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Risk factors and socio-economic burden of neurocysticercosis in Uganda

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Content:

Dedicated to my parents:

Joachim & Elisabeth Dupont

1 Abstract

Introduction: Over 50 million people suffer from epilepsy worldwide with more than 80% in resource poor countries. Neurocysticercosis (NCC) is the most common helminthic infection of the central nervous system, causing approximately 30% of epilepsy cases in endemic areas. Northern Uganda is endemic for *Taenia solium*, whose larvae cause NCC and secondary epilepsy. In addition, *T. solium puts* financial strains on affected communities. The present study evaluates the prevalence of NCC, risk factors for contracting NCC in northern Uganda and both the DALY (disability-adjusted life years) and economic burden of NCC for the whole country.

Method: This study combines data from field surveys, clinical diagnoses, CT - and serology results from a total of 38,303 individuals (2009-2012). We calculated prevalence estimates and risk factors attributed to NCC status using univariable and multivariable logistic regression models as well as other statistical analyses. Our DALY and economic calculations are based on internally validated data by applying the WHO-DisMod II model on a model population, based on sociodemographic data from Uganda. Both epilepsy and headache were included as NCC symptoms to estimate economic and DALY burden.

Results: 1245 people with epilepsy (PWE) among 38,303 people screened were identified. 300 PWE based on most recent seizure onset were further examined by using CT scan and serology testing. 40 NCC patients were subsequently identified. An epilepsy prevalence estimate of 3.3% [CI: 3.1-3.4] and a NCC prevalence estimate of 13.3% [CI: 10-18] (within the PWE population) was calculated for northern Uganda. We further found that the NCC infection risk increases by 4% (OR 1.04 [CI: 1.02-1.06]) with every year of age. Farming was associated with a higher risk of contracting NCC: aOR=3.22 [CI: 1.33-8.23]. Pork consumption was not found to be statistically significant: OR 1.46 [CI: 0.69-3.38]. There was evidence that education plays a protective role: OR: 0.18 [CI: 0.07-0.43]. Especially late seizure onset ($p<0.001$), seizure motor activity (tonic/clonic/myoclonic) ($p=0.014$), a history of bad headaches ($p=0.049$) and pre-existing conditions such as cerebral malaria ($p=0.035$) and meningitis ($p=0.020$) were identified to be statistically different between NCC and non-NCC PWE. Our DisMod II model identified 9,000 new NCC-epilepsy cases per year and 2,000 new NCC-headache cases per year based on the Ugandan population modelled for 2010. The DALY burden for all incident cases, based on the country specific life expectancy, was 182,614 [CI: 142,547-228,459] DALYs in 2010. The DALY rate per lifetime incident case was: 17 [CI: 14-20]. The DALY burden per 1,000 person years was: 5.5 [CI: 4.3-6.9]. The economic burden was found to be USD 75,470,055 [CI: 56,386,713-108,895,694] for all incident cases. On an individual level this equals to USD 8,068 [CI: 6,825-11,323] per lifetime case.

Conclusion: This study is one of the largest epidemiologic studies on NCC in Africa. The results may help identify a "typical NCC patient" and increase pre-test probability. Some of the clinical predictors may establish a clinical prediction rule that can be used for pre-screening in resource poor countries. Our DALY and economic burden assessment makes the burden comparable and its progress measurable. It will put potential public health investments into perspective, and facilitate policy design for local and international decision makers.

2 Keywords:

Neurocysticercosis (NCC), *Taenia solium*, tapeworm, epilepsy, headache, parasitic zoonoses, risk factor analysis, economic cost evaluation, , disability-adjusted life year (DALY), cost-of-illness, one-health, Uganda, cost-of-illness

3 Abbreviations/Glossary

AB: antibody

AED: anti-epileptic drug

AG: antigen

aOR: adjusted odds ratio (multivariable analysis)

CC: cysticercosis

CC-AB: cysticercosis- antibodies

CC-AG: cysticercosis-antigen

cCt: cranial computed tomography

CDC: Centers of Disease Control and Prevention, Atlanta, USA.

CI: confidence interval

CNS: central nervous system

CWGESA: Cysticercosis Working Group in Eastern and Southern Africa

DALY: disability-adjusted life years

DHC: direct healthcare costs

DNHC: direct non-healthcare costs

DW: disability weight

EITB: enzyme-linked immuno electro-transfer blot

Gbd: generalized seizures with diffuse brain damage

GBD: global burden disease (-study)

Gfs: generalized seizures with focal signs

Goa: generalized seizures outside a specific age range

Gwa: generalized seizures within a specific age range

HRQoL: health related quality of life

ICP: intracranial pressure

ILAE: International League Against Epilepsy

INHC: indirect non-healthcare costs

LLGP: lentin-lectin glycoprotein

LRA: Lord's Resistance Army

Mo: month old

N.a.: not available

NCC: neurocysticercosis

NTD: neglected tropical diseases

OR: odds ratio

PSA: prostate specific antigen

PWE: people with epilepsy

QALY: quality adjusted life years

rES: recombinant excretory secretory (protein group that is targeted by antibodies)

RR: relative risk

T. solium: Taenia solium

T-AB: taeniasis antibody

TTH: tension type headache

UI: uncertainty interval

UN: United Nations

USD: United States dollar

W/: With

W/o: Without

WHO: World Health Organization

YLD: year lived with disability

YLL: year of life lost due to premature mortality

Yo: year old

4 Introduction

Neurocysticercosis (NCC) is the most common helminthic infection of the central nervous system in resource poor countries (Coyle et al. 2009). It is also the most likely cause of acquired epilepsy in resource poor countries. The Word Health Organization (WHO) estimates 50 million cases of epilepsy, 80% of which live in resource poor countries (WHO 2016d). In endemic areas 30% of all epilepsy cases are considered to be caused by NCC ((WHO 2016d). The distribution of NCC is especially high in countries with free roaming pigs (WHO 2016d). *Taenia solium* is endemic in South America, Sub-Saharan Africa, and South- and South-East Asia. It causes two distinctive diseases: cysticercosis and taeniasis. In Figures: 11.1 Figure 1, a detailed map with the world's distribution can be seen. NCC is responsible for a large variety of symptoms and creates a high burden for the affected population. After the ingestion of *T. solium* eggs, the larvae develops and travels mainly to muscle and brain tissue, where it turns into a dormant state, called cyst. The life cycle of *T. solium* is dependent on pigs and humans and distinguishes between main and intermediate host. For a detailed description please refer to Tables: 12.1 Table 1. In order to understand NCC and its consequences, it is crucial to understand the reproductive cycle of *T. solium*. In Figures: 11.1 Figure 2, humans are portrayed as carriers of the intestinal tapeworm. Eggs are stored in gravid proglottids that are separated from the main body and excreted. Especially human feces, or pig food contaminated with human feces, represent a possible source of infection for pigs. When pigs ingest *T. solium* eggs, they develop into oncospheres, hatch and migrate to muscle tissue, where they encapsulate and form cysts.

Taeniasis can be due to *T. solium* (pork tapeworm) and *Taenia saginata*. From a human healthcare perspective, *T. saginata* is the less significant form (beef tapeworm), which can be contracted by eating under- cooked beef (see: Figures: 11.1 Figure 3). Other than *T. solium*, *T. saginata* does not affect human health significantly, as it does not enter brain tissue. Even if the intestinal tapeworm of either species may cause some minor symptoms, the main burden of *T. solium* lies with the larval stage of the disease. When trying to measure the human burden of *T. solium*, the main interest lies on the neurological signs and symptoms of NCC. As our study only focusses on the human burden, we did not consider the consequences of porcine cysticercosis. It plays a larger role in animal health and value, which is essential for smallholder pig farming. Family run farms play a major economic role in securing basic income and food supply (food security) for the majority of the population in rural Africa.

In 2010, the WHO added cysticercosis to the list of neglected tropical diseases (NTD) and estimated a burden of 2.8 million healthy life years lost (Disability-Adjusted Life Years, DALYs. See: Material and Methods: 6.7.1 Disease burden (DALY) due to NCC (WHO 2016d). *T. solium* affects mainly rural and underdeveloped regions in Africa, Latin America and Asia. It affects human health, lowers the value of livestock and threatens the livelihood of the community. Many development programmes support family/small scale farming to encourage self-sufficiency and to combat famine (United-Nations 2013).

As with many other tropical diseases, NCC and its impact on a country and its economy is directly linked to poverty and economic standing (Pal et al. 2000). Western countries experience hardly any *T. solium* related infections and consequences due to high living standards and hygiene levels. Poor countries still suffer from the consequential burden of NCC on human lives (both in terms of morbidity and mortality), quality of life and its impact on community livelihood, as well as the country's economy. This thesis focusses on the impact of NCC in PWE (people with epilepsy) in nine categories:

1. Prevalence of epilepsy in a NCC endemic area of northern Uganda
2. Prevalence of NCC in a population of PWE
3. Detailed characterization of PWE in northern Uganda
4. Headache characterization in a population of PWE due to NCC
5. Risk factors of NCC within a population of PWE
6. Behaviour pattern of a standardized NCC patient (decision tree analysis)
7. NCC incidence modelling (DisMod II standardized model population)
8. Economic impact of NCC in Uganda: direct and indirect human costs
9. Disability adjusted life years (DALYs) due to NCC (epilepsy and headache based).

4.1 Country and geopolitical situation

Uganda is a country in East Africa. It is one of the countries belonging to the great lakes region. As this region is geographically very comparable to the other countries of the great lakes region, due to its rich soil and vast water supplies, it shows many economic developments similar to other countries of this region. A detailed map and research area specific information can be found in Figures: 11.2 Figure 4. In 2013, agriculture and small scale family farming are the main source of income for 72% of the population in Uganda. However, its contribution to the GDP (gross domestic product) is much smaller (25.5% in 2014) (The-World-Bank 2013, 2014, UBOS 2015). Small scale farming is a major pillar of maintaining income security and it is a

main point of action for the Ugandan government to combat under-development and the lack of financial self-sustainability of families in rural Uganda. To quote the Ugandan agriculture report from 2010: "*The war-affected population of Northern Uganda* [is to] *engage in productive and profitable agricultural and agribusiness activities to ensure food security and increase household income"* (Ministry of Agriculture 2010*).* This has led to more sustainable and reliable family income, however it has endangered food safety and increased the likelihood of transmitting food- and animal borne diseases. From the year 2000 to 2001 the number of intestinal worms have increased by 59% (cases 2000-2001: 778,463-1,235,399) (Food-and-Agriculture-Organization:-United-Nations 2004). Some of the key components are contaminated food and water, as well as the lack of hygiene. They have been implicated in the high prevalence of NCC in such areas. In addition, freely roaming pigs that feed on human feces further contribute to the prevalence of NCC. In some areas, NCC is responsible for 30% of the overall number of epilepsy patients (WHO 2016d). Conflicts, poverty and poor food safety promote a rise in food borne diseases in the affected area. Direct vigilance has shown to be an effective mean to combat poor food safety (United-Nations:Relief-and-Works-Agency 2015). Current studies are executed to investigate the impact of preventive measures on the prevalence of epilepsy. A good example is the American field intervention, run by Helène Carabin in Burkina Faso, who tried to assess the impact of direct interventions in pig farming on the prevalence of epilepsy (Carabin 2010a). Eastern and Southern Africa has been the scene of ongoing research on epilepsy and NCC, trying to identify risk factors and to understand the local ways of transmission. Some papers for other countries found that the actual consumption of pig meat may not be the main risk factor: People who do not consume any pork do not have a lesser chance to be affected by a *T. solium* infection. Interestingly, *T. solium* also has a tradition in local traditional medicine, either to heal or to deliberately poison the "patient" (Mafojane et al. 2003).

Our work focusses on assessing the impact on humans. In order to assess the aforementioned studies, it is essential to understand and name the precise risk factors and burden created on an economic -as well as on disability-adjusted life year (DALY) level. This understanding on a national level is crucial in order to evaluate possible success of any type of intervention that aims to combat NCC prevalence.

4.2 Historical background and civil war in Uganda

Uganda has undergone tremendous social and economic changes during the last century. After its independence from the British Empire in 1962, Uganda experienced a period of political, economic and social instability. During this period, there have always been conflicts between the northern part of the country and the southern regions closer to the capital. This period was mainly influenced and triggered by the dictatorship of Idi Amin and the National Resistance Army (NRA) based in northern Uganda. The leader (Museveni) of the NRA became head of state (president) after seizing power in 1986. His major struggle during his presidency was the fight against the Lord's Resistance Army (LRA) (Chowdhury et al.), under Joseph Kony, head of the LRA. The north of the country remained stricken by civil war until late into Museveni's second term of office. Due to an amnesty-offer to all members of the LRA, their activity in northern Uganda was reduced during the end of the last decade. Since 2006, the LRA activities have mainly shifted to the Democratic Republic of Congo (DRC) (United States of America 2015). International organizations like the International Foundation of Agriculture and Development (IFAD), a specialized organization of the United Nations, as well as initiatives by the Ugandan government have tried for decades to promote small scale farming in order to increase food production, self-sustainability and economic prosperity in rural areas (Ministry of Agriculture 2010, Ifad 2012, United-Nations 2013). Due to the living conditions brought to the north of Uganda by decades of civil war and unsettlement, NCC has increasingly become a problem in northern Uganda. An international study from 2009 showed that there was a high prevalence of cysticercosis in pigs in southeast Uganda (Waiswa et al. 2009). They asked for further studies into NCC prevalence and studies of risk factors and impact.

4.2.1 Burden assessment based on 2010

The time frame for our study begins only a few years after the last attacks of the LRA in Uganda in 2006. Many improvements were established through the aid of international help in the aftermath. Some healthcare and social services in the region are therefore artificially high in comparison to other regions in Africa. A similar phenomenon was seen in Rwanda after the genocide in 1994. Rwanda is now a country leading the East African Association in many fields. The impact of international help on prevalence and infection rates is very hard to predict. However, new local riots and civil disturbances have occurred in 2016, which may also influence the further development in Uganda. Even though we are looking at a 10 year interval in our DALY and economic analyses, it is hard to predict the actual precise value, leaving our calculations always as the rough estimates they were made out to be.

4.3 Risk factors and their value in combating neurocysticercosis

Risk factors are defined by the WHO (WHO 2017) as follows:

"A risk factor is any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury. Some examples of the more important risk factors are underweight, unsafe sex, high blood pressure, tobacco and alcohol consumption, and unsafe water, sanitation and hygiene."

With regard to NCC, it is important to understand to what extend certain factors play a role in the transmission of a disease. Risk factor analysis enable us to identify where certain potential interventions disturb the overall survival of *T. solium*. The WHO states that it is on its way and already has "*taken the first steps towards identifying the "best-fit" strategy to interrupt transmission of T. solium and improve case detection and management of neurocysticercosis using the tools currently available (WHO 2016d)*. As the WHO focuses mainly on China, Brazil and Madagascar for its pilot programmes, further data is needed for every country affected by NCC (WHO 2015a, 2016d). Figures: 11.3 Figure 5 illustrates this further.

4.4 Disease specific cost and economic burden assessment

It is important to properly define the impact of a disease to make informed choices. Impact is a difficult parameter in medicine, as it possesses contradictory ethical viewpoints. When accepting the assumption that resources are limited, a certain selection of what public health intervention is the most promising is needed. Bearing this in mind, economic strategists have a straight forward way of defining success. A net gain for every dollar spent is called success, whereas a net loss is called failure. Transferring the same line of thought to public health: a medical case creates both direct and indirect costs. Direct costs include the money the patient spends on doctors, transport, medicine et cetera. Indirect costs mean money that one loses by not working, or by being less effective in the patient`s usual occupation. This includes being made redundant et cetera. When looking at a disease like NCC, there are not only human direct and indirect costs involved. Animal health becomes also affected. In principal, this relates to a market value loss for its owner, and/or potential medical treatment or preventive measures that need to be paid for. Pigs are considered productive livestock. In practise, it means that the market value (value of a pig) will not surmount the potential health costs (money spent on preventing/curing diseases), in order to stay economical. In frank words that means, a farmer will only spend as much money on a sick animal as it will still attain in market value after

successful treatment. As there is no treatment available for cysticercosis that could re-establish the pig's pre-disease market value, the medical (direct) costs for animals are often negligible: Therefore: no veterinarian costs are not included in this study.

In the second part of this thesis we evaluate the human direct and indirect costs of NCC by focussing on epilepsy and headache, the two main signs and symptoms present in an active NCC case. Any intervention with the aim to decrease NCC prevalence, will essentially also be measured by the financial benefit created by this method.

The major criticism of this monetary measuring unit is that people or populations with a smaller per capita income or unemployed people count less in terms of prospective gain created by an intervention. This means that an intervention method may be more beneficial if wealthier people have a higher benefit, whereas a large number of poor people may have a smaller economic impact on productivity or overall missed income. A non-monetary unit is therefore needed for a less biased analysis. We chose DALY's.

4.5 Disability-adjusted life year assessment

DALY stands for Disability Adjusted Life Years. DALYs are the sum of years lived with disability (YLD) and years of life lost due to premature mortality (YLL). Please refer to Figure 9 and 10 in Chapter 11 for illustration. Based on statistical information this method is applied to a population as a whole. The WHO estimated that NCC caused up to 2.8 million DALYs in 2015 (WHO 2016d). DALY measures disease specific healthy life years lost based on mortality and morbidity. It was developed as a means to measure burden in a non-financial way by Harvard University for the World Bank. It was subsequently adopted by the WHO as an official metric in different health related reports(Murray 1994). The WHO defines DALYs as follows (WHO 2016c): "*One DALY can be thought of as one lost year of "healthy" life. The sum of these DALYs across the population, or the burden of disease, can be thought of as a measurement of the gap between current health status and an ideal health situation where the entire population lives to an advanced age, free of disease and disability*."

YLD is based on specific health states with a specific value attributed to each symptom. This value is called disability weight (DW). It describes the percentage of quality of life lost due to the given cause. One represents one healthy life year fully lost due to death, whereas 0 corresponds to no loss of quality of life, or full health. The impact of a DW over a lifetime is therefore dependent on the overall life expectancy of a population and the average length of

disease as well as the disease specific mortality and incidence. See Figure 9 in Chapter 11 for further details.

DALY assessments also have some drawbacks that need to be considered before putting too much value into its interpretation. In terms of interventions, DALY does not distinguish between life saved and quality of life improved. It also does not distinguish between large gains in quality of life for few people in comparison to a slight improvement for many. Also, as old people are more likely to die regardless of the specific disease, an improvement in their quality of life is valued less than an equal improvement for a younger person. This is because the younger person may profit for more years from a possible improvement. This phenomenon is taken into account by trying to assess the duration of the disease impact. In chronic diseases such as NCC, this is an effect that needs to be kept in mind when assessing the final DALY burden. Even if DALY does not weigh income or financial loss, readers should bear in mind that domestic gross product and life expectancy correlate (Acemoglu et al. 2007). When presuming a causative link between those variables, it means that a certain intervention measure with a certain effect on a certain number of people in one country can have a different DALY based on the life expectancy specific to that country and therefore related to the economic standing of that country. DALYs do not consider the impact of zoonoses on farming or on animals, but only evaluate human health burden, excluding all economic impact. The One Health approach tries to view zoonotic diseases from both the animal and human health perspective. This new research field proposes more profound intervention options, as it recognizes the influence of the porcine infection rate on the consequential human NCC burden.

It is therefore important that DALY burden is combined with financial impact calculations, as both factors provide complimentary information. A profound understanding of what DALY and economic burden studies represent is needed, in order to avoid confusion or wrong deductions. This is important when planning interventions in any type of healthcare setting. It needs to be one major step of intervention preparation. It also helps to set healthcare spending into perspective when comparing it with potential economic loss prevented. Even though the long term goal of international organizations may be a world-wide universal health coverage, limited resources force governments to prioritize cost-effective intervention and prevention techniques. When accepting the fact that only limited resources are available, resource allocation needs a foundation, both financially but also humanistic, where the amount of suffering is put into perspective. Both economic burden and DALY values play an important yet distinctive role.

When talking about quality of life, different units and tools are available. When trying to understand burden assessments, it helps to distinguish between DALY and QALY (quality adjusted life years). QALY are used to identify the outcome of interventions and procedures. It puts a value to a certain number of years gained through a therapy or intervention. It was developed as an alternative assessment of health. It supports the argumentation that not any type of life extension is worth wile. Other than DALY, QALY considers 1 as perfect health and 0 as death (also see Figures: 11.5 Figure 10).

DALY calculations can either be based on prevalence alone or on incidence and duration. Both calculations represent specifically different traits when analysing the consequential results. In this study, DALY was calculated from an incidence perspective. Standardized WHO formulas were applied, without age-weighting or time discounting. Prevalence DALY calculations estimate the current health loss and do not consider past events that may have changed the current public health situation affecting one specific disease. Even though NCC is an infectious disease, this plays an important role when looking at time intervals. A patient may have had contact to *T. solium* years before he starts developing symptoms. He may also still have symptoms even though current infections rates are much lower. In case of NCC, it makes more sense to consider incidence rates multiplied with the length of symptoms. Incidence does not mean time of infection, but rather start of symptoms. In DALY, the process of infection is irrelevant, as long as no corresponding symptoms are present. We calculated DALY out of the product of symptom incidence and average duration of symptoms. By doing so, we portray the future health loss, caused by NCC, without only relying on current health loss due to NCC (prevalence).

Parallel to DALY calculations and economic burden assessment, we applied our findings to the population of Uganda as a whole. With a population modelling software (DISMOD model, see Material and Methods: 6.11.1 Population modelling for socioeconomic burden study) we were able to model the impact of a disease over time for one specific population. DISMOD was used to create an internally consistent set of epidemiological estimates.

4.6 Prior research efforts on *T. solium* (neuro)cysticercosis

4.6.1 *T. solium* (neuro)cysticercosis: Prevalence and risk factors

Even though NCC is mostly associated with epilepsy, it is important to remember that this only represents NCC patients that are symptomatic. Up to 53% were found to be asymptomatic in a post-mortem study (De Almeida et al. 2011). As this increases the actual prevalence for NCC

tremendously, it shows that there is a large underreporting when talking about total number of NCC patients. This number may not affect burden studies, as asymptomatic patients do not contribute to either DALY or economic burden, however, it shows that there is a large group of people that may present with symptoms at any time during their life. Why and when NCC PWE start presenting with symptoms is poorly understood until now.

Prior studies assessed prevalence estimates of NCC in Africa. An imaging study from Tanzania, found an NCC prevalence in PWE of 13.7% (Winkler et al. 2009b). In Burkina Faso, in a small study with only 33 patients a NCC prevalence of 47% (Millogo et al. 2012) was found. Another more recent study from Tanzania with 176 patients demonstrated a NCC prevalence of only 1.1% (Hunter et al. 2015). In Zambia, a study with 51 patients established a NCC prevalence of 57.1% (Mwape et al. 2015). These results show large variation between countries and study years, which may be due to the variation in sample sizes and methods applied. For a detailed overview refer to Tables: 12.2 Table 2.

Winkler et al. published a review of NCC in 2015, where the number of asymptomatic patients is discussed (Winkler et al. 2015): "WHO landscape analysis: management of NCC with an emphasis on low-and-middle-income countries."

Due to the civil war, there has not yet been any detailed analysis of risk factors in northern Uganda. From Uganda as a whole, some papers have been published to assess the animal impact and prevalence for *T. solium* cysticercosis. Five works that focus on animal health and infection rate are listed below. (Phiri et al. 2003, Waiswa et al. 2009, Nsadha et al. 2014, Zirintunda et al. 2015, Kungu et al. 2016)

In 2012, Winkler published an article on NCC in Sub-Saharan Africa in a special edition of "Pathogens and Global Health": "Neurocysticercosis in sub-Saharan Africa: a review of prevalence, clinical characteristics, diagnosis, and management" (Winkler 2012)

In this article the author discusses the special situation of NCC in Africa. She states that in comparison to South America, where NCC is much better explored, very little data and information is available for Sub-Saharan Africa. Winkler roughly estimates in her paper that 631 million people live in *T. solium* NCC endemic areas in Sub-Saharan Africa and are therefore potentially at risk. She emphasizes the need for more detailed data on possible risk factors and intervention plans to combat NCC in Sub-Saharan Africa.

New insights regarding elimination come from South America. “Elimination of taenia solium transmission in northern Peru“ (Garcia et al. 2016). This paper is based on an intervention study from South America which was also supported by the Bill and Melinda Gates foundation. In this study, the authors compared different intervention techniques in northern Peru. They presume that *T. solium* NCC is a priori eradicable. Based on possible intervention methods they examined the impact of each method. As procedure and intervention methods they chose: 1) screening of humans and pigs; 2) antiparasitic treatment of humans and pigs; 3) prevention education in affected areas; 4) pig replacement of diseased animals. Garcia et al. found that one method on its own only accomplishes limited success. However, when combining different interventions, they were able to decrease the number of live cysts in pigs to zero. One year after the intervention live cysts were found again however. This shows that one-off interventions may have very limited benefit for the local population. Any intervention programmes will therefore need to try to target different points of the life-cycle of *T. solium*. Also, similar studies are needed for interventions in Sub-Saharan Africa. Even though studies from different continents are indicative for Africa, local operational challenges may be very different in different cultures and regions.

4.6.2 *T. solium* (neuro)cysticercosis: DALY and related costs

DALY and economic burden assessments are new research fields in neglected tropical diseases. Some studies have assessed NCC or cysticercosis and DALY/economic burden in recent years.

Carabin et al. published a burden assessment for cysticercosis and echinococcosis (Carabin et al. 2005). Unfortunately this paper does not name DALY for NCC. It mainly focuses on financial burden for NCC. The author states that 1 patient in Mexico costs: US$ 2,173. She also states that in the United States direct medical and indirect costs through loss of income amount to US$8,750,490 for 1,100 patients (direct medical costs: US$ 6,539 per case & loss in income of US$1,416 per case). Unfortunately she uses different scales and time intervals for all these values making direct international comparisons difficult. No DALY was given for NCC. However, she values the implementation of both DALY and economic burden assessment and calls for further healthcare interventions.

Praet et al. published a burden assessment of *T. solium* for Cameroon in 2009 (Praet et al. 2009). This study includes both human and pig economic burden. They show, that only 5% of total financial burden are based on animal health, even though porcine cysticercosis prevalence is higher than human prevalence. The author also calculates the DALY due to NCC: 9.0 per

thousand person years. However, his NCC prevalence is based on percentages within the epilepsy community only. Also, his DALY analysis only includes epilepsy as only symptom caused by NCC.

The Global Burden of Disease (GBD) study is based on meta-analyses identifying DALY for the most common diseases including NTD. One study was published in 2010 and a second review in 2012 (Lim et al. 2012). In the GBD study, it was clearly remarked that current health concerns differ greatly between low and high income countries.

In 2014, Hotez et al. (Hotez et al. 2014) commented on the GBD study. The authors state that the DALY estimate for NTDs was 26.1 million DALYs in 2010. However they point out that there is a large range of results due to different epidemiologic methods. One main reason is that research data availability and in-field work appear to be much more difficult in Africa than in high income countries. Also, DALY calculations are often based on specific symptoms, leaving out other potentially equally important symptoms. This makes an exact burden assessment very difficult, especially in poor resource conditions. Criticism on the application of DALYs in NTD had already been voiced prior to his statements in 2006 (Engels et al. 2006). Based on this publication DALYs are often described to possibly underestimate the actual burden, as the fight against NTDs appears to be still very complex.

One study from 2012, (Bhattarai et al. 2012) evaluates the non-monetary burden of NCC in Mexico. In this study, headache is used in addition to epilepsy in order to portray NCC burden. However, no sub-categories are applied to either headache or epilepsy. The authors state a DALY of 0.25 per 1000 person years. No comparable study with both epilepsy and headache as DALY criteria is available from Africa to date. Estimates from the study in Cameroon (Praet et al. 2009) evaluate burden based only on epilepsy as 9.0 per 1000 person years. In Tanzania, a study from 2016 (Trevisan et al. 2016) found 0.7 per 1000 person years for NCC-associated epilepsy.

The economic impact of *T. solium* for other regions worldwide is shown in a study published in the Lancet (Conteh et al. 2010). All values were converted to 2008 USD equivalent: "*The societal monetary cost of Taenia solium cysticercosis was estimated at $152 7million (95% CI $51·6-299·0 million) in India,$28 3 million ($7·1-42·9 million) in Honduras, and $16 6 million ($8·3-22·8 million) in the Eastern Cape Province."* The aim of the current thesis is to give a broader perspective of the NCC burden. Both headache and epilepsy are considered together to estimate a more realistic DALY burden. Also, we used mostly data from Uganda. Only for

epilepsy and NCC specific mortality, comparable countries from Africa were used. Ultimately, our research will help to put those economic and DALY values into perspective and suggest ways how to best represent NCC burden in the future.

5 Objective of this thesis

The current thesis has three major objectives:

1) Calculation of the prevalence of epilepsy and NCC in northern Uganda.

2) Estimation of risk factors associated with NCC in northern Uganda.

3) Calculation of socioeconomic burden (DALY and monetary burden) for both epilepsy and headache. We achieved this by designing a model population and applying behavioural patterns and internally validated population specific data to our model population.

In addition, we defined two overarching aims, making use of the results obtained from objectives one and two. Sociodemographic and clinical data will be used in order to design a "typical NCC patient". This provides criteria that may help make the diagnosis of NCC in resource poor countries. We will also use the identified risk factors in order to suggest intervention points in the life cycle of *T. solium*, which may help facilitate the eradication of the parasite.

