human, the gastric secretions dissolve the substance that links the embryophor blocks together and the oncosphere is released in the duodenum (Webbe, 1994). The oncosphere is activated by biliary secretions, gains mobility and uses its six hooks to penetrate the mucosa, reaching the basal membrane of the intestine, 3 to 120 minutes after hatching (Webbe, 1994).

After penetration, the larvae are transported haematogenously to the site where they become metacestodes, known as cysticerci. In pigs, this has been observed in the muscular tissues and in organs, six days after infection, reaching its complete development and infectious capacity in 2 to 3 months. At this time they reach a diameter of 8 to 15 millimeters (Webbe, 1994; Flisser, 1998; Barry et al., 1993; Schantz et al., 1995; Dumas et al., 1989).

3.1.4. Types of cysticerci

Two morphologic types of cysticercus are known: the *C. cellulosae* and *C. racemosus*. The vesicle of the first one is small (0,5 to 1,5 centimetres), oval or

round, depending on the pressure exerted by the adjacent tissues. It is white or yellow, with a translucent wall through which it is possible to observe the scolex (Flisser, 1998). This type of cysticercus frequently has a capsule of collagen separating it from the tissue of the host.

The *C. racemosus* is much bigger, is lobulated and can measure up to 20 centimetres in diameter. It may contain 60 millilitres of liquid and it is impossible to observe the scolex through in the cyst wall (Flisser, 1998; Dumas et al., 1989). This type of cysticercus has only been found in humans, especially in the cerebral ventricles (Flisser, 1998; Dumas et al., 1989).

The small *C. cellulosae* cysts usually are located in the gray matter of the brain due to the richer vascularization of this tissue, but may also appear in the subcortical white matter. In severe cases of parenchymal cysticercosis, the number of parasites may reach several hundred, but commonly only a scattered few are seen. Cysts also may be found in the subarachnoid location, and less frequently inside the ventricles and in the spinal cord. Cysts also may reach muscle tissue of the host (Carpio, 2009).

3.1.5. Transmission of *T. solium*

Eggs may be released in the intestine and due to their viscous nature they may adhere to the perianal zone, thus easily contaminating the hands and nails of the carrier (Barry et al., 1993; Schantz et al., 1998; Pawlowski et al., 1982). For this reason *Taenia* eggs are frequently found in the clothes and under the nails of the definitive host (Schantz et al., 1998; Dumas et al., 1989; Pawlowski et al., 1982).

When the definitive host does not observe proper rules of hygiene which would prevent the adherence of eggs to the hands, he or she may become auto infected (faecal-oral route) or can contaminate food that is handled; he can also contaminate others, becoming an infection focus (Barry et al., 1993; Schantz et al.,1998; Bern et al.,1999).

Flies, ants, termites and birds (including domestic chicken) have been suggested to be vehicles transporting eggs in the environment. The role of wind dispersal is negligible since the eggs are sensitive to dessiccation and are viscous – they have the necessary conditions for being transported by other animals (as they adhere to different parts of their bodies) but not by the wind (Gemmell et al., 1982; Lawson et al., 1990).

Flies in particular play a key role in the egg transport process since they are attracted by the smell of fresh faeces. The eggs adhere to their bodies and are transported both to food items and to other animals (Pawlowski et al., 1982).

Water contaminated by human faeces constitutes another way of transmitting the T*. solium* parasite by direct ingestion of the water or through watering vegetables which are subsequently consumed raw or insufficiently washed with the contaminated water (Barry et al., 1993; Bern et al. 1999).

3.1.6. Immune responses to the cysticerci

The presence of cysticerci in the host may not cause any inflammation or symptomatic disease. The immune response may be unpredictatable, ranging from complete tolerance to intense inflammatory responses. It is also possible that same patient can have an intense inflammation around a cyst and no inflammation in other viable or calcified cysts. Carpio (2009) reported that necropsy of victims of accidents revealed that a large proportion of NCC infections was asymptomatic and discovered incidentally.

Studies have analyzed the mechanisms of the immune response against *T. solium* cysticercus such as the heterogeneity of the humoral immune response, the existence of immune evasive mechanisms and the fact that the immune response can both protect and harm the host.

Several immunoglobulin (Ig) classes are produced as specific antibodies against the parasite. The most frequent is immunoglobulin G (IgG), which can be detected in serum, CSF and saliva suggesting that the infection is of long duration.

Carpio (2009) revealed that the immune response against *T. solium* cysticerci appears to have components of both T helper type 1 cells (Th1) and T helper type 2 cells (Th2), although the underlying mechanisms are yet to be clarified. The parasite is probably killed by eosinophils, which are attracted to the site by lymphoid cells. It is assumed that this specific response is mediated by Th2 cytokines.

3.2. *Taenia solium* Life Cycle

T. solium is a zoonotic tapeworm transmitted among humans and between humans and pigs (the life cycle is shown in figure 7). *T. solium* is a cestode that in its adult phase parasites only humans (its definitive host); the intermediate phase or larvae phase of the parasite is known as the *Cysticercus cellulosae* and it hosts itself in the tissues of the different mammals (its intermediate hosts), mainly in pigs.

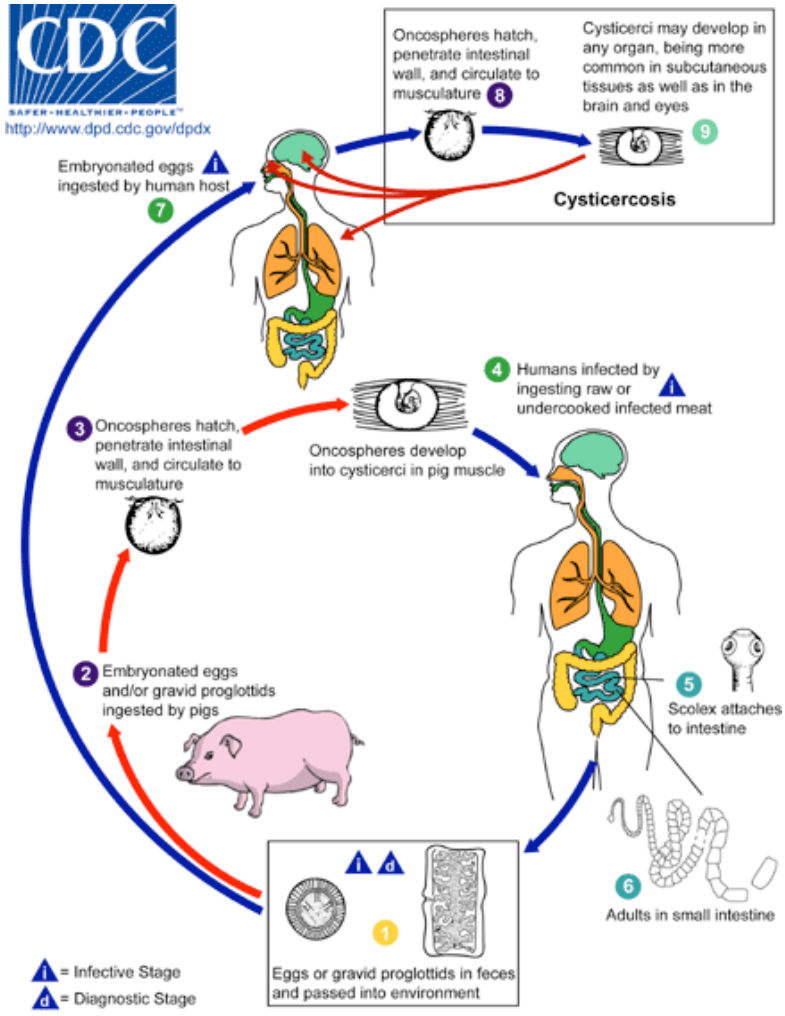
When humans act as intermediate hosts the larvae may be located in many different tissues. For unknown reasons, cysticerci have a predilection for the brain, striated muscle and subcutaneous tissue. Involvement of other sites, such as the heart, epicardial fat, optic nerve, liver and parotid glands, has been reported rarely in the literature. Involvement of the thyroid gland is even rarer. It is the location in the central nervous systems that is especially problematic and may lead to NCC and several CNS complications (Garcia et al., 2000).

Humans acquire taeniosis (tapeworm infection) when eating raw or undercooked pork meat contaminated with cysticerci, the larval form of *T. solium*. When

ingested, the cysticerci migrate to the intestine of humans where they establish and become adults. These adult worms shed eggs in human faeces that can in turn infect other humans and pigs by direct contact or by indirect contamination of water or food. In developing countries, pigs are often allowed to roam and to eat human faeces. Ingested eggs result in larval worms that migrate to different parts of the pig and human body and form cysts (cysticercosis). A principal site of migration in humans is the CNS. Human NCC occurs when the cysts develop in the brain.

Pigs can harbour thousands of these cysts making the pork from these animals unsafe to eat, often resulting in total condemnation of the pig's carcass.

Figure 7 – *T. solium* Life Cycle



Source: CDC Website

3.3. Neurocysticercosis

Human NCC, an infection of the human brain by the larvae (cysticercus cellulosae) of the pork tapeworm *T. solium*, occurs when cysts develop in the brain. NCC is considered to be the most common parasitic infection of the human CNS and most frequently preventable cause of epilepsy in the developing world (Román *et al*., 2000; Del Brutto et al., 1992, Garcia et al., 2003, Rajshekhar et al., 2003).

The condition may remain asymptomatic for years; asymptomatic individuals are occasionally detected at autopsy and in serological surveys by EITB, but their real frequencies remain unknown (Takayanaqui and Odashima, 2006). seizures are the most common presentation of symptomatic NCC affecting from 70% to 90% of cases (Carpio *et al*., 2002). In addition to seizures, manifestations can include severe headaches, blindness, hydrocephalus, chronic meningitis, symptoms due to space-occupying CNS lesions and dementia (Carabin et al., 2011).

Clinical cases have been reported where the neurological symptomatology occurred between 2 months to 5 years after infection, and there are also records of latency periods longer than 30 years (Smith, 1994). Symptomatic cases of NCC occur frequently in the productive age group; once the symptoms are established, patients frequently become incapable of working (Garcia et al., 1993; WHO, 1983; Forlenza et al. 1998).

Three distinct anatomic forms of NCC are frequently described. These are:

i) Parenchymal forms where the cysticercus type *C. cellulosae* is located in the cerebral hemispheres, usually in the cortex, meninges and cerebellum. They are differentiated into the vesicular (active cyst type) and colloidal type

(already starting to degenerate) (Webbe, 1994; Barry et al., 1993; Del Brutto et al., 1993).

ii) *C. cellulosae* forms, with ventricular location, with an increased frequency at the level of the fourth ventricle and more rarely in the lateral ventricle and Sylvian aqueduct. These cysts can be free and mobile in the cerebrospinal fluid (CSF) and can migrate from one cavity to another or adhere to their respective wall. After the death of the cysticerci, an inflammatory reaction usually develops (Webbe, 1994; Barry et al., 1993).

iii) *C. racemosus* form constituted by cysts of larger dimension without scolex with a grape-like morphology and a preferred location in the subarachnoid areas (Webbe, 1994).

An improved and widely accepted classification system has been proposed by Carpio (2009), based on the viability and location of the parasite in the host CNS: this classification distinguishes between active (when the parasite is alive), transitional (if it is in the degenerative phase) and inactive (if evidence of the death is apparent) cysts.

Each viability category is subdivided into parenchymal and extraparenchymal forms. On the basis of this classification, relating clinical manifestations to each category of the proposed classification is possible. No definitive data exists regarding the duration of individual stages. Evidence indicates that, once the parasite lodges in the brain, it may remain viable from months to years. The transitional phase can vary from 4-6 months. Finally, the dead parasite is reabsorbed or it calcifies in the CNS (Carpio, 2009).

NCC is of great economic relevance due to the related disease burden, cost of medical treatment, loss of working days and losses of condemned livestock. A minimum estimate of the cost of admission to hospital and wage loss for NCC in

the United States (a non-endemic country) was USD 8.8 million annually, whereas the estimated treatment cost in Mexico was USD 89 million and Brazil USD 85 million (Roberts et al., 1994). Carabin et al. (2006) showed that the overall monetary burden (in million of USD) to the Eastern Cape, South Africa, was estimated to vary from 18.6 to 34.2 million USD depending on the method used to estimate productivity losses.

3.4. Population at Risk

T. solium taeniosis/cysticercosis complex is associated with poor sanitation and hygiene, poor methods of pig husbandry and lack of proper meat inspection and disease control measures. Ingestion of larvae (cysticerci) in raw or inadequately cooked pork meat results in human tapeworm infection (taeniosis) as reported by Phiri et al. (2003) and discussed in the preceding sections.

The most important risk factor for human NCC is the existence of a carrier of *T. solium* who contaminates the surrounding environment (Flisser, 1998; Sarti et al., 1992; Garcia et al., 1995; Michault et al., 1990; Allan et al., 1996). Some studies show that the risk of a positive serology is two to three times higher in an individual who lives with a *T. solium* carrier (Webbe, 1995; Diaz Camacho et al., 1990; Flisser, 1987; Goodman et al., 1999; Garcia-Noval et al., 1996). The indirect transfer of eggs either through uncleaned hands or contaminated water, and vegetables watered or enriched with latrine residues, as well as through flies and other insects can result in human infection (Flisser, 1987; Noormahomed, 2005).

According to Engels et al. (2003), cysticercosis is related to a number of the most burning problems in the world today, namely, poverty in marginalized rural regions, subsistence animal husbandry and migration from rural to urban areas.

Murrel (2005), Pawloski, Allan and Meinardi (2005) and Kyvsgaard and Murrel (2005), summarised the major risk factors related to the transmission of eggs to pigs as follows:

- Extensive or free-range pig rearing in households lacking toilets (see Figure 8 and 9); in many communities, pork constitutes an affordable source of proteins, and pigs contribute actively to the maintenance of cleaning in the housing areas as reported by Schantz et al. (1998).
- Outdoor human defecation near or in pig rearing areas (see Figure 10 and 11). Schantz et al. (1998) also reported that the practice of defecation in open areas also contributes to massive infections in pigs;
- Allowing pigs to scavenge and eat human faeces;
- Deliberate use of human faeces as pig feed;
- Connecting pig pens to human latrines (see Figure 12); and
- Human carriers involved in pig rearing and care.

Figure 8 – Smallholder pigs scavenging for food.

Figure 9 - Smallholder pigs often allowed to roam freely.


Figure 10 – Latrines are easily acessible to pigs.


Figure 11 – Pig pens (especially during the crop growing season) are quite primitive and often only adult pigs are confined while piglets escape.

Figure 12 – The proximity of different facilities: family house, latrine and pig pen.

According to the same authors, the risk factors important for the transmission of *T. solium* to humans are:

- Lack of comprehensive and satisfactory meat inspection at pig slaughtering sites (see Figure 13);
- Clandestine marketing of pigs to avoid inspection (see Figure 13); and
- Cultural preferences for eating raw or improperly cooked pork meat.

Figure 13 – Meat is slaughtered and sold without any type of control or meat inspection.

Murrell (2005), Pawloski, Allan and Meinardi (2005) and Kyvsgaard and Murrell (2005) also report that the most important risk factors involved in human-to-human transmission are:

- Low economic status, low level of household sanitation and low level of personal hygiene standards;
- History of passing proglottids by a member of a household or a member of the community in frequent contact with the household (household or community food handlers and childcare givers are potentially very high risk factors); and
- Frequent pork consumption.

Summarising, the risk factors associated with NCC include: personal history of taeniosis; low level of scholarship; deficient level of personal hygiene; bad sanitary conditions of the environment the individual is living in, independent of it being a rural or urban area; and age older than 20 years old. According to Schantz et al. (1998) and Garcia et al. (1998), seroprevalence is generally higher in individuals with several of the risk factors.

3.5. Diagnosis of Cysticercosis / Neurocysticercosis

3.5.1. Clinical diagnosis

The clinical signs and symptoms of cysticercosis are dependent upon the number, location, size, and viability or stage of degeneration of cysts. Garcia et al. (2005) also reported that symptoms can be particularly varied because of the existence of multiple cysts at various locations and stages.

Asymptomatic individuals are occasionally detected at autopsy and in serological surveys by enzyme-linked immunotransfer blot (EITB), but the real frequency of infection remains unknown (Takayanaqui and Odashima, 2006).

3.5.1.1. Seizures

Seizures are usually the first sign of NCC. According to Schantz et al. (1998), Vasquez et al. (1992) and Zenteno-Alanis, (1982), it is estimated that in an endemic area NCC may be the cause of epilepsy in 30 to 50% of cases.

Patients with NCC usually have partial-onset seizures with or without secondary generalization (Carabin et al., 2011). When the first seizure occurs, most patients show an active cyst on CT scan of the brain – either a vesicular cyst or a colloidal cyst – as reported by Medina et al. (1990) and Del Brutto et al. (1992). New-onset seizures are commonly associated with an active cyst rather than a calcified cyst. Carpio et al. (2002) reported that chronic epilepsy is usually associated with calcified cysts.

Epileptogenesis in patients with NCC is related to several different factors: inflammation, gliosis and predilection for the cysts to travel to the frontal and temporal lobes, as reported by Sanchez et al. (1999) and Stringer et al., (2003). Sotelo (1995) contributed to this discussion by reporting that the host response to degenerating cysts plays an important role in the associated epileptogenesis. Children and young women tend to present a more intense host reaction to a

parasitic infection of the brain while adults usually have a variable response (Sotelo, 1995).

3.5.1.2. Symptoms due to space-occupying lesion

According to Del Brutto et al. (1992) and Berman et al. (1981), both parenchymal and subarachnoid cysts can cause symptoms if the cyst is very large. Large cysts usually result in symptoms and signs related to mass effects as described by Proano et al. (2001). The mass effects are especially prominent when the cysticerci give rise to an inflammatory response either due to spontaneous degeneration or following treatment with antiparasitic drugs such as praziquantel or albendazole (Proano et al., 2001).

3.5.1.3. Headache

A significant statistical association has been found between migraine-like headache and the presence of antibodies against C. *cellulosae* using the EITB technique in communities in Ecuador, as reported by Plancarte et al. (1994). In addition, according to DeGiorgio et al. (2002), headache usually indicates the presence of increased intracranial pressure, hydrocephalus or meningeal inflammation.

3.5.1.4. Hydrocephalus

Lobato et al. (1981) and Estanol et al. (1983) reported that free-lying ventricular cysts may result in acute obstruction of the CSF flow; when this occurs in the fourth ventricle, it may lead to drop attacks, episodic vomiting or even, in more extreme situations, death. In the same way, chronic inflammation and fibrosis can obstruct any of the ventricle foramina, leading to hydrocephalus.