6 Materials and Methods

6.1 Overview of work steps done by doctoral candidate

This thesis consists of several parts, as described in the Introduction (4) and Objective of this thesis (5). The chapter Material and Methods will therefore be sub-divided into several sub-chapters in order to illustrate the detailed work steps that were implemented. The summary below shows the work performed by the author and impact on the work distribution and publications, as proposed by Technische Universität München: medical graduate school (TUM MGS) statute. All work processes were supervised by Prof. Dr. Dr. Winkler, Neuro-Kopf Zentrum, Klinikum rechts der Isar, Technische Universität München. Formal head of the project was Prof. Dr. Hemmer, head of Neuro-Kopf Zentrum, Klinikum rechts der Isar, Technische Universität München.

1) **Summer semester 2014:** Preparation of field work. Literature research. Implementation of TUM MGS guidelines. This included setting up the TUM MGS doctorate (Dr.med.) contract, time frames and supervision agreements, securing funding and introducing the doctorate candidate into the work field and the respective teams.
2) **Winter semester 2014/2015:** Data acquisition and coding. For this purpose: three months field work in Uganda.
3) **Summer semester 2015:** Data cleaning, application of diagnostic criteria, basic correlation analyses and establishment of a central data base containing:
    a. Basic patient data
    b. Diagnostic information: Final diagnosis based on (Gabriel et al. 2012).
        i. Neurological examination
        ii. Serological data
        iii. Computer tomography results
        iv. Data from an in-depth patient questionnaire
        v. Information from the CWGESA questionnaire (Cysticercosis Working Group in Eastern and Southern Africa) (Mukaratirwa 2010)
        vi. Data from headache questionnaire written by Hélène Carabin for Burkina Faso and kindly given to our study group for the purpose of this study (Carabin 2010b)

4) **Winter semester 2015/2016**: Risk factor analysis; in cooperation with Brecht Devleesschauwer PhD, University of Florida.
    a. Establishment of basic risk factor analyses as well as multivariable analyses of NCC
    b. Prevalence calculations of epilepsy/NCC/headache
5) **Summer semester 2016**: Institute de la Santé Publique: Brussels, Belgium:
   health and economic burden assessment NCC in Uganda
    a. DisMod II population model
    b. Decision trees modelling basic patients behaviour based on analyses from CWGESA questionnaire, headache questionnaire and in-depth patient protocol
    c. Mapping prevalence design
    d. Economic impact calculations
    e. DALY calculation for NCC patients suffering from epilepsy and headache
    f. Composing thesis
    g. Accomplishing all compulsory steps required by TUM MGS prior to initiating submitting process
    h. Finalization of thesis before August 1rst 2016. Submission to Prof. Dr. Dr. Winkler
6) **Winter semester 2016/2017**: Review of thesis by Prof Dr. Dr. Winkler and Brecht Devleesschauwer PhD
7) **Summer semester 2017:** Review of thesis by Prof. Dr. Dr. Winker
8) **Winter semester 2017/2018**:
    a. Review of thesis by Prof. Dr. Dr. Winker
    b. Review of thesis by Prof Dr. Hemmer
9) **Summer semester 2018**
    a. Based on TUM MGS statute: submitting thesis in 2018

6.2 Study population and data acquisition

Uganda had a population of 31.8 million in 2010 during the beginning of our study (UBOS 2010, United-Nations 2015). This number was used as the basis for our prospective population model. In 2014, the population had grown to 34.9 million people (UBOS 2015, United-Nations 2015), demonstrating continuous growth, as to be expected in a resource poor country. For our analysis model we used the United Nations population data set provided for Uganda. DALY and economic evaluations refer to the time period of 2005-2015.

Prior to the author's participation in the study, all raw examination and questionnaire data were collected in the districts of northern Uganda: Moyo, Gulu and Adjumani in 2010 and 2011. The data collection period was managed and executed by Dr. J Kaducu Moriku and her team. The work was supervised by Prof. E Ovuga and Prof Dr. Dr. Winkler. All sub-counties and parishes were included in the study. Random cluster sampling was used to select villages and households. On a household level, every household member was interviewed. This method ensured an equally attributed number of examined patients in each district. Affected families where included as a whole by cluster sampling. The work was executed by surveying on a door-to-door approach. In total 38,303 people were screened with a screening epilepsy questionnaire. The screening test focuses on characteristics of epileptic seizures and basic differentiation to e.g. febrile seizures. Epilepsy was diagnosed by a team of international neurologists, applying the official ILAE (International League against Epilepsy) 2005 definition of epilepsy, together with the locally adapted diagnostic criteria for epileptic seizures, as EEG and neuroimaging techniques are widely unavailable in rural Africa (Winkler et al. 2007). In total 1245 PWE were diagnosed with epilepsy. The in-depth epilepsy questionnaire was completed by all 1245 patients identified with epilepsy. PWE were fully examined by a neurologist. The questionnaire included the seizure history and other relevant present and past medical history of the patient.

A second questionnaire on headache (screening and in-depth) was used to assess concomitant symptoms besides epilepsy. The screening and in-depth headache questionnaire was provided by Hélène Carabin (Carabin 2010b) (Carabin et al. 2015). All 1245 PWE answered the screening questionnaire for headache. Those patients complaining of severe and/or progressive headache also completed the in-depth section. A third questionnaire: Cysticercosis Working Group in Eastern and Southern Africa (CWGESA) was used to assess the socioeconomic- and past medical history. The focus was on assessing the life and socioeconomic impact on the infection probability. CWGESA questionnaire was taken from Mukaratirwa (Mukaratirwa 2010). The CWGESA questionnaire has already been used in several other studies on risk factors and prevalence for NCC in Africa (Mwanjali et al. 2013, Carabin et al. 2015). The CWGESA and the headache questionnaire was completed by the 300 PWE selected for the study. For all questionnaires and sources see Appendix: 13.1-13.5.

The 300 PWE that were chosen based on seizure recency received additionally:

- Cranial computed tomography (CT) with contrast (see: Material and Methods: 6.5.2. Computed tomography)
- Serology testing for *T. solium* taeniasis and cysticercosis (see: Material and Methods: 6.5.1. Serology)

As well as an ophthalmological exam to scan for retinal cysts. This additional step was based on recommendations from several prior publications (Del Brutto et al. 2001, Del Brutto 2012, Gabriel et al. 2012).
CT was performed in Kampala: (Kampala Imaging Center, P.O.Box 28305, Kampala Wampewo Ave, Kampala, Uganda, subcontracted by the Makarere University of Kampala, Mulago Hospital). Blood was drawn and stored locally by J. Kaducu. Samples were transported to the CDC and Zambia. Blood serology was performed and analysed by Veronika Schmidt (a serology specialist at Technische Universität München, Neuro-Kopf-Zentrum). For details on the analysis, please refer to Material and Methods: 6.5.1 Serology.

Due to financial constraints we were only able to fully diagnose 300 patients. Our selection was further limited by the local ethics committee, which only allowed the inclusion of patients twelve years and older. Only patients that could comply with the study regulations and that signed a written consent were included.

6.3 Diagnostic criteria for epilepsy and its role in neurocysticercosis

According to current knowledge, symptomatic NCC mainly presents with epileptic seizures. This is why epilepsy was chosen as one of the mandatory inclusion criteria (Carabin et al. 2011). "*Clinical manifestations associated with neurocysticercosis: a systematic review"* 78.8% of all NCC patients present with epilepsy, making it a better inclusion parameter than e.g. headache (37.9%) or focal deficits (16.0%). Epilepsy is defined through the International League Against Epilepsy (ILAE) (Fisher et al. 2005, Fisher et al. 2014) as follows: *"[a] disorder of the brain characterized by an enduring predisposition to generate epileptic seizures*". In its official statement Fisher et al. define three possible ways that lead to the diagnosis of epilepsy (Fisher et al. 2005):

1) epilepsy is defined as two or more seizures with more than 24 hrs apart
2) one seizure (unprovoked) and a >60% chance of further seizures over the next 10 years
3) the diagnosis of any epilepsy syndrome, explaining the present seizures

In resource poor settings, 2) and 3) are almost irrelevant for the diagnosis of epilepsy. In our study, we resorted to the definition given under 1), excluding epileptic seizures due to withdrawal from alcohol and drugs. Winkler et al. further divide epilepsy in resource poor settings in the following four categories (Winkler et al. 2007):

- Generalized seizures within a specific age range (gwa): Gwa refer to seizure onset mainly between 6 and 25 years of age without apparent sign of brain damage, but possible family history. This group can also be called "idiopathic generalized seizures".
- Generalized seizures outside a specific age range (goa): Goa refer to an onset of seizures outside the age range of gwa and also without any signs of apparent brain damage or focal start of the seizures. They are also called "cryptogenic generalized seizures".
- Generalized seizures with diffuse brain damage (gbd): Gbd refer to a group of patients where diffuse brain damage such as encephalopathy is present, most likely causing the generalized seizures.
- Generalized seizures with focal signs (gfs): Gfs refer to secondary generalized seizures with either a focal or unilateral beginning. Mild/progressive encephalopathy may be present but no major brain damage.

The first two of those categories can be summarized under the nowadays less commonly used term "primary generalized seizures", where consciousness is lost from seizure initiation. Also, no apparent cause for the seizure can be identified. The last two categories can be summarized under the nowadays less commonly used term "secondary generalized seizures", where focal neurological signs or symptoms are apparent.

6.4 Diagnostic criteria for headache

One of the main distinguishing factors of this study is the examination of both epilepsy and headache as symptoms of NCC. Headache DALY and epilepsy DALY estimates were both included in the overall NCC DALY calculations. Other African studies have thus far only included epilepsy in DALY and economic evaluations (Trevisan et al. 2016).

Headache with NCC is normally described as chronic progressive headache interfering with daily activities reminiscent of tension type headache (TTH); (Winkler 2012). However, migraine-like headaches have also been described with NCC. In order to diagnose TTH or migraine we used the International Headache Classification (IHS 2013). Migraine headache can

be sub divided into two different groups: 1) Migraine with aura (ICD 10: G 43.1) and 2) Migraine without aura (ICD 10: G 43.0).

Migraine with aura manifests with a focal neurologic manifestation that gradually develops over 5-20 minutes and remains present for less than 60 minutes. A headache equivalent to the headache without aura subsequently follows the neurologic manifestation. Two similar attacks define migraine with aura, as long as no other disorder attributed to the headache is known.

Migraine without aura manifests for 4-72 hours mostly unilateral, pulsating headache aggravated by physical activity. It is often associated with nausea, photophobia and phonophobia. Five headache attacks are needed for the diagnosis.

Tension type headache (TTH) (ICD 10: G44.2) is a dull, band-like, generally bilateral, non-pulsatile headache with mild to moderate intensity. It is the most common form of headache, with about 30-78% lifetime prevalence within the general population

In our burden assessment, the distinction between migraine and TTH becomes important, as both types of headache are associated with different DALY burden values: Migraine has a value of 0,433, whereas TTH only has 0,040. For further understanding of DALY values please refer to Material and Methods: 6.7.1 Disease burden (DALY). Headache information was taken out of the CWGESA questionnaire. Question 48 asked for bad headaches in the patient's past medical history. An additional screening questionnaire was completed asking for sever and/or progressive headache. Patients reporting this type of headache, continued with an in-depth questionnaire to describe their headache further. In this study, migraine with aura was identified by question 10 (aura) of the headache in-depth questionnaire.

6.5 Relevant tests and diagnostic criteria for neurocysticercosis

6.5.1 Serology

10 mL phlebotomy blood samples were obtained by employees of the Department of Microbiology at Mulago Hospital, Entebbe, Uganda. Serum was obtained and samples were deep frozen at -80 °Celsius until subsequent shipment. They were transported on dry ice via Entebbe to the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, United States of America. Laboratory procedures followed the same flow as described in (Schmidt et al. 2016). Laboratory testing was performed by Mag. Veronika Schmidt (Centre for Global Health, Department of Neurology, Klinikum Rechts der Isar, Technische Universität München) at the CDC. The analysis is based on Del Brutto et al. and Gabriel et al. publications (Del Brutto

et al. 2001, Gabriel et al. 2012). More recent criteria from Del Brutto et al. (2017), include both CC AB and CC AG as diagnostic criteria. This new publication was not used in this publication.

The serology AB test is based on an EITB (enzyme-linked immunoelectrotransfer blot) assay for LLGP (lentin-lectin glycoprotein) and the rT24H-EITB. The EITB subclassifies different proteins within the serum and is superior in detecting cysticercosis (CC) to the more commonly known ELISA (enzyme-linked immunosorbent assay) (Diaz et al. 1992). Additionally, an AB test was used as serology detection for cysticercosis (B158/B60-ELISA). This test is explained separately below. The LLGP and the rT24H-EITB was set to detect specific ABs for cysticercosis. The LLGP-EITB is based on 7 crude sub-AGs obtained from the *T. solium* cysticerci: Glyco Protein (GP)13, GP 14, GP 18, GP 21, GP 24, GP 39, GP 42-39 (Rodriguez et al. 2012). The numbers refer to the specific weight in kilo Dalton of the GP. The rT24H-EITB is based on recombinant CC specific AG to detect CC specific ABs (Noh et al. 2014). For the detection of taeniasis ABs, another immunoblot with a specific recombinant protein (rES33) was used (Levine et al. 2007). The rES33 recombinant protein was derived from the excretory and secretory proteins of the adult tapeworm. It indicated current or past intestinal infestation with the adult tapeworm. Both recombinant ABs were combined in one immunoblot strip. An additional test was used to detect cysticercosis specific AG: B158/B60-ELISA. This test uses monoclonal ABs (Anti-B158/B60). This test is a commercial test version produced and marketed by Advanced Practical Diagnostics, Turnhout, Belgium. This serology test was performed and analysed based on a modified protocol published by Dorny et al. (Dorny et al. 2004). By using not one serology technique, but several serology tests, we tried to represent the current diagnostic situation and make sure we diagnose most NCC cases within our study collective to the current best of our knowledge available in 2012 and accessible in rural Uganda. All 300 selected PWE received the full serology panel explained above.

Tables: 12.12 Table 12 shows all positive serology results (NCC+). It gives details on what specific serology results were found for each NCC+ patient. The serology results are portrayed in CC-AB and CC-AG columns. A categorizing system to structure and stage individual serology was used. A grading system was developed for the results: 0= all serological tests negative; 1= taeniasis-Ab test positive; 2:= only CC-AG test positive; 3=CC-AB and/or CC-AG test positive. All sub categories consist of several tests:

CC-AB: The LLGP-EITB and/or the rT24H-EITB are both included in the CC-AB column.

CC-AG: It displays the B158/B60-ELISA results.

T-AB (taeniasis-antibody): This is based on the rES33-EITB test used to identify taeniasis ABs.

Those ABs are present after a *T. solium* infection with the adult worm (current or past infection). (Levine et al. 2007). The rES33-EITB is however not positive in patients only suffering from NCC without any adult *T. solium* tapeworm contact in the past. T-AB status was therefore not used in the NCC diagnostic algorithm described in Material and Methods: 6.6 Diagnostic algorithm of neurocysticercosis.

6.5.2 Computed tomography

Neuroimaging was assessed by Dr. V. Richter at the Department of Neuroradiology at Technische Universität München. In Munich, the allocation to different Del Brutto radiology-diagnostic groups was established by Fabian Dupont based on the publication: (Del Brutto et al. 2001, Del Brutto 2012). Del Brutto defines three different neuroimaging categories:

1. Absolute criterion for NCC diagnosis: lesion where scolex is visible (see Figures: 11.4 Figure 6).
2. Major criterion for NCC diagnosis: highly suggestive lesions. For example cyst without scolex, round nodules, typical parenchymal calcifications, (see Figures: 11.4 Figure 7)
3. Minor criterion for NCC diagnosis: compatible lesions. For example enhancement of leptomeninges or hydrocephalus, (see Figures: 11.4 Figure 8)

The neuroimaging results represent one important pillar for the final diagnosis of NCC. For more information on the full diagnostic criteria of NCC, please refer to the paragraph below.

6.6 Diagnostic algorithm of neurocysticercosis

In our study we based our diagnosis on the Del Brutto criteria and its additions made by Gabriel et al. (Del Brutto et al. 2001, Del Brutto 2012, Gabriel et al. 2012). Based on serological, radiological, clinical and epidemiological criteria, a diagnosis of NCC (definitive, probable, no NCC) was established by Fabian Dupont in Munich.

According to the aforementioned criteria; a patient can attain different strengths of diagnoses ranging from definitive over probable to unlikely. Those categories have different prerequisites that need to be fulfilled in order to attribute a patient to a certain category. NCC can be diagnosed through a combination of different parameters. Depending on their predictive value they are classed as:

-Absolute

- Histologic proof (biopsy or autopsy); (not done in this study)
- Scolex seen on neuroimaging (see Figures: 11.4 Figure 6)
- Subretinal parasite visible though ophthalmoscopy

-Major

- Highly suggestive lesions on neuroimaging (see Figures: 11.4 Figure 7)
- AB or AG (Gabriel et al. 2012) linked to NCC
- Treatment success proven in neuroimaging after albendazole or praziquantel treatment (not done in this study)
- Single enhancing lesion with spontaneous resolution (not relevant in this study)

-Minor

- Compatible lesions on neuroimaging (see Figures: 11.4 Figure 8)
- Suggestive clinical manifestations of NCC (e.g. epilepsy (Carabin et al. 2011))
- Cerebral spinal fluid (CSF): serology (not done in this study)
- Signs of cysticercosis other than central nervous system. (not done in this study)

-Epidemiological

- Individuals from endemic areas
- Travel history to endemic areas
- Evidence of infection of *T. solium* within household

6.6.1 Definitive neurocysticercosis

In order to reach a definitive diagnosis there are two options out of which one needs to be fulfilled:

1. Any one **absolute criterion** will immediately link to a definitive NCC diagnosis.
2. At least **two major criteria**, and at least **one minor** and **one epidemiological** criteria.

6.6.2 Probable neurocysticercosis

In order to reach a probable diagnosis there are three different options:

1. **One major** and at least **two minor** criteria
2. **One major**, at least **one minor** and **one epidemiological** criteria

3. **Three minor** and **one epidemiological** criteria

Referring to Del Brutto et al., any form of proof of viable cysts or scolices (CT, retinal cyst, histology or pathology) is considered an absolute criterion and is seen as a definitive NCC diagnosis. In our study, we only included radiologic proof to be considered as definitive diagnosis, as no post-mortem material was available during the study and brain biopsies were ethically not justifiable. Full body exams for nodules was performed by neurologists in all 1245 PWE. During our ophthalmologic exam no viable sub-retinal cysts were found. No control CT was done after potential NCC treatment, due to lack of funding. No CSF serology was performed. As our study was set in northern Uganda, an endemic area for *T. solium*, the entire study population was considered as epidemiologically at risk, fulfilling the last (epidemiological) category of Del Brutto et al. per se.

6.7 Data sources and definitions for disease and socioeconomic burden calculations

Based on our patient data from the epilepsy examinations, the CWGESA questionnaire and the headache questionnaire, we established behavioural patterns for patients within the local healthcare system based on questionnaire data. The questionnaire was completed with the help of a locally trained healthcare assistant:

- What healthcare provider was contacted?
- How many visits per provider were needed=
- How many days of hospitalization were needed?
- What treatment was received?
- What further type of treatment, besides pharmacotherapy?
- How many days of treatment were completed?
- How was the patient's compliance?
- Was there any treatment success in terms of seizure frequency?
- How many days of work force loss?

6.7.1 Disease burden (DALY)

For epilepsy-DALY calculations, categorical disability rates were used, distinguishing between controlled epilepsy with less than 1 seizure per month and severe epilepsy with 1 or more seizures per month. For epilepsy, continuous treatment after first healthcare provider contact was assumed. For adherence, questionnaire data on compliance was used. DALY calculations,

the individual lifetime affected by epilepsy is relevant for the amount of disease burden per individual. Based on prevalence and life expectancy, individual DALY values may very between sexes. For epilepsy due to NCC; distribution by age- and sex, please refer to Tables: 12.13 Table 13.

For headache-DALY calculations, two headache types were identified, based on patient description. Migraine and tension type headache was attributed to different DALY. Both epilepsy and headache categorization is based on (Salomon et al. 2015). Treatment was considered to be only symptomatic during periods of headache and non-continuous. Only one type of medication was assumed accessible as standard headache treatment: paracetamol (Para-Acetylaminophenol) was used on a tablet based cost estimation (see also: Material and Methods: 6.9 Cost-of-illness). Based on prevalence and life expectancy, individual DALY values may vary between sexes. For headache due to NCC age distributions by sex, please refer to Tables: 12.14 Table 14.

6.7.2 Disease burden (economic impact)

Local financial cost data is based on a survey among local professionals and foreign professionals with local knowledge within the healthcare system in northern Uganda. We contacted local and national healthcare and social experts in Uganda in 2015 and 2016. Only four answered the questionnaire fully.

We used unified standardized arithmetic averages based on minimum and maximum values taken from the provided information in our set questionnaire. For detailed information on questions, please refer to Tables: 12.22 Table 22 and Appendix: 13.6 Economic calculations in northern Uganda: Expert opinion.

6.7.3 Data review

The following data review and search optimization was done and executed by Chiara Trevisan. Peer- reviewed literature was searched systematically. Grey literature (government agencies, NGO, university libraries) was used to complete epidemiologically necessary data for our calculations. Where no information was obtained, expert opinion was collected with a questionnaire and a unified standardized arithmetic average was drawn to increase reliability.

Search parameters were: Uganda AND ("tapeworm” OR "taeni" " OR "neurocysticercosis” "cysticerc" OR "epilepsy" OR "seizure" OR "migraine" OR "headache" OR "neurological disorders") AND ("case fatality" OR "mortality"). Four phases of data search were applied: 1)

Identification; 2) Screening; 3) Eligibility; 4) Inclusion. First, the following list of journals and databases were identified and included (see Tables: 12.3 Table 3): Inclusion was finished on 1rst of April 2016. We also searched online publications in national libraries or journals. Burden-, meta-analyses and comparable studies from neighbouring countries were reviewed. Eligible publications were read and the quality of the published data was assessed by Chiara Trevisan. It was discussed with F. Dupont and B. Devleesschauwer. All eligible data was screened for exclusion criteria. It needed to be: 1) Parasite specific; 2) Country specific; 3) Aim specific. Only original data was selected. Relevant data was collected on an Excel spreadsheet. Where possible, study population reference values such as age and sex distribution were included. The following parameters were extracted:

- (NCC-)epilepsy mortality rate
- (NCC-)epilepsy case fatality ratio
- (NCC-)headache mortality rate
- (NCC-)headache case fatality ratio
- Age-specific (NCC-)epilepsy prevalence

The following list of publications were identified to fulfil all aforementioned criteria.

(Matuja et al. 1995, Kaiser et al. 1996, Kaiser et al. 1998, Barendregt et al. 2003, Kaiser et al. 2007, Katabarwa et al. 2008, Katwere et al. 2009, Winkler et al. 2010, Dent et al. 2011, Kaiser et al. 2011, Dewhurst et al. 2013, Kaddumukasa et al. 2013, Ngugi et al. 2013, Kamuyu et al. 2014, Bigelow et al. 2015, Kariuki et al. 2015).

6.8 Decision trees

In order to model the burden of a population, a behaviour pattern of a standardized NCC patient needs to be established. It contains the behaviour possibilities available within the Ugandan population as well as the probabilities and consequences of certain healthcare related decisions. It also contains relevant financial and cost related information. It is a valid method to structure infection frequencies within a population and diseases specific behavioural algorithms. It serves as the foundation for our large scale economic impact assessment. It also plays a role in the DALY calculations, as treatment success reduces the effective burden of a disease. Access to healthcare will therefore influence the burden but also the financial strain of a disease within a population. The final decision tree including all relevant results can be seen under Results: 7.3.1 Decision tree: Model behaviour options for neurocysticercosis patients.

Prevalence was obtained through the analysis of CT-, serology-, clinical- and questionnaire results. Junction points (nodes) were established based on data available through CWGESA questionnaire. Percentages on healthcare provider choice, means of travel, distance travelled and hospitalization rate are also based on results from CWGESA questionnaire. Prices for transport, treatment and hospitalization are based on expert opinion questionnaires.

Cost estimates are based on local expert opinions. All monetary values are in Ugandan Shillings (UGX) only. It is assumed that for hospitalization, a second relative is needed to be present for basic healthcare purposes. This justifies additional direct non-medical costs for transport, food, accommodation etc.

In many African countries, a special professional group exists: Clinical officers. They usually have 2-3 years of non-tertiary academic training. In many healthcare institutions they are considered as equivalent to medical doctors (MD. Based on our data, no neurologist was consulted from any of the studied epilepsy patients. This might be due to several reasons. Neurologists are not very broadly distributed over rural Uganda. Also, a neurologist appointment is the most expensive diagnostic option available to epilepsy patients. Neurologists are therefore not very likely to be chosen as healthcare provider. Also, it is important to understand that epilepsy is still considered a stigmatized disease in Uganda. It is also often considered as a psychiatric disease.

6.9 Cost-of-illness

Cost-of-illness is the term used to describe the financial burden created by a disease. It contains direct healthcare costs (DHC) and direct non-healthcare costs (DNHC), as well as indirect non-non-healthcare costs (INHC) caused by a disease over time. Tables: 12.4 Table 4 shows an overview with examples of costs that need to be taken into consideration to get a good estimation of the costs created through one specific disease. Cost-of-illness was calculated from an incidence perspective without any time discounting. Time discounting (or temporal discounting) refers to the phenomenon that humans tend to value future events less than current burden/financial strains. USD (2015) was used as calculation currency. (3.300 Ugandan Shilling/USD). Tables: 12.16-18 Table 16, Table 17 and Table 18 list the cost of illness related to NCC. Direct costs include spendings that are triggered directly through a disease or its consequences. DHC include everything that is paid for diagnostics, treatment, prevention, rehabilitation etc. DNHC mainly relate to transport to and from medical appointments. Also, in most African countries, patients' families provide many basic healthcare work, as this is not

provided by the hospital during hospitalization. This replaces costs that are normally covered by direct medical costs in western countries (hospital costs), for example through additional healthcare assistants who help with personal hygiene or feeding. In our Ugandan model this is included under indirect non-healthcare costs (INHC), as the relative has a certain loss of productivity during the period of hospitalization. However, no active salary for relatives taking over healthcare responsibilities (normally under DHC) is included in our model.

INHC are losses attributed to the disease, such as loss in salary, because of hospitalization or for being less effective. In Uganda, it also includes the loss of work force of the accompanying relative, who is not able to work during his time at the hospital, in order to care for his sick relative. Redundancies or lost job opportunities through the disease are also considered to be indirect causes. An overall average in working loss, based on average income figures from Uganda were included in indirect costs. Potentially missed job opportunities and work efficiency decreases are hard to evaluate and were not specifically included. This may have led to a possible under-reporting of economic impact. In order to visualize all incurred costs diagnostic and treatment algorithms have been established. Epilepsy and headache algorithms need to be explained separately.

Tables: 12.14-15 Table 15-18 use (fitted) parameters of the corresponding distributions. Fitted distributions try to better represent a distribution of questionnaire replies within the preexisting width of possible answers. A Beta distribution models a continuous value between 0 and 1. The parameters can be interpreted in terms of data: alpha is number of positives of a hypothetical trial, beta is the number of negatives. Thus alpha / (alpha + beta) is the average of the distribution. The larger (alpha + beta), the larger the hypothetical sample size (valid replies), and thus the larger the precision for the given value. The Dirichlet distribution extends the Beta distribution, in that it allows more than two categories (for Beta: “positive” and “negative”). The interpretation is similar, eg, alpha_i / sum(alpha) is the mean proportion of category i, and the larger sum(alpha), the larger the precision.

Epilepsy: Based on CWGESA data, current compliance rate was calculated. The drug treatment distribution can be seen in Tables: 12.8 Table 8. The anti-epileptic drugs (AED) used were in 63% phenytoin, in 24% phenobarbitone and in 13% carbamazepine. For epilepsy burden assessment, relevant data from questionnaires was used to establish the average time of no treatment between seizure onset and start of treatment. Average seizure reduction rate was calculated out of total number of seizures for each patient. Through treatment a reduction in

DALY was included. It was assumed that under lifelong treatment, no further seizure frequency increase happens, but that no full convalescence was assumed either. Average yearly non-compliance rates based on questionnaire data was respected. Costs for medication was calculated based on AED adherence and NCC prevalence, drug type distribution between start of treatment and death based on average mortality.

Headache: We were able to attribute 33% of the headache symptoms to NCC within the NCC+ population. This number is based on headache incidence in NCC patients compared to PWE control group. Headache treatment option in Uganda are limited. It was assumed that only paracetamol, herbal remedies were used and traditional healers were consulted. It was further assumed that in 80% of headache cases paracetamol, in 50% of cases herbal/local remedies was used and in 10% a traditional healer was consulted. It was assumed that no western healthcare provider was consulted due to headache. Costs for paracetamol, traditional healer and herbal remedies were identified through expert opinion. No preventive headache treatment was included. Based on questionnaire analysis, the average headache frequency under PWE patients was 8.9 times per month. Expert opinion provided headache treatment cost per month for each category, which, combined with headache prevalence, established the average costs of treatment for headache.

Average income and employment rate, overall mortality and age distribution was taken from the United Nation data base, Indexmundi and from the Uganda Bureau of statistics (Uganda-Bureau-of-Statistics 2004, UBOS 2010, UBOS 2015, United-Nations 2015, Barrientos 2016, Uganda-Bureau-of-Statistics 2016). INHC were calculated using the human capital approach. The 2010 gross national income, provided by the World Bank, was applied: 550 USD per capita (The-World-Bank 2010).

Tables: 12.16-18 Tables 16-18 present all major input parameters for calculating cost-of-illness. Travel information and frequencies were derived from CWGESA questionnaire analysis. Unit costs come from expert opinion. Three expert opinions were accepted, giving a minimum to maximum range of each price item. Prices for hospitalization, local transport and all other form of local treatment options were acquired through expert opinion questionnaires. It was taken into consideration that healthcare staff was counted to DNHC instead of DHC in Uganda.

All results were averaged and weighted to represent the average economic situation in Uganda. As the population consists mainly of less affluent people, it cannot be assumed that the arithmetic mean of healthcare prices represents the actual health costs, as opportunities to

receive average to high end healthcare is based on financial prosperity. By weighting the monetary average price for each item, we adjusted the price level to represent the realistic affordability for a standard patient. This step represents the financial decision making process of the population better and it avoids unrealistic over-estimation. For NCC-headache, only treatment costs were included as DHC.

6.10 Disability-adjusted life years

YLL (years of life lost, see Introduction: 4.5 Disability-adjusted life year assessment) are based on standardized life expectancy tables as defined by the official DALY guidelines (Murray 1994, Devleesschauwer et al. 2014b).

Disability weights (DW) are used to assess the burden for every individual patient has to face per year when suffering from a specific condition (Devleesschauwer et al. 2014b, Vos et al. 2015). In DALY calculations we focused on the two main symptoms caused by NCC: Headache and epilepsy. With this said, it is important to define those symptoms further within our patient population. Headache can be sub-divided into migraine and tension type headache (TTH). Migraine has a DW of 0.441 whereas TTH only has 0.037 in terms of DW.

For DALY calculations, it is important to distinguish between two different types of seizure frequencies. The DALY calculation for epilepsy is based on the classification:

- One or more seizures/month= severe epilepsy: DW of 0.552
- Less than 1 seizure/month= controlled epilepsy: DW of 0.263

Epilepsy causing less than one seizure per month is considered treated or under control. Severe epilepsy is defined as one or more seizures per month. Severe epilepsy has a DW of 0.552, which is more than two times higher than the treated/controlled form (Vos et al. 2015, Wagner et al. 2015a). Attribution to different severity groups as well as transition between different epilepsy groups after treatment initiation was done based on our in- depth and CWGESA survey data. For more details on all used DW, please refer to Tables: 12.15 Table 15.

6.11 Statistical analyses

We calculated the prevalence of epilepsy, taeniasis and NCC, as well as its corresponding 95% exact confidence intervals (95%-CI). In order to evaluate the association between epidemiological criteria (results from the CWGESA-; In-depth-, and headache- questionnaire) and our final NCC diagnosis, based on the aforementioned criteria, we used univariable logistic

regressions. Regression analysis was also used for Odds ratios (OR). OR give a likelihood of association between two variables. An association is considered established, if OR is greater than 1. They are used to give the infection risk attributed to a certain exposure. The Fisher Exact test was used for categorical values for variables with less than 5 entries per field. For more variables per field and categorical values, the Chi-Square test was applied. The Mann- Whitney-U test was used for non-normally distributed metric, continuous values and the T- test was used for normally distributed metric values. Distribution was approximated by visual evaluation of graphical demonstration and the application of the Kolmogorov-Test. Most items in the attached, final tables have NCC yes/no as binary variable, thus logistic regression was the standard form of analysis Selected qualitative analyses with few options (yes/no) or small sample sizes were done through Firth's penalized-likelihood logistic regression and profile likelihood in order to increase reliability. The number of replies (n) received per questionnaire item is indicated in each line in all tables. Statistical calculations were executed using SPSS V. 23.0.0.0 provided by Neurokopfzentrum Munich for 2015-2017 and R-version 3.2.0 (R-Core team, 2015, including add-on packages). Data management was performed in Microsoft Excel. Microsoft Word and Power Point Version Office 365 for students was used for text and graphics management. All three Microsoft Office applications run under licence: 15.0.4823.1004, licensed through the student account licence agreement by Technische Universität München. As citation manager for publications & thesis EndNote X7.4 V1.7.4.0.8818 was used, also licenced by Technische Universität München.

6.11.1 Population modelling for socioeconomic burden study

In the present thesis we used the DisMod II model in order to obtain the variables needed for the calculation of the burden of NCC (epilepsy and headache based) and the economic impact of NCC. The DisMod II population model is used to predict disease specific incidence, based on internal and external population specific data. This model was used to finally evaluate DALY- and economic impact of NCC in Uganda. DisMod II is an epidemiological tool provided by the WHO for consistent disease specific scenarios (Barendregt 2003). Its calculations are based on the fact that disease specific facts are not independent of each other and therefore evolve in a connected way. It enables researchers to predict unknown values, based on other data and its consequential confidence intervals. For further details see Figures: 11.6 Figure 11. Studies often use data from other countries to bridge incomplete data gaps. In summary, DisMod II creates internally-validated, age-stratified epidemiological parameters, based on disease and population specific input. The main output values were: 1) NCC epilepsy

incidence; 2) NCC headache incidence based on NCC epilepsy incidence. The DisMod II model uses a Markov-chain model, applying four different population categories. That means it hypothetically divides the population in individual life lines that live through certain events, based on the statistical input provided. The relevant events are: 1) Death caused by specific disease; 2) Death through other causes; 3) Healthy individual; 4) Diseased individual (NCC)

Attribution to different groups are linked to diseases specific transition hazards. This means that all life lines are determined by disease specific events or NCC specific likelihoods that accumulate over time. The transition hazards are dependent on: 1) NCC incidence; 2) Case fatality ratio; 3) General mortality rate; 4) Remission rate.

DisMod II allows the estimation and the internal validation of related epidemiological parameters, such as duration of disease, age at disease onset, age at death, standardized mortality rate and prevalence,. The underlined parameters were used as input parameters for DisMod II. The DisMod II model needs at least three disease specific input variables to receive the full disease specific range of epidemiologic parameters. It also requires the population distribution by age and sex and the aforementioned overall mortality. This was taken from (United-Nations 2015) The NCC epilepsy prevalence was taken from our own data analyses for Uganda. The standard mortality rate was adopted from (Wagner et al. 2015b): 2.6 (CI: 1.7-3.5). Due to the chronic aspect of NCC, we assumed spontaneous remission of NCC to be zero for both headache and epilepsy. This is based on the idea that patients continue to live in a highly endemic area and may be re-exposed to NCC at any time. Even after the death of a cyst, the calcified remnant may be responsible for epileptiform discharges. Nash et al. describes chronic calcific NCC as the most common form and does not become clinically inactive. (Nash et al. 2004, Nash et al. 2015). Also, zero mortality for NCC headache was assumed. All other data was taken from our own data sets and analyses of serology and CT-result analysis. The full process can be seen in detail in Chapter 11: Figure 11.

DisMod II was developed by J. Barendregt of the Department of Public Health: Erasmus University Rotterdam, Netherlands and has its copyright with the World Health Organization (Barendregt 2003). It is free to use for research purposes. The implementation of DisMod II for our study is visualized in Chapter 11: Figure 11. It is common to use data from different sources that may come from different population backgrounds. Often, data is unavailable leading to the need of using either less suitable data or to estimate possible values based on either expert opinions or comparable situations in other countries. In comparison to other models, DisMod

II guarantees a higher data quality and therefore a better final burden estimate. As all of our data input sources come from the years 2005 to 2015 we used this decade as a baseline for our simulation. This time period represents a post conflict development due to the civil war of northern Uganda that officially ended in 2009. Data on population, age distribution, average income, unemployment rate, percentage of working population and overall mortality was taken from the United Nations database on population statistics by country, from the Statistical Abstract Report 2010 and 2015; the National Population and Housing Census 2014, Poverty Status Report and the State of Uganda Population Report, all from the Uganda Bureau of Statistics. Further relevant financial statistics was taken from the raw data base: IndexMundi.com. (UBOS 2010, Ministry of Finance 2015, UBOS 2015, United-Nations 2015, Ministry of Finance 2016, Barrientos 2016, Uganda-Bureau-of-Statistics 2016).

Mortality by population indicators (birth rate, death rate, and life expectancy), epilepsy specific mortality, and crude death rate, prevalence of epilepsy, cysticercosis and headache by age distribution was collected by a systematic data base search including 16 different publications (details see Material and Methods: 6.7.3 Data review) (Matuja et al. 1995, Kaiser et al. 1996, Kaiser et al. 1998, Kaiser et al. 2007, Katabarwa et al. 2008, Katwere et al. 2009, Winkler et al. 2010, Dent et al. 2011, Kaiser et al. 2011, Dewhurst et al. 2013, Kaddumukasa et al. 2013, Ngugi et al. 2013, Kamuyu et al. 2014, Bigelow et al. 2015, Kariuki et al. 2015, Wagner et al. 2015b). For overall standardized mortality rate of epilepsy, data from (Wagner et al. 2015b) was used. All other publications were disregarded, because the study population was not close enough to our designated population.

For overall standardized mortality rate of epilepsy, data from (Wagner et al. 2015b) was used. All other publications were disregarded, because the study population was not close enough to our designated population.

Detailed information on the statistical methods of the DisMod II simulation tool can be found in: "*A generic model for the assessment of disease epidemiology: the computational basis of DisMod II* " by Barendregt et al. (Barendregt et al. 2003). As our predictions are only valid for NCC patients that also suffer from epilepsy, we assumed 78.8% of NCC patients to suffer from epilepsy, based on (Carabin et al. 2011). By dividing the relevant value by the epilepsy likelihood of NCC, this gives, among other results, the overall incidence of NCC in Uganda. Based on that number, we were able to evaluate the overall incidence of headache and epilepsy due to NCC in the Ugandan population (see also Figures: 11.6 Figure 11). For our DALY and

economic burden calculations, we based our findings on the two main symptoms of NCC: epilepsy and headache.

6.12 Ethical clearance

Ethical clearance was issued and granted, after application by Prof Dr. Dr.Winkler, by Prof. Dr. E. Ovuga in the name of the ethics committee at Gulu University, Uganda. A copy of the local, Ugandan ethical approval document and the German statement by Ludwig-Maximilian-Universität (LMU) ethics committee chair holder Prof. Dr. Paumgartner can be found in in Appendix: 13.7 Ethics-approval documents. As this study was implemented in Uganda, local ethical clearance was decisive for the implementation of this study. The German ethical statement reiterates the necessity and validity of the local document from the University of Gulu, Uganda. The only critical aspect was radiation burden for PWE follow-up. This led to the exclusion on PWE under 12 years of age.

7 Results

Based on the methodology described in Materials and Methods, the results of this thesis can be sub-divided into three different fields: The first step is the characterization of the NCC population. The second step evaluates the risk factors associated with NCC including clinical predictors such as headache and coexisting conditions. The final and third step analyses socioeconomic disease burden of NCC.

7.1 Study population

Out of 38,303 surveyed individuals in three districts in northern Uganda, 1245 epilepsy cases were identified. Within our 38,303 individuals a triangular age distribution was found. This is a typical age distribution for resource poor countries, showing many young people, but relatively few old people. The arithmetic mean age was 19.6 years (median: 14 years). There was an approximately even sex distribution: (Male: 16,351 (43%); Female: 21,952 (57%). Our study revealed an epilepsy prevalence of 3.3% (CI: 3.1-3.4). 300 PWE were selected for further investigations based on the recency of their last seizure (active epilepsy). Active epilepsy is officially defined as seizure events within the last 12 months (M. Zack et al. 2017). Within our selected 300 PWE sub-set of patients no significant difference in age (p=0.224) in sex distribution (p=1.000) was found (Tables: 12.5 Table 5). The aforementioned triangular age distribution was preserved.

Among the 300 PWE, who underwent further diagnostic work up, 40 PWE were diagnosed with NCC (prevalence: 13.3% [CI: 10-18]). Those cases were evenly distributed over the three districts: Moyo/Adjumani/Gulu (13% [CI 7.3-22]; 15% [CI 8.6-24]; 11% [CI 6.4-19]). Sex was distributed evenly (166 vs 134). An even age distribution was maintained. (Male: 166 [55%] vs. female 134 [45%]). Due to ethical restraints, children under the age of 12 were excluded. Population figures including age and sex as well as prevalence can be seen in Table 5.

Our diagnosis was made based on the Del Brutto et al. criteria explained in Material and Methods: 6.6 Diagnostic algorithm of neurocysticercosis. 18 cases were defined as definitive NCC (6.0% [CI: 3.3-8.9]) and 22 as probable NCC (7.3% [CI: 4.9-11]). For details refer to Figures: 11.7 Figure 12 and Figure 13.

7.1.1 Serology diagnosis of cysticercosis and taeniasis

Out of our 300 PWE population, 30 patients were positive for either CC- AB or AG. Out of the 30 serologically positive NCC patients, 29 were positive for CC-AB. Out of the 29 patients'

positive for CC-AB, 7 were positive for both CC-AB and CC-AG. Only one of the 30 serologically positive patients was only positive for CC-AG and negative for CC-AB. Based on Gabriel et al., all 30 positive serologic results ought to be considered as positive in the Del Brutto et al. diagnostic criteria (Del Brutto et al. 2001, Gabriel et al. 2012).

Adult tapeworm ABs represent either active *T. solium* infection or a serology scar from a past tapeworm carrier status. Out of the 300 PWE, 15 had ABs (anti-rES33) against the adult tapeworm. This represents 5% (CI: 2.8-8.1%) of the overall PWE population. 13 out of those 15 anti-rES33 positive PWE were subsequently diagnosed with NCC. All those 13 patients had also either CC-AG and/or CC-AB positive. Two NCC negative PWE also had ABs against the adult tapeworm: 2/260 (0.7% [CI: 0.1-2.4]).

Adult tapeworm contact increases the risk 62 times (OR) to additionally suffer from NCC ($P<0.001$) [CI: 16-411]. Being a tapeworm carrier is a risk factor for attaining NCC. For discussion details, please refer to Discussion: 8.1.1 Tapeworm carrier status in people with epilepsy.

Further details on the serology analysis and the distribution of the results in the various patient groups is shown in Tables: 12.12 Table 12 and Figures: 11.7 Figure 14.

In Figure 14, the PWE serology distribution can be seen in detail. The different serology tests are explained in Material and Methods: 6.5.1 Serology. 40 out of 300 PWE were diagnosed with NCC based on (Del Brutto et al. 2001, Gabriel et al. 2012) . 260 were diagnosed with non NCC epilepsy. 30 out of the 40 NCC positive patients had positive CC-ABs or CC-AGs. Every positive serologic finding led to a positive NCC diagnosis. Only 75% of all NCC positive patients showed CC-AB or CC-AG conversion when disregarding CT findings. All 30 patients with positive CC-AB and/or CC-AG results showed sufficient further epidemiologic, clinical or radiologic evidence to be subsequently diagnosed with NCC, based on Del Brutto et al. (Del Brutto et al. 2001) as the gold standard diagnostic criteria.
Also, out of the 270 CC-AB or CC-AG negative patients, another 10 patients were diagnosed with NCC based on CT-results, endemic risk factor and clinical factors, as described in Del Brutto et al. (2001). 260 out of 270 PWE with negative CC-AB or CC-AG were not diagnosed with NCC.
As an overview, the serology tests based on CC-AB and CC-AG showed the following descriptive values:

- Sensitivity: 75% (30/40) [serology pos./(serology pos.+false neg.)]
- Specificity: 100% (260/260)) [serology neg./(serology neg.+false pos.)]
- Positive predictive value: 100% (30/30) [serology pos./(serology+ and NCC+)]
- Negative predictive value: 96.3% (260/270)
  [(NCC neg.+serology neg.)/serology neg.]

In this case: false negative refers to the 10 patients that were serologically negative, but that had positive CT findings. There were no false positive patients. This needs to be contemplated with caution, as serology is part of the diagnostic criteria. For further Information see Discussion: 8.2.1 Serology tests in the diagnostic algorithm of neurocysticercosis

7.1.2 Computed Tomography diagnosis of neurocysticercosis

In Figures: 11.7 Figure 15 the study population is divided into sub-categories based on their neuroimaging results. Out of the 300 PWE, who underwent further diagnostic work-up, 3 patients presented with scolices on their CT findings. 23 fulfilled the criterion of highly suggestive for NCC. 12 patients had findings that were compatible with NCC. 100% of patients who fulfilled the absolute criterion of a scolex found on their CT results were finally diagnosed with NCC. In the sub-group of patients with compatible lesions, only 1 out of 12 (8.7%) patients was diagnosed with NCC, based on the Del Brutto criteria. In the Del Brutto criteria, a scolex is considered proof of NCC. A scolex is the structure within the cyst that later develops into the head (scolex) of the tapeworm. Cysts without scolex were considered as highly suggestive lesions. For further details on how the CT criteria were met, please refer to Material and Methods: 6.5.2 Computed tomography. Out of the 23 patients, where highly suggestive lesions were found, 100% were finally diagnosed with NCC, based on the Del Brutto criteria. When combining the two strongest sub-groups: absolute and highly suggestive, all 26 (3+23) patients were found to suffer from NCC, after having included serology, epilepsy and endemic origin as diagnostic requirements in the Del Brutto criteria (Del Brutto et al. 2001).

When referring to CT results only, the final NCC diagnosis based on the Del Brutto et al. criteria (Del Brutto et al. 2001), correlates with highly suggestive and absolute criteria ($p<0.001$). When including absolute and highly suggestive categories, both as positive test results, we receive the following values for sensitivity and specificity. The denominator represents the total number of NCC diagnoses. Those diagnoses were met with the Del Brutto et al criteria and the Gabriel et al. amendments (Del Brutto et al. 2001, Gabriel et al. 2012). We set those criteria as gold

standard. The results of the CT scan cannot be considered totally independent of the gold standard and the calculations below have to be interpreted in this context.

- Sensitivity: 65.0% (26/40) [CT-pos./(pos+false neg.)]
- Specificity: 100% (260/260) [CT-neg./neg+false pos.)]
- Positive predictive value: 100% (26/26) [CT-pos./(CT-pos. and NCC+.)]
- Negative predictive value: 94.9% (260/274). [(CT-neg. and NCC-)/CT-neg.]
    - *(compatible. and negative CT results considered as CT-neg)*
    - *(absolute and highly suggestive CT results considered as CT-pos)*

As CT diagnostic testing is part of the Del Brutto criteria gold standard, this is a rough estimate, as quality criteria for statistical analyses are not met. Further information and analysis of the CT diagnostic- and the serological test results can be found in: Discussion: 8.2 Analysis of diagnostic criteria. There, the option of a standalone serological kit alongside a pre-screening catalogue is discussed.

7.1.3 Overall diagnosis of neurocysticercosis

This study shows details for every individual NCC case identified. Tables: 12.12 Table 12 shows the characteristics of all 40 PWE that were diagnosed with NCC. Each line stands for the individual patient and the diagnostic decision making process. It illustrates the complexity of the diagnosis. Each step of the NCC diagnosis can be retraced. One may also find a characterization of each patient's epilepsy type, other neurologic findings and neuroimaging results together with its relevant staging. As this thesis focuses more on the epidemiologic impact on NCC, more details on the clinical characteristics will be given in Results: 7.2.3 Clinical characteristics of neurocysticercosis.

Among all 40 NCC positive PWE 13 patients showed no apparent lesions on neuroimaging. One diagnosis was compatible with NCC, 23 were considered as highly suggestive and three patients presented with viable cysts on neuroimaging. Even though 13 patients presented without clear NCC-linked lesions in neuroimaging, they displayed serology results that sufficed to diagnose NCC. The diagnostic criteria are further explained in Materials and Methods: 6.6 Diagnostic algorithm of neurocysticercosis and more details on the diagnosis of NCC can be found in Tables: 12.12 Table 12.

Based on CT and serology results, every patient could be attributed to absolute, major and minor criteria according to the Del Brutto et al. criteria, which in turn define the final diagnosis. As

the entire study population comes from an endemic area, they all fulfilled the epidemiologic criterion. The diagnostic process is based on the Del Brutto criteria and the amendments done by Gabriel et al. (Del Brutto et al. 2001, Gabriel et al. 2012). In Tables: 12.12 Table 12, all details on the diagnostic process are listed.

7.2 NCC risk factor analysis

7.2.1 Sociodemographic risk factors

In Tables: 12.6 Table 6, a detailed sub-analysis by sex and age group is shown. There was no statistically significant difference in sex and district distribution in the NCC patient population. An equal prevalence in all districts suggests that risk factors and infection pressure can be considered comparable between the three different districts. A statistically significant difference can be observed when comparing the age distribution between NCC positive and NCC negative PWE. The average age of NCC patients was 38 years whereas it was 24 in the NCC negative population ($p < 0.001$). Also, seizure onset differed in NCC positive and NCC negative patients (24 years vs 14 years; $P<0.001$). For more details, refer to Results: 7.2.3 Clinical characteristics of neurocysticercosis.

The prevalence distributions listed by age are shown in Tables: 12.14-16 Table 14 and 15 and Figure 16. Being a student or white collar worker decreases the likelihood of an NCC infection. (OR 0.18[CI: 0.07-0.43]). Farming however, represented a risk factor with a reverse odds ratio of 5.6 OR ($p<0.001$). As age presents a confounder, we corrected the analysis for age. And calculated new adjusted odds ratios (aOR) for age and farming. On multivariable analysis, we found: adjusted effects for age: (aOR=1.04 [CI: 1.01-1.07]; p=0.013) and farming (aOR=3.22 [CI: 1.33-8.23]; p=0.011). Both remained statistically significant. Another risk factor found through univariable analysis was alcohol consumption (OR: 3.65 [CI: 1.2-10.1]; p= 0.024). 15% of NCC positive PWE report regular alcohol consumption whereas it was only 4% in the NCC negative PWE. However on multivariable analysis this risk factor lost its statistical significance. Possible confounders were again age, but also socioeconomic standing and occupation.

7.2.2 Behavioural risk factors

Tables: 12.7 Table 7 shows the characteristics of consumer behaviour and pig farming habits. No statistical significance was found for consumption of pork (p=0.337) and pork cooking habits, although the latter showed a trend for people that prefer barbecued pork (p=0.094).

Another assumed risk factor included in our questionnaire was knowledge about porcine cysticercosis. As we have only 300 PWE with further diagnostics, this question only shows a tendency that is not statistically relevant (p=0.148). Pig keeping and related practices including home slaughter were not found to be associated with NCC. Knowledge on porcine cysticercosis did not seem to play a role, at least in our study (Table 7). 29 PWE had prior knowledge about cysticercosis, whereas 268 declined prior knowledge about cysticercosis. Only 1 patient (3%) of the knowledgeable PWE has NCC, whereas 39 patients (15%) of the non-informed PWE suffer from NCC. We obtained similar results when looking at knowledge about tapeworm infections in humans (p=0.105; Table 7). Interestingly, interviewed individuals indicated that they got their knowledge from family members and social contacts, rather than healthcare systems or the media.

7.2.3 Clinical characteristics of neurocysticercosis

Clinical predictor rules are based on both medical signs and symptoms obtained in a clinical setting. They help predict certain probabilities about the outcome of diagnostic interventions or treatment success. They represent the base for many clinical scores and are consequentially an important tool used in the evidence based clinical decision making process.

Tables: 12.8 Table 8 shows the seizure characteristics associated with NCC within our study population of 300 PWE. Winkler et al. (2007) proposed that her suggested categories may help to further classify epilepsy in resource poor countries. “[D]iagnostic and therapeutic implications” may be deducted from those categories. In our group of 300 PWE we were only able to establish a tendency towards goa (p=0.225). As per definition, patients with goa are suspected to have an unknown (cryptogenic) cause for their epilepsy. However our findings were not statistically significant. In order to elucidate this further, a larger study population is needed.

When only looking at the basic ILAE diagnostic groups, we found a statistically significant distinction (p=0.049) between primary and secondary generalized epilepsy. 80% (32/40) of NCC positive PWE showed primary generalized seizures. 20% (8/40) NCC positive PWE showed secondary generalized seizures. In the NCC negative PWE population 64% (166/260) had primary generalized seizures and 36% (94/260) had secondary generalized seizures. Based on a univariable analysis, people with secondarily generalized seizures have a 2.3 times lower change of suffering from NCC than PWE suffering from primary generalized seizures (OR 0.44 [CI: 0.18-0.95]).

Another factor that seems to relate to NCC is the motor activity during seizures (p=0.014). Considering all PWE, the most common type of generalized seizures are tonic-clonic seizures. Those seizures have a three times lower chance of being caused by NCC than seizures with tonic motor activity (OR: 0.33 [CI: 0.16-0.70]). However, it needs to be considered that among NCC patients still 55% of all patients have tonic-clonic seizures.

Most of the NCC patients (55%) have their seizures only during the day, whereas only 28% of PWE without NCC present with day-time seizures only. In PWE without NCC, 57% of patients' seizures occur at any time, without following a specific pattern. This distribution shows a statistical significance (p=0.004). PWE with seizures at any time including nights, have a 3.4 times lower risk of having NCC than patients with only day-time seizures (OR: 0.29 [CI: 0.14-0.60]).

One of the most important risk factors was seizure onset (p<0.001). As suggested by Winkler et al. (2007) in: "Epilepsy in resource poor countries--suggestion of an adjusted classification" cryptogenic epilepsies with a pathologic cause occur more likely in patients older than 25 years of age. In our study, we found that the average seizure onset in NCC patients was 24 years and in the PWE control group 14 years. This corresponds to a 4% risk attribution increase per year (OR 1.04 [CI: 1.02-1.06]).

7.2.3.1 Treatment of people with epilepsy and neurocysticercosis

The distribution of antiepileptic medication between NCC patients and PWE without NCC did not show any statistical differences (p=0.582). There was no statistical difference in adherence to medication (p=0.473) and no statistical difference in seizure frequency reduction before vs. after treatment (p=0.163). Also, there was a tendency that people with NCC and epilepsy responded better to AEDs than PWE without NCC (p=0.163, Table 8): Overall, the arithmetic average values of seizure reduction are (median in brackets):

NCC+: 77.7% (91.8%); NCC-: 48.2% (87.5 %)

7.2.3.2 Headache characteristics in people with epilepsy and neurocysticercosis positive patients

22.5% (9/40) of our NCC positive PWE complained of bad headaches, whereas only 11.8% (27/227) of NCC negative PWE reported bad headaches (p=0.0.49). Details on headache type distribution and further analyses can be found in Tables: 12.9 Table 9. Bad headaches refer to results from item 48 in the CWGESA questionnaire. Severe and/or progressive headaches refer

to the headache screening questionnaire results. Details on which specific patient out of our NCC positive PWE suffered from bad headache can be found in Tables: 12.12 Table 12. We also linked the severity of the neuroimaging results to the likelihood of suffering from severe headache (Tables: 12.10 Table 10). Even though a tendency of people with NCC suffering more from headaches compared to those without NCC was observed, (67% of patients with scolices visible have severe headache) the total number of NCC patients identified may be too small to yield a statistically relevant result (p= 0.379; Table 10). In addition, we analysed the type of pain by describing its characteristics and by using a pictogram pain scale. Even though not statistically significant, there seemed to be a tendency towards an average to severe pain level with a more punctual (piercing) and continuous characteristic (p=0.089). For absolute numbers, please refer to Tables: 12.9 Table 9. More research might specify headache type and may help screen patients for NCC-symptomatic headache. A detailed list of all analysed headache specific data can be seen in Table 9.

As we only had 40 NCC patients, it is difficult to define a typical NCC headache. In further studies this could be important to help define the "typical NCC patient". Some conclusions however can still be drawn:

Among those NCC patients with headache, most showed their pain peak more than one year before the interview. It means that 67% of NCC patients with headache reported their worst headache pain level over one year ago, whereas in the control PWE population only 44% reported their headache peak more than a year ago (OR:3.66 [1.20-10.17]). NCC patients also described their pain much rather as piercing headaches (58%: 7/12) vs. (19%: 11/58), (p=0.044). Non NCC-patients describe their headache mostly as stabbing/sharp pain (8%: 1/12) vs. (31%: 18/58), (p=0.044), also see Table 9. Through the analysis of our pain pictograms, NCC patients described their headache more like a medium pain and seldom as extremely strong or as faint pain (p=0.086). PWE without NCC described their headache in a broader distribution from faint to extreme pain.

We determined whether headache prevalence and severity of CT diagnosis (absolute-highly suggestive-probable-negative) correlated. There is an increase in headache prevalence in the more severe CT diagnosis categories within the NCC positive PWE: 1) Negative: 23% (2/13) suffer from headache; 2) Compatible: n.a. (no data); 3) Highly suggestive: 33% (7/21) suffer from headache and are NCC+; 4) Absolute: 67% (2/3) suffer from headache and are NCC+.

No statistically significant association between headache and CT results could be found (overall: p=0.379; sub groups: p=0.476), due to a small sample size (n=37). For details see Tables: 12.10 Table 10.

The same reasoning applies to serology. Serology was only done on specific AB and AG testing available for NCC and *T. solium*. No link between both serology & CT results and headache could be found (p=0.739; p=0.476 respectively).Further details can be found in Table 10.

7.2.3.3 Coexisting medical conditions in people with epilepsy and neurocysticercosis positive patients

In our study we assessed reported coexisting medical conditions for their association to NCC. All analyses can be found in Tables: 12.11 Table 11. Even though we studied admission history, psychiatric and average sick day distribution, we only found two factors that can be linked to an NCC infection were associated with NCC in a statistically significant manner.

Patients that had suffered from meningitis had a 2.49 times higher risk to also suffer from NCC during their life (OR: 2.49 [CI: 1.16-5.14]; p=0.020).