Bickerstaff et al. (1952) reported that cysts located in the subarachnoidal space can develop abnormally to form a membranous and/or cystic mass, known as racemose cysticercosis. According to Del Brutto, (2002) this mass can continually grow and commonly results in meningeal inflammation and basilar arachnoiditis with inflammation and fibrosis around CNS structures. This is also a cause for hydrocephalus due to CSF outflow obstruction as reported by Estanol et al.

(1983) or cerebrovascular complications as reported by Pittella, (1997); Del Brutto,(1992) and Cantu et al.(1996).

3.5.1.5. Chronic Meningitis

In a less common and more malignant form of the disease, the cysticerci are located in the subarachnoid space, where they induce an intense inflammatory reaction leading to chronic meningitis. This form of the illness is little altered by the use of praziquantel or any other form of therapy (Estanol et al., 1983).

3.5.2. Serological diagnosis

Advances in serologic diagnosis include the identification and synthesis of specific antigens to produce highly sensitive and specific as well as simple and affordable assays to detect either circulating antibodies or antigens.

3.5.2.1. Antibody detection methods

Different techniques have been described to detect antibodies to *T. solium* infections in humans and pigs, such as the complement fixation test, hemagglutination, radioimmunoassay, enzyme-linked immunosorbent assay (ELISA), dipstick-ELISA, latex agglutination and immunoblot techniques (Ferreira et al., 1997; Garcia and Sotelo, 1991; Ito et al., 1998; Miller et al., 1984; Rocha et al., 2002 and Tsang et al., 1989).

According to Tsang et al. (1989) the most specific test developed is the enzyme-linked immunoelectrotransfer blot (EITB), which is widely used for the diagnosis of cysticercosis in human and pig serum samples. This test is an immunoblot of seven cysticercus glycoproteins, purified by lentil lectin-purified chromatography, which gives close to 100% specificity and a sensitivity varying from 70 to 90%. However, Wilson et al. (1991) reported a sensitivity of only 28% in cases with single cysts in the brain.

Because of issues related to availability, simplicity and cost, ELISA testing is often preferred to immunoblot tests. Rosas et al. (1986) reported that this is the

choice made by most developing countries since the test may provide a suitable alternative and may also provide a tool for serological monitoring of anti-parasitic therapy.

Ito et al. (1998) reported also that the purification of glycoproteins from cyst fluid by single-step preparative isoelectric focusing produced very specific antigens which can be applied in both immunoblot and ELISA with comparable specificity and sensitivity. The specificity and sensitivity of ELISA matched those of immunoblot methods in Ito's study.

There are two major problems related to antibody detection in clinical settings: (i) as reported by Garcia et al. (2001), antibodies indicate the exposure to infection but not the presence of an active infection, and (ii) as reported by Harrison et al. (1989) and Garcia et al. (1997), antibodies may persist long after the parasite has been eliminated by immune mechanisms or drug therapy.

Thus antibody testing does not necessarily reflect the true prevalence of cysticercosis and may lead to unnecessary use of antiparasitic therapy in cases where no active infection exists (Bern et al., 1999; Garcia et al., 2000).

3.5.2.2. Antigen detection methods

Antigen detection may provide a suitable alternative to antibody detection. It may also provide a tool for serological monitoring of anti-parasitic therapy.

Several assays as reported by Correa et al. (1989); Wang et al. (1992) and Erhart et al. (2002) have been developed to detect parasite antigens, but only the monoclonal antibody-based tests directed at defined parasite antigens were able to ensure sensitivity, specificity and reproducibility.

Antigen detection may be performed on serum as well as on CSF according to Choromanski et al. (1990) and Garcia et al. (1998, 2000). Because of the

localization of the cysts in the brain, antigen detection in CSF may be more appropriate for diagnosis than in the serum; however, sampling of CSF is more demanding and with higher risk of complications than blood sampling.

The sensitivity of the antigen detecting ELISA test is reported to be high. Garcia et al. (2000) found a sensitivity of 85%, however, in their study only patients who were seropositive on EITB were examined with ELISA. The sensitivity in patients with a single viable cyst was 65% as reported by Garcia et al. (2000). Erhart et al. (2002) found a very high agreement between an ELISA for detecting circulating antigen, computerized tomography scanning and biopsy examination of subcutaneous cysticerci.

3.5.2.3. Serum antibody and antigen detection in the diagnosis of NCC patients

Serological tests can also be used in NCC patients. Correa et al. (1989) and Zini et al. (1990) reported that depending on the viability and the localization of the cysts, testing on CSF can be more sensitive than using serum.

Chang et al. (1988) and Del Brutto et al. (1996) reported that serological tests can also be particularly useful in the confirmation of imaging techniques for the differential diagnosis of other lesions, including echinococcosis, brain tumours and tuberculosis.

Garcia et al. (2000) and Dorny et al. (2003) mentioned that the use of ELISA for the detection of circulating parasite antigens is a promising technique specifically in the monitoring of NCC patients being treated because of the excellent correlation between the presence of circulating antigen and active brain cysts.

Dorny et al. (2003) reported that ELISA-Ag results became negative three months after the treatment was started and proved to be successful. This technique was also much cheaper and more accessible than neuroimaging.

3.5.3. Electroencephalographic findings

Electroencephalography (EEG) may be normal or may show focal or generalized abnormalities in cases of NCC (Carpio et al., 2009). If the signs, symptoms and abnormal EEGs are correlated with the neuroanatomic location of specific calcifications on imaging, it is clear that some calcified lesions are able to initiate seizure activity.

Abnormal electric activity correlates with the locations of brain calcifications in 26% to 55% of the cases (Singh et al., 2000). Failure to localize seizure activity to more of the calcified lesions can be due to inherent limitations and constraints of the methodology, duration, or timing of the studies, spread of electrical activity from silent regions along anatomic pathways, or other lesions or processes as the cause of seizure activity (Nash et al., 2004).

The role of the EEG recording in NCC patients is important to achieve a more precise classification of seizure types. Partial seizures may be differentiated from generalized ones, especially when the partial onset is sudden and followed by a secondary generalization which is not always possible to determine from the history (Nicoletti et al., 2005).

3.5.4. Neuroimaging diagnosis

Modern neuroimaging techniques, including computerized tomography (CT) and magnetic resonance imaging (MRI), have improved the accuracy of NCC diagnosis by providing objective evidence on the number and topography of lesions, their stage of evolution and the degree of inflammatory reaction of the host against the parasites (Garcia and Del Brutto, 2000).

Garcia et al. (2002) and Sotelo et al. (1985) revealed that developments of clinical classifications of NCC based on the topography and stage of the lesions were critically important in the determination of the appropriate therapeutic approach for the different forms of the disease.

Intracranial calcifications are a common finding in patients with NCC and in many cases represent the only evidence of the disease. The sensitivity of MRI for the detection of calcified lesions is poor and therefore CT remains the best screening neuroimaging procedure for patients with suspected NCC as reported by Garcia and Del Brutto, (2003).

The WHO reported that MRI is the imaging modality of choice for the evaluation of patients with intraventricular cysticercosis, brainstem cysts and small cysts located over the convexity of the cerebral hemisphere. The image definitions suggest that MRI is superior to CT in the follow-up of the patients after therapy. However, the costs of MRI are high and the equipment is not available in many endemic countries (Garcia and Del Brutto, 2003).

CT and MRI findings in parenchymal NCC depend on the stage of development of the parasites. Vesicular cysticerci appear on CT as small and rounded low-density areas that are well demarcated from the surrounding brain parenchyma. These cysts present without perilesional edema and do not enhance after the administration of contrast medium. Most of these cysts show in an eccentric hyperdense nodule representing the scolex on the inside. The scolex is usually visualized within the cyst as a high intensity nodule giving the lesion a pathognomonic “hole-with-dot” imaging. Sometimes, these parasites are so numerous that the brain resembles a “swiss cheese” (Garcia and Del Brutto, 2003).

The process of degeneration of parasitic cysts has been categorized by Escobar (1983) into four histopathological stages: viable, colloidal, nodular-granular and calcified.

Colloidal cysticerci appear on CT and MRI as ill-defined lesions surrounded by edema and represent the so-called “acute encephalitic phase” of NCC in which

the host's immune system is actively reacting against the parasite (Escobar, 1983).

A particular neuroimaging pattern of parenchymal NCC is observed in patients with cysticercotic encephalitis. In this severe form of the disease, both CT and MRI show diffuse brain edema and collapse of the ventricular system without midline shift. Rangel et al. (1987) reported that after contrast medium administration, multiple small ring-like or nodular lesions appear disseminated within the brain parenchyma.

Calcified cysticerci normally appear on CT as small hyperdense nodules without perilesional edema or abnormal enhancement after contrast medium administration. As previously noted and reported also by Nash et al. (2001), these lesions are usually not visualized on MRI.

The racemose cysts are located most frequently either in the basal cisterns or inside the Sylvian fissure. With MRI, cysts are well visualized, as hypointense CSF-like image in all the phases. The MRI permits direct visualization of the intraventricular cysticerci by identifying the cyst wall, scolex, or both. The ventricular ependymal lining reacts to the cysts and an inflammatory reaction or ependymitis occurs, with can be visualized on CT scan or MRI as a high-intensity signal in the ependymal layer. The cysts deform the surrounding structures, and may lead to hydrocephalus (Carpio et al., 2009).

Estanol et al. (1983) and Sotelo and Marine (1987) reported that hydrocephalus, caused by inflammatory occlusion of the foramina of Luschka and Magendie, is the most common neuroimaging finding in patients with subarachnoid NCC. The fibrous arachnoiditis that is responsible for the development of hydrocephalus is seen on CT or MRI as areas of abnormal leptomeningeal enhancement at the base of the brain after contrast medium administration (Martinez et al., 1989).

According to Del Brutto, (1992) ischemic cerebrovascular complications of subarachnoid NCC are well visualized with CT or MRI; however, such findings are non-specific since the neuroimaging appearance of cysticercosis-related cerebral infarcts is the same as that of cerebral infarcts from other causes.

Ventricular cysticerci appear on CT as hypodense lesions that distort the ventricular system causing asymmetric or obstructive hydrocephalus. As reported by Madrazo et al. (1983), ventricular cysts are usually isodense with the CSF.

3.6 Management and Treatment of Cysticercosis

As seen in the previous section, there is a wide variability in the presentation of cysticercosis and as a consequence, the treatment should be individualized as far as possible.

There are five treatment strategies that can be offered to patients (Garcia et al., 2002; Nash, 2003):

1) Larvicidal agents to kill the cystic larvae;
2) Corticosteroids or other immunosuppressive agents to decrease or prevent inflammation;
3) Anti-seizure medication to prevent or decrease the severity and number of seizures;
4) Surgical-based therapies including emergent measures to decrease the mass effect of cysts with or without accompanying inflammation, remove cysts causing obstruction of the ventricles, shunt placement for hydrocephalus and sometimes for removal and/or decompression of large or critically located cysts prior to use of cysticidal agents; and
5) General supportive measures in impaired individuals and symptomatic treatments.

Numerous animal (Flisser et al., 1990 a, b; Gonzalez et al., 1995) and human studies recently reviewed by Garcia et al. (2002) and Sotelo et al. (1984) have documented the ability of larvicidal agents to kill viable larvae with either praziquantel or albendazole resulting in decrease in size or disappearance of cysts. However, the clinical benefits following treatment vary depending on the clinical situation and the results of studies are contradictory for most common clinical presentations.

A number of reports have documented the dramatic effect of albendazole or praziquantel on regression of lesions causing mass effects. In one recent series, Proano et al. (2001) reported that 33 patients with giant subarachnoid cysts associated with intracranial hypertension treated with courses of either albendazole or praziquantel resulted in disappearance of the cysts and almost all showed significant clinical improvement.

Whether there is clinical benefit from larvicidal treatment of patients with a single parenchymal cyst showing contrast enhancement on CT imaging is controversial. Chandy et al. (1991) and Rajshekhar et al. (1993) reported patients with single inflammatory lesions (less than 20 mm in size with or without the presence of edema) which were mostly due to degenerating cysticerci. A number of studies have documented spontaneous resolution of most of these lesions (Rajshekhar, 2001; Rajshekhar and Abraham, 1990; Ahuja et al., 1989; Wadia et al., 1987).

Del Brutto et al. (1992a) and Vasquez and Sotelo, (1992) retrospectively reported patients with varying numbers of cysts who, after treatment, demonstrated a decreased number of seizure episodes; however, both studies were non-randomized.

In patients with massive infections, there is a general hesitation to use larvicidal drugs because of the resulting massive inflammatory response which could be detrimental to the patients. In patients with mild and moderate infections cure

rates ranged from 60 to 85% when the drugs were given in standard doses with most series showing albendazole as slightly superior (Garcia et al., 2002).

Praziquantel at the usual dose regimen of 50-75 mg/kg per day in three divided doses was the first drug available and has few side effects. It was initially administered for 30 days but in later studies was employed for 14 days, because of the high cost associated with a long course of treatment (Garcia et al., 2002). Corona et al. (1996) advocated 1-day therapy using 75 mg/kg every 2 h for three doses.

In an effort to increase CSF levels, others have used higher doses of praziquantel (100 mg/kg) in four divided doses from 10 days to 1 month without observing an increase in toxicity. This regimen was reported by Bittencourt et al. (1990a,b) and Proano et al. (2001).

Due to drug interactions, praziquantel blood levels are lowered by concomitant medication with anti-epileptic drugs such as phenytoin and carbamazepine (Bittencourt et al., 1992) as well as with corticosteroids (Vasquez et al., 1987).

Albendazole has largely supplanted praziquantel because of slightly higher cure rates, apparent increased efficacy in subarachnoid or ventricular cysts, decreased cost and increased availability.

Albendazole is converted to its active metabolite, albendazole sulphoxide, in the liver. Nash (2003) reported that the usual dose is at 15 mg/kg per day with a maximum of 400 mg/bid (higher doses have been given) for 7-30 days with repeated courses as clinically warranted.

Praziquantel has well documented drug interactions while albendazole has not been well studied. However, similar compounds to albendazole demonstrate significant interactions with anti-seizure medication. Few side effects directly

related to the drugs have been documented in treating cysticercosis. It is unusual to experience serious side effects with praziquantel, but serious side effects, including agranulocytosis, liver function abnormalities and balding have been documented with long-term albendazole administration in the treatment of hydatid disease as reported by Nash (2003).

Corticosteroids are commonly used to suppress and/or prevent ongoing or treatment-induced inflammation that usually occurs 2-5 days after initiation of therapy. Although some clinicians wait until symptoms develop, others begin corticosteroids before or just after administration of larvicidal drugs. There is a general consensus that corticosteroids should be used prophylactically when patients have numerous, large or critically located lesions (Nash, 2003).

Corticosteroids decrease blood levels of praziquantel and result, theoretically, in decreased efficacy (Vasquez et al., 1987). According to Takayanagui et al. (1997), elimination of albendazole sulphoxide is decreased by corticosteroids but it is unknown if this increases the efficacy of albendazole. The duration of corticosteroid treatment is determined clinically but it is practice to use 10-16 mg per day of dexamethasone in divided doses and taper the dose following therapy over 1-3 months (Nash, 2003). According to Del Brutto et al. (1993), up to 32 mg of dexamethasone per day is needed to reduce the brain edema accompanying this condition.

Patients with subarachnoid cysts or chronic meningitis may require immunosuppression chronically and in these patients switching to alternate day prednisone lessens the side effects (Nash, 2003). Corticosteroids are frequently used to decrease neurological symptoms due to the death of the parasite and subsequent edema and are also used in the primary management for chronic cysticercosis such as with arachnoiditis or encephalitis (Nash, 2003).

Since seizures are the most common clinical manifestation of cysticercosis as previously mentioned, there is a requirement for anti-seizure medication. The use of anti-convulsants is no different in cysticercosis than in other seizure disorders, but the continued use depends on the patients clinical situation. Baranwal et al. (2001) report, for instance, that patients with single enhancing lesions tend not to require long-term anti-seizure medication.

The need for surgical interventions has decreased dramatically over the past two decades. According to Sotelo et al. (2001), placement of intraventricular shunts is probably the most common surgical intervention in NCC.

Colli et al. (1986) reported that the protracted clinical course of patients and their high mortality rates (up to 50% in two years) were directly related to the number of surgical interventions because shunts tend to obstruct and require repeated replacements.

Suppressive corticosteroid therapy is sometimes required to depress inflammation and to maintain a functioning shunt as recommended by Roman et al. (1996). According to Garcia et al. (2002), maintenance corticosteroids therapy may decrease the frequency of shunt blockages. Proano et al. (1997) also reported that many authors advocate shunting combined with antiparasitic drugs to further reduce the incidence of shunt failure.

Intraventricular cysts not responsive to medical therapy should be surgically removed. Although successful medical therapy of fourth ventricular cysts with or without the presence of intraventricular shunts is well documented (Proano et al., 1997), some neurosurgeons believe that medical therapy alone is too dangerous and advocate endoscopic removal of these cysts (Garcia et al., 2002). In addition, we have removed easily approachable cysts that impinged on critical structures before larvicidal treatment to prevent serious complications following treatment and to decrease the duration of corticosteroid use.

NCC is not a single disease for which one therapy can be recommended. Because of the variability in presentation, probably the best advice on the treatment of NCC would be not to generalize but to approach and assess each case individually.

3.7 Prognosis

Forty-eight years ago Dixon & Lipscomb (1961) observed that some patients with NCC and epilepsy improved spontaneously. Other authors confirmed that many patients with NCC and epilepsy had a good prognosis. Nevertheless, no case-control or longitudinal prospective studies have been undertaken to analyze the factors associated with the occurrence and remission of seizures in NCC patients. It is therefore impossible to establish the ideal duration of treatment with anti-epileptic drugs.

Seizure recurrence is high following a first acute symptomatic seizure due to NCC, but this risk seems related to persistence of active brain lesions. Recurrence risk is low and in keeping with seizure risk following other brain insults in patients where the NCC lesion resolves (Carpio et al., 2009).

Prognosis is best for those patients whose image pathology normalizes, spontaneously or after treatment. The seizure recurrence rate for those patients with persisting, active cysts (61%) is more than double the rate of those patients with normal imaging (22%) (Carpio et al, 2009).

Most morbidity and mortality in human cysticercosis occurs when the parasite invades the CNS and causes epilepsy, hydrocephalus and other neurological manifestations (Cook, 1998).