Those that had a past medical history of cerebral malaria showed a 2.4 times lower risk of attaining NCC during their life (OR: 0.42 [CI: 0.17-0.95]; p=0.035).

Discussion and interpretation of those findings can be found under: Discussion: 8.1.4 Coexisting conditions in neurocysticercosis.

7.3 Economic and disability-adjusted life year burden assessment of neurocysticercosis

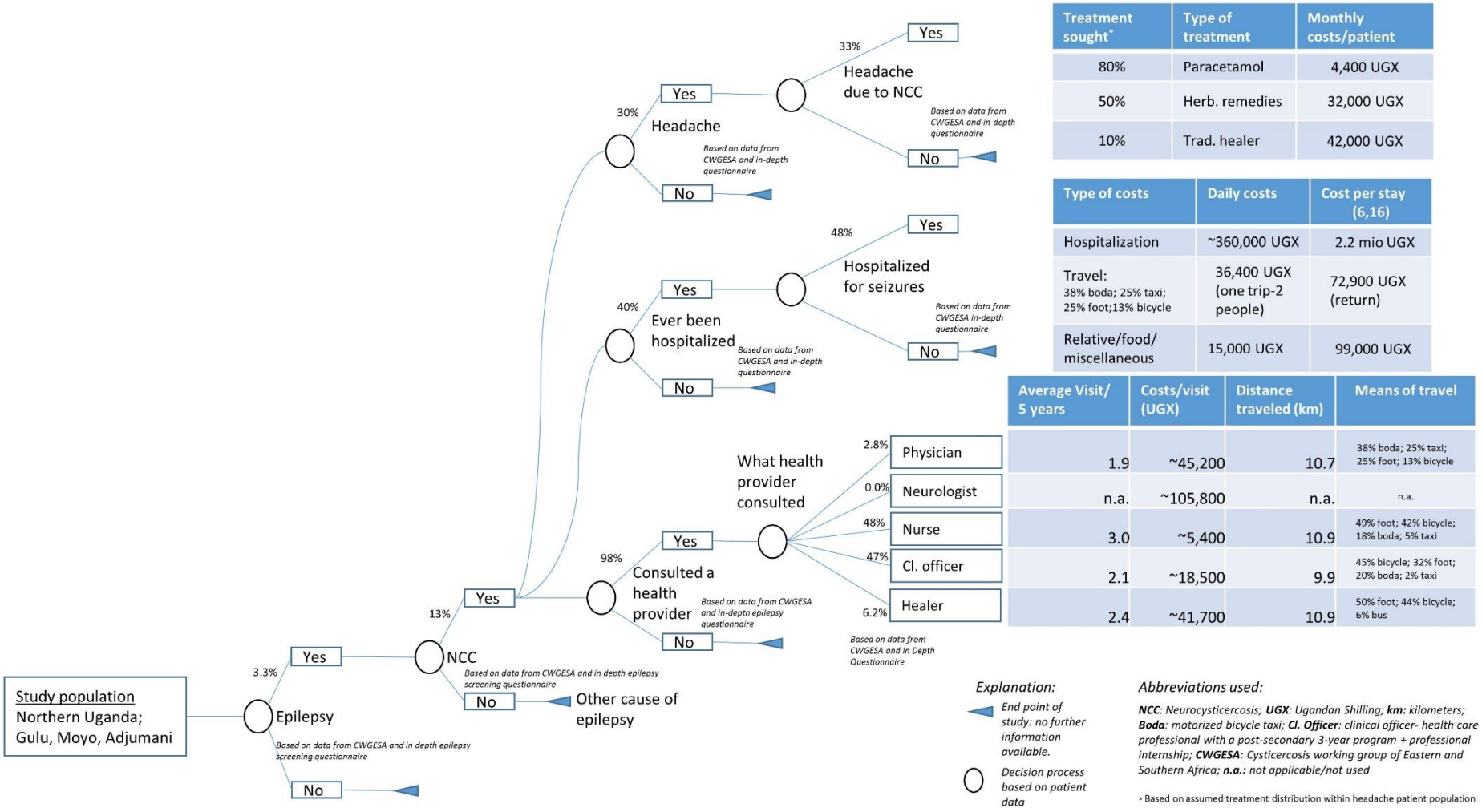
In our study we also assessed the human burden of NCC in terms of DALYs and economic impact. This includes direct medical and non-medical costs, as well as indirect human costs. The new aspect of this analysis is the implementation of a DISMOD model to internally validate all relevant data. Also, we included headache costs and epilepsy as symptoms secondary to NCC.

7.3.1 Decision tree: Model behaviour options for neurocysticercosis patients

In order to establish a cost and DALY estimate, a decision algorithm is needed for both epilepsy and headache in Uganda. Based on NCC epilepsy, certain healthcare options are chosen by patients. It is therefore important to analyse patient behaviour prior to implementing

calculations. In Graphic 1, see below, the decision making process is represented in form of a decision tree. It is based on several screening questionnaires (epilepsy screening/in-depth questionnaire/CWGESA/headache) used within the study population of northern Uganda.

The present paragraph is intended to help understand and read the decision tree. Percentages next to an arbitration line give the prevalence of this option. For example it means that 3.3% of the study population was identified with epilepsy, or that 30% of the NCC patient group was found to report headaches; of which 33% could be attributed to NCC in comparison to the control group. Italic font next to every decision point names the information source used for a certain decision probability. A blue triangle indicates a chosen end point that was not followed further, but may have relevance on a broader public health level. On the right hand side, associated costs are listed in tables. The named costs are only a selection that are associated with the decision end points. Further indirect costs and detailed direct medical costs that are associated with NCC are not listed, but can be found in Material and Methods: 6.9 Cost-of-Illness. Parameters that define the weight of certain points are left out, but can be found in Tables: 12.16-18/21 Tables 16-18 and 21. This graph has been kept incomplete in order to maintain simplicity and basic understanding of work steps. Graphic 1 also represents the basic process for all relevant decision steps needed in DALY and economic impact calculations.



Treatment sought*	Type of treatment	Monthly costs/patient
80%	Paracetamol	4,400 UGX
50%	Herb. remedies	32,000 UGX
10%	Trad. healer	42,000 UGX

Type of costs	Daily costs	Cost per stay (6,16)
Hospitalization	~360,000 UGX	2.2 mio UGX
Travel: 38% boda; 25% taxi; 25% foot;13% bicycle	36,400 UGX (one trip-2 people)	72,900 UGX (return)
Relative/food/ miscellaneous	15,000 UGX	99,000 UGX

Average Visit/ 5 years	Costs/visit (UGX)	Distance traveled (km)	Means of travel
1.9	~45,200	10.7	38% boda; 25% taxi; 25% foot; 13% bicycle
n.a.	~105,800	n.a.	n.a.
3.0	~5,400	10.9	49% foot; 42% bicycle; 18% boda; 5% taxi
2.1	~18,500	9.9	45% bicycle; 32% foot; 20% boda; 2% taxi
2.4	~41,700	10.9	50% foot; 44% bicycle; 6% bus

Graphic 3: Decision tree for NCC patients suffering from epilepsy and headache with prevalences and associated costs. Explanations in 7.3.1 Decision tree: model behaviour options for neurocysticercosis

7.3.2 Disability-adjusted life years of neurocysticercosis in Uganda

The DisMod II model estimated 9,344 (CI: 7,685-11,071) NCC epilepsy incident cases and 1,426 (CI: 0-3,254) NCC-headache incident cases for 2010. Those incident cases led to 2,749 (CI: 2,346-3,167) NCC-epilepsy related deaths. Further relative values, besides the aforementioned absolute numbers can be found in Tables: 12.19 Table 19. Overall, our study estimates 182,614 (CI: 142,547-228,459) healthy life years lost, due to the incident cases of 2010. Per 1,000 person years it means a loss of 5.5 (CI: 4.3-6.9) healthy life years. Per NCC-case the loss amounts to 17 (CI: 14-20) healthy life years. Details on the mentioned results can also be found in Tables: 12.20 Table 20. The main impact on the final DALY estimate had epilepsy, whereas headache only contributed to 5% (95%UI: 0%-13%) of the overall DALY. However headache provided the highest patient level morbidity impact (YLD). This is based on the high cases of migraines (53% within the NCC headache population) and the high DW of 0.441. For more details see Tables: 12.15 Table 15. Non-fatal health outcomes were the largest contributors to the total health impact (68%; 95%UI: 58%-75%).

7.3.3 Economic burden assessment of neurocysticercosis in Uganda

The economic burden of NCC in Uganda was USD 75,470,055 (CI: 56,386,713-108,895,694). These costs represent the overall lifetime costs created by all 2010 incident cases from the beginning of their symptoms until their future death. Per symptomatic NCC case the costs amount to USD 8,068 (CI: 6,825-11,323). A detailed summary of all cost-of-illness results can be found in Table: 12.21 Table 21. These numbers represent the sum of all DHC, DNHC and INHC created between the onset of symptoms in 2010 and the remaining disease specific life expectancy. The overall cost-of-illness was headed by production loss, caused by severe epilepsy (INHC). Hospitalization contributed most to DHC and represented the second largest position in the overall costs-of-illness.

8 Discussion

8.1 Study population, epilepsy prevalence and identified cases of neurocysticercosis

In this study, the epilepsy prevalence was 3.3% and the NCC prevalence among PWE was 13%. Prior studies in neighbouring countries found a similar NCC prevalence (Winkler et al. 2009b, Hunter et al. 2015). Our results are within the margins of prior findings and represent a rather low-conservative prevalence estimate. For further details on prior research and results, please refer to: Introduction- Prior research efforts on *T. solium* and cysticercosis. In our study, the NCC prevalence rate refers to the prevalence within a PWE population screened for active generalized epilepsy. Strictly speaking we are therefore assessing a sub category of NCC PWE. Other studies did not define their included patients' condition precisely, such as (Carabin et al. 2011). It is very common that only the terms "seizures" or "epilepsy" are used, without any further details on the type of epilepsy and its definition.

Epilepsy is a great problem in Sub-Saharan Africa. Its annual incidence is about two times higher than in industrialized countries (81·7 per 100 000 (CI 28·0–239·5) compared with 45·0 per 100 000 (CI: 30·3–66·7) (Preux et al. 2005, Ba-Diop et al. 2014). The disease burden study from 2010 defined severe, uncontrolled epilepsy as the second highest DW, only topped by HIV (Ba-Diop et al. 2014). The stigma of witchcraft and the large treatment gap make it a very substantial problem in the affected countries. A Lancet study from 2014 estimated an overall meta-analysis prevalence of epilepsy in Sub-Saharan Africa of 9·39 per 1000 (0.939%). The included prevalences varied strongly between countries: Cameroon 10.5% (2008) and Ghana 0.2% (2013) (Ba-Diop et al. 2014). This study's epilepsy prevalence of 3.3% is comparable to other studies, but a bit higher than the overall estimate from the Lancet 2014. In (Millogo et al. 2012) a prevalence estimate of 4% was calculated for Burkina Faso. Our epilepsy prevalence was highest in 10-18 year olds and decreased further with age. This might indicate that the relative NCC prevalence can be expected to rise with age, when presenting with a new seizure condition.

In this study, the NCC prevalence among PWE was 13%. The corrected overall NCC prevalence within the general population (epilepsy and non-epilepsy population) would be 16.5%, if applying Carabin's 78.8% of epilepsy prevalence among NCC patients (Carabin et al. 2011). In Zambia, Mwape et al. found a NCC prevalence of 57.1% in a population of 49 PWE (Mwape et al. 2015). No confidence interval (CI) was given. Their very small study

population would most likely give a large CI. In Burkina Faso, Millongo et al. found a NCC prevalence of 45.5% (CI: 19.0-74.1) and 46.9% (CI: 30.2-64.1) in two separate villages from a total PWE population of 68 patients (Millogo et al. 2012). A study from Tanzania found a very small NCC prevalence of 1.1% (CI: 0.3-4.0) (Hunter et al. 2015) and Winkler et al. found a very comparable NCC prevalence of 13.7% (no overall CI) in Tanzania a few years previously(Winkler et al. 2009b). The confidence intervals in those cited studies are also very wide. As we fully examined 300 PWE, we were able to produce a rather small confidence interval (prevalence: 13% [CI: 10-18]). A general association of factors can be assumed: The larger the study population→ the smaller the confidence interval → the more low-conservative the prevalence result, when assuming a comparable disease burden in all studied countries.

Our values appear to be internally validated by showing comparable results in all three districts studied: (13% [CI: 7.3-22]; 15% [CI: 8.6-24]; 11% [CI: 6.4-19]). The global difference of NCC prevalence estimates might be partly due to a lower infection pressure, or different risk factors in different countries. At the same time, the variation in results also explains why it is so important to individually verify prevalence and risk factors in each affected region, as they may vary depending on a rather complex situation. This becomes especially relevant when implementing intervention plans on a national level.

When evaluating the changes made to the Del Brutto criteria by (Gabriel et al. 2012), it only changed our final NCC diagnosis from 39 to 40 positive NCC cases. Therefore, it did not have a major impact on the final prevalence value (13% to 13.3%).

8.1.1 Tapeworm carrier status in people with epilepsy

As one tapeworm produces 50-60 x 10^3 eggs per day, one individual within one population can easily infect a large number of people and turn them into accidental, intermediate hosts (cysticercosis or NCC). As intermediate hosts do not close the life cycle of *T. solium*, they do not actively participate in *T. solium*' s reproductive cycle, and therefore pose less risk to a population from a healthcare point of view. Even though prevalence for tapeworm infection seems to be lower, their overall impact, when battling NCC, can be considered to be much higher than other risk factors for NCC alone. 87% of all *T. solium* infected PWE, were additionally diagnosed with NCC. This result could mean that auto-infection attributes a lot to the actual NCC burden. 13 out of 40 (33%) NCC positive PWE, but only 2 out of 260 (1%) non-NCC patients, had ABs against the adult tapeworm. In our population, the NCC risk was increased by 62 times (OR) ($p<0.001$; [CI: 16-411]) by being a tape worm carrier. Tape worm

carrier status was defined through AB tests (RES 33 EITB). This test does not distinguish between current or past infections (serology scar). Having positive AB for RES 33 is one of the most important risk factor findings in our study. It is hard to say whether this risk factor stands for a higher likelihood of auto-infection or generally a higher probability of living in a more contaminated environment. Because of its impressive strength, it can be said that there is strong correlation between *T. solium* tapeworm carriers and NCC patients. This makes sense when looking at the life cycle of *T.solium*, were tapeworm carries are necessary to infect pigs and humans, in order for them develop cysticercosis. It promotes the idea that breaking through the NCC life cycle will help fight NCC. Consequentially, many preventive measures fighting porcine cysticercosis have been proposed as methods to combat NCC (Carabin 2010a). Another famous method is anti-helminthic mass treatment to prevent cysticercosis (WHO 2006, Lightowlers 2013) In mass treatments, taeniasis is targeted to break through the life cycle and prevent future cysticercosis or NCC infections. There have been some trials of mass treatments in order to specifically combat NCC, however, the results were not as strong as the very high odds ratio suggests. Often, structural local problems make a large implementation difficult. For further details, see also: (Garcia et al. 2016). It is therefore important to identify, why mass treatment was unsuccessful in the past and how to improve it, in order to enhance preventive measures against NCC. Another thought would be to combine it with different consecutive preventive measures, such as hygiene or pig infection control measures. Mass treatment may also have adverse effects on NCC patients (Abba et al. 2010). Criticism of mass treatment can be found in (Winkler et al. 2015), as it may be detrimental to those people that harbour cysts from NCC. Anti-helminth treatment may convert asymptomatic to symptomatic NCC, as it may lead to an inflammatory reaction and may entail increased intracranial pressure and death.

A study in 2009 showed significant cysticercosis clusters around tapeworm carriers (Lescano et al. 2009). This finding also supports the assumption that human-to-human transmission is a major cause of NCC and suggests the possibility of “cluster targeted” anti-helminthic mass treatment. In this context increased surveillance for potential side effects could be conducted much easier than when treating the whole population.

8.1.2 Epilepsy in people with neurocysticercosis

Other than headache, epilepsy is a much bigger problem in Africa than on other continents. Other door-to-door surveys show that the prevalence is more than twice as high as it is in Europe or northern America (Ba-Diop et al. 2014). Epilepsy is based on stringent diagnostic criteria in western countries. In Sub-Saharan Africa many preconceptions are still in place. Often, epilepsy

patients are sent to a psychiatry ward instead of the neurology department. Epilepsy is also still associated with evil witchcraft. Traditional healing ceremonies for epilepsy include scarification. This involves cutting the patient and waiting for evil spirits to leave the body. Scars and keloid as well as lasting disabilities may be the case. Epilepsy also has got tremendous social impact for the people affected and may even lead to exclusion from a social circle (Ba-Diop et al. 2014). This may have led to a certain underreporting, as people may not have liked to admit to suffer from epilepsy. Especially under women the social consequences are more severe. Our data portrays that, as we have slightly more men reporting seizures than women (see Tables: 12.5 Table 5). Also the reliability of treatment compliance needs to be read with caution. There might be a certain over-reporting, as people are not prepared to admit that their treatment adherence was lower than admitted in the questionnaire. Therefore there might be an under-reporting of associated symptoms and seizure frequency. This issue is also described in (Ba-Diop et al. 2014).

8.1.3 Headache in people with neurocysticercosis

22.5% (9/40) of our NCC positive PWE complained of bad headaches, whereas only 11.8% (27/227) of NCC negative PWE reported bad headaches (p=0.0.49). When trying to relate headache to serology and CT-results, no statistically significant results were obtained. (p=0.739; p=0.476 respectively). Headache characteristics were not statistically different between NCC positive PWE and non- NCC PWE. An overview of all analyses can be seen in Tables: 12.9 Table 9. This is probably due to the very small sample size of NCC positive PWE with headache. Migraine was only identified by question 10 (aura) of the headache in-depth questionnaire. This study therefore only included migraines with aura. As Migraines without aura could only be identified insecurely by question 9 (vomiting/photophobia) and only one headache patient reported vomiting but no aura, it was decided to focus only on the migraine with aura patients. This may have triggered an under reporting in our DALY calculations. Also, we only identified 60 headache patients in our 300 PWE. Only 51/60 chose to reply to question 10. It is therefore unreliable to look into further sub-analyses of headache types and characteristics, as the sample size is insufficient for a clear answer.

Headache is a very common symptom in any population. The WHO estimates that approximately 75% of the entire world's population suffer or have suffered from headaches over the last year (WHO 2016b). Both TTH and migraine headaches seem to be less common in Sub-Saharan Africa than in western countries (Winkler et al. 2009a, Winkler et al. 2010). Migraine prevalence is estimated to be about 11% worldwide (Dent et al. 2011). A lower age

adjusted value of about 6% in northern Tanzania has been found by Winkler et al. The authors also found an overall headache prevalence of 12.1% with a TTH part of 7% of the overall population. They also stated that it was difficult to clearly identify headache types in northern Tanzania, as the diagnostic criteria were often hard to meet. This also applied to our study (see above). We did not analyse the age structure of our headache patients, as we did not have a large enough sample group to successfully test for statistical significance. The average age in the migraine group was 32 years and the average age in the TTH group was 28 years. Our data also only portrays the headache subgroup within PWE and it is therefore not directly comparable with a headache study that screens the general population. Winkler et al. found for the general population of northern Tanzania that the highest prevalence for TTH was in the >40 yo group. It can therefore be concluded that headache is generally a less important issue in Sub-Saharan Africa than in western countries. In turn, this might increase the portion of secondary headaches in those countries.

Epilepsy is less common than headache with 50 million suspected cases world-wide (WHO 2016a). Also, as the likelihood of having a NCC patient suffering from epilepsy is 78.8%, but only 37.9% for the same sample group presenting with headache, epilepsy is the better pre-screening parameter to identify NCC patients. The last two values were taken from (Carabin et al. 2011). However, some studies have been conducted using headache as their primary screening parameter to assess NCC (Del Brutto et al. 2012). Its value and informative significance remains to be seen. Based on our query for clinical factors that may help to identify NCC patients. The following "typical NCC patient" can be imagined: It is the combination of a piercing headache of medium intensity that is not new to the patient in addition to an already established epilepsy. The combination of both diagnoses (epilepsy + headache) may even have a stronger predictive power of NCC in endemic areas than current tests. However, calculations could not be performed, as only PWE were recruited.

8.1.4 Coexisting conditions in neurocysticercosis

Childhood meningitis represents a risk factor for NCC (OR: 2.49 [CI: 1.16-5.14]). Meningitis is a common disease in Sub-Saharan Africa. Approximately 400 million people contracted meningococcal meningitis in the African meningitis belt in 2014 (WHO 2014). It affects especially the age group of 7-14 year olds and it is lethal in up to 50% of cases (WHO 2015b). Meningitis is contracted though the exchange of bodily fluids and maintains its infection rate through close and prolonged contact. It is mainly droplet-carried and its infection rate increases through being present close by (WHO 2015b). NCC has similar risk factors. Even though it's

transmitted through contaminated soil and food, smear infections are more likely to happen in poor hygiene settings where many people live in close proximity to one another. As meningitis often causes structural damage to brain and surrounding tissue, the blood-brain-barrier might be especially compromised through a prior meningococcal infection, enabling an easier entry for larvae into the brain tissue. Childhood meningitis was a statistically relevant risk factor (OR: 2.49 [CI: 1.16-5.14]; p=0.020). Further research on how meningitis might affect the susceptibility to NCC is needed to fully understand this phenomenon.

As malaria is transmitted through the anopheles mosquito, hygiene and close physical proximity do not play a major role in transmission (Cdc 2015). The causative organism of malaria in Sub-Saharan Africa is *plasmodium falciparum,* a eukaryotic organism. On a phylogenetic level it is therefore closer related to *T. solium* than to bacteria. It is known that the T-cell response plays a crucial role in malaria infection (Langhorne 1989). The intracellular forms trigger an early Th1 response. However, a Th2 response and IgE levels play a major role in long term parasite contact and in cerebral malaria (Perlmann et al. 1994, Perlmann et al. 2002). Perlmann et al. also stated that the IgE levels could not clearly be traced back to either malaria or a prior helminth infection.

A prior Th2-stimulating infection, with parasite specific immune responses in the CNS might therefore help fight a possible infection with *T. solium* cysts happening at a later stage. No publication clearly supporting this hypothesis has been found so far. An argument against this hypothesis is that both malaria and NCC are potential causes of epilepsy based on structural brain lesions. The statistical significance could therefore only be a representation of the PWE that attained epilepsy through a prior CNS malaria infection regardless to their NCC status. However, this does not explain why there seems to be a protective aspect about prior cerebral malaria, but a positive risk attribution to meningitis, which can also cause consecutive epilepsy. The main difference between the two forms of infection is the triggered immune reaction which is comparable in parasites (*plasmodium falciparum and T. solium),* but different in bacterial infections. Further research is therefore needed to understand the relation between malaria, meningitis, epilepsy and NCC.

8.2 Analysis of diagnostic criteria

8.2.1 Serology tests in the diagnostic algorithm of neurocysticercosis

Our serology test procedures combined both AG and AB testing to increase reliability. Details on how serology has changed over the last years, please see: Material and Methods: 6.5 Relevant tests and diagnostic criteria for neurocysticercosis.

The rES33 is a recombinant protein that helps detect a taeniasis specific AB. A serology tool in order to detect tapeworm infections was first described in 1999: (Wilkins et al. 1999). It describes the Excretory Secretory (ES) protein group as a possible AB target, which can be used to detect tapeworm infections in humans. rES33-EITB results are not part of our NCC diagnostic criteria, based on findings from: (Levine et al. 2007, Handali et al. 2010). rES33-EITB was however used to identify adult tapeworm carriers with current or sero-scar status. This becomes relevant when analysing clinical risk factors, as tapeworm carrier status represents one of the principal risk factors found in this study. RES 33 EITB helps to broaden and to better understand the relevant infection criteria in Uganda, as it shows that tape worm carrier status is a great risk factor for suffering from NCC at the same time.

Current Del Brutto et al. criteria also include AG as major criteria in their NCC diagnostic process (Del Brutto et al. 2001, Del Brutto et al. 2017).

In our work, AG testing was added alongside with the prior AB testing as another major criteria for the final NCC diagnosis. The states of diagnostic strength are based on the original Del Brutto criteria, as proposed in 2001. AG testing to be included was initially proposed by (Gabriel et al. 2012).

In this thesis B158/B60-ELISA helps to identify additional patients that are AB negative but AG positive. In accordance with the Gabriel et al. criteria we also used the B158/B60-ELISA as equivalent to other major criteria, such as *T. solium* cysticerci specific ABs (Gabriel et al. 2012).

100% of patients that were positive in either tests were subsequently diagnosed with NCC in this thesis. There is no test to fully distinguish between cysticerci within or without the CNS. In our study we therefore assumed that clinical signs and a positive test result is considered as NCC positive, even though patients could also suffer from epilepsy and/or headaches caused by a different agent and the cysticerci might be placed somewhere else in the body.

It is always complicated to define a gold standard when trying to assess NCC serology reliability. As both AB and AG tests were part of our diagnostic criteria. The following values

needs to be considered with caution, as we do not have another, separate gold standard to compare both tests to. As both tests are part of our diagnostic algorithm, it is a systematical error which still permits to give a tendency as to what test is more effective within the diagnostic framework. AB tests ended up identifying 29 out of 40 NCC cases (73%), whereas AG test only identified 7 out of 40 NCC cases (18%). Only one patient was identified through AG tests alone. When comparing those aforementioned values, AB testing was more than 4 times more sensitive to detect NCC. AG testing should therefore only be used as an addition to AB testing to identify recently infected patients. This result was also suggested in: (Bueno et al. 2005). Our data distribution supports this proposition. Rodriguez et al. clearly stated that AG testing is not as sensitive or specific as AB testing. However, it is a good tool for follow-up, as circulating AG correlates with the quantity and type of cysts(Rodriguez et al. 2012). This relation was found in both humans and pigs. This might play a role in point of care tests to control treatment success in the future.

Quality criteria for statistical analyses are not fully met by the sensitivity/specificity values given in Results: 7.1.1 Serology diagnosis of cysticercosis and taeniasis. However, those numbers help compare the different aspects of the diagnostic criteria amongst each other and they are therefore useful to identify what serology tests do within the diagnostic criteria.

8.2.2 Applicability and future approaches of the neurocysticercosis diagnostic criteria

Neuroimaging appears to be the most direct way to diagnose NCC, as the cyst may be directly detected. Both serology and CT alone can be seen to have a highly predictive value (100%) (see also Results: 7.1.2 Computed Tomography diagnosis of neurocysticercosis). It needs to be noted that we did not use a separate gold standard to calculate those diagnostic test values. Both, serology and CT, are separate indicators that point to the final diagnosis. The results for neuroimaging test strength are similar to the results for serology, with a slight superiority of serology over CT. In order to receive high diagnostic security, a combination of serology and neuroimaging is used in current diagnostic criteria (Del Brutto et al. 2001). This approach is problematic in resource poor countries, because of the lack of neuroimaging facilities. The option of relying on serology alone, alongside with a risk factor analysis in resource poor countries is one of the central propositions of this thesis.

As both serology and CT scan results yield a low sensitivity for the diagnosis of NCC, both do not qualify as a screening test. It is therefore important to pre-screen the population in endemic areas for individuals at risk. Here, epilepsy types, headache types and clinical characteristics

and other risk factors such as age, economic details and information about their endemic origin may help with pre-selecting a patient pool with a higher likelihood of a positive NCC diagnosis. This approach may help to increase sensitivity without creating essential extra costs. It is also used in other chronic diseases, such as prostate specific antigen (PSA) screening for prostate cancer (Li et al. 2015). PSA or better the development of PSA over time is a pre-screening criteria that helps to decide whether further, more invasive diagnostics are necessary (biopsy).

By combining serology and CT results, as indicated in the Del Brutto criteria, the final sensitivity to detect NCC is improved (Del Brutto et al. 2001). In order to fully define the sensitivity for the Del Brutto criteria as a whole, pathology findings are needed to identify patients with positive NCC status with a unified gold standard. This was not available in this study. Therefore, the Del Brutto criteria were considered as the gold standard for all calculations.

As positive predictive value depends on prevalence, by better defining our pre-selection criteria (epilepsy recency etc.), we were able to receive a positive predictive value of 100% in both serology and CT-scan results. If we apply this to the current situation in resource poor countries, it might be sufficient to develop a pre-screening catalogue of risk factors from various fields: 1) Endemicity of residence area; 2) Age (and sex); 3) Seizure type/history; 4) Seizure onset; 5) Headache type/history; 6) Occupation; 7) Social/socioeconomic background
After effective risk factor pre-screening, the application of a compound serology kit, combining different serology approaches, easily applicable in resource poor countries, might be sufficient to receive a high positive predictive value for the final diagnosis of NCC. In our research we could show that pre-screening leads to a better positive predictive value. Current advances in serology testing (Noh et al. 2014), may lead to more applicable tests in resource limited areas. Even if a combination of serology and neuroimaging, as defined in the Del Brutto criteria, still remain the most favourable diagnostic approach, neuroimaging still remains sparse in basic healthcare settings. This is different for serology kits that are easier to handle and to distribute and therefore have a great diagnostic potential in resource poor countries.

8.3 Risk factor analysis

8.3.1 Sociodemographic risk factors

The average age of NCC positive and NCC negative PWE population is statistically significantly different. This result confirms findings in other studies that NCC prevalence increases with age and it is more common in older PWE (Fleury et al. 2010), (Millogo et al.

2012), which might be due to a long incubation period between the contact with *T. solium* and the symptoms. This reasoning is supported by the fact that the difference in age of seizure onset is also statistically significant. It is higher in NCC positive PWE (24 years vs 14 years; P<0.001). Another interesting fact is a difference in age at marriage. Even though only borderline statistically significant (p=0.065), the average age at marriage is 26 years in NCC positive and 23 years in NCC negative PWE. To receive further information about the reliability of this fact, a bigger study population is needed. However, assuming that NCC patients are somehow socially more noticeably unhealthy, it might decrease the social standing required for an earlier wedding in comparison to other PWE. This is especially interesting, when bearing in mind that there is no statistical difference in seizure frequency between the NCC groups.

Due to ethical constraints we were not able to include children younger than 12 yo into this study. Other papers however support our finding and show that NCC prevalence is lower in younger people. This might be due to the fact that genetic disorders causing epilepsies typically manifest during childhood, whereas acquired causes of epilepsy only manifest at a later date in life. This hypothesis is further discussed in the book: *"Taenia solium Cysticercosis: From Basic to Clinical Science"* Gagandeep Singh, Sudesh Prabhaka (Singh et al. 2002). From a study point of view, excluding children may create an over-representation of the NCC population within PWE. As NCC is less common in children, excluding children will lead to a higher overall prevalence, leading to an over-estimation of prevalence. As the ethics committee requested to exclude children under 12, a certain amount of inaccuracy is present. We had to make assumptions about NCC distribution in under 12 yo. As the average seizure onset of NCC patients is 24 yo, in comparison to 14 yo in the remaining PWE population, and a long period between infection and seizure onset can be assumed, in our model we decided to set prevalence to be 0 in children under 12 see Tables: 12.6 Table 6.

Education seems to have a protective effect. Even though no relationship between level of schooling and NCC could be established (p=0.104), we accepted the completion of level four primary school as formal education. This basic measure of schooling provided a protective Odds ratio of 0.18, which makes it a protective risk factor of 5.6 (OR 0.18[CI: 0.07-0.43]). A possible confounder could be a lower average age for students, than in the average study population (average: 15.26 years [SD: 3.9] for students [111 students] and 25.7 years [SD: 13.41] for the total study population; P<0.001). Age could therefore in parts explain the high OR. However, from an epidemiological point of view, a higher education level will also influence living conditions and therefore decrease potential infection. For more details about

the impact of confounders on univariable risk analysis, please see Discussion: 8.3.4 Causality in risk factor analysis.

The schooling analysis was done with reference to the farming population, as farming was the biggest occupational group. The design of the test also implies that farmers have an increased risk of attaining NCC. OR 5.6 (inverse of 0.18 [CI: 0.07-0.43], p<0.001) (see Tables: 12.6 Table 6). From an epidemiological point of view, age might also play a role as a possible confounder for farming as well as for student status. In order to identify a confounder, three prerequisites need to be fulfilled (Breslow et al. 1980, Hennekens et al. 1987, PHAST 2016):

1. Age needs to be a risk factor for NCC: Age is the main risk factor (p<0.001), with a 6% (CI: 3-8%) increase in risk per year of life lived.
2. There needs to be a correlation between farming and age: The average age of farmers is: 35 years (SD: 13.3years) (116 farmers), whereas the average age of the overall study population is 26 years (SD: 13.4 years) (p<0.001). The farming population is therefore older than the average population and this difference is statistically relevant.
3. Confounders cannot be an intermediate step between risk factor and disease. This prerequisite is fulfilled. Age is not an intermediate step between farming and an NCC infection.

Age needs to be considered as a relevant confounder, explaining at least in parts the large risk attribution to farming or student status. It also relativizes the risk reduction attributed to being a student.

When considering the life cycle of *T. solium*, it is likely that both farming and student status are relevant factors. Farmers have more contact to soil and farm animals, whereas schooling and academic work happens away from potential sources of infection. In order to fully understand and exactly quantify its impact, a new study is needed with equal age distributions in both risk groups and overall population. Unfortunately no definite figure can be attributed to both farming and academic progress due to possible confounding through age. Based on the information below, it is likely that at least some risk may be attributed to occupation. If you cannot implement a new study or change the study design, there is another way to work with confounding factors or at least assess their impact on relevant risk factors: multivariable analyses and linear regression models. Based on an epidemiological publication from 2012: (Pourhoseingholi et al. 2012): "*How to control confounding effects by statistical analysis"*, we evaluated the impact of age on occupation and student status. We included all types of

occupations reported (see Tables: 12.6 Table 6) and analysed it against age. On multivariable analysis, we found adjusted effects for age (aOR=1.04 [CI: 1.01-1.07]; p=0.013) and farming (aOR=3.22 [CI: 1.33-8.23]; p=0.011). Both remained statistically significant. In practical words this means the adjusted risk attributed to age is: 1,036. This amounts to $1{,}036^{10} = 1.42$ in ten years. The result states that the risk of attaining NCC increases by 42% in ten years. This result bears in mind other possible interlinked ratios like occupation, student status and drinking habits that also change over time, and also seem to have an impact on the infection rate (Tables: 12.5 Table 5). However, this is only a linear model with a static risk situation for each year gained. If using a non-linear attribution model, implying that not every year yields the same risk of infection, this number decreases to 38% over ten years. The different models all yielded a statistically significant odds ratio to both age and farming.

As non-flexible risk factors (age) are not susceptible to change through policies, further work ought to be focused on reducing infections in high risk jobs such as farming. Farming has been in the focus of developmental aid for years (Ampaire et al. 2010, United-Nations 2013). However, self-sufficiency has mostly been the focus of possible intervention programmes trying to promote family farming as a sustainable source of income. Food safety has rarely been an issue, as the production was mainly aimed for family and close-by neighbours. This policy, especially promoting pig farming without ensuring basic food and hygiene safety measures, may have reduced famine and financial dependency of people in resource poor countries, but has also enabled food borne diseases to become an important healthcare threat in those countries. It is therefore important to consider and evaluate possible consequences of intervention programmes, before they are implemented. It is also important to review current measures taken and to rethink whether certain amendments in policy at NGO, national and international level may be able to reduce infection rates. For proposed intervention methods proposed by the WHO please refer to Figure 5 in Chapter 11. For a complete overview of what factors can be influenced please refer to Chapter 9 Overall summary and conclusions: Graphic 2.

Alcohol consumption was statistically relevant in univariable analysis as a risk factor consumption (OR: 3.65 [CI: 1.2-10.1]). No statistical significance was found when correcting for age and occupation. As alcohol is freely available in Uganda, it is often consumed openly on the street. It is cheap when comparing it to average food prices. 72% of the population are dependent on farming. As farming is also a social indicator, for less affluent families (The-World-Bank 2013), a correlation between drinking habits and economic prosperity may

influence the actual risk factor. Socioeconomic standing could therefore be a confounder that will need to be assessed in more detail. This phenomenon might explain the relatively high odds ratio for alcohol. To fully understand the risk attribution, an equal socioeconomic background ought to be guaranteed in both study groups.

8.3.2 Behavioural risk factors

Pork consumption was no risk factor for contracting NCC (OR: 1.46 [CI: 0.69-3.38], p=0.337). At first thought this might be surprising, but when looking at the *T. solium* life cycle, NCC is not contracted through the consumption of pig meat, but through the accidental infection with eggs from human faeces. As pork consumption is relevant to maintain the life cycle of *T. solium* and maintain a sufficiently large number of infected humans, in order to spread a high enough number of eggs throughout the community, meat inspections have proven effective when combating NCC, even though pork consumption could not be linked directly to the NCC infection.

Another, yet poorly examined, approach is the development of a pig vaccine against cysticercosis (Jayashi et al. 2012). In studies, cc-vaccines are often combined with oral anti-cyst treatment (oxfendazole). This new approach, may be a key component in battling the *T. solium* prevalence in Sub-Saharan Africa, helping to fight the replication of *T. solium* and therefore the potential infection of humans with NCC, based on Professor Marshall Lightowlers, University of Melbourne, Australia. As one of the leading scientists in this field with many new advances and strides against tapeworm infections. He postulated many times that the solution to the NCC epilepsy symptoms might be an animal vaccine (Lightowlers 2006, 2010, Lightowlers 2013, Lightowlers et al. 2017). However, vaccines are often not affordable by farmers and up to now not supported by the government.

Meat barbeques are very common in northern Uganda. However, large pieces of meat are prepared at one time, which does not guarantee a fully cooked piece of meat. Often, parts of the consumed food are still raw and have therefore a higher infection risk. Further research is needed to fully assess the risk of barbequed pork meat in Uganda. The CDC in Atlanta proposes a 63-71°C cooking temperature in the deepest layer of the meat to prevent transmission (CDC 2013c). However, in Uganda, based on current socioeconomic developments, it is unlikely that people will start using kitchen appliances to measure pork temperature while cooking.

8.3.2.1 The role of knowledge in neurocysticercosis

As knowledge is an interesting toe hold for future interventions, it would be worthwhile assessing how much difference an information campaign could evoke in terms of change in prevalence. Studies should also ask for a detailed description on patients' definition of current knowledge. From our data, it becomes apparent that many of the information thought correct by the patient are based on hearsay and do not reflect a solid understanding of the impact of tapeworm infections. Often, even though knowledge is presumed through questions in questionnaires, facts on transmission and risk factors are largely incorrect. 10% (14/135) of people link NCC mainly to walking bare foot. Only 44% (60/135) of 135 people who answered that they know and comprehend the source and infection process of NCC, relate it to the consumption of contaminated food or water. The real number may be bigger, as the questionnaire as such creates a certain information bias, as it does not check knowledge directly. It contains many questions on pigs and hygiene safety. This makes it easy to deduct that pigs and hygiene may play a role in the infection process. It therefore indirectly provides answers to questions that come up later in the questionnaire. Further research is necessary, especially as knowledge training is a favourable method used in many tropical disease settings. The WHO provides a large variety of training materials in other fields: e.g. malaria. Similar approaches are needed for *T. solium* endemic areas.

When asking about the source of NCC and relating it to NCC rates, no statistical evidence was found (p=0.561). It is interesting to see however that 57% of respondents received their information not from the healthcare system or the media, but through family and social surroundings. This might be a sign that hardly any effective awareness training for NCC has happened so far in northern Uganda. We were not able to show that awareness training has a relevant statistical impact on the infection rate, this may largely be due to wrong and imprecise information available on NCC, even among those patients who reported to have positive knowledge. In order to implement awareness training campaigns it will be worth wile to assess prevalence change over time when using media and traditional information platforms like schools etc. A study such as the study on NCC prevalence change through farming interventions granted in 2010 to H. Carabin (Carabin 2010a), but with an additional analysis of precise information distribution, would be interesting, in order to understand the relation between knowledge and NCC infection rate better. During field work time in Uganda, I was able to support the implementation of a pig farm at a regional detention centre (Remand home, Gulu (King 2014)),trying to make sure that all players in this project knew about potential risk factors

and sources of infection. Working on knowledge and understanding of how NCC infections happen, appear to me as one essential intervention technique, when trying to further decrease NCC prevalence. Offering advisory services in local farming projects may be one very important feature in disrupting the life cycle of *T. solium*.

Questions on pig keeping and meat inspection techniques were all not statistically significant (home slaughter: p=0.728) (house inspector: p=0.512) (free roaming p=0.865). The total number of replies we received in this field sometimes only represented 10% of the entire study population. From other studies, there is some evidence especially from Mexico and South Africa that those factors do influence NCC prevalence within a population (Murrell et al. 2005, Morales et al. 2008, Foyaca-Sibat et al. 2009). Those factors also need to be addressed with especially targeted education and guideline programmes for pig owners. The detailed questions and their relevant statistical answers can be found in Tables: 12.7 Table 7 and the Appendix: 13.1-13.5 (questionnaires).

8.3.3 Clinical prediction rule for neurocysticercosis

Our epilepsy diagnosis is based on the ILAE criteria (Fisher et al. 2005, Fisher et al. 2014)). We also sub-divided our epilepsy patients in four groups, based on a locally adapted epilepsy classification by Winkler et al. (Winkler et al. 2007). Also, see Material and Methods: 6.3 Diagnostic criteria for epilepsy and its role in neurocysticercosis). The same classification was already used in a similar study in Tanzania (Blocher et al. 2011). No statistical relevance was found when characterizing seizures in the proposed four sub categories: (p=0.225). Further research is needed to verify the mentioned classification as a pre-test method.

8.3.3.1 Treatment of people with epilepsy and neurocysticercosis

We tried to assess whether PWE with NCC had different seizure reduction rates than the control group PWE. However, neither the overall fit frequency-, before or after treatment was different. There was also no significant difference in relative reduction in seizure frequency (p=0.163). Even though the arithmetic averages appear to be very different (77.7% reduction to 48.2% reduction), due to a non- normally distributed reduction distribution, we had to analyse median differences (91.8% to 87.5%), where no statistical significance was found. In further studies, it is advisable to explore the causes for epilepsy further, as refractory epilepsy due to brain lesions may have caused the few patients not responding at all to treatment within the PWE control group. This may have caused the reduction distribution to be non-normally distributed. There are a couple of reasons why this sub-group of people has not experienced any improvement on

treatment. One option is always possible non-adherence. Within the NCC population, treatment was just as successful as in the control group when comparing median values alone. In all patients, 76 out of 294 (26%) reported no further seizures after treatment start. Within the NCC group 15 out of 40 (37.5%) and within the control group 61 out of 260 patients (24%) reported no further seizures after the start of treatment. This difference was not statistically significant (p=0.298). As no difference in adherence/compliance was found (p=0.473), we assume that symptomatic epilepsy treatment is just as successful in the NCC sub-group as in the PWE control group. As the likelihood of secondary epilepsy is higher in resource poor countries, it would be interesting to see the NCC response in comparison to a more uniform control group of only generalized epilepsy without obvious cause such as brain lesions on imaging.

8.3.3.2 Headache characteristics in people with epilepsy and neurocysticercosis positive patients

Headache details are given in Tables: 12.9 Table 9. Please beware that the table values give percentages per line, whereas in this paragraph, we look at headache percentage within patient groups (columns). This is due to the fact that each paper presents their data differently. Our value of PWE and NCC suffering additionally from headache (23%) is lower than proposed in the clinical review: (Carabin et al. 2011): 37.9%. However, Carabin et al. refers to all NCC cases, whereas we only measured NCC patients within the PWE population. She also says that 78.8% of NCC patients present with epilepsy. When you combine these two values you can assess the quantity of NCC patients with epilepsy that have headache:

0.788 x 0.379=0.298.

Based on that calculation her study reports 29.8% of headache patients within a PWE population. This number is close to what we found (23%). PWE, who additionally to epilepsy, present with headache, have a 2.44 times higher risk of suffering from NCC (OR: 2.44 [CI: 1.01-5.52]). When referring to prior literature in the field of NCC, there is a large variety of diagnostic items required to reach the diagnosis of NCC. As described by Del Brutto in 2012, there is an association between NCC and headache (Carabin et al. 2011, Del Brutto et al. 2012). They explain that NCC is more prevalent in headache-prone patients. Our data supports that hypothesis. Our population showed a statistically significant result of a higher headache prevalence in the NCC positive population within our PWE group. .We have also retrieved additional headache type information. However, our study population with its 40 NCC positive

patients was too small to analyse more information on headache in PWE and NCC with confidence.

8.3.4 Causality in risk factor analysis

When talking about risk factors in epidemiology, one key element is the question on how causality can be attributed to correlation. Odds ratios and statistical significance describe a similar distribution in two variables in two or more study populations. It does not explain why or how certain risk factors may influence each other.

In 1965, Sir Bradford Hill defined a list of causative agents that are used to verify whether a correlation indeed represents a causation (Hill 1965). His list contains:
1) Strength; 2) Consistency; 3) Specificity; 4) Temporality; 5) Biological gradient;
6) Plausibility; 7) Coherence; 8) Experiment; 9) Analogy
He tries to establish a basis on which "*observed association"* can be considered as causation. When assuming his factors to be correct, this means that each odds ratio needs to be seen in the light of the aforementioned points:

1) There should be a strong correlation. The stronger a correlation the more likely there is a causative agent. This means a high odds ratio or a very small p value makes causality more likely.
2) Consistency of results: Findings should be externally validated. Possibly through other independent and individual studies.
3) The correlation should be specific. This means there needs to be a possible link in theory that can explain a possible interaction.
4) There should be a chronological order. The impact must have happened prior to the visible effects measured.
5) There should be a biological gradient. This implies that a higher burden leads to a measurably higher effect.
6) Findings should be coherent. When talking about coherence, it implies that a plausible explanation is found that, if possible, does not contradict the current state of knowledge.
7) Interventions should trigger change. Based on the risk factor, possible interventions ought to lead to possible improvement or deterioration.
8) The theory should be reinforced by experimental findings. If there is a correlation based on biological premises, experimental results should confirm the aforementioned findings.

9) There should be analogy within the risk factors. This means that similar influences should produce similar results. For example two risk factors that influence hygiene should yield similar risk attributions.

Points free after: Hill 1965: "The Environment and Disease: Association or Causation?"(Hill 1965)

When working with risk factors, it is therefore always important to reflect on what a risk factor is and what it really represents. Only after a long line of confirmatory steps, can a risk factor be taken for what it is. In theory, these steps appear to be logical and concise. However, newer papers acknowledge that realistically, not every risk factor will be verifiable by the Hill criteria. Rothman et al. say that it is more of an exercise that needs to be pursued and that this ought not to be seen as a check list that needs to be fulfilled before a causality can be assumed (Rothman et al. 2005).

One further aspect when talking about risk factors is their attribution to actual predicting values. Clinical risk factors refer to values that can physiologically be measured in a clinical setting e.g.: blood pressure or high cholesterol as a clinical risk/predictor factor for diabetes: (Lyssenko et al. 2008). Clinical predictors define a broader field of values. They are often used in scores to better define one specific patient population. Scores ,such as the Ranson score, Wells score, are based on clinical predictor rules. They are also called clinical decision rules, as they are important for clinical algorithms (Mcginn et al. 2000). This is an important application for risk factors and predictors, as it applies them to clinical settings of prospective patients and helps the attending physician to base his decision on facts rather than gut feeling. This approach is also taken in this study. When we describe a "typical NCC patient", our values try to reflect pre-selection criteria for future clinical algorithms to diagnose NCC in resource poor countries.

8.3.5 Complexity of risk factor analysis

One important factor in all epidemiologic studies is the strength of possible risk factors. Especially when bearing in mind possible confounders, it is important to be able to attribute some proportions to certain risk factors that influence each other. Multivariable analyses try to include an allowance for possible interference with other risk factors. The number of factors included in a multivariable analysis depends on the strength of a risk factor and the chosen study population. A bigger sample size within a larger study population will produce more reliable results. Field research in Africa is often difficult to organize and execute, as many standardized procedures and resources are not available or cannot be relied upon. This was also

the case with regards to some aspects of our study. For instance, we could only allow 300 PWE to undergo further exams. We complemented some of the univariable analyses we complemented with multivariable analyses to increase reliability: Risk factors /protective factors such as alcohol consumption farming and studying, are all influenced by age as well as by each other. Farmers are mostly older than students, they are more likely to have a drinking habit and less likely to have an academic background. Consequentially, this thesis tried to give both univariable and multivariable data for major risk components of the risk factor range. The problem with risk factors or odds ratios is that with only a small number of patients (40 NCC cases) only very strong correlations become apparent. Also, confounders and bias are a problem at every level of the analysis. Because we had to use different interviewers translating or explaining questions in different languages, the individual understanding of a question often led to imprecise replies that were not usable and this reduced our study population further. In our tables (Tables: 12.6-12.11 Tables 6-11) this is indicated with the total number of answers received per one question (n=…). Also, some administrative problems led to different ID numbers in patient questionnaires and CT-scans, making data attribution at times difficult.

Further limitations were that we had to choose 300 PWE for further diagnostic work-up based on their last seizure, as a way to measure active epilepsy. Active epilepsy has already been used in other studies as an indicator for NCC (Raina et al. 2012). Also, Del Brutto et al. described active epilepsy as a valid pre-selection criteria for NCC (Del Brutto et al. 2001). Even though this is done in many studies, it might lead to an over representation of NCC within the total population of PWE. Often, this value is generalized to the prevalence within the epilepsy community in resource poor countries. As the definition for active vs. controlled vs. in remission (without and with treatment) is an ongoing discussion in expert groups (ILAE 2013), the exact impact of this generalization remains unknown.

8.4 Burden assessment

For our socioeconomic burden assessment, an incidence based human burden approach was used. We found more than 9,000 new NCC-epilepsy cases and approximately 1,500 new NCC-headache cases in 2010 alone. The NCC-epilepsy cases lead to nearly 3,000 NCC-epilepsy related deaths, due to a higher disease specific mortality than the mortality of the average population. 29.4% (case fatality ratio) of the total 2010 annual cases statistically experience a disease related death in their lifetime. Other studies calculated case fatality rates (per year), which are difficult to compare with our result:

- (Praet et al. 2009): 6.2% of the total annual incident cases in Cameroon
- (Bhattarai et al. 2012): 0.5% of the total annual incident cases in Mexico
- (Devleesschauwer et al. 2014a): 1.5% of the total annual incident cases in Nepal
- (Trevisan et al. 2016): 1.2% of the total annual incident cases in Tanzania

In our study, different data sources were used as input. Instead of extrapolating missing data from studies in other countries, we calculated epidemiological parameters using the DisMod II model, making our data internally consistent (Barendregt et al. 2003).

In (Mafojane et al. 2003), Uganda is assumed to be just as endemic for *T. solium* than the neighbouring countries: Tanzania, Zambia and Kenya. More recent studies show that there is no effective control of porcine cysticercosis (Nsadha et al. 2014). In (Waiswa et al. 2009), *T. solium* porcine prevalence is considered to be a good indicator for the threat of *T. solium* to humans. Therefore, we attributed prevalence attributions from the north to the entire country. By doing so, we may create a certain under-assessment, as we did not specifically adapt for more affluent areas like Kampala or Entebbe, where healthcare expenditure may be higher. On the other hand, the prevalence of NCC might most likely be lower in more affluent, urban areas. Northern Uganda seems to be a good representative for the average population suffering from poor financial- and healthcare resources, which is the case in most parts of Uganda. As this group will be the main beneficiary of possible healthcare interventions, this generalization to the national level appeared to us as the most prospective form of data handling, in order to secure a high reliability for the outcome. If more data on epilepsy and NCC were available for Uganda, this would largely simplify matters for further studies. As national data on age structures, mortality rates and life expectancy is more reliable than data from local or regional authorities, is was easier to use standardized statistical data distributed by the Ugandan Bureau of statistics, the United Nation or the World Bank for Uganda as a whole. Even though Uganda is subdivided in regions and municipalities, the specific borders and regions have undergone many changes over the last decade, making it hard to verify what part was included in a certain data base and what part was left out. Also, specific data, such as age distribution for mortality rates, were not available from regional sources.

8.4.1 Disability-adjusted life year burden assessment

The DALY disability weight for epilepsy and headache is based on the classification adopted from the GBD (Global Burden of Disease Study 2015, Salomon et al. 2015, Vos et al. 2015).

8.4.2 Disability-adjusted life years for epilepsy

The aetiology or any international epilepsy classifications are not taken into consideration:

- 1 or more seizures / month= severe epilepsy
- Less than 1 seizure/month= controlled epilepsy

This is a simplified model trying to attribute burden to crude seizure frequency. We used this model for the DALY attribution. Patients that have one or more seizures per month are considered severe since the start of symptoms. Patients that show a seizure frequency of less than 1 per month, were considered as severe epilepsy patients until the start of treatment. The vast majority (approx. 95%) were able to reduce seizure frequency through treatment. Ideally, there should be a continuous increase of seizure frequency and attributed DALY burden. As this becomes a very complex mathematical model, the simplified categorization of epilepsy takes a possible under reporting of burden into consideration, in order to maintain a clear comparable value. Based on our data, the difference in treatment adherence in PWE was assessed. This was done by asking whether the patients were taking AED at any one time during the last year (298/299). We used this as a base line and compared it to the results of whether they were currently taking any AED (224/300). From that difference we calculated the current adherence rate. We also used this result for our DALY and economic calculations, assuming that the adherence/compliance rate was 100%- 24.7% =75.3%. In The UK 89% of all recently prescribed AED drugs were taken and only 76% of all doses (Packham 2009). As our data is based on patient feedback and not on directly observed therapy, there might be a certain uncertainty due to patients reporting higher compliance than what they really took.

For a resource poor country, this number is however rather high. Many of the factors identified for non-compliance, such as feeling stigmatized, side effects, and financial burden (Packham 2009), apply also to the PWE in Uganda. A study from 1993 in Tanzania reported a strong influence on peoples' perception of epilepsy though local and traditional theories about epilepsy (Rwiza et al. 1993). In a study from 2003 (Murthy 2003), a treatment gap of 80-94% was assumed in resource poor countries. The term treatment gap refers to the number of people who are not treated for a certain disease for whatever reason. As our numbers are based on interview reports and not on blood sample-testing for substance levels, it can be assumed that the actual adherence rate to AED in Uganda may be lower. When comparing our adherence rate to the average reduction in seizure frequency and the percentage of patients that are fully seizure free, AED treatment appears to be a valuable method to control epileptic seizures caused by NCC.

Even though the aforementioned factors may explain the different treatment success rates between different patients, non-adherence also creates a higher burden in terms of DALY. As patients from resource poor countries have access to less treatment options and face more social and financial restraints due to epilepsy and its therapy, the actual quality of life lost due to epilepsy may be higher than in resource rich countries. However, DALY calculations do not include economic restraints directly into its burden assessment. There is only one DW for epilepsy with one or more seizures per month and for controlled epilepsy with a seizure frequency of less than once a month. This approach was chosen to equally value the quality of life regardless to the economic or political situation of a population. This is one of the major differences between monetary impact assessments and quality of life burden. However, it is far from perfect and only represents one perception of suffering. In reality, there is a connection between monetary and DALY burden. Some factors such as adherence and consequentially seizure frequency are dependent on financial sustainability.

8.4.2.1 Disability-adjusted life years for headache

For our burden assessment we roughly subdivided the NCC headache population in tension type headache and migraine type headache. We only included migraine with aura into our burden assessment, which is very likely to under report the actual burden of migraine, as we did not have sufficient information to diagnose migraines without auras. Visual aura migraine patients represent only 15%- 30% of all migraine patients (Gutman 2008, Gilmore et al. 2011). As tension type headache has a much lower disability weight than migraine (0.037 and 0.441), this will largely under-report the YLDs caused by headache due to NCC. In order to maintain a conservative estimate, it was important not to include speculations on possible migraine patients, where the full diagnostic criteria for migraine could not be clearly fulfilled. Our diagnostic criteria for headache was based on the classification of the International Headache Classification (IHS 2013) as explained in Material an Methods: 6.5 Diagnostic criteria for headache. This is only the second NCC study to include headache symptoms in their burden assessment. The first study was done in Mexico (Bhattarai et al. 2012). However, headache type was not specifically subdivided in TTH and migraine type headache. In this previous study, severe chronic headache was defined as: Duration of more than three days. Based on whether the headache was treated or not, they applied 0.028 and 0.007 for untreated and treated severe headaches accordingly. They took this information from: Global Burden of Migraine in the Year 2000, published online (Leonardi M 2000), which again is based on the GBD 2000 study.

We chose, based on the GBD 2013, to use the official disability DW proposed in the aforementioned publication (Salomon et al. 2015):
TTH: 0.037 and migraine: 0.441. Also, we used a zero remission rate for NCC related symptoms. Bhattarai et al. used a remission rate of 2.9-4.8 years. Those differences resulted in a much higher per incident case burden. Our study found 7.1 DALYs, whereas Bhattarai et al. found 0.09 DALYs per incident case. Due to different epidemiological choices, comparison on a study to study level is difficult in this situation.

For economic evaluations, one-off paracetamol treatment was assumed main treatment option based on average headache frequency. Other direct costs, both medical and non-medical were not included. No indirect headache costs were included in the overall estimation of the NCC burden. This may create a possible under- reporting of actual economic burden due to headache.

8.4.2.2 Overall DALY estimates

We estimated 5.5 (95%UI: 4.3-6.9) DALYs per 1,000 person years. In comparison to other studies, our value was somewhat higher. All results are given in DALYs per 1,000 person years.

- (Bhattarai et al. 2012): Mexico: 5.5 (95% UI: 4.3-6.9)
- (Devleesschauwer et al. 2014a): India: 0.553 (95% UI: 0.207-1.054)
- (Trevisan et al. 2016): Tanzania: 0.7 (95% UI: 0.2-1.6)
- (Singh et al. 2016): India: 1.7 (95%UI: 0.82-3.39)

However, Praet et al found a higher burden estimate: 9 (95%UI: 2.8-20.4) DALYs per 1,000 person years in Cameroon (Praet et al. 2009). Comparability is a major issue in burden studies, as almost every study seems to develop its own way to estimate burden in a country specific context. It also depends on data availability and quality, as well as level of assumptions. Some studies apply a 3% discount rate or age weighing (Mexico and Cameroon). Discount rates or age weighing mean that future life years have a slightly lower value than current years. We did not use that assumption for our calculations. Assumptions about remission and mortality also differ. Therefore, not too much value can be put into direct comparisons between different studies. It is more interesting to re-compare burden studies within one country over time.