No reliable information is available regarding mortality rates. This is probably because a large percentage of patients (50%) with NCC are asymptomatic (Carpio, 2009). Most patients with parenchymal NCC have a benign clinical course. However, patients with subarachnoidal cysticercosis (approximately 10-15%, including intraventricular cysts) may develop complications such as vasculitis and hydrocephalus. Permanent neurological deficits may result secondary to infarction in the case of vasculitis, and high mortality rates or severe clinical morbidity such as dementia may result from hydrocephalus. Patients with intraventricular cysts can experience sudden death due to acute obstruction of the intraventricular system, particularly the aqueduct of Sylvius (Carpio, 2009).

3.8 Control of *Taenia solium*

Elimination strategies which were successful in developed countries are not suitable for most developing countries. Most developed countries controlled the parasite as an indirect consequence of the development of living conditions. Improvements in environmental hygiene and meat inspection procedures were implemented mainly to ensure food safety and raise living standards. A disease elimination programme that takes into account the socio-economic factors and country-specific context is more likely to be successful, sustainable and also result in the acceptance of health education campaigns (Gilman et al., 1999).

In the past, the WHO suggested that control programmes would be successful if inspection of pig carcasses in slaughterhouses were rigorously enforced as reported by Gemmell et al. (1983). But so far, this strategy has failed in developing countries.

Targeting slaughterhouses as the primary intervention fails to influence the animal husbandry practices which occur before the pigs are brought to the market. Instituting a policy in which pigs that are detected to have cysticercosis

are confiscated without payment to the owner leads to the establishment of a clandestine market for pigs that may be infected with *T. solium*.

For example, in Peru, if porcine cysticercosis is detected, the pig is confiscated and no payment is given to the peasant. Consequently, 55% of pigs are illegally slaughtered and this figure is close to 100% in many rural areas (CWGP, 1993).

Pigs are mostly sold alive to intermediary agents who in turn take them to the cities. If a pig is found infected, the intermediary will still try to sell its meat. Any program to be sustainable must aim to decrease the supply of infected meat to consumers. To the purchaser diseased meat has the advantage of being cheaper in price but the disadvantage of being illegal and dangerous (CWGP, 1993).

Efforts to educate villagers at schools, village meetings and on an individual basis have been highly successful in terms of teaching villagers the parasite life cycle as reported by Keilbach et al. (1989) and Sarti et al. (1997). The connection between infected pigs and themselves or others getting cysticercosis is also an important part of this education effort. As a consequence, villagers were able to describe how *T. solium* infection was transmitted and how it could be prevented.

Sarti et al. (1997) reported that Knowledge, Attitude and Practice (KAP) studies have demonstrated that villagers understand the role of *T. solium* infection in pigs and the *T. solium* larvae's relationship to NCC or epilepsy. However, the knowledge acquired does not appear to result in dramatic changes in risk behaviour (Garcia and Del Brutto, 2000).

Other proposed strategies for control emphasise eliminating egg dissemination in the environment using mass human chemotherapy (Allan et al., 1997; Diaz Camacho et al., 1991; Sarti et al., 2000; Pawlowski et al., 2005)). This strategy is based on the assumption that if egg dispersion is stopped, then the disease transmission cycle will be broken.

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 (Gilman et al., 1999). For example, a study performed in a community in Mexico and reported by Keilbach et al. (1989) found that swine cysticercosis prevalence increased from 6,6% to 11% one year after mass human chemotherapy.

In terms of human carriers, two categories exists: (1) those living in rural areas with direct contact with pigs and involved with life cycle perpetuation; and (2) those living in urban areas, with little or no access to pigs, but playing a considerable role as a source of human NCC. This category, being dispersed and more difficult to identify and treat, is often neglected in control studies according to Pawlowski, (1991) and Garcia-Garcia et al. (1999).

Effective treatment of infected pigs is the next logical addition to mass or focused treatment of humans in control programmes (Gonzalez et al., 1997, 1995). Since humans can only become infected with the adult stages of this parasite when they eat contaminated pork, treatment of pigs prior to slaughter would block the transmission cycle of cysticercosis.

Implementation of taeniasis/cysticercosis control in national programs is politically unpopular since it is frequently seen as a low priority problem of poor and illiterate rural people rearing pigs in unsanitary conditions and a problem which can be solved only by long term education, economic and social developments.

The following arguments can be used to positively influence government decisions:

1) The public health impact of human NCC in some regions is serious and requires immediate control in order to lower the morbidity and mortality caused by *T. solium* and the social and financial costs related to the disease (Schantz et al., 1998; Bern et al., 1999).

2) Although the rural poor are the major disseminators of infection to pigs, NCC can potentially affect any person, rural or urban, exposed to *T. solium* eggs, especially productive young adults (Shantz et al., 1992; Allan et al., 1996a; Garcia-Garcia et al., 1999; Shandera et al., 2002).

3) Contamination of the environment with taeniid eggs can be common even in the urban centres (Schantz et al., 1992; Garcia-Garcia et al., 1999).

4) Control measures do not necessarily need to be implemented nation-wide but may be limited to areas of heavy transmission and to some identifiable focus of active transmission (Pawlowski, 1991; Pawlowski et al., 2005).

5) Control activities can be logistically and administratively included in existing health systems, leading to the improvement in the overall health infrastructure (Engels et al., 2003; Pawlowski et al., 2005).

In addition, the efficacy of control programmes according to Cruz et al. (1989) and Gonzalez et al. (1994) can be easily monitored by measuring the cysticercosis rate in sentinel or slaughtered pigs.

In 1988 the International Task Force for Disease Eradication (ITFDE) established criteria to assess the feasibility of eradication of some infectious and parasitic diseases. *T. solium* cysticercosis fulfilled some of the biological criteria necessary

for eradication but some issues of a technical, societal and political nature remained (Schantz et al., 1993).

However, the experience gained to date has shown that worldwide eradication of *T. solium* NCC in humans cannot be achieved in the near future.

3.9 Rationale for the study

As mentioned previously cysticercosis/NCC seriously affects health in a number of ways. Thus the disease is a serious constraint for improving the livelihoods of smallholder farming communities and a food security and safety issue for pork consuming populations in both rural and urban/peri-urban areas.

The study is hoped to generate results to help in assessing the epidemiology of NCC in the study area and its possible relationship to epilepsy. Thus, it may generate knowledge that could be used to increase awareness of cysticercosis/NCC and its impact on human health and well-being, pig production, domestic food supply and marketing and trade oppurtunities for pigs in Mozambique, in turn contributing to the alleviation of poverty.

The results of this study will hopefully provide an important evidence-base for making appropriate and relevant policies concerning sustainable livestock development in Mozambique, while mitigating the risks to human health.

In Mozambique there is a lot of focus on provision of health facilities by the government. Our study will aim to provide basic information on epidemiology and applied diagnostics for cysticercosis.

The study will demonstrate whether there is a link between the prevalence of epilepsy and cysticercosis in Angonia, district of Mozambique.

The study will strengthen the veterinary public health infrastructure in Mozambique and promote cross-sectional, integrated approaches to zoonotic diseases.

The study will help fulfil the CWGESA Regional Action Plan for Combating Cysticercosis.

3.10 Objective

3.10.1 General Objective

To assess the prevalence of NCC in people with epilepsy in the district of Angonia, Tete Province, in Mozambique.

3.10.2 Specific Objective

i) Determine the prevalence of epilepsy in the district of Angonia;

ii) Determine the prevalence of NCC in humans in the district of Angonia;

iii) Identifty the risk factors associated with NCC and epilepsy in the district of Angonia.

CHAPTER FOUR
METHODOLOGY

4.1 Study Area and Population

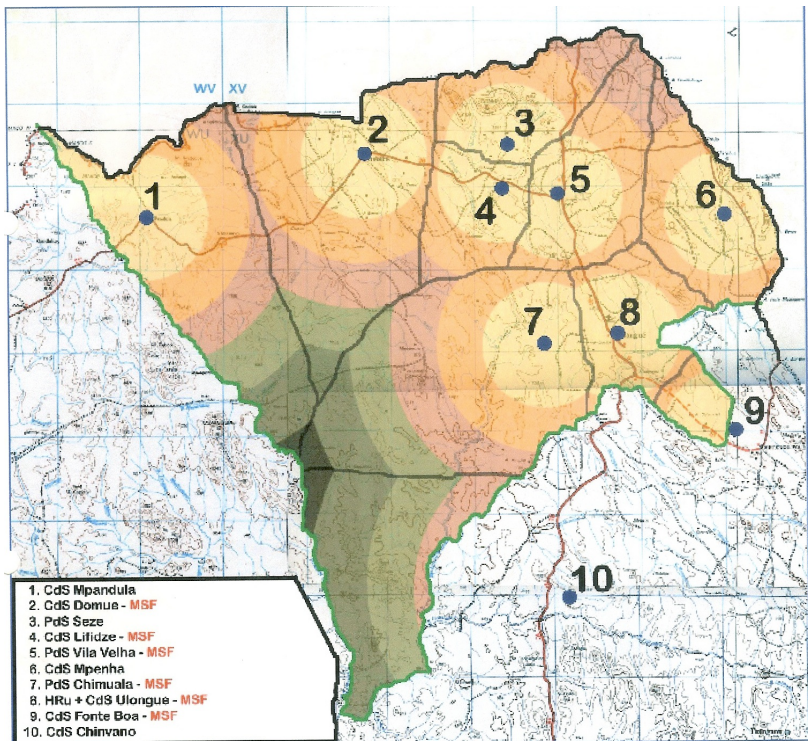
The study was conducted in the district of Angonia, located in the Tete Province, which is in the central region of Mozambique in 2008 (see Figure 14 and 15).

Figure 14 – Mozambique and Tete Province within Mozambique

The Angonia district is located at the northeast area of the Tete Province, between the parallels 14º 46' and 15º 14' south and between the meridians 33º 46' and 34º 54' east and has the following limits:

- North and Northeast: Malawi Republic
- South and Southeast: Tsangano District
- West: Macanga District.

Figure 15 – Angonia District



Source: DDS, Angonia, 2008

The district administrative town Ulongue is located 235 km from Tete city, the provincial capital. The district is crossed by Rural Road 223, which is a section of National Road 103 that connects the district with the provincial capital and the Malawi Republic.

The District has two administrative posts - Ulongue and Domue (8 and 2 on the map above) - and sixteen towns which in turn are subdivided into three hundred and seven villages and communities.

Table 1 - Distribution of Towns by Administrative Posts

Administrative Post	Towns
Ulongue	Ulongue, Calomue, Chimuala, Dziwanga, Mangane, Monequera and Namingona.
Domue	Calio, Catondo, Kamphessa, Chikumbe, Khombe, Mpandula, Ndaula, Mkame and Seze.

The following towns were included in the study:
(i) Ulongue: Ulongue (villages of Ndundu and Matewere), Calomue, Chimuala (village of Kungua) and Namingona (village of Majawa);
(ii) Domue: Ndaula (village of Chilitse), Binga, Calio (village of Ndumbo), Lilanga (village of Dinga), and Seze (village of Ntsimeza and Malitene).

The district is characterized by a humid climate that receives an annual rainfall ranging between 1100 and 1200 mm. The rainy season extends from about October to March and the dry period extends from April to September. Relative humidity is about 70% and mean annual temperature ranges from 18 to 22 ºC.

The population of Angonia was estimated to be 227.437 in 1999 (National Statistics Institute, 1999) of which 107.309 are men and 120.128 are women. Estimated population density is around 72,2 inhabitants \ km^2 .The total number of households in the district is 1080 and pig population is 3005 in Ulongue and 1.171 in Domue (Direccao Distrital de Agricultura, 2006; census performed in 2006).

The district inhabitants are mainly of the Chewa ethnic group, of which the family structure is matrilineal. They occupy mostly highland areas and practice mixed peasantry farming. Environmental and feeding conditions are favourable for the development of taeniosis/cysticercosis. The district has also health infrastructure to support the study, including human resources required for the success of the study.

The initial field visit proved to be very important as it allowed the investigators to establish contact with local individuals and institutions and promoted the grounds for the conduction of the study.

All individuals and institutions contacted understood the objectives and importance of the study and were available to help and contribute to the study. It

was very positive to note that all local / traditional heads expressed willingness to support the study. They reported on the presence of cysts in pork and described cases of human epilepsy.

4.2 Study Design

A survey was conducted to determine the overall prevalence of epilepsy in the district of Angonia and to evaluate the presence of human cysticercosis among people with epilepsy. Risk factors for the presence of human cysticercosis were also investigated.

4.3 Sampling and sample size calculation

A sampling frame was constructed using information from the National Statistics Institute. The sampling stategy consisted of the following steps: select the villages, list of all households within selected villages, select the households from the list and finally interview individuals from the selected household. A sampling with probability proportional to size (PPS) was used to select the villages. In total 54 enumeration areas were selected and 30 households visited in each area. In each numeration area, a list of households was made. A systematic random sampling was used to select the households to be included. Briefly, every fourth household in the list was selected at random from the first fourth household. At each household a list of all household members was obtained from which a participant was then randomly selected. The sample size was calculated based on an expected 20% prevalence of cysticercosis in the study area. Using single proportion calculation, sample size was estimated to be 1600 in the district (p=0.2, SE=0.01).

4.4 Methods

Several methods were used for data collection in order to answer all study objectives.

4.4.1 Interviews

Structured interviews with the person sampled, or in case of children or otherwise incapable persons, the family head, mother or father, were conducted using validated questionnaires from CWGESA including questions on: age, gender, place of birth, profession/occupation, educational level, place of residence, household characteristic, information on drinking water and sanitation, information on pork consumption and management, information on human cysticercosis/taeniosis and clinical manifestations compatible with NCC, eg., epilepsy. Interviews have been conducted by paramedical staff that had received training during the pilot study phase.

4.4.2 Inspections of sites

Observations regarding factors related to the presence or absence of cysticercosis, eg, type of latrine of the household, evidence of recent use of the latrine, pork consumption and free roaming pigs were made.

4.4.3 Clinical examination

All participants were examined by a physician for signs and symptoms compatible with NCC (focal signs, papilloedema, nodules under the tongue, in the subcutaneous tissues and in the eyes, headache, vomiting, epilepsy, mental disorders).

4.4.4 Blood sampling

A venous blood sample (4.5ml) was obtained from individuals sampled. Sera were separated by centrifugation in the field and stored at -20 C in cryotubes

(Nunc, Roskilde, Denmark) in the blood bank of the Rural Hospital. The samples were transported by aeroplane from Tete to Maputo, duly protected by dried ice, and stored at Department of Parasitology, Medical Faculty, Eduardo Mondlane University, Mozambique before transportation to Zambia.

4.4.5 Analysis of specimens

For the diagnosis of human cysticercosis, sera specimens were analyzed by ELISA for the detection of parasite antigens at the School of Veterinary Medicine, University of Zambia, Lusaka, Zambia by the team of Prof. Isaac Phiri of the Department of Clinical Studies. Serum samples were examined using a monoclonal antibody (MoAb) based ELISA for the detection of circulating antigens of T. *solium* metacestodes in the serum as described by Brandt et al. (1992) and slightly modified according to Nguckam et al. (2003, b). Briefly, the serum was pre-treated using trichloroacetic acid at a final dilution of ¼. Two MoAbs was used in a sandwich ELISA. MoAb B158C11A10 was diluted at 5 microgram/ml in carbonate buffer (0.06 m/pH 9.6) for coating and a biotinylated MoAb B60H8A4 (1.25 microgram/ml in phosphate-buffered saline containing 0.05% Twin 20 and 1% new-born calf serum) was included as detector antibody.The incubation was carried out at 37ºC on a shaker for 30 min for the coating of the first MoAb and for 15 min for all subsequent steps. The chromogen/substrate solution consisting of a phenylene diamine (Dako, Glostrup, Denmark, #S2045) and H_2O_2 was added and incubated without shaking for 15 min at between 30 and 33ºC. To stop the reaction, 50 microlitre of H_2SO_4 was added to each well. The plates were read using an ELISA reader (Labsystem Multiskan RC, Brussels, Belgium) at 492 nm. Negative reference control sera from local people and one reference positive control serum from a patient with confirmed cysticercosis were included in each ELISA run. The optical density (OD) of each serum sample was compared with the mean of the eight negative reference sera at a probability level of p = 0.001 to determine the result using a modified students t test (Sokal & Rohlf, 1981). The ELISA ratio was calculated by

dividing the OD of the sample by the calculated cut-off value of the eight negative controls. An ELISA ratio of > 1 was considered as positive.

4.4.6 Neuroimaging and Electroencephalography

All persons with a positive ELISA test and clinical manifestations, or a history of symptoms presumptive of NCC, underwent neuroimaging and electroencephalography. The patients were transported by bus from Angonia district to Beira city. These examinations were carried out in Beira Central Hospital using a somatom emoton helicoidal, version A45A (Germany). Ultravist-370, Lopramida no ionic (Germany) was used as the intravascular contrast agent. Each patient was monitored before and after contrast injection by a physician and image series on slides were made. In addition, all patients underwent electroencephalography, using an E.E.G. Nihon Khoden, 4421K (Japan) machine. Electrodes were placed according to the international 10-20 system, by using referential and bipolar montages. Hyperventilation and intermittent photic stimulation were used routinely during EEG recording. EEG records and Brain CT Scans were analyzed independently by two observers. These observers are neurologists from Beira and Maputo Central Hospital.

4.4.7 Definition of epilepsy

In this study the definition of epilepsy proposed by the International League Against Epilepsy (ILAE, 2005) was used: “an epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain”; “epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological and social consequences of this condition”. An epileptic seizure is a clinical event, demarcated in time, with a clear start and finish.

4.4.8 Diagnostic criteria for neurocysticercosis

Considering clinical, serologic, neuroradiologic and epidemiologic data, NCC was diagnosed according to the criteria proposed in 2001 (Del Brutto et al., 2001).

The criteria include four categories – absolute, major, minor, and epidemiologic – stratified on the basis of their individual diagnostic strength.

Figure 16 – Diagnostic Criteria for Neurocysticercosis

Categories of Criteria	Criteria
Absolute	1. Histologic demonstration of the parasite from biopsy of a brain or spinal cord lesion 2. Cystic lesions showing the scolex on CT or MRI 3. Direct visualization of subretinal parasites by fuduscopic examination
Major	1. Lesions highly suggestive of neurocysticercosis on neuroimaging studies 2. Positive serum EITB for the detection of anticysticercal antibodies 3. Resolution of intracranial cystic lesions after therapy with albendazole or praziquantel 4. Spontaneous resolution of small single enhancing lesions
Minor	1. Lesions compatible with neurocysticercosis on neuroimaging studies 2. Clinical manifestations suggestive of neurocysticercosis 3. Positive CSF ELISA for detection of anticysticercal antibodies or cysticercal antigens 4. Cysticercosis outside CNS
Epidemiologic	1. Evidence of a household contact with *Taenia solium* infection 2. Individuals coming from or living in an area where cysticercosis is endemic 3. History of frequent travel to disease-endemic areas

We included two degrees of diagnostic certainty: definitive and probable.