8.4.3 Economic burden

INHC dominated the NCC cost-of-illness calculation, especially the productivity loss due to severe epilepsy. The other burden assessment studies mentioned above also found that INHC contributed substantially to the overall economic burden. Our INHC burden was higher than in

those studies, as we included the productivity loss for one relative, who has to be present during hospitalization periods for healthcare purposes. In other studies, professional healthcare staff was considered as part of hospitalization costs (DHC). Other indirect costs such as lost business opportunities, missed pay rises or possible redundancy, because of NCC are not included in our calculation, possibly leading to an underestimation of costs created by NCC. DHC was the second biggest contributor to the economic burden of NCC. Similar distributions were found in two of the aforementioned studies (Praet et al. 2009, Trevisan et al. 2016).

In our analysis (for algorithm steps see: Material and Methods: 6.8 Decision trees), we tried to map the decision process and the attributed costs. However, often this is not easily done, as some costs are covered by the government or national health insurance, but some hospitals charge additional fees. We tried to represent the full scope of costs generated, by scoping the estimates through our expert opinions. Expert opinion is an important and reliable tool in regions where either no official information on costs is available, or the information available appears to be untrustworthy. It has become clear that at some hospitals in Uganda, an admission charge is paid, when registering in the waiting room. Officially, no quote of that fee can be found. Also, the payment system in hospitals can vary tremendously. After examination, a prescription for further diagnostic tests is written, which needs to be paid by the relatives at a central payment post at the hospital. If this prescription cannot be paid for, no further treatment steps are taken. This payment is often an access-charge, covering only a certain percentage of the actual price for an examination or treatment. The remainder is subsidised by the government (in public hospitals). However, this charge may vary from hospital to hospital and also from day to day. The final price structure found in hospitals does not necessarily represent the official statements from the Ministry of Health. This is why we used expert opinion and not official quotes from the hospital carrier or agency. Even though expert opinion may be considered as a less valid source of information, in certain regions, they may be more representative than values published by local or national authorities. Unfortunately, we were only able to include three experts as sources. After several months of trying to encourage further input from local partners, we were not able to convince any more participants to qualify as experts. In further studies it would be desirable to implement an expert opinion questionnaire from the beginning. In most countries the pricing structure in the medical sector is very complex and varies depending on the patient's resources. In Uganda, there is a large price range possible, depending on insurance, financial situation of the patient, standard of medical care and region where the patient lives. We asked each specialist for possible minimum and maximum fees charged and calculated an

overall arithmetic average. In order to prevent an over-estimate, we implemented a gamma distribution to each expert due to the local situation in Uganda. It caters for the fact that more people are poor and will therefore use the lower end of the scale more often. Another problem with hospitalization costs are the additional costs due to medical imaging, or further diagnostics. Even though recommended in certain scenarios by guidelines, they are often not readily available. Their realistic use does not correlate with the number of patients treated for a specific diagnosis that should receive special diagnostics, based on guidelines. As no centralized information system is available at most hospitals in Uganda, the number of patients actually undergoing diagnostic procedures is lost and only rough estimates from experts can be used. For hospitalization, our study was based on a 0.192 seizure hospitalization rate, extracted from our survey data. We used this figure with an estimate of 0.1 for further diagnostics such as EEG. We further considered that CT, serology or MRI were hardly ever done (zero), outside of our study.

As provided by the UN and World Bank, we used 550 USD/year as an average per capita income and a 66% productivity loss in patients with severe epilepsy. In consequence, economic burden assessment will value the health of a high income population higher, but attribute the same DALY burden regardless to financial affluence. Changes in life expectancy and treatment options will influence both DALY results and economic burden. Over time the overall social behaviour and the living conditions may change, changing current risk factors and their relevance. Regular verifications of our results are therefore needed, especially if specific aid programs are implemented to combat NCC prevalence.

8.5 Diagnostic criteria of neurocysticercosis

The diagnostic criteria for NCC are an ongoing process. For more information on those criteria, see also Material and Methods: 6.6 Diagnostic algorithm of neurocysticercosis. We used the latest criteria available at the time of the study. We also used a variety of different serology tests to differentiate between cysts and tapeworm infections. These tests are however impractical when looking at the healthcare situation in rural Uganda or in resource poor countries as a whole. One needs imaging and serology tests that are expensive and not available in most parts of resource poor countries. The American epilepsy society defines steps that ought to be taken if epilepsy secondary to another disease is suspected; see guidelines: (AES 2015). In order to do so, it is important to try and find a clear cause for the suspected epilepsy. In that context, it is desirable to develop a NCC serology kit that is economically affordable and easy

to use in simple infrastructure settings. Pre-screening should be based on risk factors and on epilepsy criteria. This could reinforce a diagnosis of NCC, without causing too many healthcare related costs. New advances in serology (Noh et al. 2014), have made serology tests, developed by the CDC, more affordable for other laboratories. This may change serology testing in resource poor countries in the future.

In 2017, Del Brutto et al. published a revised version of their official NCC diagnostic criteria (Del Brutto et al. 2017). As data analysis was done between 2012 and 2016, we based our diagnostic criteria on the then current criteria. For details on used criteria, please refer to Material and Methods: 6.6 Diagnostic algorithm of neurocysticercosis. In the new version, Del Brutto et al. included recent changes in serology into the diagnostic criteria, such as the inclusion of AG into the diagnostic algorithm, as proposed by Gabriel et al. in 2012. More emphasis is put on MRI and specific imaging findings. The authors also define clinical signs of NCC more precisely, naming chronic headaches, focal deficits and cognitive decline besides epileptic seizures. He also included more clinical and epidemiologic factors. Close proximity to tapeworm carriers is now a major criteria, as suggested by our risk factor analysis in Uganda. For more information also see Results: 7.1.1 Serology diagnosis of cysticercosis and taeniasis and Discussion: 8.1.1 Tapeworm carrier status in people with epilepsy.

8.6 Drawbacks of the study

The data acquisition for our study was done in rural Uganda, which presented with several practical and clinical difficulties. Current ILAE criteria were applied (Fisher et al. 2005, Berg et al. 2010, Fisher et al. 2014). Due to language difficulties, local staff was needed for some of the history taking and diagnostic steps required for the diagnosis of epilepsy. This might have led to some degree of bias due to a different understanding of what a seizure is and how to precisely transfer information between different local languages. Some problems arose with the interpretation of how to stick to certain work instructions. Questionnaire replies that required personal inspection of toilet/hygiene facilities by the interviewing person were not met comprehensively, leaving this thesis with values that could not be used for further risk factor analyses. Many of the replies to the questions requiring inspection by staff were given by patients. Most patients reported a fully enclosed toilet. This does not represent the average living condition in northern Uganda and it implies a certain degree of imprecise answers due to possible social pressure experienced during the interview process. We did not analyse the data attained from those questions, as the amount of patient bias can be assumed to be high. In further

studies, it is important to clearly communicate to every participant the need to adhere to all requests mentioned in the questionnaire. Also, there should be a supervision system in place, verifying that all relevant steps are upheld during the interview/data collection period.

As our NCC prevalence is based on a PWE population and not on the general population, it under-reports the actual burden of NCC in northern Uganda. When using the 78.8% epilepsy rate among NCC patients from (Carabin et al. 2011), symptomatic NCC prevalence can be statistically corrected to 16.5% (see Discussion: 8.1 Study population, epilepsy prevalence and identified cases of neurocysticercosis).This was also done for our calculations using DisMod II values for the DALY and economic impact study.

We also excluded children under 12 yo from inclusion into our diagnostic study. This exclusion was necessary as a prerequisite for ethics approval from the local ethics committee. We assumed the prevalence for under 12 yo to be zero. We made this choice based on a list of logical conclusions. The NCC average age of seizure onset was 10 years above the actual seizure onset age in non-NCC PWE (24 yo vs. 14 yo). Moreover, PWE between 12 and 18 yo showed a NCC prevalence estimate of 7%, whereas over 35 yo had a NCC prevalence estimate of 33%. As it has been suggested that there is a period of a few years between infection and seizure onset (Dixon et al. 1934), it is a valid conclusion to consider NCC prevalence to be low in young children. For further analysis, we therefore assumed that NCC prevalence for under 12 yo was zero. However, this assumption creates an artificial selection bias within our study population that needs to be mentioned and taken into consideration when talking about resulting implications. This is especially significant in a resource poor country with a triangular age distribution. When doing further NCC research in the region, this point ought to be re-discussed with the ethics committee in detail, especially as children may have a larger benefit from a possible NCC diagnosis. One of the local arguments was the unnecessary risk of radiation exposure. The impact of NCC and epilepsy on children in Uganda is assumably higher than the statistical radiation risk undergone by a cCT with adequate protection. Also, a pre-screening catalogue for headache, epilepsy and further risk factors will yield a more narrow study population and may increase possible individual benefits. (Details see Material and Methods: 6.12 Ethical clearance.)

8.7 Future outlook

Scientific research on risk factors enables well-planned intervention policies. Economic and DALY burden help to put healthcare spending into perspective. Ideally, the results from the

current thesis may lead to an implementation study, similar to what was done in Northern Peru (Garcia et al. 2016). The authors compared different intervention techniques in northern Peru. For more information refer to Introduction: 4.6 Prior research efforts on T. solium (neuro)cysticercosis. In addition, the DisMod model we used, may be applied to different scenarios in order to quantify burden in different regions in Africa.

In the future, additional research is needed in order to overcome our shortcomings described. Another interesting study would be to assess the non-human impact of *T. solium* with regards to the consequences of animal health and market value loss due to porcine cysticercosis, to cater for the one health approach in combating *T. solium.*

With all this said, irrespective of knowledge etc., many farmers operate under very severe financial restraints. When bearing this in mind, knowledge on disease and hygiene management may not be the only factor important to combat NCC. If a farmer realizes that his pig is infected and burns the meat, his full investment is lost. When he sells it, however, he is able to refinance other pigs during their upbringing. Therefore, the farmer has no financial interest in elimination or prevention of porcine cysticercosis, or consequentially NCC, as it means a great personal loss to him in the short term. It is therefore important to implement compensation methods, where farmers are reimbursed at market value when reporting an infected pig. Otherwise, his economic standing forces him to sell his infected livestock, in order to not jeopardize the wellbeing of his family.

Resource poor countries harbour many causes for a higher prevalence of epilepsy and a higher overall mortality in epilepsy (Nevalainen et al. 2014), compared to high income countries. The authors state that the final mortality rate for epilepsy is largely dependent on the most likely cause of epilepsy within a country. Especially in resource poor countries, the causes of epilepsy differ from the ones in industrialized countries, so that our values are likely to be an under estimate, due to a higher percentage of symptomatic epilepsy in resource poor countries.

It is important to understand the exact causes and how to implement effective procedures to identify and support affected patients based on their disease etiology. Further research is needed in the different fields of identified risk factors and health systems, especially at primary health care level.

9 Overall summary and conclusions

This thesis portrays data of one of the largest NCC study conducted so far. This study elucidated relevant questions about risk distribution in northern Uganda. It assessed the prevalence of epilepsy, the prevalence of NCC in PWE and the clinical as well as the sociodemographic factors of PWE and NCC. It established a decision algorithm for PWE and NCC. It calculated the human burden of NCC (DALY) and the economic impact Uganda had and still has to face, due to NCC. It aims to help decision makers put their public health interventions into perspective and monitor success and progress when combating NCC.

Based on our data, we established a more profound knowledge about what defines a "typical NCC patient", by describing clinical characteristics and risk factors. This work may help to establish a pre-screening catalogue. A list of epidemiologic, sociodemographic and clinical predictive information may simplify the current diagnostic criteria. These new criteria will help identify patients who will benefit from blood testing and further diagnostics, as they may not have access to diagnostic tests routinely. If combining our suggested criteria for a "typical NCC patient" with the new advances in serology, a cheaper and more attainable diagnostic tool might become available soon in resource poor countries.

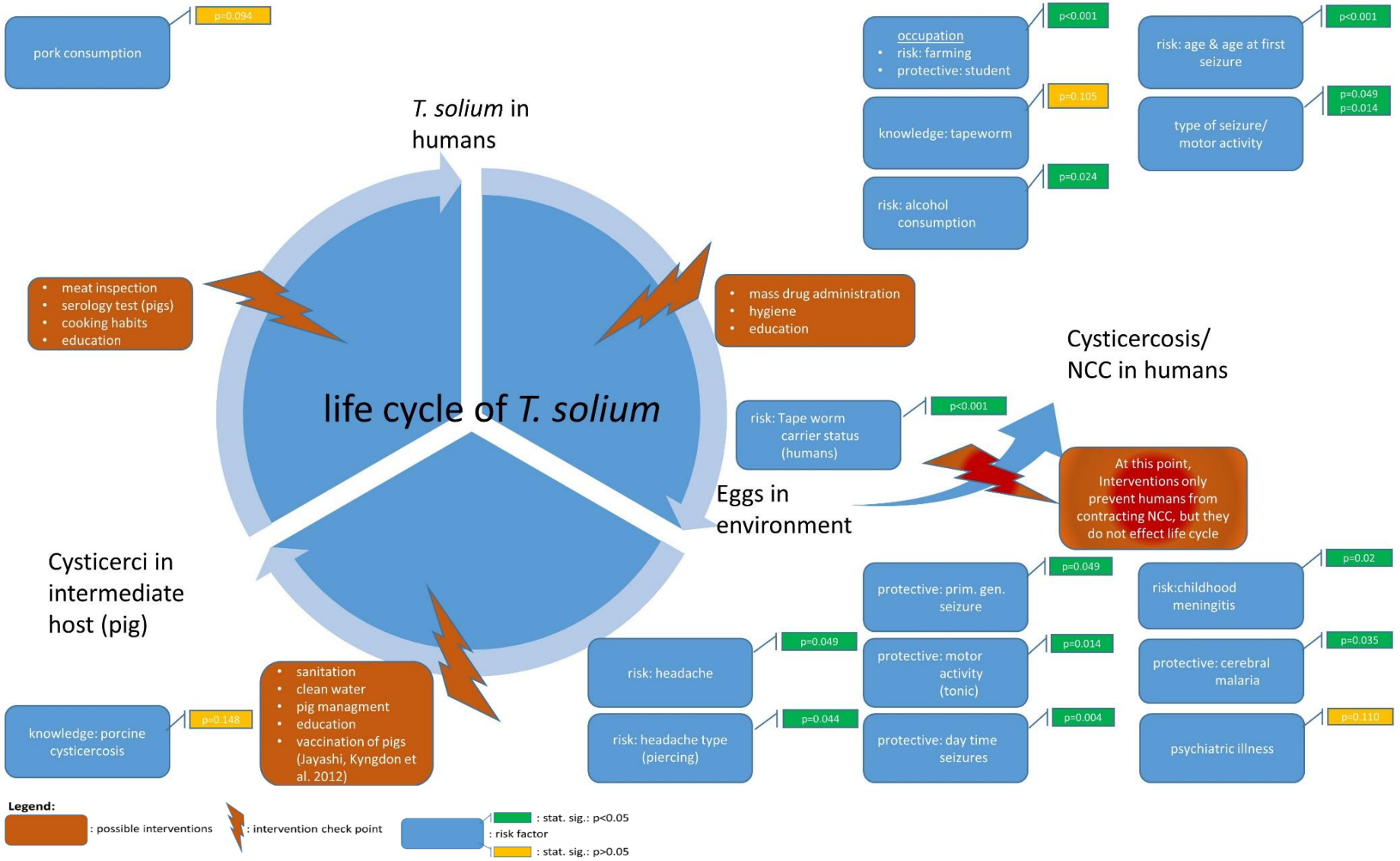
In northern Uganda the epilepsy prevalence is: 3 %. NCC prevalence in PWE is 13%. A summary of all risk factors and their statistical significance can be seen in Graphic 2 (see below). It shows the most important statistically significant risk factors organized in groups, as well as their location within the *T. solium* life cycle and their respective p- values. Some risk factors were included, even though not being statistically significant, as they are commonly assumed to be responsible for NCC (e.g. pork consumption). Based on those risk factors, certain interventions may become obvious. They are indicated in orange. Recent studies could show that certain interventions such as targeted treatment or pig treatment/vaccination can make a difference on *T. solium* prevalence (Garcia et al. 2016). In future studies, it is important to combine different interventions in order to achieve the highest success rate.

On multivariable analysis, one life year increased the risk of contracting NCC by 4% (OR 1.04 [CI: 1.02-1.06]). Farming was one of the most important sociodemographic risk factors identified. Studying had a preventive effect. On univariable analysis the average seizure onset in NCC positive PWE was 24 years and 14 years in PWE without NCC ($p<0.001$). Results suggested that knowledge about hygiene and NCC may have had an influence on NCC, but no statistically significant data was found. In our study, pork consumption could not be identified

as a risk factor for NCC. Contact with *T. solium* represented a risk factor for NCC. It increased the risk for contracting NCC by 62 times (OR: 62; CI: 16-411). This becomes especially important when discussing intervention options to combat NCC. Our study showed that there was a strong correlation between adult tapeworm carriers and NCC patients ($p<0.001$). Clinical risk factors associated with NCC were headache ($p=0.049$), primary generalized seizures ($p=0.049$), tonic seizures ($p=0.014$) and day-time seizures ($p=0.004$). From NCC patients' history, meningitis was identified as risk factor ($p=0.020$), whereas cerebral malaria had a protective benefit ($p=0.035$). This correlation might have been caused by a similar immune response between NCC and cerebral malaria, potentially protecting the patient from further eukaryotic parasite infections. Further research is needed in this field.

Other studies that tried to assess the burden of NCC, only focussed on the main symptom epilepsy. In this thesis we also included headache with its sub-categories in NCC patients into both DALY and economic calculations. This enabled us to depict a more precise image of the human and economic burden of NCC. Also, by applying the DisMod II model on our data input, we were able to use internally conclusive data, based on population data from Uganda. We were also able to calculate missing incident values, which furthermore enabled us to estimate future losses due to NCC. We estimated an overall economic burden of more than USD 75 million and more than USD 8,000 per NCC case. Our DALY burden was more than 180,000 healthy life years lost due to NCC. Per NCC case this amounted to 17 DALYs.

In this study we only focused on the human burden through NCC. Porcine cysticercosis was not included. In 2016, new prevalence data for porcine cysticercosis in Uganda became available (Kungu et al. 2016). With this information, future burden studies could additionally estimate the impact of porcine cysticercosis on Ugandan economy. Such a study would further complete the information on burden caused by *T. solium* from both a human and animal perspective. In order to significantly reduce Uganda's burden of NCC, specific interventions and augmented awareness are needed now.



Graphic 4: Summary of risk factors and possible intervention check points for *Taenia solium* and NCC

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11 Figures

11.1 Figures 1-3: *Taenia solium* related information

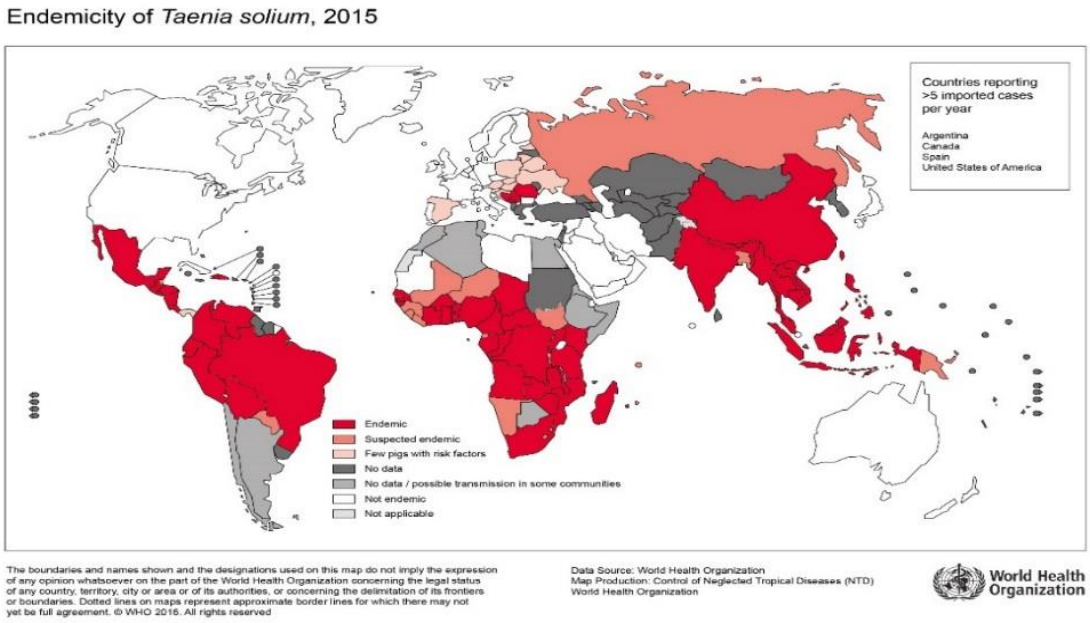


Figure 2: Endemic areas of T. solium (WHO 2016d)

In Figure 1, endemic areas for *T. solium* can be seen. Dark red coloured labels designate endemic countries and white labels non endemic countries. Uganda is labelled as an endemic country. Neighbouring countries like the youngest country in 2016: South Sudan are indicated as suspected-endemic and Somalia as well as Ethiopia do not provide any information regarding *T. solium* endemicy (Figure 1).

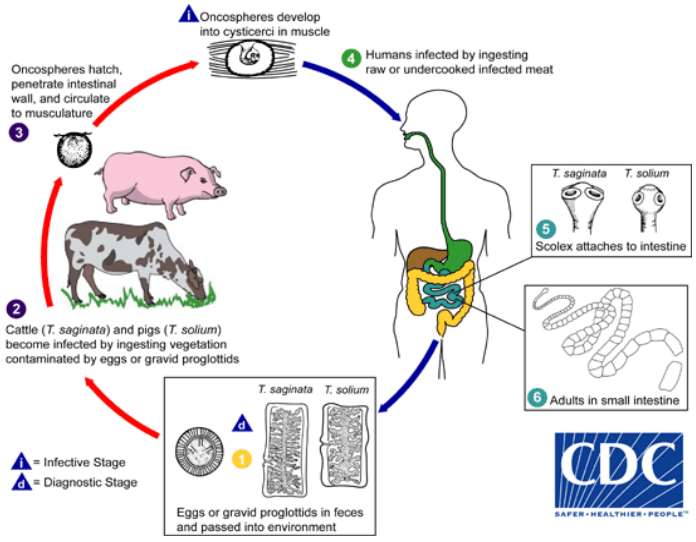


Figure 3: Life cycle of *Taenia solium* and saginata.

The cycle shows humans as main hosts and pigs/cattle as intermediate hosts. (CDC 2013b)

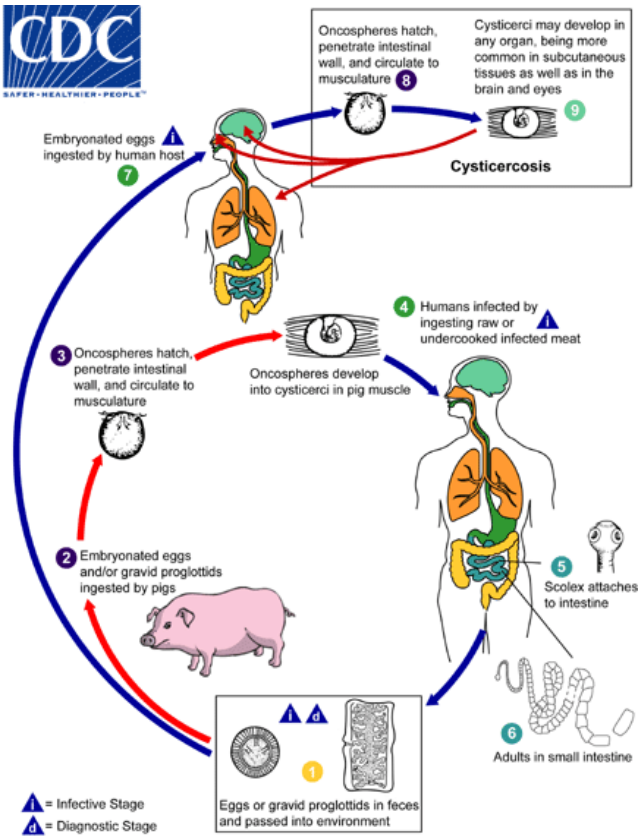


Figure 4: *T. solium* life cycle

Figure 3 explains the infectious cycle for accidental human cysticercosis and NCC (CDC 2013a)

11.2 Figure 4: Map of the research area

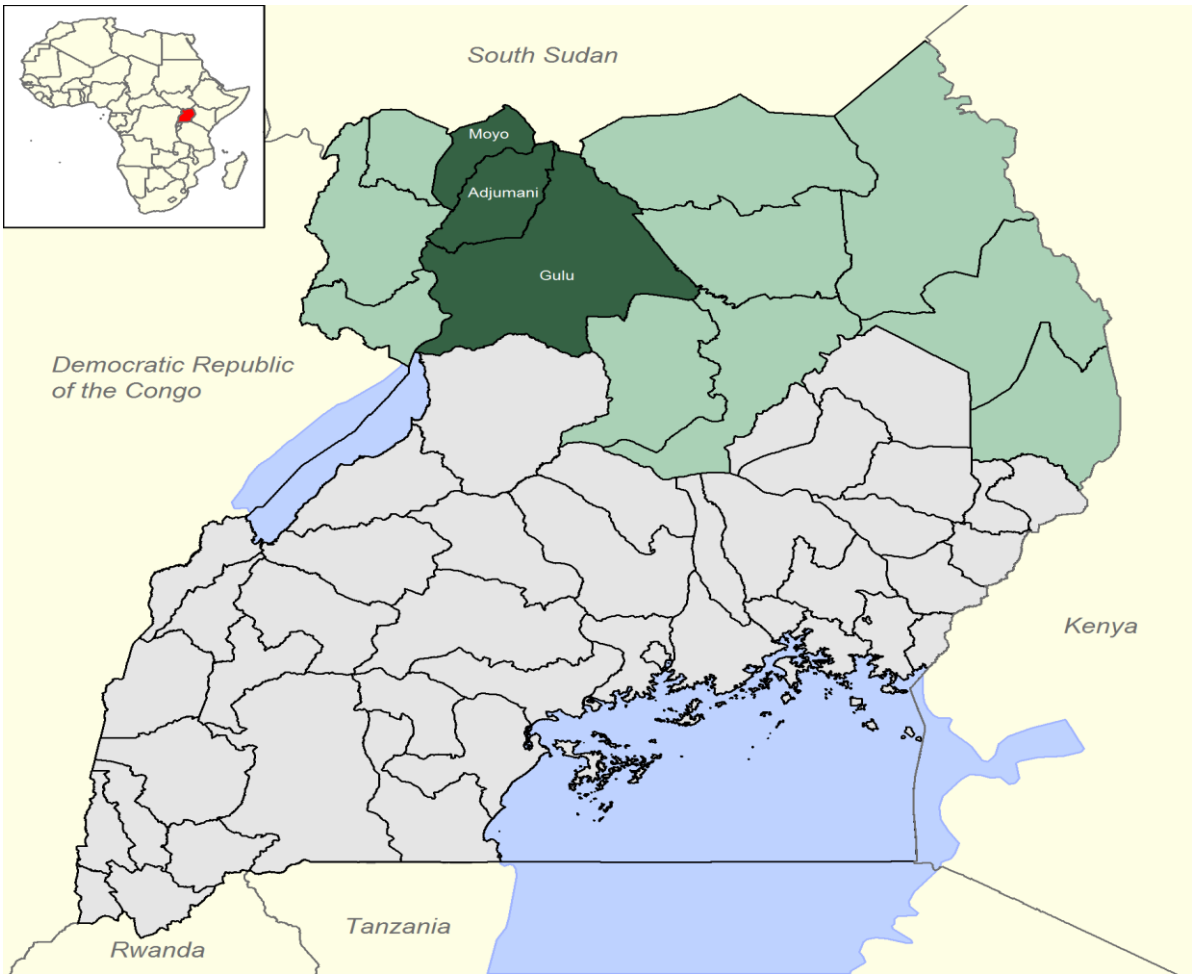


Figure 5: Top left corner: Map of Africa highlighting Uganda (red). Detailed map of Uganda (2015) with all regions: Green: Northern Uganda. Dark green: regions of this study in northern Uganda.

In the top left corner, Figure 4 shows an overview of the African continent. Uganda is highlighted in red. The detailed map shows Uganda as a whole, subdivided in regional districts as defined in 2015. Also, the two great lakes of Uganda can be seen. To the west: Lake Albert and to the south: Lake Victoria. Many smaller lakes and the Nile delta are not included in the map. The country has many fresh water supplies, however clean drinking water distribution still plays a major role in domestic political struggles, especially in rural areas. This situation facilitates food- and water borne diseases to spread easily in all of Uganda. Due to many recent changes in district distribution, there have been changes in the exact borders between districts, and affiliations to certain regional district boards. In green, the districts associated to northern Uganda are marked. In dark green, the three study areas (Moyo/Adjumani/Gulu) are highlighted. This is the part of northern Uganda, where prevalence and risk factor analysis were performed.