Figure 17 – Degrees of certainty for the diagnosis of neurocysticercosis

Diagnostic Certainty	Criteria
Definitive	1. Presence of one absolute criterion 2. Presence of two major plus one minor and one epidemiologic criterion
Probable	1. Presence of one major plus one minor and one epidemiologic

	criterion 2. Presence of three three minor plus one epidemiologic criterion 3. Presence of three minor plus one epidemiologic criterion

4.5 Data Management and Analysis

Data forms were initially stored and checked for consistency using EpiInfo 2002 (Center for Disease Control, Atlanta, Georgia, USA) and analysed using the SPSS version 12 (SPSS Corp., Chicago, IL), STATA software package (Stata Corporation, College Sation, TX, USA). Descriptive analysis and univariate analysis were performed by the author. The distributions of potential risk factors were examined among negative and positive subjects. Crude odds ratio (OR) and 95% confidence interval (CI) were used for the interpretation of univariate analysis. P values of less than 0.05 were considered significant. To identify independent risk factors for cysticercosis, adjusted odds ratio and 95% CI were calculated by logistical regression analysis.

4.6 Ethical Considerations

This study was submitted to and approved by the following Ethical Committees:

- Ethical Committee of the Medicine Faculty of Eduardo Mondlane University, Mozambique;
- Ethical Committee of the Ministry of Health of Mozambique, Mozambique
- Danish National Committee on Biomedical Research Ethics , Denmark
- Faculty of Health Sciences Ethics Committee of the University of Pretoria, South-Africa.

A project meeting was held in each village prior to the implementation of the study to explain the project and to obtain community consent for the study. Informed consent (orally or in writing) was sought from all adult participants (or, in case of children, their parents or guardians) prior to participation. Project

participation was voluntary, and participants were free to withdraw from the study at any time.

Voluntarity: Project staff collected written informed consents from all participants prior to conducting an interview. The interviewer explained the contents of the form to the participant and asked the participant to sign the form. A translator for local languages was also present to facilitate full understanding of the form and of its contents. Participants who could not sign their name were allowed to use the respective fingerprint in the lign of the signature. The participants also received an explanation that they could withdraw from the study at any time and even so the health services would continue to be available.

Confidentiality: Interviewers were trained to project confidentiality to all individuals who approached in view of participating in the study. All project staff have completed security and confidentiality training and subsequently signed a statement indicating their understanding of all security and confidentiality policies. Furthermore, the questionnaire contained minimal personal indentification.

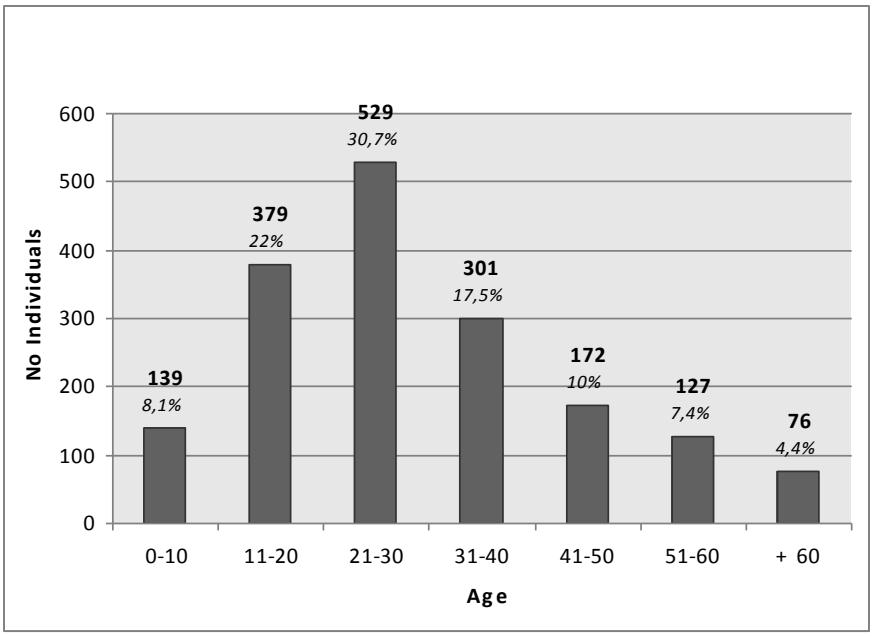
Appropriate safety precautions were taken to protect project staff and participants. Individual results were kept confidential. Feedback was provided to participants. Any person had the right to decide whether to obtain his or her result from any test or examination performed. The research findings were communicated to all stakeholders, to relevant authorities and will be communicated to the national and international research communities. The study was carried out under the supervision of a medical doctor. For those with NCC, treatment was offered according to treatment guidelines and was free of charge. If at any time the patient developed any clinical complication or side effects, the patient or parent/guardian was instructed to report immediately to the local health centre.

CHAPTER FIVE
RESULTS

1.723 individuals were included in the study as described in the chapter four, (4.3 sampling and sample size calculation).

5.1. Socio Demographic Characteristics

Figure 18 – Age Distribution



The age group of 21 to 30 years comprised 30,7% of all individuals. The mean age was 22 years with a median of 17 years and a range of 2 – 91 years.

Table 2 - Gender Distribution

Gender	No Individuals	%
Male	473	27,5
Female	1.250	72,5
Total	**1.723**	**100,0**

Table 3 - Education Level

Education Level	No Individuals	%
None	940	54,6
Primary School	599	34,8
Middle School	182	10,6
High School	2	0,1
Total	**1.723**	**100,0**

Amongst the individuals interviewed 72,5% were female and 27,5% were men. No education was reported by a majority (54,6%), followed by primary school

education (34,8%). Few had higher levels of education. Most of interviewed individuals did not pursue further studies (87,5%). Only a small number of individuals studied at College level (10,2%), Higher Education (1,7%) or Technical / Vocational Training (0,7%).

5.2. Drinking Water and Sanitation Information

Table 4 - Drinking Water Source

Drinking Water Source	No Individuals	%
River	74	4,3
Well	999	58,0
Bore-hole	597	34,6
Tap	37	2,1
Rain catchments	10	0,6
Others	6	0,3
Total	**1.723**	**100,0**

The well was the most frequent source of water (58%) followed by borehole (34,6%). Other sources of water have also been reported but the frequency is less, as described in the table above (river, tap, rain catchments and others). There was no general habit of boiling the drinking water (93,2% did not).

Table 5 – Existence of Latrines at Households: reports by individuals

Existence of Latrine at Household	No Households	%
Yes	386	89,8
No	44	10,2
Total	**430**	**100,0**

When questioned about the existence of latrines in the respective households most individuals replied that a latrine existed (89,8%). However, when checked by the interviewers, through direct observation, the number of latrines was less than reported as shown in the table below.

Table 6 – Existence of latrines at Household: observation of existence

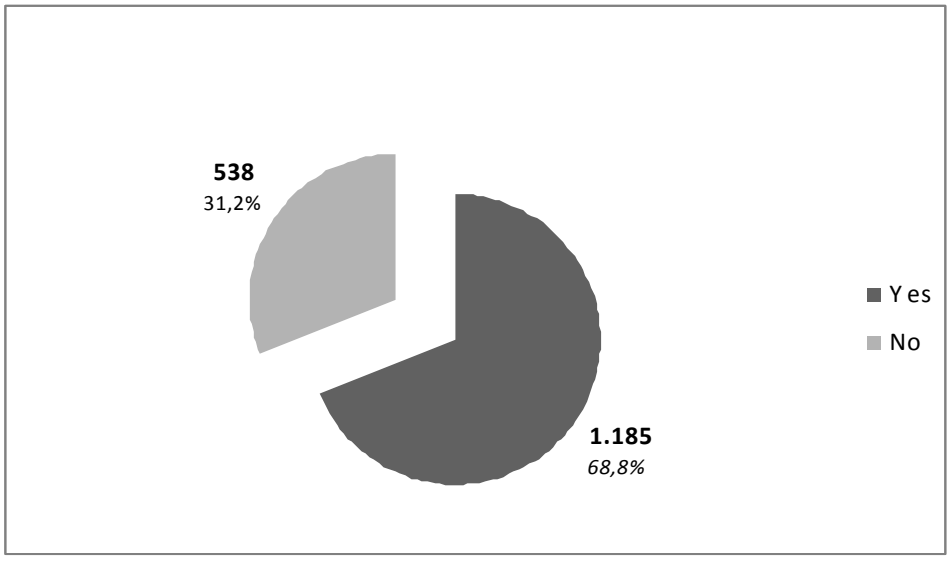
Observation of Existence of Latrine at Household	No Households	%
Absent	125	29,1
Present and completely enclosed	96	22,3
Present and partially enclosed	194	45,1
Present and open	15	3,5
Total	**430**	**100,0**

In the households with verified latrines, some latrines were completely enclosed (22,3%), some were partially enclosed (45,1%) and only a small part were open and allowed access to roaming pigs (3,5%). Additionally the interviewers found by direct observation that approximately 60% showed signs of being used by the respective households.

5.3. Pork Consumption and Management Information

Pork was consumed by 68.8% of the individuals interviewed (Fig. 17).

Figure 19 – Pork Consumption



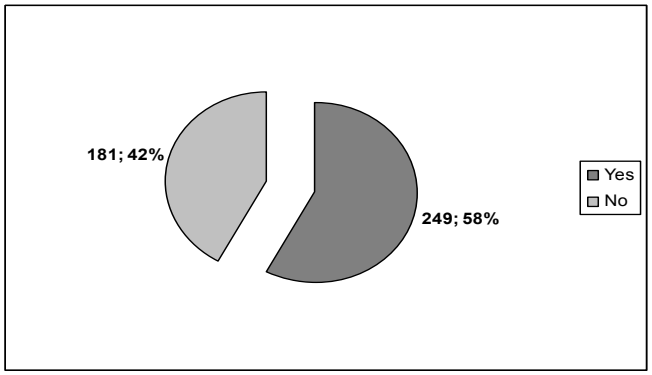
Of those individuals, 47,2% consumed pork at least once a month. The most common way of preparing the meat was by cooking (92,6%).

Table 7 – Gender and Pork Consumption

Gender	Consumption of Pork				Total	P value
	Yes	%	No	%		
Male	380	80,5	93	19,5	473	0,001
Female	805	64,4	445	35,6	1.250	
Total	**1.185**	**68,8**	**538**	**31,2**	**1.723**	

Men are twice more likely to consume pork than women (OR=2.25, 95% CI, 1.75 – 2.91).

Figure 20 – Keeping of Pigs in Household



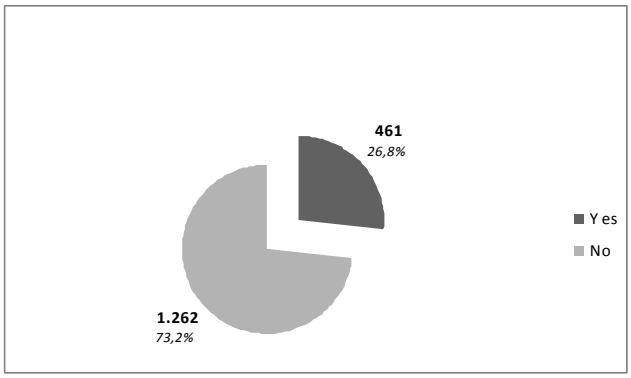
Pigs are kept in 58% of households of the study but of those, 78,4% have never been inspected by a meat inspector.

5.4. Human Cysticercosis / Taeniosis Information

5.4.1. Knowledge of condition

73,2% of the individuals interviewed had never heard of tapeworm infection in humans. This is presented in the Figure below.

Figure 21 – Knowledge of tapeworm infection in humans



5.4.2. Clinical symptoms

Table 8 – Clinical history and symptoms

Clinical history or current symptoms	Nº individuals	%
Mental disorders	21	1,22
Epileptic crisis	268	15,55
Headache	532	30,88
Subcutaneous nodules	41	2,38
Neurological focal signs	38	2,21
Asymptomatic	823	47,77
Total	**1723**	**100**

Among all interviewees, 8,3% reported the presence of previous skin nodules and only 2,38% currently had skin nodules.

A total of 63,2% did not complain about repeated episodes of severe headaches like migraine while 30,9% were currently suffering from this symptom.

5.4.3. Clinical signs

Clinical signs occurred in 3,4% of individuals. The following signs were found: isolated hemiparesis in 25 (1,19%) individuals, the association between dysarthria and hemiparesis ocurred in 2 (0,1%), cranial nerve fall-out occurred in 6 (0,35%) while bilateral papiloedema occurred in 5 (0,3%) individuals. Mental disorders were registered in 21 (1.22%) individuals.

5.5. Epidemiology of epilepsy in the study area

Among those interviewed 84,1% were never told that they had epilepsy / epileptic seizures. A total of 268 [(15,6%), 95% CI, 14,9 – 16,2)] were informed that they did have epilepsy / epileptic seizures by traditional healer (67.8%), nurse (27,4%), physician (3.6%) and neurologist (1.2%).

Table 9 – Information about epilepsy status

History of epilepsy or epileptic seizures	No Individuals	%
Yes, currently has	188	10,9
Yes, in the past year, not currently	20	1,2
Yes, one year or more ago, not currently	60	3,5
No	1.449	84,1
Cannot remember, do not know	6	0,3
Total	**1.723**	**100,0**

From the total of individuals with epilepsy (15,6%), 5,2% reported a past history of head injury with loss of consciousness, 1,5% reported meningitis “brain infection” during childhood and 9,7% had cerebral malaria. 15,7% (50) have hurt themselves when loss of consciousness occurred during a seizure (more than half reported falls in the fire).

In the same households of these individuals who reported epilepsy or seizures, a total of 28,7% also reported that other members in the same household also had epilepsy or seizures.

Table 10 – Epilepsy status by education level

Education Level	No of Individuals with Epilepsy				*p* value
	Yes		No		
	N.º	*%*	*N.º*	*%*	
No Education	144	15,7	793	84,6	0,09
Primary Education	101	16,9	497	83,0	
Secondary +	23	10,3	165	89,4	
Total	**268**	**15,6**	**1.455**		

There is no difference in the proportion of people suffering of epilepsy with level of education (p= 0,09).

Table 11 – Epilepsy status by sex

Gender	No of Individuals with Epilepsy				TOTAL	*p* value
	Present		Absence			
	N.º	*%*	*N.º*	*%*	*N.º*	
Male	134	28,3	339	71,7	473	0,001
Female	134	10,7	1.116	89,3	1.250	
Total	**268**	**15,6**	**1.455**	**84,4**	**1.723**	

There was association between gender and epilepsy status. Men were 3.29 times more likely to have epilepsy than women (OR=3.29, 95% CI, 2,51 – 4,30).

Table 12 – Epilepsy status by age group

Age	Epilepsy Yes	%	Epilepsy No	%	TOTAL
0-10	60	41,4	85	58,6	145
11-20	79	20,9	299	79,1	378
21-30	41	7,8	482	92,2	523
31-40	43	14,3	258	85,7	301
41-50	23	13,4	149	86,6	172
51-60	13	10,2	114	89,8	127
61 +	9	11,8	68	88,2	77
Total	**268**	**15,6**	**1.455**	**84,4**	**1.723**

Children aged 0-10 years (41,4%) are more likely to suffer from epilepsy than the older ages.

Table 13 – Association between neurological symptoms/signs and epilepsy

Neurological symptoms/signs	Epilepsy		*p*
	Yes (%)	No. (%)	
Loss of consciousness			
Yes	189 (77.5)	55 (22.5)	0.001
No	79 (5.3)	1398 (94.7)	
Period of absence			
Yes	149 (74.1)	52 (25.9)	0.001
No	119 (7.9)	1392 (92.1)	
Uncontrollable twitching			
Yes	176 (73.0)	65 (27.0)	0.001
No	92 (6.2)	1385 (93.8)	
Period of hearing and smelling			
Yes	31 (40.8)	45 (59.2)	0.001
No	235 (14.3)	1408 (85.7)	

The predictors for epilepsy are: loss of consciousness (OR= 60.81, 95% CI 41.47-88.58); period of absence (OR = 33.5, 95% CI 23.22-48.38); uncontrollable twitching (OR= 40.7, 95% CI 28.60-58.08) and; period of hearing or smelling or seeing things that are not there (OR= 4.12, 95% CI2.55-6.66).

Table 14 – Hospitalization due to seizure / epilepsy

Hospitalised because of seizure/epilepsy	No Individuals	%
Yes	38	14,2
No	226	84,3
Cannot remember	4	1,5
Total	**268**	**100,0**

Among individuals diagnosed with epilepsy, 38 (14,2%) were hospitalized. Most of them (62%) were hospitalized once and they were in hospital for an average of 13 days.

Table 15 – Individuals treated for seizure/epilepsy

Treatment	No Individuals	%
Yes	166	61,9
No	99	36,9
Cannot remember	3	1,1
Total	**268**	**100,0**

61,9% of individuals received treatment for seizure / epilepsy while the remaining 38,1% did not. Treatment was mainly traditional medicine (65,3%), phenobarbital and phenytoin (14,2%) and the remaining can not remember the medication.

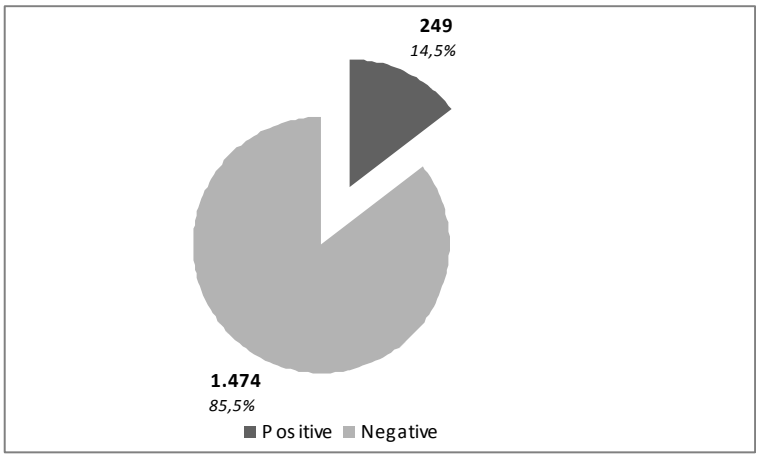
Table 16 – Association between selected variables and epilepsy

Variable	Frequency		OR (95% CI)	*p*
A. Source of Water				
Safe Water	112/643	17,4%	Ref	
Non Safe Water	156/1077	14,5%	0,8 (0,61 - 1,06)	0,1
B. Latrine				
Yes	236/1543	15,5%	Ref	
No	32/179	17,9%	1,21 (0,79 - 1,84)	0,4
C. Consumption of Pork				
Yes	183/1184	15,5%	0,98 (0,77 - 1,37)	0,8
No	85/537	15,8%	Ref	
D. Keeping of Pigs				
Yes	105/756	13,9%	0,83 (0,63 - 1,09)	0,2
No	161/964	16,7%	Ref	

The prevalence of epilepsy in the study was 15,6% (95% CI, 14,9 – 16,2). None of the variables considered – Source of Water, Existence of Latrine in Household, Consumption of Pork, and Keeping Pigs in Household – had a direct association with epilepsy. A very small increase of prevalence was been observed in the households without latrines and who keep pigs.

5.6. Serological diagnosis of cysticercosis

Figure 22 – ELISA Cysticercus Antigen Results



249 individuals (14,5%) , (95% CI, 13,7 – 15,2) had a positive ELISA antigen test.

Figure 23 – Elisa Ag status by gender

Gender		ELISA Ag Result		Total
		Positive	Negative	
Male	N.	101	372	473
	%	21,4	78,6	100
Female	N.	148	1102	1250
	%	11,8	88,2	100
Total	N.	249	1474	1723
	%	14,5	85,5	100
			Pearson x^2	25,1
			P value	0,001

It was observed that more male patients had positive results of ELISA Ag than females (21,4% Vs 11,8%). Males are twice as likely to be infected than women (OR= 2,02, 95% CI, 1,51 – 2,70).

Table 17 – Ag Status by age group

Age group	Elisa Ag Test				Total	
	Yes	%	No	%	N	%
> 15 yrs	232	15.6	1.259	84.4	1.491	100.0
≤ 15 yrs	17	7.3	215	92.7	232	100.0
TOTAL	**249**	**14.5**	**1.474**	**85.5**	**1.723**	**100.0**

The group of patients older than 15 years of age showed more positive results for ELISA Ag than the younger (15,6% vs 7,3%). Patients aged 15 and older have twice the risk of having a positive ELISA Ag test than young patients (OR= 2,33, 95% CI, 1,36 – 4,04).

5.7. History of epilepsy and positive serology

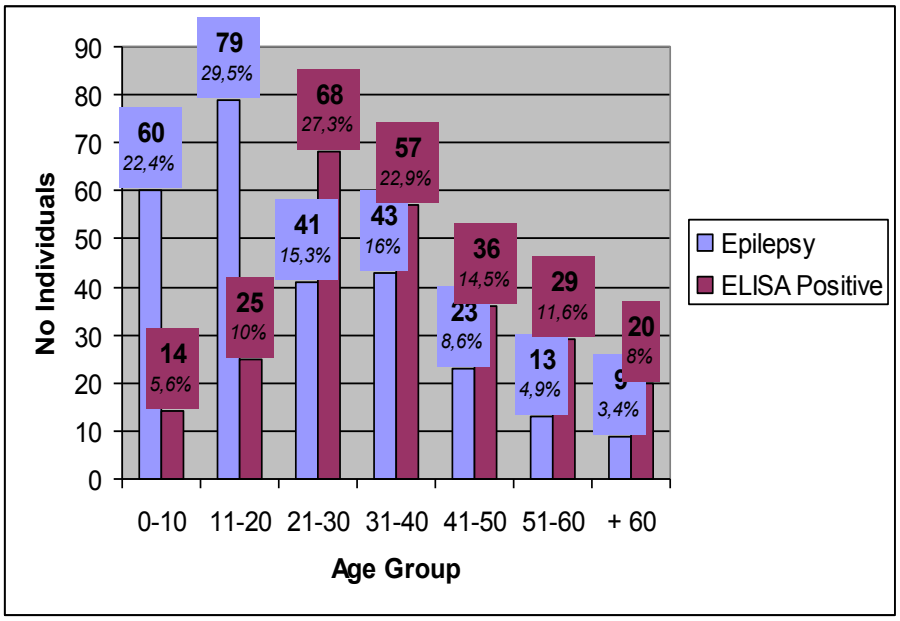
Table 18 – Elisa Ag Status and epilepsy

Elisa Ag	Epilepsy				Total	
	Yes	%	No	%	N	%
Positive	118	47.4	131	52.6	249	100.0
Negative	150	10.2	1324	89.8	1.474	100.0
TOTAL	**268**		**1455**		**1.723**	**100.0**

From the total of 249 individuals who tested positive for ELISA for the detection of parasite antigens, almost half (a subtotal of 118) had epilepsy while from the 1.474 individuals who tested negative for ELISA antigens a subtotal of only 10,2% had epilepsy (OR= 4,65, 95% CI, 3,50 – 6,19).

Thus, epilepsy was observed to be much more frequent in individuals who were seropositive than seronegative [(118/249 or 47,4%) vs (150/1474 or 10,2%); p<0,001].

Figure 24 – Epilepsy and Seropositivity for Cysticercosis: Distribution by Age Group



It was observed that the prevalence of cysticercosis grows with age and is more frequent between 21 to 40 years.

5.8. Environmental factors and serology

Table 19 – Association between selected variables and positive ELISA

Variable	Frequency Positivity for antigen *T. solium*		OR	*p*
A. Source of Water				
Safe Water	91/644	14,1%	Ref	
Non Safe Water	158/1077	14,7%	1,01 (0,75 - 1,34)	0,7
B. Latrine				
Yes	212/1544	13,7%	Ref	
No	37/179	20,7%	1,64 (1,09 - 2,64)	0,01
C. Consumption of Pork				
Yes	186/1185	15,7%	1,48 (1,06 - 2,08)	0,03
No	63/474	11,7%	Ref	
D. Keeping of Pigs				
Yes	107/756	14,2%	Ref	
No	141/965	14,6%	1,02 (0,73 - 1,28)	0,7

The prevalence of AgELISA positives in the study was 14,5%. Absence of latrine in household (OR 1,64 ; p=0,01) and consumption of pork (OR 1,48 ; p = 0,03) – was significantly associated with antigen positivity.

5.9. Risk factors for NCC

Table 20 – Association between Gender and NCC

Gender	No Individuals \ NCC					
	Yes		No		Total	
Female	81	6,5	1169	93,5	1250	100,0
Male	74	15,6	399	84,4	473	100,0

P = 0.001

It was observed that more male patients had NCC than female (15,6% Vs 6,5%).

Table 21 – Association between Education Level and NCC

Education Level	No Individuals \ NCC					
	Yes		No		Total	
No Education	92	9,8	848	90,2	940	100,0
Primary School	55	9,2	544	90,8	599	100,0
Middle and High	8	4,4	174	95,6	182	100,0

P = 0.1

There is no difference in the proportion of individuals suffering of NCC with level of education.

Table 22 – Association between Age Group and NCC

Age	NCC Yes	%	NCC No	%	NCC Total	%
0-10	13	9,0	132	91,0	145	100,0
11-20	20	5,3	359	94,7	379	100,0
21-30	28	5,4	495	94,6	523	100,0
31-40	37	12,3	264	87,7	301	100,0
41-50	25	14,5	147	85,5	172	100,0
51-60	16	12,6	111	87,4	127	100,0
+ 60	16	21,1	60	78,9	76	100,0

P = 0.001

It was observed that the prevalence of NCC is more frequent between 21 to 40 years.

Table 23 – Association between selected variables and NCC

Variable	NCC Yes		NCC No		NCC Total		*p*
A. Source of Water							
Safe Water	66	10,2	578	89,8	644	100	P=0.1
Non Safe Water	89	8,3	988	91,7	1.077	100	
B. Latrine							
Yes	133	8,6	1.411	91,4	1.544	100	P=0.1
No	22	12,3	157	87,7	179	100	
C. Consumption of Pork Meat							
Yes	117	9,9	1.068	90,1	1.185	100	P=0.06
No	38	7,1	499	92,9	537	100	
D. Keeping of Pigs							
Yes	53	7,0	701	93,0	754	100	P=0.03
No	99	10,3	866	89,7	965	100	

Keeping of pigs was significantly associated with NCC. No difference between proportions of consumption and non-consumption of pork meat to have NCC (P=0.06).

5.10. Seropositivity, brain CT scan and EEG exam

151 individuals (107 ELISA antigen positive with a history of epilepsy and 44 ELISA antigen negative and history of epilepsy) underwent a CT scan of the brain and an EEG exam.

Figure 25 – Individuals who underwent Brain CT Scan and EEG Exam

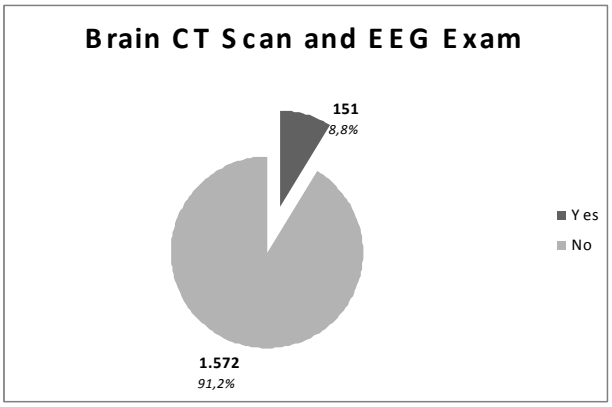


Table 24 – Age distribution of patients who underwent Brain CT Scan and EEG Exam

Age	No individuals	%
0-10	27	17,9
11-20	33	21,8
21-30	21	13,9
31-40	32	21,2
41-50	20	13,2
51-60	10	6,6
61 +	8	5,3
TOTAL	151	100,0

Table 25 – Association between age and CT abnormality

Age group	CT abnormality				Total	*p* value
	Yes	%	No	%		
≥ 21 yrs	65	71,4	26	28,6	91	0,001
< 21 yrs	19	31,7	41	68,3	60	
	84		**67**			

Patients aged 21 or more with epilepsy are five times more likely to present abnormal Brain CT Scans than younger patients (OR= 5,39, 95% IC 2.65 – 10.96).

Table 26 – Results of Brain CT Scan Exam

Brain CT Scan Exam Findings	Positive Elisa + Epilepsy		Negative Elisa + Epilepsy	
	No Individuals	%	No Individuals	%
Vesicular	19	17,8	1	2,3
Colloidal	8	7,5	1	2,3
Nodular-Granular	4	3,7	4	9,1
Calcified	35	32,7	2	4,5
Fibrous Arachnoiditis	1	0,9	0	0,0
Cysticercotic Encephalitis	3	2,8	0	0,0
Vesicular + Calcified	7	6,5	0	0,0
No alterations \ Other injuries	30	28,0	36	81,8
Total	**107**	**100,0**	**44**	**100,0**

The table above summarizes the CT Scans findings. In the group of individuals with positive ELISA Ag and epilepsy the most frequent type of lesion was calcifications (32,7%) followed by cystic (vesicular) lesions (17,8%). In the group of individuals with negative AgELISA and epilepsy the most frequent type of lesion was nodular (granular) (9,1%) followed by calcified lesions (4,5%). In the ELISA Ag positive patients, 28% did not show alterations on brain CT scan, while 81,8% who were ELISA Ag negative had no alterations or other injuries on brain CT scan. It must be noted that despite of having a negative ELISA Ag, 8 patients were submitted to brain CT Scan and presented with lesions suggestive of NCC.

Table 27 – Univariate analysis of Brain CT scan findings in relation to clinical features

Clinical feature	Abnormal CT Yes (%)	Abnormal CT No (%)	p	OR
Age of onset of loss of consciousness				
0 – 5 yrs	12 (37.5)	20 (62.5)	0.04	OR=0.41, 95% CI 0.17-0.97
+ 5 yrs	42 (59.2)	29 (40.8)		
Duration of seizure disorder				
0-2 yrs	17 (54.8)	14 (45.2)	0.7	OR= 1.14 , 95% CI 0.49-2.67
> 2 yrs	37 (51.4)	35 (48.6)		
Family history of epilepsy				
Present	24 (58.5)	17 (41.5)	0.9	OR= 1.16, 95% CI 0.56-2.42
Absent	58 (54.7)	35 (45.3)		
EEG				
EEG normal	46(58.2)	33 (41.8)	0.09	OR= 1.24, 95% CI 0.65-2.37
EEG abnormal	38 (52.8)	34 (47.2)		

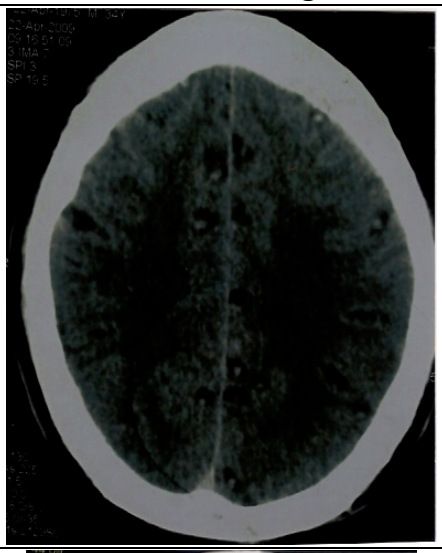
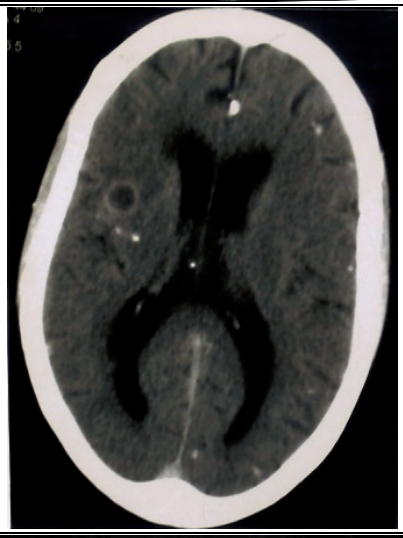
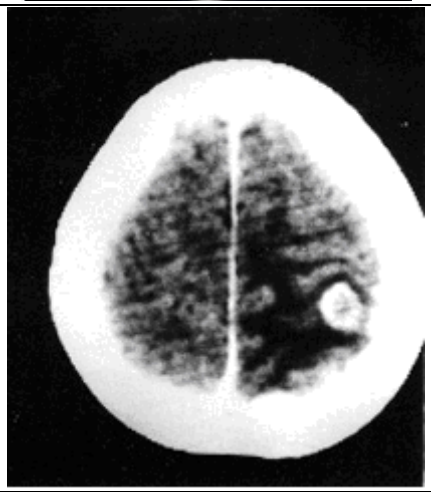
Univariate analysis revealed that taking abnormal scan as the outcome, only age of onset of loss of consciousness was significantly associated with an abnormal scan (OR= 0.41, 95%b CI 0.17– 0.97).

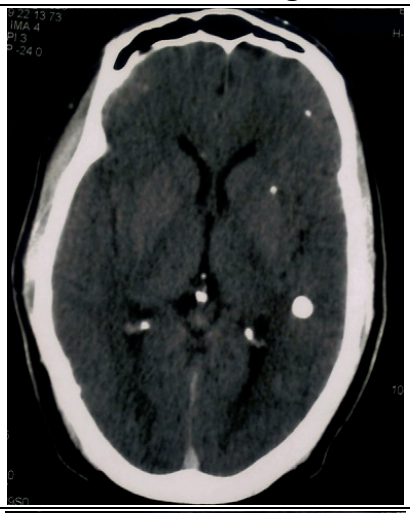
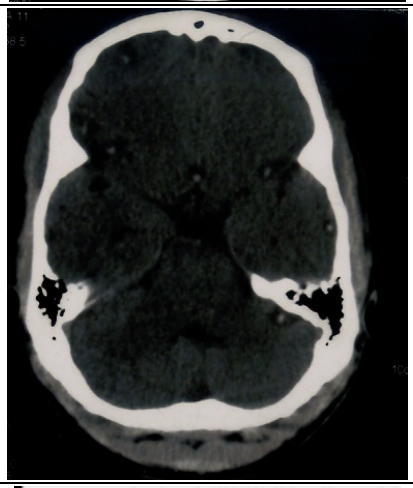
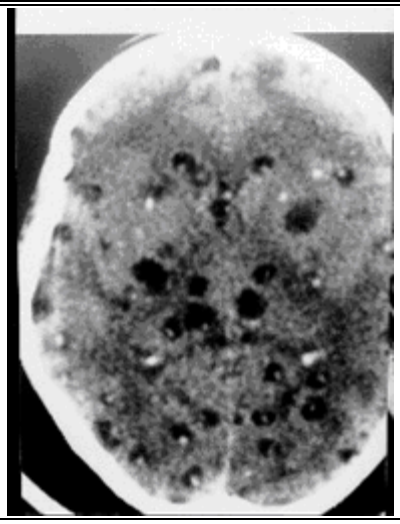
Table 28 – Findings of Brain CT Scan Exam and ELISA

Brain CT Scan Findings	Positive Elisa + Epilepsy		Negative Elisa + Epilepsy	
	No Individuals	%	No Individuals	%
Normal	36	31,9	30	78,9
Abnormal	77	68,1	8	21,1
Total	**113**	**100,0**	**38**	**100,0**

Patients with ELISA Ag positive and epilepsy present more abnormalities in the Brain CT Scan exam than patients with ELISA Ag negative and epilepsy (OR=11,55, 95% CI, 4,49 – 30,65).

Figure 26 – Images of Brain CT Scan

Type	CT Scan Image	Description
1. Vesicular		Vesicular cysticerci appear as small and rounded low-density areas that are well demarcated from the surrounding brain parenchyma. The scolex is usually visualized within the cyst as a high intensity nodule giving the lesion a pathognomonic imaging.
2. Colloidal		Colloidal cysticerci appear as illdefined lesions surrounded by edema. Most of them show a ring pattern of enhancement after contrast medium administration.
3. Nodular-Granular		This pattern corresponds to the granular stage of cysticerci and is commonly referred as to “cysticercus granuloma”, “single enhancing lesion”.

Type	CT Scan Image	Description
4. Calcified		Calcified (dead) cysticerci normally appear as small hyperdense nodules without perilesional edema or abnormal enhancement after contrast medium administration.
5. Fibrous Arachnoiditis		The fibrous arachnoiditis is seen as areas of abnormal leptomeningeal enhancement at the base of the brain after contrast medium administration.
6. Cysticercotic Encephalitis		Cysticercotic Encephalitis shows diffuse brain edema and collapse of the ventricular system without midline shift. After contrast medium administration, multiple small ring-like or nodular, lesions appear disseminated within the brain parenchyma.