11.3 Figure 5: *Taenia solium* possible intervention stages

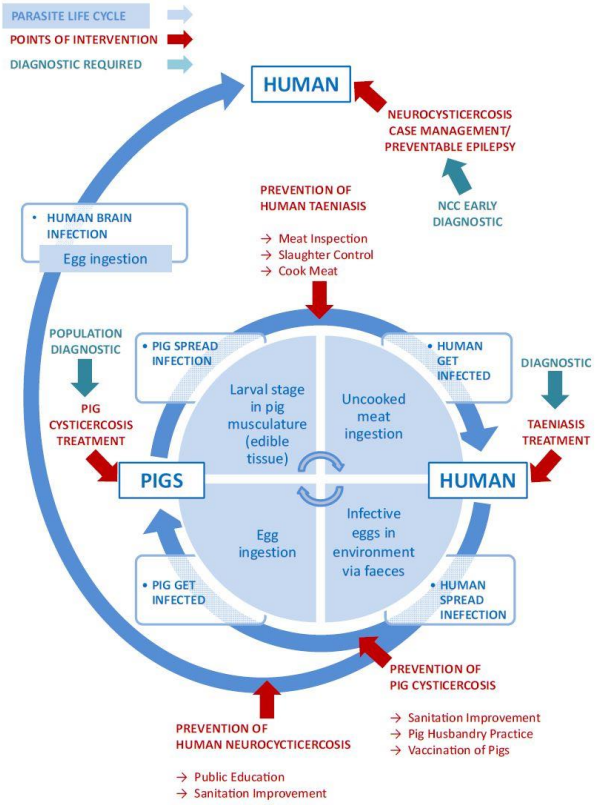


Figure 6: WHO life cycle of *T. solium* with possible stages of interventions (red) (WHO 2016)

Figure 5, not only shows information on *T. solium*. It also shows the different clinical manifestations it may trigger and where more specific diagnostic steps might be most beneficial for future diagnoses. For more information on current diagnostic steps see (Material and Methods: diagnosis of NCC). Figure 5 also shows how to interrupt the cycle at specific points. It displays the complexity and it envisages that a public health measure is not at all only a medical concern, but needs the active participation of different stakeholders from all parts of society. This includes veterinarians for the assessment of pigs, it refers to teachers and media specialists to distribute essential information about the life cycle to the affected people and also it includes concerted governmental activities to ensure basic hygiene and food safety measures to be kept. Figure 5 is only a simple diagram trying to demonstrate how complex public health interventions may become. In recent WHO reports, scientists could show that: "[interventions] *resulted in the absence of cyst-infected pigs in almost all intervened villages by the end of the intervention and one year after"* [in Peru] (WHO 2015a). It shows that there are current efforts in some countries to decrease the burden caused by *T. solium.* In order to plan and execute intervention measures, as shown in Figure 5, it is crucial to fully understand the impact of specific risk factors and the burden of a disease within the country.

11.4 Figure 6-8: Computed tomography imaging with typical lesions

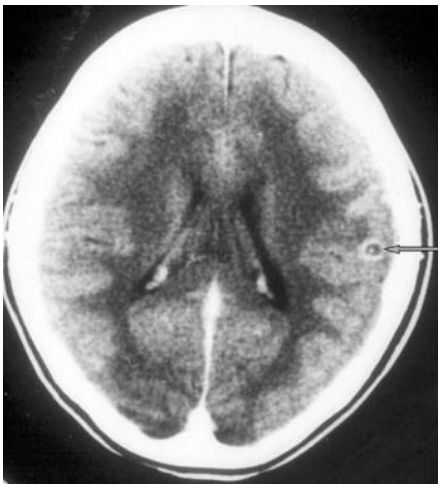


Figure 7: CT of head: Single viable cyst (arrow) with eccentric scolex present (Absolute criterion for NCC diagnosis) Source: (Anil Khosla 2015)

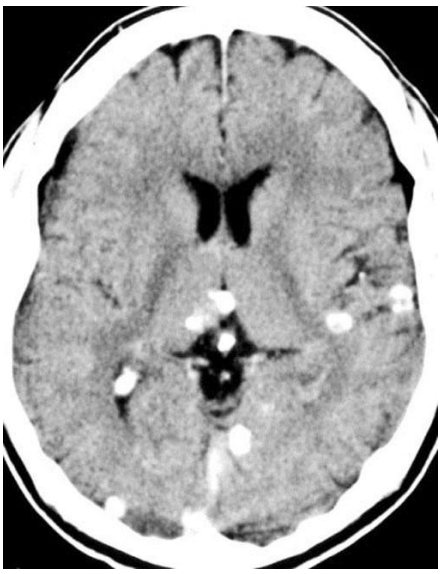


Figure 8: CT of head: Multiple parenchymal calcifications (Major criterion for NCC diagnosis) Source: (Anil Khosla 2015)

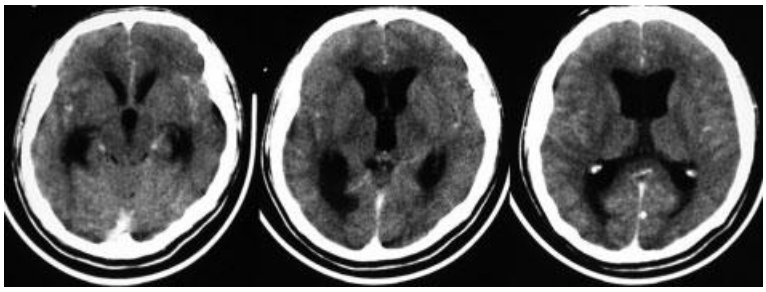
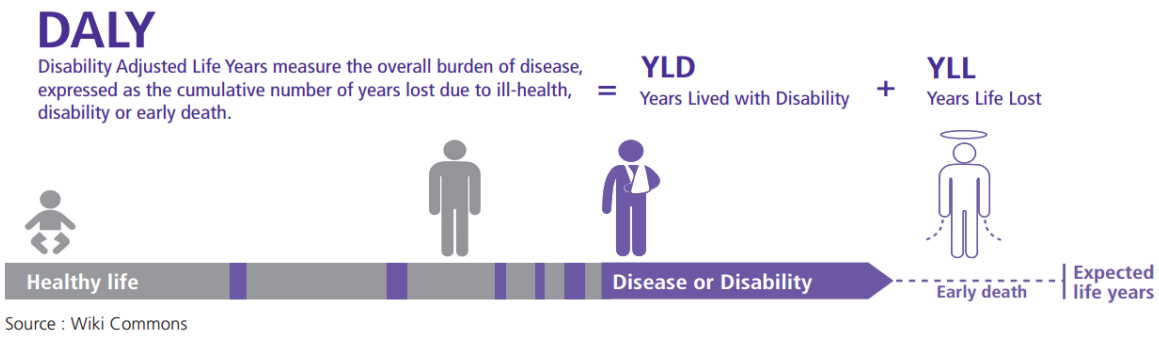


Figure 9: CT of head: Occlusive hydrocephalus with mild enhancement of leptomeninges. (Minor criterion for NCC) Source: (Del Brutto 2012)

11.5 Figure 9 and 10: DALY visualization



DALYs = Years of life lost due to premature mortality (YLL) + Years lived with disability (YLD)

Figure 10: DALY: Dependencies and distribution of disability-adjusted life years (Nccid 2013)

Figure 9, illustrates how the individual DALY per person is calculated. It shows the DALY calculation based on the life of one specific person from birth to his potentially premature death due to one specific disease.

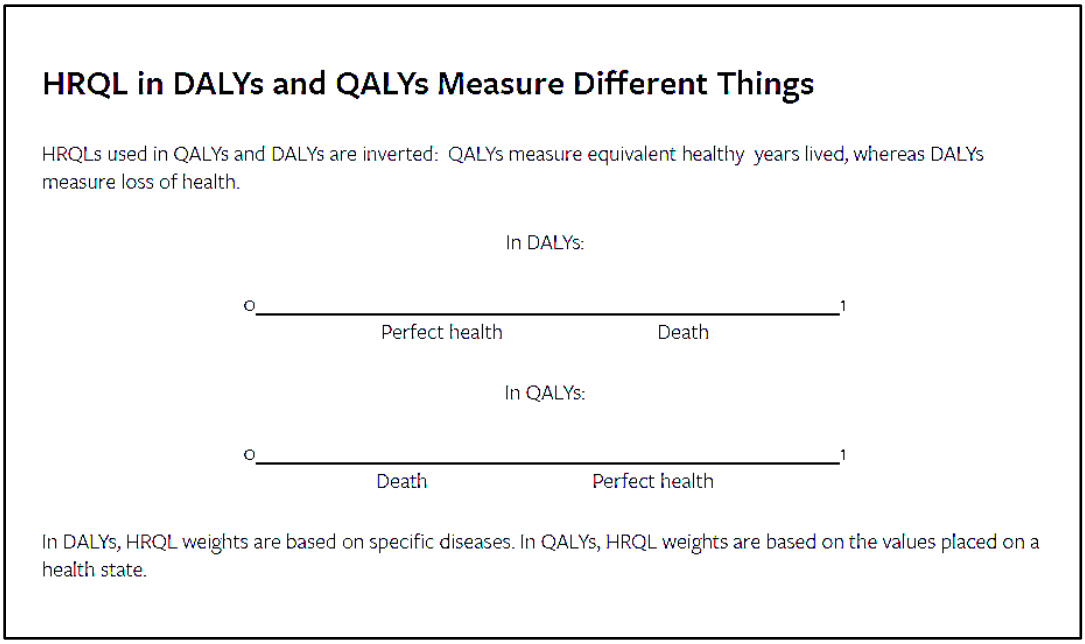


Figure 11: DALY vs QALY: both measure HRQL: Health Related Quality of Life (NCCID 2013)

Figure 10 shows a direct comparison between DALY and QALY, which are both Health-Related Quality of Life (HRQL) epidemiologic burden tools.

DALY: It measures the burden of one specific disease in one specific population as in healthy years lost. It is important for current and future interventions, because it helps to understand and therefore lessen the impact of a disease.

QALY: It measures the life years lived in perfect health in relation to a certain intervention. It gives a tool to clinicians and scientists to evaluate the impact or improvement through a certain treatment without putting a monetary value to the time period of life gained.

11.6 **Figure 11: Sources and procedures to estimate burden of NCC in Uganda**

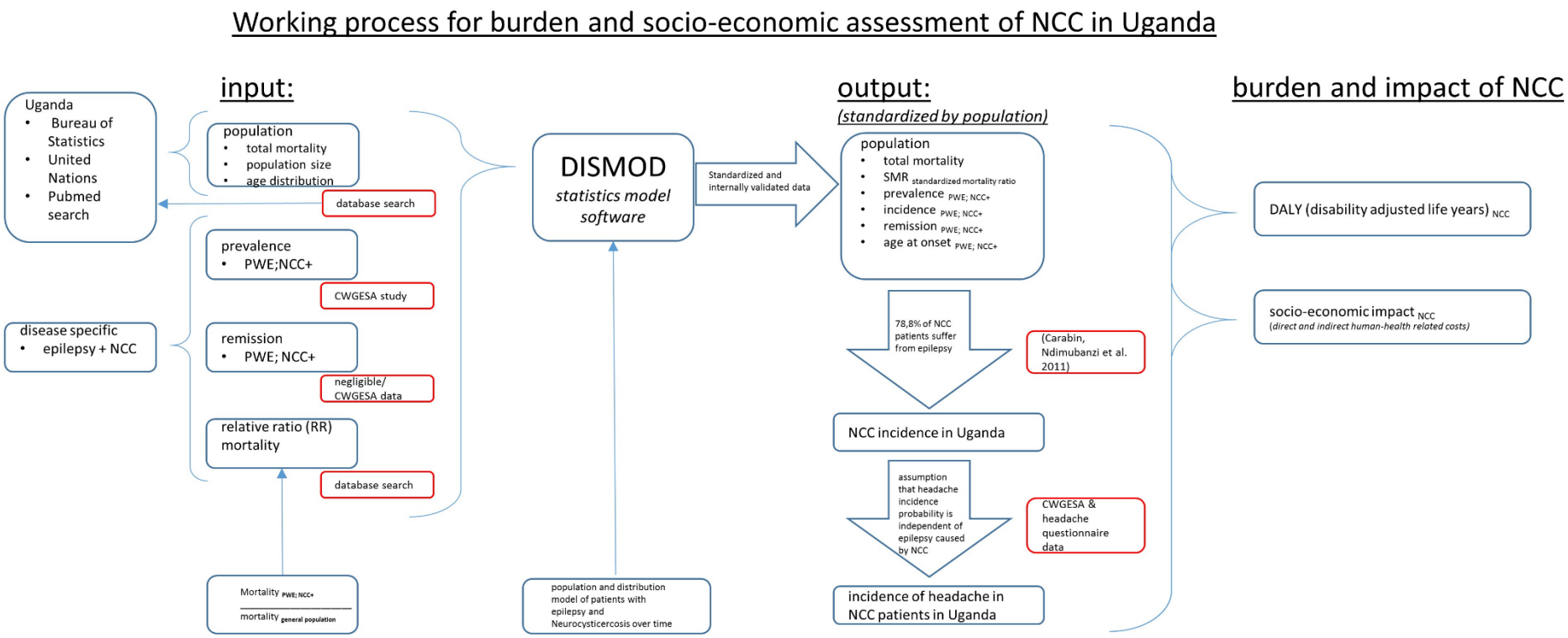


Figure 12: Sources and procedures to estimate burden of NCC in Uganda

11.7 Figures 12-16: Distribution of study population

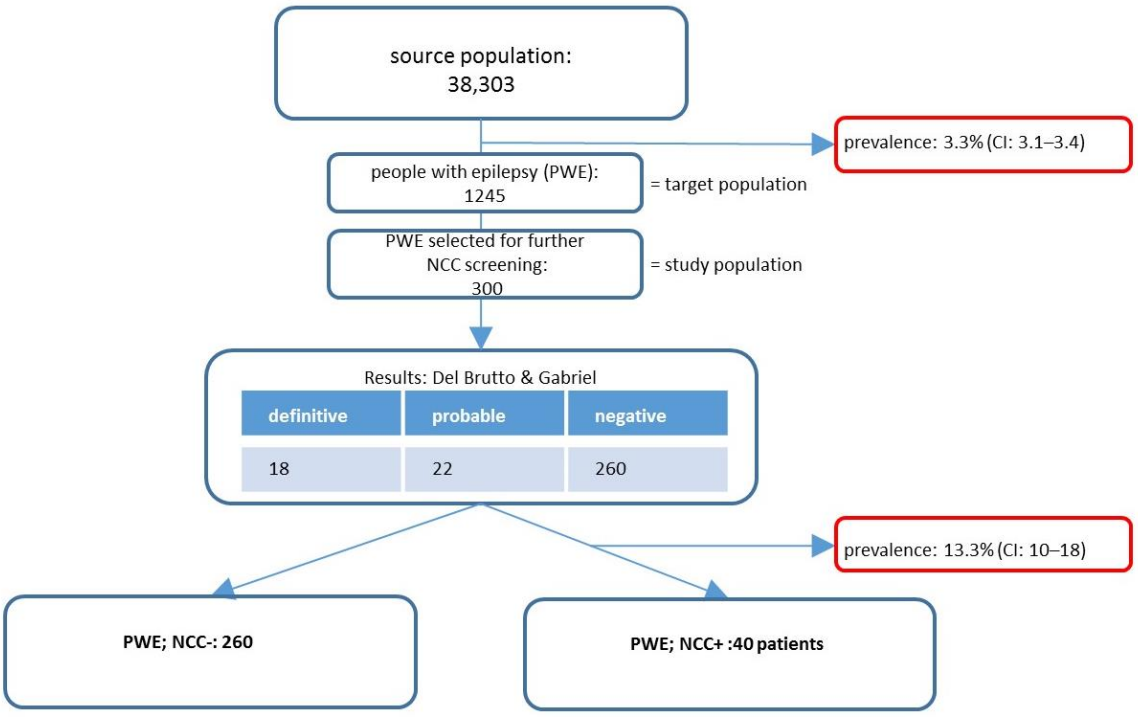


Figure 13: Total distribution of study population

PWE: People with epilepsy; NCC: Neurocysticercosis; CI: Confidence interval

Figure 12 shows details on the selcection process of the study population. The overall source population contained 38,303 people. Out of which, the target population of 1245 PWE was identified. Due to financial restrictions, we ended up with a study population of 300 PWE.

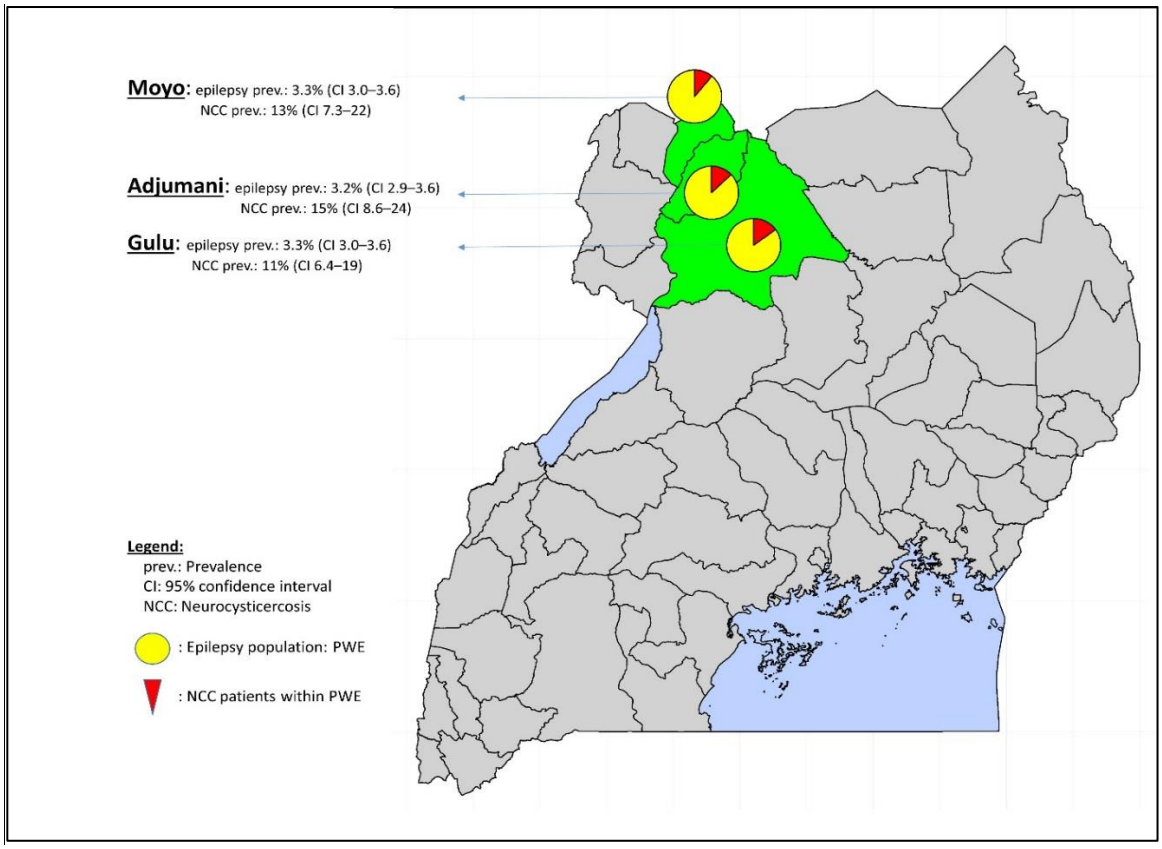


Figure 14: Epilepsy and NCC prevalence in Moyo/Adjumani/Gulu in northern Uganda

In Figure 13, prevalence data for epilepsy and NCC can be seen on a map of Uganda. The pie chart illustrates that the NCC distribution within PWE in all three districts is comparable. Bright green highlights the three districts in question: Moyo, Adjumani and Gulu.

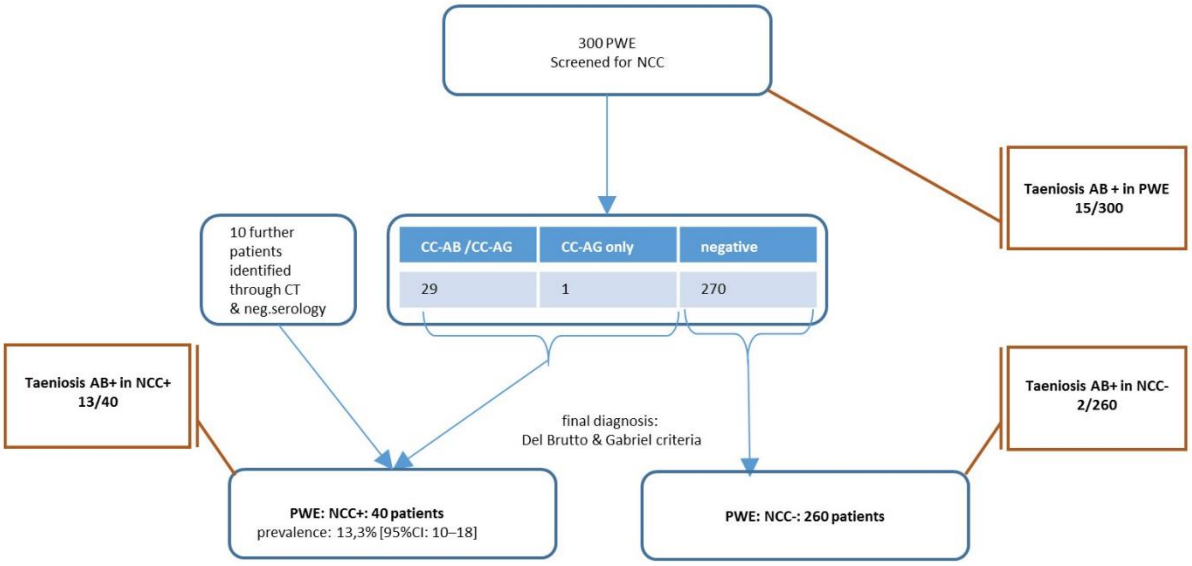


Figure 15: NCC serology distribution within PWE population

Taeniasis within sub-populations in red;

PWE: People with epilepsy; NCC: Neurocysticercosis; CC: Cysticercosis; AB: Antibody; AG: Antigen; +: positive; -: negative

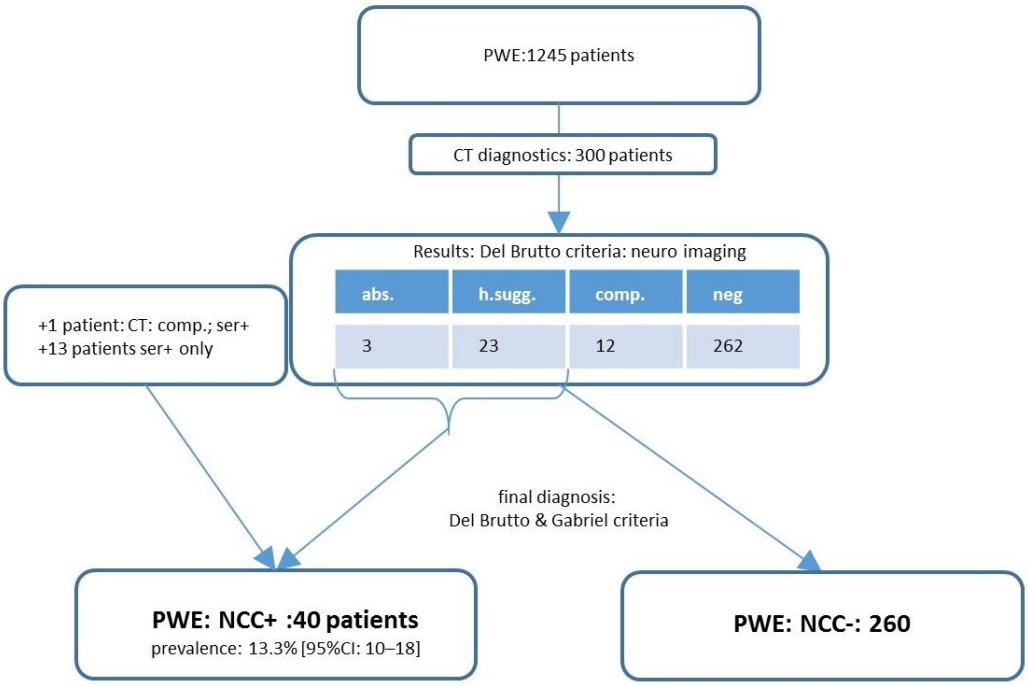


Figure 16: NCC neuroimaging distribution within epilepsy population

PWE: People with epilepsy; NCC: Neurocysticercosis; CT: Computed tomography; CI: Confidence interval; abs.: absolute criteria; h.sugg.: highly suggestive for NCC; comp.: compatible with NCC; neg.: negative; CT image (findings not related to NCC); ser+: serology results that prove NCC

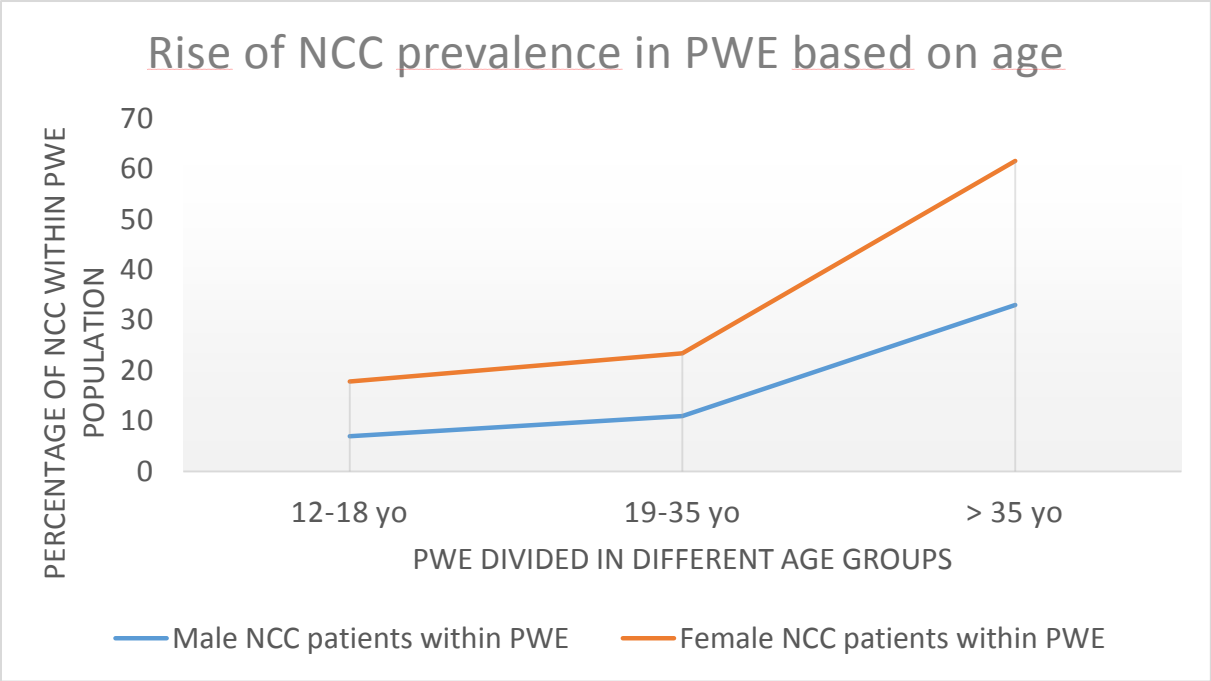


Figure 17: Line chart comparing NCC prevalence increase based on age

Even though NCC cases within age groups are not evenly distributed, it shows that there is a clear increase in NCC cases over age.

Men:

- 12-18 yo: 7% (0.014-0.179)
- 19-35yo: 11% (0.044-0.234)
- >35yo: 33% (0.118-0.616)

Women:

- 12-18 yo: 8% (0.027-0.178)
- 19-35yo: 12% (0.051-0.237)
- >35yo: 58% (0.366-0.779)

Addendum:

12: Tables

13: Appendix

14: Acknowledgements

12 Tables

Tables follow the logic flow of the text. Thex also represent the working process of this thesis. In order to simplify cross-referencing, the following strategy has been implemented:

Tables 1-4: Introduction and clarification of terms/workflow

Table 5: Prevalence of epilepsy and NCC

Tables 6-11: Risk factors and NCC associated correlations

Table 12: details on PWE w/ NCC

Tables: 13-22: Data from DisMod II and burden assessment

12.1 Table 1: Different types of hosts.

Based on p. 7: "Lehrbuch für Parasitologie für die Tiermedizin, 112 Tabellen"(Eckert 2008)

Main host	Organism in which sexual reproduction takes place: For *T. solium*: humans. The small intestine is the habitat where the adult worms reproduce and produce eggs. The worm sheds proglottids containing eggs. They are excreted in feces.
Intermediate Host	Organism which is essential for the life cycle of the parasite, but where no sexual reproduction takes place. For *T. solium*: pigs. After pigs ingest the *T. solium* eggs, the larvae develop and migrate to muscle and brain tissue.
Accidental host	A host where the parasite can develop but where, based on its life cycle, the infection is not effective for its dissemination. For *T. solium:* humans with cysticercosis/NCC.

Explanation to Table 1: Whilst pigs are commonly considered as intermediate hosts, accidental infections of humans happen on a regular basis causing human cysticercosis or NCC. NCC does not close the life cycle and therefore does not actively participate in the reproductive cycle of *T.solium.* In order to maintain the life cycle, the worm needs to reproduce within the human organism. When humans consume pork infected with cysts, the larvae hatch and develop into the adult worm. The transformation to the adult worm takes up to two months.(García et al. 2003) Then it produces approximately 50-60 x 10^3 eggs per day that are excreted through

feces (Flisser 1994). If, through insufficient hygiene and sanitation, human feces reaches the food supply of pigs, the life cycle is complete.