5.11. EEG Results

Table 29 – Findings of EEG Exam

EEG Exam Results	No Individuals	%
Normal	72	47,7
Abnormal	79	52,3
Total	**151**	**100,0**

The 151 patients who underwent CT scanning were also examined by EEG and 52% (79 patients) had abnormal results. Considering the type of seizures of the 79 individuals, 73,4% (58) were affected by partial seizures and the remaining by generalised seizures.

Partial seizures were reported more often than generalised seizures and were either complex partial seizures with motor manifestations (38 patients) or partial seizures secondarily generalized, and the most commonly observed generalized seizures was tonic-clonic.

Slow theta and delta abnormalities were found in 23,1% of cases, and isolated deterioration of basic rhythms was observed in 18,7% of cases. Electroclinical agreement was considered to be satisfactory in 28 patients, and was better with epileptiform abnormalities than with slow wave abnormalities. The existence of epileptiform EEG abnormalities confirmed clinically diagnosed epilepsy, but did not allow etiological diagnosis.

Table 30 – Demographic, clinical, serological and radiological characteristics of 151 patients with seizures

Characteristic	Category	Nº	%
Age range	5-66 yrs		
Age group	≥ 15 yrs	115	76,2
Gender	Female	88	58,3
Self-reported frequency of seizures	Single seizure	8	5,3
	More than one	132	87,4
	No answer	11	7,3
Primary seizure type	Partial seizures	58	73,4
	Generalized seizures	21	26,6
Reported duration of seizure disorder	≤ 1 year	43	28,5
	2-4 years	39	25,8
	5-9 years	25	16,6
	≥ 10 years	44	29,1
ELISA Ag	Positive	58	54,2
Brain CT	Abnormal	38	52,8

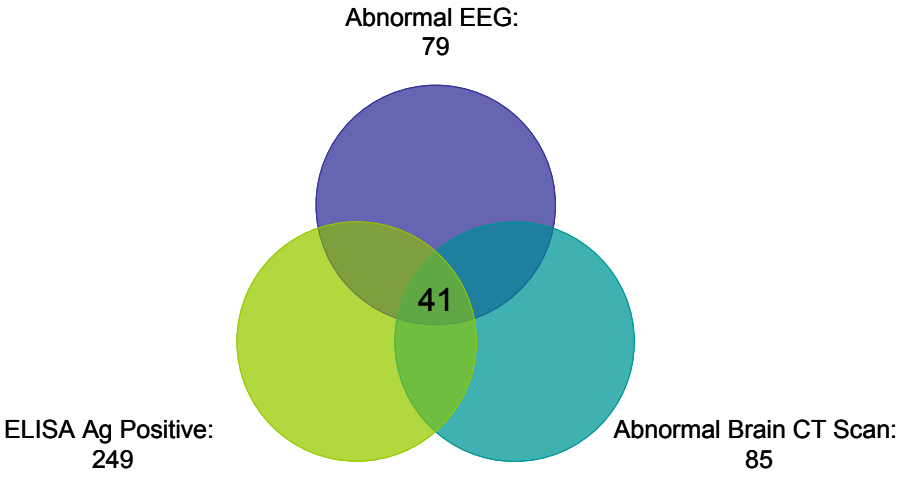
Table 31 – Findings of EEG Exam and ELISA Results

Results	Abnormal EEG		Normal EEG		TOTAL	
	Nº	%	Nº	%	Nº	%
ELISA Positive and Epilepsy	58	54,2	49	45,8	107	70,9
ELISA Negative and Epilepsy	21	47,7	23	52,3	44	29,1
Total	**79**	**100,0**	**72**	**47,7**	**151**	**100,0**

Patients who were ELISA Ag positive and had epilepsy were more likely to present abnormalities on the EEG exam than patients who were ELISA Ag negative, but the difference was not significant (OR=1,30, 95% CI, 0,61 – 2,78).

Electroserological agreement was good in 58 patients. A significant association (Chi Square, p=0,03) existed between slow focal abnormalities and positive cysticercosis serology. Conversely, no significant association was detected between epileptic patterns and serology results.

Figure 27 – Association between ELISA Ag Positive, Abnormal EEG and Brain CT Scan (No of Individuals)



A subtotal of 41 individuals presented simultaneously ELISA Ag Positive with Abnormal EEG and Brain CT Scan.

CHAPTER SIX
DISCUSSION

The main aim of the present study was to provide information on the prevalence of NCC, the distribution of epilepsy and possible relationships between NCC and epilepsy in humans in the district of Angonia, so that the control programme planned for the near future could be made effective and monitored well.

In several villages in Mozambique, patients with neurological abnormalities mostly use traditional medicines as they believe that the traditional doctor contacts the spirits that cause the disease and because of that can treat them more effectively. This situation can contribute to a underevaluation of the problem.

Considering the spiritual cause of epilepsy, people may not address this entity openly and it becomes difficult to collect reliable data. To avoid this limitation, a project meeting was held prior to the implementation of the study to explain to the communities' leaders and all the participants, the importance of the study for the communities (reduced incidence of cysticercosis and improved livelihoods of farming communities and consumers).

The low sensitivity/specificity of the serological examination with a single viable cyst may result in a problem due to the fact that many patients may also be infected with others helminthoses (cross reacts with others cestode parasites). To avoid this limitation, all the individuals with positive ELISA and clinical manifestations or history of symptoms presumptive of NCC underwent computerized tomography scanning and electroencephalographic studies.

6.1. Socio Demographic Characteristics

1.723 individuals were included in the study. The age group of 21 to 30 years of age comprised 30,7% of total individuals. Amongst the individuals interviewed 72,5% were female and 27,5% were male.

Male migration, characterized by the moving of men in search of work opportunities, is a very frequent situation in the district under study and therefore women and children were more available to participate in the study. This is also consistent with other similar population based studies performed in Mexico (Dumas et al., 1989; Keilbach et al., 1989) where study participants tended to be females and younger age groups.

The ELISA antigen test showed that males were twice more likely to be infected than women, with a greater frequency in the group of patients older than 15 years of age. This finding is in contrast with the observation by Cruz et al. (1999) who found a higher proportion of epileptic females with positive ELISA Ag results and attributed it to food handling activities and their relationship with infection with cysticerci. Other studies have given inconsistent results, with no difference (Sarti et al., 1994), or a higher seroprevalence in women than in men (Garcia-Noval et al., 1996). It is likely that cultural differences may affect the behaviour of men and women influencing the proportions. In Angonia, most cysticercotic pork is eaten by the largely rural communities and, for cultural reason, men eat more pork meat than women. It is also possible that the men who had epilepsy, were unemployed and thus stayed at home becoming part of the study.

Communities of Angonia in general do not access any sort of education; the majority of the individuals interviewed never frequented a school. These data are also in accordance with the data from the National Inquiry on Living Condition in Mozambique (Simler et al., 1998).

It was observed that there was a tendency of a higher prevalence of epilepsy in persons with no formal education, in other words, the prevalence of epilepsy decreased with higher levels of education, but this trend did not reach statistical significance as figures were too small.

There is also a positive relation between level of education, age and the knowledge of preventive measures regarding cysticercosis. More educated and older individuals were better able to give examples of how to prevent the transmission of parasitic infections.

Efforts to educate villagers at schools, village meetings, and on an individual basis have been highly successful in terms of teaching villagers the parasite life cycle and the connection between infected pigs and themselves or others getting cysticercosis (Keilbach et al., 1989; Sarti et al., 1997). Villagers were able to describe how *T. solium* infection was transmitted, and how it could be prevented. Knowledge, Attitude and Practice (KAP) studies can demonstrate that villagers understand the role of *T. solium* infection in pigs and the *T. solium* larvae's relationship to NCC or epilepsy (Sarti et al., 1997). However, the knowledge acquired did not appear to result in dramatic changes in risk behaviour and this need to be investigated in our current population studied.

6.2. Drinking water and sanitation information

In Angonia, wells are the most frequent sources of water and there is no practice of boiling the drinking water. Fruit and vegetables that grow at ground level are eaten unpeeled and uncooked. Consumption of unclean vegetables and water contaminated with infected human feces and poor personal hygiene (e.g., inadequate washing of hands before eating and after defecating) may contribute to infection with *T solium* and ensuring the perpetuation of cysticercosis (Sarti et al., 1988, 1997; Flisser et al., 1994; Garcia et al., 1991).

During the interviews, the majority of individuals reported that they had a latrine in the household. Nonetheless, when the interviewers observed the households in questions, 28,9% of the individuals did not have latrines and 45% had either open or only partially enclosed latrines. Futhermore only about 60% of the latrines showed signs of being in use by the respective household.

This important fact shows how ready access pigs and other coprofagos animals, including flies and insects, have to human feces, thus facilitating and potentiating the transmission of the parasite. One study failed to incriminate domestic flies as mechanical vectors of *Taenia* eggs in the community of Tianquizolco, Guerrero State, Mexico; the authors concluded that pigs roam freely in the village consuming human faecal material immediately after defecation, thereby limiting fly contact with *T. solium* eggs (Martinez et al., 2000).

The study did not specifically focus on this, but in Angonia, where there are many flies, they could play a role in the transmission of *Taenia* eggs.

Some of the variables like existence of latrines in households (OR=1,51; p=0,01) and consumption of pork (OR=1,34; p=0,03) had a direct and significant association with cysticercosis in the studies. An association between human cysticercosis and poor sanitation has been observed in many other studies (Sarti et al., 1992; Morales et al., 2002; Phiri et al., 2002; Ngowi et al., 2004) and our study supports these findings.

For many communities, pigs are considered to be a replacement of the municipal cleaning service (Letonja, 1975; Verster, 1974) and they may also replace latrines. Thus, they can gain weight and produce a profit without the need for investment in supplementary food. The limited use of latrines in the Angonia district implies that people use the nearby bush for defecation, resulting

in pigs having ready access to human feces, resulting in porcine cysticercosis which is essential for the life cycle of *T. solium* taeniasis (Garcia et al., 2003). Pigs raised in endemic countries have greater access to human feces due to poorer sanitation, undergo incomplete or inadequate meat inspection, and are frequently consumed incompletely cooked (Carpio, 2002).

If slaughtered pork is not inspected adequately and is consumed incompletely cooked, the cycle for cysticercosis is completed.

6.3. Pork consumption and pork management

A pig is one of the few assets available to the farmer that can be quickly and easily converted into cash. A pig can be fed at little cost by permitting it to range free in villages or on free farm land and in this way obtain a variety of foods to supplement its diet, including human and other animals feces (Gilman et al., 1999).

Meat inspection and meat dissection findings confirm that porcine cysticercosis is common in the Angonia district and is potentially a serious health problem to pigs and humans (Gule, 2008). Important risk factors responsible for transmission and maintenance of porcine cysticercosis in the Angonia district were described as poor management of pigs, lack of pork inspection, pork consumption, and ignorance about the mode of transmission of *T. solium* taeniasis/cysticercosis (Gule, 2008).

In Angonia, as in many other endemic areas, very few rural pigs, with or without cysticercosis, are made available for inspection at abattoirs, partly because the dealers who buy such pigs do not want to risk the loss of a cysticercotic animal. This would explain why estimates of pigs cysticercosis that are based on routine meat inspection are often far lower than those observed in cross-sectional surveys (Aluja et al., 1982; Anon, 1993).

Inspection in the abattoirs, at least as performed now, would appear to be a very ineffective method of cysticercosis control in Angonia. Although meat-inspection programmes in the late 1800s and early 1900s did appear to be successful in eradicating cysticercosis from most of Europe (Hitchcock, 1987), their success may have been partially attributable to the relatively small numbers of pigs then moved between endemic and non-endemic regions. The confiscation of infected meat in abattoirs like in Central America, with no attempt at compensation, has undoubtedly promoted the transmission of *T. solium* by encouraging the clandestine and unregulated marketing of infected pork (Pawlowski et al., 2005).

In order to avoid losses by condemnation of infected carcasses at official meat inspection, owners often detect infection in vivo, sell these pigs at a cheaper price to pig traders or kill them at unofficial slaughterhouses or at home. In this way transmission of *T. solium* is perpetuated in endemic rural areas and infected pork commonly enters the market, including urban areas, away from the regions where pigs are reared. Unlicensed pig traders and ineffective food safety regulations and meat inspection as well as lack of consumers' rights agencies facilitate a spread of taeniosis/cysticercosis.

In Angonia, the type of pig production represents a paradigm of the complete cysticercosis cycle: animals are produced extensively, feeding on what they find; they are slaughtered with no inspection and a general lack of knowledge about the disease and how to prevent it is seen in the population.

In the Angonia district, communities visited reported that pigs are usually confined during the rainy season and released after harvest or during the dry season. During confinement, pigs were mainly fed farm and kitchen residues, but in some households also human feces. After the harvest, free roaming pigs have access to human faecal material. Many pigs are slaughtered outside the

slaughterhouses without any veterinary supervision. Pork is widely consumed in the area especially during funerals and other traditional events.

There was no significant difference in the proportion per household with evidence of human cysticercosis between those who owned pigs and those that did not (OR= 1,02; p= 0,7). This is not surprising, given the fact that there is a lot of social interaction between houses, with people visiting each other. It was also reported by people that pigs sometimes entered in the gardens of households which did not own pigs, in search for food.

The existence of cysticerci in the pork that is consumed in the district was reported by several pig farmers. Some of the individuals interviewed reported that they had consumed meat that was “full of balls and was spongeous when chewed”, a description that reminds of Aristotle in his “History of Animals” (Aristotle, 1969).

In Angonia, most cysticercotic pork is eaten by the largely rural communities where the pigs have been raised – communities are very familiar with the cysticerci and tolerate them rather than attempt to control them. The transport of pigs with cysticercosis and the migration of villagers from rural communities to urban areas, help spreading *T. solium* – and the risks of futher human taeniosis/cysticercosis – througout the Angonia District and into neighbouring areas. The consumption of raw or partly cooked meat is a part of the local culinary habit.

6.4. Human neurocysticercosis \ taeniosis

NCC is the most frequent parasitosis of the brain and mainly prevalent in developing countries, where sanitary conditions are sub-standard such as poor control of water supply, food handling and personal hygiene (Avode et al., 1998; Newell et al., 1997). Once the parasite reaches the brain parenchyma, there is a

focal reaction that later on may produce chronic granuloma, which may produce epileptogenic foci. The prevention of NCC, will therefore, lead to the prevention of many cases of epilepsy (Grunitzky et al., 1995).

The impact of NCC on human health is difficult to estimate, because of the highly variable clinical picture of the disease, ranging from asymptomatic to severe headache, blindness, mental disturbance, epilepsy and even death (Cruz et al, 1999; Houinato et al, 1998; White, 2000).

In Mexico, NCC is currently the primary cause of adult-onset epilepsy (Medina et al., 1990; Del Brutto et al., 1994) and is responsible for 11% of all neurological consultations (Vasquez and Sotelo, 1992) and 25% of craniotomies (Sotelo et al., 1985). Cysticerci can be detected, at autopsy, in the brains of 2-3% of the general population (Villagran and Olvera, 1988).

Symptomatic NCC is known to appear years after exposure (Dixon and Lipscomb, 1961). Studies have shown that the frequency of taeniosis in patients with NCC may reach 15%, and that patients with many cerebral cysticerci have a higher probability of carrying a tapeworm at the time of diagnosis (Garcia et al., 1999; Gilman et al., 2000).

Recent epidemiological studies have shown that household contacts of patients with NCC had a risk of positive serology for cysticercosis that was three times higher than the general population. While these findings are still consistent with a common envinronmental source of infection with *T. solium* eggs, they also suggest a potential for direct human-to-human contamination (Carpio, 2009).

In Angonia a history of headache was three times more frequent in women than in men. This is also expected for the general population (Siberstein et al., 1999) and probably because of the low specificity of the symptom, there was no association between the complaint of headache and seropositivity for

cysticercosis. A significant statistical association has been found between migraine-like headache and the presence of antibodies against *C. cellulosae* using the EITB technique in communities in Ecuador, as reported by Plancarte et al. (1994). In addition, according to DeGiorgio et al. (2002), headache usually indicates the presence of increased intracranial pressure, hydrocephalus or meningeal inflammation. Headache may be very common and unspecific symptom in rural African populations.

A survey carried out in Mexico on 205 patients with NCC (114 adults and 92 children younger than age of 15 years) reported that seizures were more frequent in children (80% vs 56%), while headache was more frequent in adults (27% vs 15%) (Teitelbaum et al., 1989). These findings are also in accordance with our data.

However, in Angonia, subcutaneous nodules were observed in only 2,4% ELISA-Ag positive individuals, which is much lower than the figures from other endemic regions of Africa and Asia (10-30%, Dumas et al., 1990; Schantz et al., 1998) and more similar to what is reported in South America (2,9-6%, Cruz et al., 1994).

No pathognomonic physical findings unmistakably identify a patient with NCC. Virtually any neurological sign or symptom can occur, depending on the CNS location of the parasite.

6.5. Epilepsy prevalence

Epilepsy is considered an important health problem in developing countries, where prevalence rates range from 2.47/1,000 to 57/1,000 (Senanayake et al., 1993).

In endemic areas in Africa, the proportion of epilepsy attributed to NCC varies from 11,7% in Burundi, 25,4% in South Africa to 48,9% in Madagascar (Newell et al.,1997).

In Africa the causes of epilepsy are often attributed to the supernatural forces which contribute to the social exclusion, stigmatization and marginalization of patients, limiting the opportunities for its study and treatment. For this reason, the patients with neurologic disorders preferably consult traditional healers whom they believe to be in contact with the spirits that cause the disease and therefore are more capable of curing them. Non-documented information, from Mozambican medical staff, report that a large number of epileptic patients are never treated within the official health system and respective facilities.

Other possible causes of epilepsy in sub-Saharan Africa include genetic factors (Zoli et al., 2003), meningitis and malaria (Carter et al., 2004) in children, and in adults, brain tumours (Sander et al., 1996), vascular diseases (Diop et al., 2003) and head injury. Malnutrition has also been identified as a possible cause (Crepin et al., 2007). Significantly, in our study from the total of 249 individuals who tested positive for ELISA for the detection of parasite antigens, a subtotal of 47,4% had epilepsy, while from the 1.474 individuals who tested negative for the ELISA antigens, only 10,2% had epilepsy (OR= 4,69, 95% CI, 3,50-6,19); it means that NCC is probably the most common cause of acquired epilepsy in Angonia. A number of studies have shown a strong association between epilepsy and NCC in areas endemic for *T. solium* (Garcia et al., 1995, 2003b).

In our study head injuries may have contributed to the development of epilepsy in 5,2% of patients while meningitis and malaria accounted for a further 1,5% and 9,7% respectively.

Although epilepsy is known as a frequent condition in Mozambique, data on its prevalence and aetiological factors are unavailable. This study confirms the

previous observation by others authors, that NCC is one of the most important causes of epilepsy in developing countries (de Bittencourt et al., 1996; Carpio et al., 1998).

Most communities fear epileptic patients, because epilepsy is considered a contagious and/or a shameful disease (Avode et al., 1996; Preux et al., 2000). According to surveys of Preux et al. (2000) in West Cameroon only 27% of epileptics get married and 39% fail to enter into a professional activity. These factors greatly contribute to an underestimation of the burden of epilepsy and its real public health importance like in the Angonia district

The frequency of individuals with seizures in older age groups in the study population and the strong association with ELISA-Ag to cysticerci probably reflect the cumulative effect of infections that occurred some time ago but only become clinically manifest years later.

There is a lack of information about the epidemiology of epilepsy in Africa, including the age of onset. Where data are available, more than half of cases report that patients developed epilepsy as adults. This pattern is not seen in high-income countries where age-specific incidence typically follows a U-shaped curve, being highest in the first year, low in young adulthood and climbing again after the age of 60 (Forsgren et al., 2005; Preux & Druet-Cabanac, 2005).

This may be because young adults comprise a very large proportion of the population in Africa, including Mozambique; in Europe, this is not the case. Thus, adults contribute a greater number of cases of epilepsy even if the prevalence is the same. At the other end of the age spectrum, the rise in incidence after the age of 60, which is typical of a high-income country, cannot be detected when few people live to this age in our environment.

6.6. Epidemiology of cysticercosis

The WHO estimates that the global prevalence of cysticercosis is between 0.7% and 1% with a tendency to twice this number in developing countries (Roman et al., 2000).

The prevalence of cysticercosis (as estimated by ELISA-Ag) was 14,5% (95% CI, 13,7-15,1) in the Angonia District. The prevalence of antigen positivity in this study is similar to findings from Latin America and Africa (Sotelo et al., 1985; Dumas et al., 1989; Heinz et al., 1965).

Hospital records from Busia District in Kenya showed a prevalence between 12-14% in one division notably where free-range pig keeping is common (Githigia et al., 2002). A study in Bulawayo reported a prevalence of anticysticercal antibodies of 13% in patients with signs and symptoms compatible with NCC (Mason et al., 1992). A prevalence of 12% was reported in hospitalized epileptic patients in the capital of Togo (Grunitzky et al., 1995)

The antigen detection ELISA was higher among adults between 21 to 40 years than among children which is in concordance with previous findings that children are usually much less affected by cysticercosis than adults. Studies in the Peruvian jungle showed that the maximum seroprevalence ages were 46-55 (Diaz et al., 1992) and in Brazil, the highest prevalence ages were 20-40 years (Agapejev, 1996).

In Angonia, the prevalence of cysticercosis by ELISA-Ag was 11,8% in women and 21,4% in men. Males have twice the risk of being infected than women (OR= 2,02, 95% CI, 1,51-2,70). Other studies have given inconsistent results, with no difference (Sarti et el.,1994), a higher seroprevalence in women (Garcia-Noval et al.,1996; Cruz et al., 1999) and a higher proportion in men (Agapejev,1996). It is likely that cultural differences may impact on the behaviour

of men and women influencing the level of infection. This result suggests that it would be advisable to include knowledges, attitudes and practices regarding *T. solium* infection in education manuals for adults.

6.7. Brain CT Scan Exam

Modern imaging techniques such as CT, which have considerably improved the diagnosis of NCC in the clinical setting, have only rarely been used in epidemiological studies or in control interventions because of the expense involved and the limited availability of equipment in endemic countries (Diop et al., 2003). In our study, 151 patients underwent cerebral CT scanning. This is the largest African cysticercosis epidemiological study using imaging to date. It should be noted that the epidemiological application of such techniques has frequently detected asymptomatic cases of NCC in endemic populations (Nash et al., 2004) as was also seen in the Angonia study.

The cost of imaging studies for the diagnosis and follow-up treatment for patients with NCC has not been determined. Moreover, these facilities are restricted to specialized hospitals in large urban centres. Thus, many efforts have been made recently to develop sensitive and specific immunological assays to support the diagnosis and follow-up of the patients (Rosas et al., 1986; Tsang et al., 1989; Ramos-Kuri et al., 1992; Garcia et al., 1995, 2000; Verastegui et al., 2003).

Calcified brain cysticerci are found in over half the cases of symptomatic NCC (Medina et al., 1990; Palacio et al., 1997), and in almost all asymptomatic individuals examined by neuroimaging in endemic villages (Sarti et al., 1994, 1997; Gonzalez et al., 1994). Intracranial calcifications may represent the only evidence of the disease (Garcia and Del Brutto, 2003). This is similar to our study, where the most frequent type of lesion was calcifications (32,7%) in the group of patients with positive ELISA Ag and epilepsy.

Colloidal lesions were seen in 7,5% of patients, confirming the observations of many different authors that dying and/or degenerated cysticerci are common in epileptic patients with cysticercosis (Sotelo et al., 1985; Garcia-Noval et al., 1996; Nash et al., 2001).

In the group of patients with positive ELISA Ag and epilepsy, 17,8% presented with vesicular lesions on brain CT. Most of vesicular (living) cysticerci have in their interior an eccentric hyperdense nodule representing the scolex. The scolex is usually visualized within the cyst as a high intensity nodule giving the lesion a pathognomonic 'hole-with-dot' imaging.

The imaging studies helped to achieve a diagnosis of definitive or probable NCC when combined with serology, as by the adopted diagnostic criteria proposed in 2001 by Del Brutto et al.

6.8. EEG Exam

It is important to stress that, of the 77 individuals with epilepsy classified as having definitive or probable NCC, (73,4%) were affected by partial epilepsy with or without secondary generalization; only 26,6% were classified as having generalized seizures.

Thus partial seizures are much more frequent among patients with NCC in our study. The role of EEG recording was important in achieving a more precise classification because of a better distinction between the partial seizures and the generalized ones, especially when the partial onset is sudden and followed by a secondary generalization. It appears that partial seizures are very strongly associated with NCC in this population.

While the EEG alone clearly does not allow aetiological diagnosis, its joint use with clinical and biological results was a key element of the etiological and therapeutic discussion. When it shows focal abnormalities in a patient with epilepsy living in a high prevalence cysticercosis area, it confirms the clinical suspicion of NCC. Morphological imagery alone can provide etiological information on the seizures by showing the nature and localization of the parenchymal lesions.

Cysticercosis is an important cause of epilepsy in this area of Mozambique. This study confirms the previous observation by other authors, that NCC is one of the most important causes of epilepsy in developing countries (Bittencourt et al., 1996; Carpio et al., 1998).

6.9. NCC Treatment

Previous studies have shown that up to 80% of patients with epilepsy from developing countries have not been treated (Scott et al., 2001). This finding was also confirmed in our study

Treatment of NCC per se may be associated with serious side-effects and often requires hospitalisation. Affected people in resource-poor areas therefore generally have limited access to adequate case management. There is also no consensus whether all cases of NCC do indeed benefit from cestocidal treatment or whether treatment with anti-epileptic drugs alone can provide them the deserved sustained comfort and quality of life (Nash, 2003).

An analysis of drugs for NCC treatment concluded that there is insufficient evidence to assess whether cestocidal therapy can be associated with long term beneficial effects (Nash, 2003).

Evidence and consensus building is needed in this area. The provision of adequate care for those suffering from the disease at all health care levels is likely to generate the largest immediate relief of burden and social stigmatization, particularly for affected poor people.

First seizures due to inflamed cysticercal lesions should be considered acute symptomatic seizures. Therefore, they should be treated only for the duration of the acute condition. However, treatment may be continued during the period when the inflammatory response is active, which might last several months.

Actually no guidelines exist regarding the duration of antiepileptic drug treatment following an acute NCC episode with seizures. The risk of seizures is substantial as long as an active ongoing process, as characterized by persistence of edema around the degenerating lesion, is present. Because of this risk, CT scans are useful for treatment decisions.

Seizures in the context of edema and a degenerative lesion should be considered acute symptomatic seizures, even if they occur many months after presentation. After resolution of the acute lesion, antiepileptic drug administration may be discontinued.

Seizures occuring after resolution of edema or when calcification of the degenerating cyst is seen, should be considered unprovoked, and, in this situation, long-term antiepileptic drug administration is warranted. Other authors also suggest that antiepileptic drugs administration can be safely withdrawn once the follow-up CT scan shows resolution of the lesion.

Clinical controversy has centered on the role of cysticidal agents for the treatment of symptomatic NCC. Antiparasitic drugs in current use for NCC include praziquantel and albendazole (Davis, 2002; Goodman et al., 1999). Antiparasitic therapy may hasten radiologic resolution of cysts but can be

associated with exacerbation of neurologic symptoms; the possibility exists of massive cerebral edema and death in some individuals who have multiple cysts.

Some authors have advocated simultaneous administration of corticosteroids to reduce the inflammatory response and exacerbation of symptoms, but the safety of this treatment has not been evaluated fully. In developing countries, most neurologists administer the corticosteroids and antiparasitic drugs at the same time (Nash, 2003).

Patients with NCC are possibly more likely to remain seizure-free if antiparasitic treatment is administered; however, recent studies have shown that there is no correlation between treatment with cysticidal drugs and seizure recurrence (Nash, 2003).

A meta-analysis of randomized trials assessing the effect of cysticidal drugs (albendazole and praziquantel) on neuroimaging and clinical outcomes of patients with NCC has been reported. In the case when the parasite is already dead the treatment with cysticidal drugs is probably worthless and the effects of treatment on neuroimaging end points were relatively small (Carpio, 2009).

Garcia et al. concluded that antiparasitic therapy in patients with viable parenchymal cysts is safe and effective; however, 6 months after treatment, 38% of patients had cysts that disappeared on neuroimaging in comparison with 15% of patients who used placebo (Garcia et al., 1991).

Carpio et al (2008) reported disappearance of cysts in 35% of patients with viable cysts in comparison with 12% of the placebo group. In both studies, these differences were statistically significant ($p<0,05$).

Based on these two studies, antiparasitic treatment using albendazole is effective in terms of disappearance of viable parenchymal cysts in one third of

patients. Therefore, we treated the patients in Angonia with albendazole. Additional studies are necessary to investigate the impact of cysticidal treatment in the Angonia District.

Large scale field interventions using mass treatment against *T. solium* tapeworm infection were undertaken in China (Allan et al., 2002), in Ecuador (Cruz et al., 1989), in Mexico, Peru, Guatemala and Honduras (Sarti et al., 1988; Garcia-Noval et al., 1996; Garcia, 1999; Sanchez et al., 1996) all of which confirmed the focal distribution of *T. solium* carriers in the endemic rural areas, suggesting that the control interventions involving treatment of human tapeworm carriers can be targeted rather than population-oriented. The definition of a *T. solium* infection focus for intervention purposes has been defined as: (1) any location with a high prevalence of cysticercotic pigs; or (2) any farm supplying cysticercotic pigs; or (3) any patient with late onset epilepsy and his or her family members; or (4) any case of detected or probable taeniasis (Pawlowski et al., 2005).

6.10. Disease burden due to T. *solium*

Two major aspects should be considered in relation to the burden due to *T. solium* cysticercosis: (i) one, its localisation in the CNS which is estimated to cause an important disease burden, particularly in terms of late-onset epilepsy. It must be taken into consideration that the majority of cases of NCC occur in individuals of productive age who may become unfit to work because of symptoms; (ii) two, as the parasite also requires pigs as intermediate hosts to complete its life cycle, its consequences also have a potentially large impact in terms of food safety and subsequent economic consequences.

The global economic costs imposed by *T. solium* have only been partially evaluated in a few studies conducted in sub-Saharan Africa and parts of Asia. In Mexico, for example, it has been reported that USD 14.5 million was spent in hospital care of only 2.700 newly hospitalised NCC cases in 1986 (Flisser,

1988). Another available example is of Cameroon where it was estimated that the actual cost of treatment of one case of NCC is 261 Euro (Zoli et al., 2003).

6.11. Control strategy

There is evidence that a comprehensive prevention and control strategy combining treatment of *T. solium* carriers with improvements in hygiene, sanitation, pig husbandry and veterinary sanitary measures could be effective and could even potentially contribute to the elimination the disease (Schantz et al., 1993; WHO, 1998). It has further been demonstrated that elimination of the human reservoir of *T. solium* infection is a key factor in control and/or elimination efforts (WHO, 1983).

Community participation and social support with input on health and municipal authorities is necessary to achieve successful prevention and control. Community responsibilities can include identification of focus of transmission, promotion of self-diagnosis in infected individuals, improving pig rearing and improvements in sanitary conditions in the area. Community participation is frequently impaired by lack of information on appropriate means to identify and eliminate risky human behaviours and activities and therefore promotion of health education; in addition to official support, it requires committed and enthusiastic community leaders for effective implementation.

The disappearance of *T. solium* in most European countries is an important evidence of the potential for the elimination and ultimately eradication of *T. solium*. Elimination of this zoonosis in Europe was attributed to countries' economic development, meaning that environmental sanitation, pig husbandry and strict meat inspection become responsible for the prevention and control of taeniosis/cysticercosis (Schantz et al., 1993; Grove, 1990; OPS, 1994).
Outside the USA there are reports of increasing numbers of "outbreaks" of cysticercosis in Australia (Walter et al., 1991), Europe (Overbosch et al., 2002)

and Kuwait (Hira et al., 2004) which require international efforts to prevent the transmission to non-endemic countries (Schantz et al., 1998; Overbosch et al., 2002; Schantz and Tsang, 2003). In order to expedite this, an attempt was made to declare NCC an international reportable disease (Roman et al., 2000).

Health education campaigns are effective in the prevention and control of many infectious diseases like NCC with participation of the community and schools in maintaining hygienic and sanitary conditions, as emphasized in several studies (Udonsi and Ogan, 1993, Rousham, 1994, Nakamura and Siregar, 1996, Sarti, 1997). Changes in knowledge, attitudes and practices with regard to the disease, as well as reduction in human taeniosis rates and rates of exposure to cysticercosis in humans were additional outcomes of this intervention (Sarti, 1997).

Health education could be effective in changing people's behaviour but requires multidisciplinary input and active participation of the community leaders. However, health education should be followed up by infrastructural improvements such as the construction of latrines, pigpens and slaughterhouses to facilitate changes in the people's practices.

In children of school going age and teenagers health education has proven to be effective with permanent change in attitudes and behaviours but with less important effect in adults. The assimilation of knowledge in adults is smaller and usually with no change in acquired habits and attitudes. Adults also tend not to consider cysticercosis a public health problem (Perera et al., 1970; Keilbach et al., 1989; Sarti et al., 1997).

There are two key aspects to consider in the control of *T. solium*:

- The zoonotic human-pig-human cycle, generally important in rural and peri-rural areas where extensive pig production is performed; and

- Transmission between humans, very difficult to control, in urban and peri-urban areas, amongst populations who emigrated from endemic rural areas. This is possibly the situation of the majority of Mozambican communities.

The control of pigs would play the largest role in the analysis of the first aspect above, underlining issues related to meat inspection, a crucial component on the fight against cysticercosis and frequently an assessment parameter in the evaluation of *T. solium* in a region. This is a criterion that can have different readings as it depends not only on the prevalence of the disease but also in the diagnostic capacity of meat inspectors and the capacity of the organization around commercialising the pork meat.

The rate at which pigs are rejected in slaughterhouses reflects the situation of the sector from which the animals come from; traders and owners who see their animals being rejected in the slaughterhouses search for alternatives. This is frequently the case of trading, cheaper and accessible to the poorest, reinforcing the perpetuation of the parasite cycle.

It is fundamental to strengthen veterinary services to control cysticercosis alongside with the search for practical solutions and sustainable alternatives for infected meat. Cysticercosis will not be controlled without the provision of good meat inspection (CWGP, 1993). Inspection is only a quality assurance for consumers and has its own limitations. Control measures should be acceptable from producer perspective considering what the animal means economically.

Treatment of pigs with oxfendazole is a potentially effective control agent because once treated, pigs are refractory to re-infection even in the event of ongoing exposure to the source of *T. solium* eggs.

In relation to human to human transmission, several factors need to be considered. Wars, conflicts, natural disasters and the search for better living

conditions have caused extensive movements of people from rural to urban settings. *T. solium* carriers migrate from rural areas, generally establish themselves in the suburbs of towns without basic sanitation and contribute to the establishment of a new infection focus. High population density in slums and the selling of food from non-licenced small street shops with no hygienic control complete the framework and consequently enhance the propagation of cysticercosis in these urban agglomerations more effectively than in rural areas.
The great number of asymptomatic patients, the variety of clinical manifestations, the lack of specificity/sensitivity and high costs of diagnostic methods available, make data about the real prevalence of the cysticercosis/NCC difficult to obtain (Sotelo et al., 2000). Improved epidemiological data on *T. solium* is essential for its control.

The most important findings from epidemiological studies performed until now include: tapeworm carriers and human cysticercosis cases cluster around endemic foci becoming useful for planning control measures (Sarti et al., 1988, 1992; Cruz et al., 1989; Pawlowski, 1991; Rodriguez-Canul et al., 1999; Garcia et al., 1999; Gonzales et al., 2003); in endemic areas late onset epilepsy is a strong predictor of NCC (Garcia et al., 1995; Pawlowski et al., 2005); autoinfection plays a very important role resulting in high rates of NCC (Garcia et al., 2003b); and the value for detecting active NCC is limited (Garcia et al., 2003a, 2003b; Sarti et al., 1988, 1992).

Cysticercosis and NCC affect health and well-being of both livestock and humans and social consequences include stigmatisation, incapacitation and decreased work productivity.

In pig rearing farming communities cysticercosis and NCC can affect the society in four ways:
(1) Infection of humans affecting their health, social and family life (stigmatization) and productivity;

(2) Causing protein-energy malnutrition due to poor pork meat quality and condemnation of pig carcasses;

(3) Seriously reducing the farmer's household income, and

(4) Creating a barrier to marketing and trade of pigs and pork.

All of these effects are likely to be long term given the duration of untreated NCC cases. Thus the disease is a serious constraint for improving the livelihoods of smallholder farming communities. In addition, stigmatization may remain after patients have been treated and could also extend to the farm itself if the farmer becomes known for selling contaminated meat (Carabin et al., 2004).

CHAPTER SEVEN
CONCLUSIONS AND RECOMMENDATIONS

This study provided new data on the sero-prevalence of *T. solium* cysticercosis in the Angonia district.

It has been concluded that human NCC caused by *T. solium* remains an overlooked public health problem in the Angonia district. On the basis of the study results, it can also be concluded that *T. solium* cysticercosis is an important cause of epilepsy in this district.

This study found a very high prevalence of epilepsy and a high prevalence of cysticercosis among this population. The prevalence of NCC was high among population with epilepsy and cysticercosis.

Results clearly show all the conditions are present for a very efficient parasite transmission in the Angonia district.

Solutions for reducing the prevalence of disease in humans must include effective education campaigns aimed at clearly explaining how we can break the pork tapeworm cycle and additionally, improving sanitary practices at the household and personal levels.

Cysticercosis is a preventable and treatable disease and study results confirm that it could play an important role in the incidence of epilepsy in endemic areas of developing countries. The study also will increase awareness among physicians and public health agencies about *T. solium* cysticercosis. Efforts should be developed to start up appropriate control programs in these areas.

Prior to any action planning, the public health and the economic relevance of cysticercosis must be defined. Simple assessment tools have to be further developed and complemented by well-targeted serological investigations. Collection of data from hospital records and slaughterhouses is also essential. The risk of disease should be mapped and interventions prioritized accordingly.
At the present, no intervention programmes have been implemented at the national level. However, several strategies for control have been piloted at a smaller scale and have proven to be successful.

Probably the best practice in the treatment of NCC would be not to generalize but to approach and assess each case individually. However, physicians who are not familiar with the disease need, at least, a basic set of principles to follow. The selection of a treatment option must include consideration of risks and benefits in addition to the economic situation of the patient.

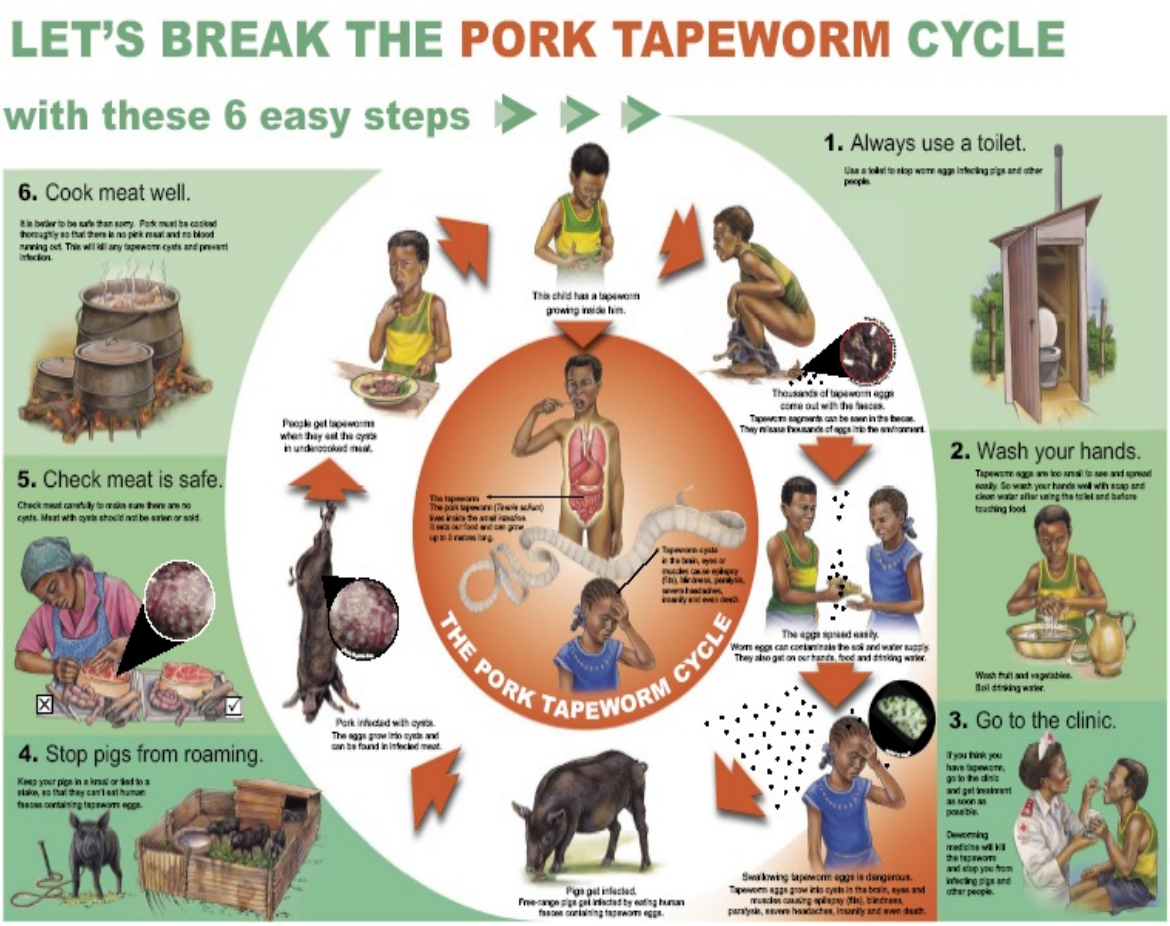
The current controversy on whether the use of antiparasitic agents is of benefit in a long-term control of epileptic seizures in NCC led to much confusion about whether such agents should be used in any form of the disease. This undesirable situation causes inappropriate use of antiparasitic drugs, i.e., in cases with already calcified parasites or in cysticercosis encephalitis. Even more dangerous, physicians may refrain from using antiparasitic treatment when it is the best treatment option.

The long-term intervention approach has undoubtedly best long-term perspectives; it is inherent to socio-economic development, establishment of adequate levels of infrastructure and general improvement of life. Focused interventions like health education and systematic treatment have a more limited impact, but are probably more immediately sustainable and can provide good short term results in term of burden relief.

One can also expect some reduction in *T. solium* prevalence within the framework of UN Millennium Declaration, endorsed by 189 countries in September 2000. *T. solium* infection fits directly or indirectly into six out of eight major goals expected to be achieved by 2015. Eradication of extreme poverty (goal 1) may for example reduce subsistence pig rearing by the rural poor. Achivement of universal primary school education (goal 2), should increase the knowledge about risky behaviours in relation to *T. solium* transmission. Promotion of gender equality and empowering women (goal 3), should decrease risk of *Taenia* infection at home by reducing consumption of food containing cysticerci and spreading *Taenia* eggs by inadequate personal hygiene (goal 4). Ensuring environmental sustainability (goal 5) includes improvement of sanitation, important for *Taenia* spread. The development of a global partnership for development (goal 6) mentions as a marker for its success an increase in the proportion of a population with access to affordable essential drugs on a sustainable basis (Pawlowski et al., 2005).

The control of NCC in humans depends not only on govermental decisions but also on the activities of individual researchers, clinicians and public health workers, who are close to the problem. Their active co-operation through exchanging information and expertise and the pressure they can exert on international organisations, national decision makers, various sponsors and, last but not least, leaders of the affected communities, will also be critical in determining how successful control of *T. solium* infection will be, but may naturally happen if the burden is evident and the proposed solutions reasonable in the local public health and socio-economic context.

Figure 28 – Steps to break the *T. solium* taeniosis-cysticercosis cycle



Source: CWGESA, 2006

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APPENDIX
Questionnaire

Human *Taenia Solium* Cysticercosis
in the district of Angónia, Mozambique:
Epidemiology and clinical aspects

Questionnaire

Part I: Interviewers Manual

1. Project presentation
2. The aim of this questionnaire is to gain information on the occurrence and knowledge of *Taenia solium* infections in humans. Similar data will be collected from the region and used to better prevent and control the disease in humans. The interviewee is free to withdraw from the interview at any time and to omit questions. The risks of participating in this survey are minimal, as all data will be kept confidential and all names will be replaced by codes. The benefits will be a direct feedback with recommendations on how to better prevent and control the disease.
3. Description on how to select the interviewee.
4. Description on how to handle non-responders.
5. Description on how to keep questionnaire forms when completed.
6. Description on translating procedure and ensuring of local terminology
7. Description on the procedure for conducting an interview:
    a. Permission
    b. How long the interview will take
    c. Read the aim, the rights, the risks, the benefits and confidentiality
    d. Write clearly on marked lines
    e. Circle the appropriate answer(s)
        a)
        b)
        c)
        d)
    f. Among other details to be provided by the PI.

ID Number (Coding)	

Questionnaire

Part II: Interview	
NOTE: Interviewer please fill in on the provided lines and circle all appropriate answers	
I. General Information	
1. Date of interview *(dd/mm/yyyy)*	
2. Country	
3. District	
4. Village	
5. Household number	
6. Name of interviewer	
II. Household Information	
7. Name of interviewee	
8. Age	
9. Sex	a. Male b. Female
10. What is the highest schooling grade you have completed?	a. None b. Primary school c. Middle school d. High school
11. What further education have you completed?	a. None b. College c. University d. Technical/vocational e. Other (please specify): _____
12. What is your main occupation?	
III. Information on Drinking Water and Sanitation	
13. From where do you usually get your drinking water?	a. River b. Well c. Bore-hole d. Tap e. Rain catchments f. Other (please specify): _____
14. Has your drinking water been boiled before you drink it?	a. Always b. Almost always c. Sometimes d. Rarely e. Never
15. Do you have a latrine at home?	a. Yes b. No (please skip to Q. 16)
16. How often do you use a latrine when you have to defecate?	a. Always b. Sometimes

	c. Never
IV. Information on Pork Consumption and Management	
17. Do you ever eat pork meat?	a. Yes b. No (please skip to Q. 19)
18. How often do you eat pork meat?	a. At least once a month b. Less than once a month but at least once a year c. Less than once a year
19. How is the pork that you eat prepared?	a. Boiled b. Fried c. Barbeque d. Other (please specify): _____
20. Do you or anyone in your household keep pigs?	a. Yes b. No
21. How often is your meat inspected by a meat inspector?	a. Always b. Almost always c. Sometimes d. Rarely e. Never f. Can not remember, do not know
V. Information on Human Cysticercosis \ Taeniosis	
22. How many days of work have you missed because of illness in the past month?	**_____ days**
23. Have you ever heard of tapeworm infection in humans?	a. Yes b. No (please skip to Q. 26)
24. How did you learn about it?	
25. How does one know that he/she has a tapeworm?	
26. How do people get tapeworm infection?	
27. Have you ever had skin nodules or hard lumps under your skin?	a. Yes, currently has b. Yes in the past year, but not currently c. Yes, one year or more ago, but not currently d. No e. Can not remember, do not know
28. Have you ever had repeated periods of time with bad headaches?	a. Yes, currently has b. Yes in the past year, but not currently c. Yes, one year or more ago, but not currently d. No e. Can not remember, do not know
29. Have you ever had sudden loss of	a. Yes, currently has

consciousness and episodes of incontinence or foaming of the mouth or tongue biting?	b. Yes in the past year, but not currently c. Yes, one year or more ago, but not currently d. No (please skip to Q. 31) e. Can not remember, do not know (please skip to Q. 31)
30. How often have you had these symptoms?	a. Only once b. More than once c. Can not remember, do not know
31. How old were you when this first happened?	**_____ years**
32. Have you ever had a brief period of absence(s) or loss(es) of contact with the surroundings that starts suddenly?	a. Yes, currently has b. Yes in the past year, but not currently c. Yes, one year or more ago, but not currently d. No (please skip to Q. 34) e. Can not remember, do not know (please skip to Q. 34)
32. How often have you had these symptoms?	a. Only once b. More than once c. Can not remember, do not know
33. How old were you when this first happened?	_____ years
34. Have you ever had uncontrollable twitching or jerking or abnormal movements of one or more limb(s) (convulsions) that starts suddenly and lasts for a period of a few minutes?	a. Yes, currently has b. Yes in the past year, but not currently c. Yes, one year or more ago, but not currently d. No (please skip to Q. 37) e. Can not remember, do not know (please skip to Q. 37)
35. How often has this happened?	a. Only once b. More than once c. Can not remember, do not know
36. How old were you when this first happened?	_____ years
37. Have you ever had sudden onset of a brief period of hearing or smelling or seeing things that are not there or feeling strange body sensations?	a. Yes, currently has b. Yes in the past year, but not currently c. Yes, one year or more ago, but not currently d. No (please skip to Q. 40) e. Can not remember, do not know (please skip to Q. 40)
38. How often has this happened?	c. Only once d. More than once c. Can not remember, do not know
39. How old were you when this first happened?	_____ years

40. Have you ever had seizures or fits?	a. Yes, currently has b. Yes in the past year, but not currently c. Yes, one year or more ago, but not currently d. No (please skip to Q. 43) e. Can not remember, do not know (please skip to Q. 43)
41. How often has this happened?	e. Only once f. More than once c. Can not remember, do not know
42. How old were you when this first happened?	_____ years
43. Were you ever told that you had epilepsy or that you had had an epileptic seizure?	a. Yes, currently has b. Yes in the past year, but not currently c. Yes, one year or more ago, but not currently d. No e. Can not remember, do not know
*NOTE: Interviewer: If the answer is **"no"** to all of the questions 45 through 60, the interview is finished. Please go to the last page and complete question A. and B based on observation. Remember to say:* **Thank you very much for your cooperation.** *[Otherwise, please continue with question 43]*	
44. Have you had head injury that made you lose consciousness?	a. Yes b. No (please skip to Q. 46)
45. When did your seizure symptoms start?	a. Before head injury b. Soon after head injury c. Can not remember, do not know
46. Have you had meningitis (brain infection) during childhood?	a. Yes b. No (please skip to Q. 48)
47. When did your seizure symptoms start?	a. Before an attack of meningitis b. Soon after an attack of meningitis c. Can not remember, do not know
48. Have you had cerebral malaria?	a. Yes b. No (please skip to Q. 51)
49. When did your seizure symptoms start?	a. Before an attack of cerebral malaria b. Soon after an attack of cerebral malaria c. Can not remember, do not know
50. What happens to you when you have a seizure or a fit?	
51. Have you ever hurt yourself when you lose consciousness or during a seizure?	a. Yes b. No (please skip to Q. 53) c. I do not lose consciousness or have seizures (please skip to Q. 53) d. Can not remember (please skip to Q. 53)
52. How did you hurt yourself?	a. Fell in the fire

	b. Fell in the water c. Fell off your bicycle d. Fell while walking along the road e. Cut yourself f. Other (specify) _____
53. Is there someone in your household with epilepsy or seizures?	a. No b. Yes, currently is c. Yes in the past year, but not currently d. Yes, one year or more ago, but not currently e. Can not remember, do not know
NOTE: Interviewer: Read the following statement: **"Now I want to ask you some questions about your treatments for seizure/epilepsy"**	
54. Have you ever been hospitalized because of seizure/epilepsy?	a. Yes b. No (please skip to Q. 61) c. Can not remember (please skip to Q. 61)
55. How many times have you been hospitalized in the past 5 years?	_____times
56. When you were last hospitalized?	_____(month)_____(year)
57. How many days did you stay in hospital?	_____ (days)
58. How much did it cost? (specify the currency)	
59. How far is the hospital from your house?	_____ km
60. How did you get to the hospital?	a. By foot b. By bicycle c. By bus d. By taxi e. By train f. Other (specify) _____
61. Have you ever consulted a health provider because of seizure/epilepsy?	a. Yes b. No (please skip to Q. 66) c. Can not remember (please skip to Q. 66)
62. When was the last time you consulted a health provider for seizure/epilepsy?	a. Within the past month b. Within the past year c. From one (1) to five (5) years ago d. More than five (5) years ago e. Can not remember, not sure
63. What kind of health provider(s) did you consult and how many times in the past 5 years?	a. A physician _____ times b. A neurologist _____ times c. A nurse _____ times

	d. A traditional healer _____ times e. Other (specify) _____ times f. Can not remember, not sure
64. How much did it cost last time you consulted with one health provider (specify the currency used)?	a. A physician _____ b. A neurologist _____ c. A nurse _____ d. A traditional healer _____ e. Other (specify) _____ f. Can not remember, not sure _____
65. How far is the health provider from your house and how did you get there (foot, bicycle, bus, train, taxi, car)?	a. Physician at _____ km reached by_____ b. Neurologist at _____ km reached by_____ c. Nurse at _____km reached by_____ d. Traditional healer at _____ km reached by_____ e. Other (specify) _____ at _____ km reached by_____ f. Can not remember
66. Were you ever tested with a diagnostic test because of this condition?	a. Yes b. No (please skip to Q. 70) c. Can not remember, do not know (please skip to Q. 70)
67. What kind of test was it (check as many boxes as appropriate)?	a. Blood test for cysticercosis b. CT scan of the brain c. X-Ray of the brain d. MRI of the brain e. Electroencephalogram f. Other (please specify) _____ g. Can not remember, not sure
68. When was the last time you were tested with a diagnostic test?	a. Within the past month b. Within the past year c. From one (1) to five (5) years ago d. More than five (5) years ago e. Can not remember, not sure
69. How much did the test(s) cost (specify the currency used)?	a. Blood test for cysticercosis _____ b. CT scan of the brain _____ c. X-Ray of the brain _____ d. MRI of the brain _____ e. Electroencephalogram _____ f. Other (specify) _____ g. Can not remember, not sure _____
70. Were you ever treated for seizure/epilepsy?	a. Yes

	b. No (the interview is finished) c. Can't remember, do not know (the interview is finished)
71. When was the last time you bought medication for seizure/epilepsy?	a. Within the past month b. Within the past year c. From one (1) to five (5) years ago d. More than five (5) years ago e. Can not remember, not sure
72. What medication was it and how many times in the past year did you have to buy some?	a. Phenobarbital _____ times b. Dilantin _____ times c. Valproic acid _____ times d. Traditional medicine _____ times e. Other (specify) _____ times f. Can not remember, not sure
73. How much did it cost <u>last</u> time you bought this medication (specify the currency used)?	a. Phenobarbital _____ b. Dilantin _____ c. Valproic acid _____ d. Traditional medicine _____ e. Other (specify) _____ f. Can not remember, not sure _____

THIS IS THE END OF THE INTERVIEW
THANK YOU VERY MUCH FOR YOUR COOPERATION

NOTE: Interviewer: The following 2 questions should be answered by you after direct observation of the household's latrine.

A. Which type of latrine does the household have?	a. Absent b. Present and completely enclosed c. Present and partially enclosed d. Present and open (easily accessible to roaming pigs)
B. Is there evidence of recent use of the latrine (by anyone)?	a. Yes b. No