12.2 Table 2: Overview of NCC prevalence in other African studies

	Burkina Faso (Millogo et al. 2012) 33 patients	**Tanzania** (Hunter et al. 2015) 176 patients	**Zambia** (Mwape et al. 2015) 51 patients
epilepsy prevalence	4.8% [CI: 2.9-7.6]	0.4% [CI: 0.34-0.42]	approx. 0.15% [n.a.]
NCC within PWE	47% [CI: 32-61]	1.1% [0.3-4.0]	57.1% [n.a.]

n.a.: not available

12.3 Data review: Table 3: List of databases screened and hits retrieved

Database	**Link**
African Journal Online	http://ajol.info
African journal of medicine and medical sciences	http://ajol.info/index.php/jmms
African Journal of Neurological sciences	http://ajns.paans.org/
African Neurology database	http://unilim.fr/ient
Annals of Medical and Health Sciences Research	http://amhsr.org/
East African Journal of Public Health	http://eajph.org/
Open Grey	http://opengrey.eu
PubMed	http://pubmed.org
WHO Africa	http://indexmedicus.afro.who.int

12.4 Table 4: Cost-of-illness: Overview of costs in economic calculations

Direct, healthcare (DHC)	Treatment, diagnosis, healthcare provider fees
Direct-non-healthcare (DNHC)	Travel costs to healthcare provider
Indirect, non-healthcare (INHC)	Productivity losses due to inability to work, job loss, dying; being accompanied by relative

The cost-of-illness calculation details can be found in Table 21.

12.5 Table 5: Epilepsy and NCC prevalence in study population

	Epilepsy prevalence		NCC prevalence	
	x/N	*% (95%CI)*	*x/N*	*% (95%CI)*
District				
Moyo	408/12,503	3.3% (3.0-3.6)	13/97	13% (7.3-22)
Adjumani	414/12,800	3.2% (2.9-3.6)	14/92	15% (8.6-24)
Gulu	423/13,000	3.3% (3.0-3.6)	13/111	11% (6.4-19)
Sex				
Male	694/16,351	4.2% (3.9-4.6)	26/166	16% (10-22)
Female	551/21,952	2.5% (2.3-2.7)	14/134	10% (5.8-17)
Age group				
0-1	3/3089	0.0% (0.0-0.3)	—	—
2-5	67/5617	1.2% (0.9-1.5)	—	—
6-10	130/7199	1.8% (1.5-2.1)	—	—
11-18	502/8062	6.2% (5.7-6.8)	8/116	6.9% (3.0-13)
19-35	356/7868	4.5% (4.1-5.0)	13/122	11% (5.8-18)
>35	187/6468	2.9% (2.5-3.3)	19/58	33% (21-46)

12.6 Table 6: Sociodemographic factors associated with neurocysticercosis among people with epilepsy

Characteristic	**NCC+ (%)**	**NCC– (%)**	**Odds Ratio (95%CI)**	**p-value**
Sex (n=300)				0.183
Female	14 (10%)	120 (89%)	—	
Male	26 (16%)	140 (84%)	1.59 (0.81–3.26)	
Age average [median] (n=300)	38 [35]	24 [20]	1.07 (1.04–1.09)	<0.001
Average number of children [median] (n=82)	2.4 [2]	2.0 [2]	1.13 (0.81–1.56)	0.445
Marital status (n=140)				0.985
Single	11 (19%)	48 (81%)	—	
Married at some point of life	15 (19%)	66 (81%)	0.99 (0.0.42–2.40)	
Average age at marriage (n=81)	26 [27]	23 [22]	1.10 (0.99–1.22)	0.065

Schooling (n=300)				0.104
None	13 (16%)	70 (84%)	—	
Primary	21 (11%)	174 (89%)	0.635 (0.31–1.40)	
Advanced	6 (27%)	16 (73%)	2.02 (0.63–5.99)	
Occupation (n=284)				<0.001†
Farmer	28 (24%)	88 (76%)	—	
Student	6 (5%)	105 (95%)	0.18 (0.07–0.43)	
White collar	2 (5%)	37 (95%)	0.17 (0.03–0.61)	
Unemployed, including housewife/man	1 (6%)	17 (94%)	0.19 (0.01–0.97)	
Regular alcohol use (n=300)				0.024
No	34 (12%)	248 (88%)	—	
Yes	6 (33%)	12 (67%)	3.65 (1.20–10.1)	
Relatives with seizures (n=292)				0.809
No	16 (13%)	109 (87%)	—	
Yes	23 (14%)	144 (86%)	1.09 (0.55–2.19)	
Latrine (n=299)				0.670
Completely enclosed	11 (14%)	67 (86%)	—	
Partly enclosed	20 (12%)	147 (88%)	0.83 (0.38–1.88)	
Open, absent	9 (17%)	45 (83%)	1.22 (0.46–3.18)	

†Based on Fisher's exact test

Unless stated otherwise, logistic regression was used
NCC: Neurocysticercosis; CI: Confidence Interval; in brackets: percentages or median; n indicates the number of replies received per questionnaire item.

12.7 Table 7: pig related factors associated with neurocysticercosis among people with epilepsy in northern Uganda

Characteristic	NCC+ (%)	NCC– (%)	Odds Ratio (95%CI)	p-value
Pork consumption (n=299)				0.337
No	9 (11%)	77 (90%)	—	
Yes	31 (15%)	182 (85%)	1.46 (0.69-3.38)	
Pork consumption frequency (n=297)				0.184
Never	9 (11%)	77 (90%)	—	
Less than once a year	13 (21%)	50 (79%)	2.22 (0.89-5.76)	
At least once a year	18 (12%)	130 (88%)	1.89 (0.52-2.89)	
Pork cooking habits (n=211)				0.094
Boiled	12 (19%)	53 (82%)	—	
Fried	14 (11%)	115 (89%)	0.54 (0.23-1.26)	
Barbecued	5 (29%)	12 (71%)	1.84 (0.51-6.06)	
Pig keeping (n=299)				0.568
No	30 (14%)	183 (86%)	—	
Yes	10 (12%)	76 (88%)	0.80 (0.36-1.67)	
Free roaming of pigs (n=87)				0.865‡
Never	0 (0%)	4 (100%)	—	
At least sometimes	10 (12%)	73 (88%)	1.29 (0.12–175) ‡	
Slaughter at home (n=89)				0.728†
No	6 (10%)	53 (90%)	—	
Yes	4 (13%)	26 (87%)	1.36 (0.32-5.18)	
House inspector (n=32)				0.512†
No	1 (25%)	3 (75%)	—	
Yes	4 (14%)	24 (86%)	0.50 (0.05-11.49)	
Price for a 4mo piglet (n=69) in Shilling [UGX] (median)	51,111 (50,000)	48,733 (40,000)	1.00 (1.00-1.00)	0.870

Knows, seen/heard nodules in pigs (n=299)				0.476†
No	36 (14%)	219 (86%)	—	
Yes	4 (9%)	40 (91%)	0.61 (0.18-1.63)	
Knows where to find nodules in pig (n=42)				0.204‡
Under tongue	0 (0%)	16 (100%)	—	
Limited knowledge	3 (14%)	19 (86%)	5.92 (0.52–819) ‡	
No knowledge	1 (25%)	3 (75%)	14.14 (0.62–2256) ‡	
Heard of porcine cysticercosis (n=297)				0.148†
No	39 (15%)	229 (85%)	—	
Yes	1 (3%)	28 (97%)	0.21 (0.01-1.03)	
Knows about tapeworm in humans (n=297)				0.105
No	26 (17%)	132 (84%)	—	
Yes	14 (10%)	125 (90%)	0.57 (0.28-1.12)	
Knowledge source (n=141)				0.561‡
Family and social surrounding	9 (11%)	71 (89%)	—	
Traditional education, books	1 (3%)	28 (97%)	0.40 (0.04–1.84) ‡	
Healthcare system	0 (0%)	3 (100%)	1.08 (0.01–12.44) ‡	
Media	4 (15%)	23 (85%)	1.44 (0.39–4.68) ‡	

†Based on Fisher's exact test

‡Based on Firth's penalized-likelihood logistic regression and profile likelihood

Unless stated otherwise, logistic regression was used

NCC: Neurocysticercosis; CI: Confidence Interval n: number; UGX: Ugandan Shilling in brackets: percentage or median; n indicates the number of replies received per questionnaire item.

12.8 Table 8: Seizure characteristics associated with neurocysticercosis among people with epilepsy in northern Uganda

Characteristic	NCC+ (%)	NCC– (%)	Odds Ratio (95%CI)	p-value
Type of seizure (n=300)				0.225†
Gwa	19 (15%)	108 (85%)	—	
Goa	13 (18%)	58 (82%)	1.27 (0.58-2.75)	
Gbd	6 (8%)	72 (92%)	0.47 (0.17-1.18)	
Gfs	2 (8%)	22 (92%)	0.52 (0.08-1.96)	
ILAE diagnosis (n=300)				0.049
Primary generalized seizures	32 (16%)	166 (84%)	—	
Secondary generalized seizures	8 (8%)	94 (92%)	0.44 (0.18–0.95)	
Motor activity during fits (n=300)				0.014†
Tonic	14 (25%)	41 (75%)	—	
Clonic	1 (8%)	11 (92%)	0.27 (0.01-1.56)	
Tonic-clonic	22 (10%)	197 (90%)	0.33 (0.16-0.70)	
Myoclonic	2 (40%)	3 (60%)	1.95 (0.24-12.99)	
No movements of limbs, but rolling of eyes and grinding of teeth	1 (11%)	8 (89%)	0.37 (0.02-2.26)	
Seizure side (n=300)				0.032†
Both sides	32 (12%)	240 (88%)	—	
Only left side	5 (38%)	8 (62%)	4.69 (1.35-14.95)	
Only right side	1 (25%)	3 (75%)	2.50 (0.12-20.20)	
None	2 (18%)	9 (82%)	1.67 (0.25-6.83)	
Time of fits (n=300)				0.004
Day time	22 (23%)	74 (77%)	—	
Any time	13 (8%)	150 (92%)	0.29 (0.14-0.60)	
Night time	5 (12%)	36 (88%)	0.47 (0.15-1.25)	

Fits during fever (n=300)				0.025†
No	38 (15%)	210 (85%)	—	
Yes	2 (4%)	50 (96%)	0.22 (0.04-0.76)	
Age at first seizure (n=300) (median)	23.9 (15.5)	14.1 (11.0)	1.04 (1.02-1.06)	<0.001
Currently on anti-epileptic drugs (n=300)				0.473
No	12 (16%)	64 (84%)	—	
Yes	28 (12%)	196 (88%)	0.76 (0.37-1.64)	
Current anti-epileptic drug taken (n=224)				0.582†
Carbamazepine	2 (7%)	28 (93%)	—	
Phenytoin	20 (14%)	121 (86%)	2.31 (0.63-15.02)	
Phenobarbitone	6 (11%)	47 (89%)	1.79 (0.38-12.77)	
Received any anti-epileptic drug during the last year (n=299)				0.048‡
No	1 (100%)	0 (0%)	—	
Yes	39 (13%)	259 (87%)	0.05 (0.00–0.97) ‡	
Received Carbamazepine during the last year (n=299)				0.750†
No	37 (13%)	240 (87%)	—	
Yes	2 (9%)	20 (91%)	0.65 (0.10-2.35)	
Received Phenytoin during the last year (n=299)				0.140
No	34 (14%)	201 (86%)	—	
Yes	5 (8%)	59 (92%)	0.50 (0.17-1.23)	
Received Phenobarbitone during the last year (n=299)				0.220
No	16 (11%)	134 (89%)	—	
Yes	23 (15%)	126 (85%)	1.53 (0.78-3.07)	

Received traditional medicine during the last year (n=7)				0.513‡
No	0 (0%)	6 (100%)	—	
Yes	0 (0%)	1 (100%)	4.33 (0.02–999) ‡	
Number of fits per month, before treatment (n=295)	21.8 (3.5)	26.9 (3.0)	1.00 (0.99-1.01)	0.517
Number of fits per month, after treatment (n=294)	1.1 (0.3)	3.0 (0.5)	0.95 (0.80-1.01)	0.162
Relative reduction in seizure frequency after treatment (n=299)	77.7 (91.8)	48.2 (87.5)	1.00 (1.00-1.02)	0.163
Relative reduction in seizure frequency after treatment for patients taking Carbamazepine (n=299)	87.5 (87.5)	46.5 (85.4)	1.02 (1.00-1.13)	0.329
Relative reduction in seizure frequency after treatment for patients taking Phenytoin (n=299)	53.1 (75.0)	31.4 (91.7)	1.00 (NA)	0.793
Relative reduction in seizure frequency after treatment for patients taking Phenobarbitol (n=299)	84.0 (97.9)	45.5 (87.5)	1.01 (1.00-1.03)	0.103
Hallucinations (n=253)				0.255†
No	8 (14%)	50 (86%)	—	
Yes, currently	3 (6%)	46 (94%)	0.41 (0.09-1.50)	
Yes, past year	7 (12%)	51 (88%)	0.86 (0.28-2.56)	
Yes, more than one year ago	16 (18%)	72 (82%)	1.39 (0.57-3.65)	

†Based on Fisher's exact test

‡Based on Firth's penalized-likelihood logistic regression and profile likelihood

Unless stated otherwise, logistic regression was used NCC: Neurocysticercosis; CI: Confidence Interval; n: number; gwa: generalized seizures within age range; goa: generalized seizures outside age range; gbd: generalized seizures with diffuse brain damage; gfs: generalized seizures with focal signs; ILAE: International League Against Epilepsy; in brackets: percentages or median; n indicates the number of replies received per questionnaire item.

12.9 Table 9: Headache characteristics associated with neurocysticercosis among people with epilepsy in northern Uganda

Characteristic	NCC+ (%)	NCC– (%)	Odds Ratio (95%CI)	p-value
History of "bad"* headache (n=294)				0.049
No	31 (12%)	227 (88%)	—	
Yes	9 (25%)	27 (75%)	2.44 (1.01–5.52)	
Headache peak (n=294)				0.055†
No headache	31 (12%)	227 (88%)	—	
Currently	1 (25%)	3 (75%)	2.44 (0.12–19.74)	
This year	2 (14%)	12 (86%)	1.22 (0.18–4.76)	
More than one year ago	6 (33%)	12 (67%)	3.66 (1.20–10.17)	
History of severe and progressive** headache (n=293)				0.066
No	25 (11%)	208 (89%)	—	
Yes	12 (20%)	48 (80%)	2.08 (0.95–4.36)	
Headache history (n=60)				0.655†
Currently	2 (25%)	6 (75%)	—	
Past year/+not currently	10 (19%)	42 (81%)	0.71 (0.14–5.37)	
Age of headache onset (n=58) (median)	22.8 (18)	21.0 (19)	1.02 (0.93–1.11)	0.634
Headache impairing daily chores (n=58)				0.625‡
No	0 (0%)	3 (100%)	—	
Yes	12 (22%)	43 (78%)	2.01 (0.18–277)‡	
Aura present (n=51)				0.505†
No	3 (16%)	16 (84%)	—	
Yes	8 (25%)	24 (75%)	1.78 (0.44–9.05)	
Nausea or vomiting (n=56)				1.000†
No	10 (21%)	38 (79%)	—	
Yes	2 (25%)	6 (75%)	1.27 (0.17–6.54)	

Type of pain (n=58)				0.044†
Piercing	7 (39%)	11 (61%)	—	
Throbbing	4 (19%)	17 (81%)	0.37 (0.08–1.52)	
Stabbing/sharp pain	1 (5%)	18 (95%)	0.09 (0.00–0.58)	
Headache character (n=58)				0.070†
Continuous	2 (67%)	1 (33%)	—	
Periodical/episodic	8 (24%)	26 (76%)	0.15 (0.01–1.81)	
Paroxysmal/sudden	2 (10%)	19 (90%)	0.05 (0.00–0.77)	
Pictogram analysis ***(n=57)				0.086‡
A little more	0 (0%)	5 (100%)	—	
Hurts even more	8 (35%)	15 (65%)	6.03 (0.56–828) ‡	
Hurts a hole lot	4 (24%)	13 (76%)	3.67 (0.30–517) ‡	
As much as imaginable	0 (0%)	12 (100%)	0.44 (0.00–86) ‡	
Headache progression since onset (n=56)				0.391‡
More severe	2 (12%)	14 (88%)	—	
The same	10 (28%)	26 (72%)	2.30 (0.56–13) ‡	
Better	0 (0%)	4 (100%)	0.64 (0.00–10) ‡	

†Based on Fisher's exact test

‡Based on Firth's penalized-likelihood logistic regression and profile likelihood

Unless stated otherwise, logistic regression was used

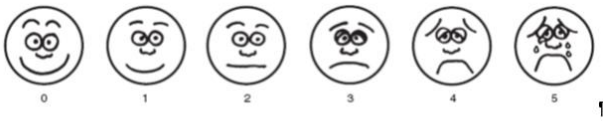
NCC: Neurocysticercosis; CI: Confidence Interval; in brackets: percentages or median

n indicates the number of replies received per questionnaire item.

*original wording used in CWGESA questionnaire

**severe and progressive follow-up headache questionnaire in the same individuals

***Pictogram scale:



0 = VERY HAPPY, NO HURT
1 = HURTS JUST A LITTLE BIT
2 = HURTS A LITTLE MORE
3 = HURTS EVEN MORE
4 = HURTS A WHOLE LOT
5 = HURTS AS MUCH AS YOU CAN IMAGINE

12.10 Table 10: Characteristics associated with severe and progressive headache among people with neurocysticercosis-associated epilepsy in northern Uganda

Characteristic	Headache+ (%)	Headache– (%)	Odds Ratio (95%CI)	p-value
CT highly suggestive for NCC or absolute (n=37)				0.476†
No	3 (23%)	10 (77%)	—	
Yes	9 (38%)	15 (62%)	2.00 (0.46–11)	
CT result (n=37)				0.379†
Normal	3 (23%)	10 (77%)	—	
Compatible	0 (NA)	0 (NA)	NA	
Highly suggestive	7 (33%)	14 (67%)	1.67 (0.36–9.23)	
Absolute	2 (67%)	1 (33%)	6.67 (0.48–178)	
Antibody status (n=37)				0.445†
Negative	2 (20%)	8 (80%)	—	
Positive	10 (37%)	17 (63%)	2.35 (0.47–18)	
Serology results (n=37)				0.739‡
Negative	2 (22%)	7 (78%)	—	
Taeniosis antibody positive, only	0 (NA)	0 (NA)	NA	
Cysticercosis antigen positive, only	0 (0%)	1 (100%)	1.00 (0.01–27) ‡	
Cysticercosis antibody positive	10 (37%)	17 (63%)	1.80 (0.39–11) ‡	

†Based on Fisher's exact test

‡Based on Firth's penalized-likelihood logistic regression and profile likelihood

Unless stated otherwise, logistic regression was used

n indicates the number of replies received per questionnaire item.

NCC: Neurocysticercosis; CI: Confidence Interval; n indicates the number of replies received per questionnaire item.

12.11 Table 11: Coexisting medical characteristics associated with neurocysticercosis among people with epilepsy in northern Uganda

Characteristic	NCC+ (%)	NCC– (%)	Odds Ratio (95%CI)	p-value
Ever been admitted (n=300)				0.293
No	27 (15%)	153 (85%)	—	
Yes	13 (11%)	107 (89%)	0.69 (0.33-1.37)	
Hospitalized for seizures (n=266)				0.392
No	31 (15%)	178 (85%)	—	
Yes	6 (11%)	51 (89%)	0.68 (0.24-1.61)	
Childhood meningitis (n=299)				0.020
No	27 (11%)	217 (89%)	—	
Yes	13 (24%)	42 (76%)	2.49 (1.16–5.14)	
Cerebral malaria (n=298)				0.035
No	33 (16%)	172 (84%)	—	
Yes	7 (8%)	86 (92%)	0.42 (0.17–0.95)	
Psychiatric illness, current (n=300)				0.118
No	35 (12%)	246 (88%)	—	
Yes	5 (26%)	14 (74%)	2.51 (0.77–7.02)	
Psychiatric signs/symptons, type (n=300)				0.110‡
None	35 (12%)	246 (88%)	—	
Behavioral problems	0 (0%)	2 (100%)	1.39 (0.01–18) ‡	
Dementia	0 (0%)	2 (100%)	1.39 (0.01–18) ‡	
Depression	2 (33%)	4 (67%)	3.86 (0.65–18) ‡	
Mental retardation	1 (20%)	4 (80%)	2.31 (0.23–13) ‡	
Psychotic episodes	2 (100%)	0 (0%)	34.72 (2.75–4827) ‡	
Suicidal attempt	0 (0%)	2 (100%)	1.39 (0.01–18) ‡	

Place of birth (n=300)				0.421[†]
Home	26 (13%)	169 (87%)	—	
Health centre, Dispensary	3 (8%)	37 (93%)	0.53 (0.12–1.60)	
Hospital	11 (17%)	54 (83%)	1.32 (0.59–2.80)	
Sick days/month due to any illness (n=282)	3.5 (3)	2.9 (2)	1.04 (0.95–1.14)	0.356

[†]Based on Fisher's exact test

[‡]Based on Firth's penalized-likelihood logistic regression and profile likelihood

Unless stated otherwise, logistic regression was used

NCC: Neurocysticercosis; CI: Confidence Interval; n indicates the number of replies received per questionnaire item.

12.12 **Table 12: Characteristics of people with epilepsy with neurocysticercosis and their respective diagnostic staging**

	Demography		Neurology				CT analysis	*T. solium* serology			NCC criteria [d & e]				NCC diagnosis	
n	Age	G	Neuro	TS ILAE [a]	TS[b]	Headache*	Lesions[c]	Staging	CC-AB	CC-AG	T-AB	Abs	Major	Minor	Epi	*Gabriel et al.*[d]	*Del Brutto*[e]
1	18	m	npf	prim	gwa	No	hs	3	p	n	n	-	2	1	1	def	def
2	50	m	npf	prim	goa	No	vc	3	p	p	p	1	2	1	1	def	def
3	22	f	p	sec	gfs	No	hs	0	n	n	n	-	1	1	1	prob	prob
4	35	f	npf	prim	goa	No	n	3	p	n	n	-	1	1	1	prob	prob
5	36	m	npf	prim	gwa	No	hs	0	n	n	n	-	1	1	1	prob	prob
6	28	f	ao	sec	gbd	Yes	n	3	p	n	n	-	1	1	1	prob	prob
7	46	f	npf	prim	goa	No	hs	3	p	p	p	-	3	1	1	def	def
8	70	m	npf	prim	goa	Yes	n	3	p	n	n	-	1	1	1	prob	prob
9	37	f	ao	prim	goa	No	n	3	p	n	n	-	1	1	1	prob	prob
10	63	m	npf	prim	goa	Yes	hs	3	p	n	n	-	2	1	1	def	def

11	14	m	npf	prim	gwa	No	n	3	p	n	n	-	1	1	1	prob	prob
12	12	m	npf	prim	gwa	No	n	3	p	n	p	-	1	1	1	prob	prob
13	52	f	npf	prim	goa	Yes	vc	3	p	p	p	1	3	1	1	def	def
14	55	m	npf	prim	goa	Yes	hs	3	P	n	n	-	2	1	1	def	def
15	16	f	npf	prim	gwa	No	hs	0	n	n	n	-	1	1	1	prob	prob
16	14	m	p	sec	gbd	No	n	3	p	n	p	-	1	1	1	prob	prob
17	22	m	npf	prim	gwa	Yes	hs	3	p	n	p	-	2	1	1	def	def
18	15	f	npf	prim	gwa	No	hs	0	n	n	n	-	1	1	1	prob	prob
19	54	m	npf	prim	gwa	No	hs	3	p	p	n	-	3	1	1	def	def
20	25	f	p	sec	gfs	Yes	hs	0	n	n	n	-	1	1	1	prob	prob
21	32	m	npf	prim	goa	No	hs	3	p	n	p	-	2	1	1	def	def
22	25	m	npf	prim	gwa	No	hs	0	n	n	n	-	1	1	1	prob	prob
23	50	m	npf	prim	gwa	No	hs	3	p	n	p	-	2	1	1	def	def
24	20	f	n.a.	prim	gwa	M	hs	3	p	n	n	-	2	1	1	def	def
25	41	m	npf	prim	gwa	No	n	3	p	n	n	-	1	1	1	prob	prob

26	49	f	npf	prim	gwa	Yes	hs	0	n	n	n	-	1	1	1	prob	prob
27	46	m	npf	prim	gwa	No	hs	3	p	n	n	-	2	1	1	def	def
28	23	m	npf	prim	gwa	No	n	2	n	p	n	-	1	1	1	prob	unlikely
29	64	m	npf	prim	goa	Yes	hs	3	p	p	n	-	3	1	1	def	def
30	55	m	ao	sec	gbd	No	hs	0	n	n	n	-	1	1	1	prob	prob
31	17	f	npf	sec	gbd	No	n	3	p	n	n	-	1	1	1	prob	prob
32	18	m	npf	prim	gwa	Yes	hs	3	p	n	n	-	2	1	1	def	def
33	34	m	npf	prim	gwa	M	hs	0	n	n	n	-	1	1	1	prob	prob
34	48	m	npf	prim	goa	No	hs	3	p	n	p	-	2	1	1	def	def
35	23	m	ao	sec	gbd	Yes	n	3	p	n	p	-	1	1	1	prob	prob
36	23	f	npf	prim	goa	No	n	3	p	n	p	-	1	1	1	prob	prob
37	48	m	npf	prim	gwa	Yes	vc	3	p	p	p	1	2	1	1	def	def
38	54	m	ao	sec	gbd	No	n	3	p	p	n	-	2	1	1	def	prob
39	30	m	npf	prim	gwa	M	hs	0	n	n	n	-	1	1	1	prob	prob
40	50	m	npf	prim	goa	No	c	3	p	n	p	-	1	2	1	prob	prob

n: case number; G: gender/sex; m: male; f: female; neuro: results of neurological examination; npf: no pathologic findings; p: paresis; ao: abnormal orientation; n.a.: data missing; TS: type of seizure; ILAE: International League Against Epilepsy; prim = primary generalized seizures; sec = secondary generalized seizures; gwa: generalized seizures within age range; goa: generalized seizures outside age range; gbd: generalized seizures with diffuse brain damage; gfs: generalized seizures with focal signs; M: missing data CT: computed tomography; CC-AB: *T. solium* cysticercosis antibody test, CC-AG: *T. solium* cysticercosis antigen; T-AB: *T. solium* taeniasis antibody;
CT: n = no relevant lesion; c = compatible with NCC, hs = highly suggestive for NCC; vc = viable cyst with visible scolex;
Serology: 0: all serological tests negative; 1: taeniasis-Ab test positive; 2: CC-AG test positive; 3: CC-AB and/or CC-AG test positive; p: positive; n: negative;
Abs: absolute diagnostic criteria; Major: major diagnostic criteria; Minor: minor diagnostic criteria; epi: epidemiologic diagnostic criteria; Diagnosis: def = definitive NCC; prob = probable NCC; unlikely = NCC unlikely.

*: Headache questionnaire item: severe or progressive headache from headache questionnaire;

[a] According to the International League Against Epilepsy (ILAE) http://www.ilae.org/ (03.09.2015) (ILAE. 2013)

[b]According to (Winkler et al. 2007)

[c] According to (Del Brutto et al. 2001, Nash et al. 2004)

[d] According to *(Gabriel et al. 2012)*)

[e] According to (Del Brutto et al. 2001, Del Brutto 2012)

12.13 Table 13: Prevalence of epilepsy and of neurocysticercosis in people with epilepsy in Uganda by sex and age used for DisMod II

Sex	Age group	Epilepsy prevalence (95%CI)	NCC prevalence in PWE (95%UI)
Male	0–12	N/A	*Assumed 0*
Male	12–18	0.051 (0.045–0.059)	0.065 (0.014–0.179)
Male	19–35	0.041 (0.035–0.047)	0.115 (0.044–0.234)
Male	36+	0.018 (0.014–0.023)	0.333 (0.118–0.616)
Female	0–12	N/A	*Assumed 0*
Female	12–18	0.085 (0.076–0.095)	0.081 (0.027–0.178)
Female	19–35	0.056 (0.048–0.064)	0.123 (0.051–0.237)
Female	36+	0.048 (0.040–0.057)	0.583 (0.366–0.779)

N/A: not available; CI: confidence interval; UI: uncertainty interval

12.14 Table 14: Estimated prevalence of neurocysticercosis associated epilepsy and headache in Uganda, 2010

Sex	Age group	NCC-epilepsy prevalence per 1000 (95%UI)	NCC-headache prevalence per 1000 (95%UI)
Male	0–12	0	0
Male	12–18	3.00 (0.64–7.09)	0.46 (0.00–1.50)
Male	19–35	4.07 (1.54–7.73)	0.62 (0.00–1.74)
Male	36+	4.37 (1.54–8.31)	0.67 (0.00–1.88)
Female	0–12	0	0
Female	12–18	5.86 (1.96–11.7)	0.89 (0.00–2.59)
Female	19–35	5.80 (2.40–10.5)	0.88 (0.00–2.42)
Female	36+	16.7 (9.86–24.7)	2.55 (0.00–6.28)

CI: confidence interval; UI uncertainty interval

12.15 **Table 15: Disability-Adjusted Life Year parameters for neurocysticercosis-associated epilepsy and headache**

Parameter	Distribution	Mean (95%UI)	Source
Proportion of NCC-epilepsy patients receiving effective treatment	Beta(α=168, β=126)	0.571 (0.515–0.627)	questionnaire analysis
Time between onset and effective treatment, age <35	Fixed	8.6	questionnaire analysis
Time between onset and effective treatment, age ≥35	Fixed	4.4	questionnaire analysis
Proportion of NCC-headache patients presenting with migraine	Beta(α=8, β=7)	0.533 (0.289–0.770)	questionnaire analysis
Proportion of NCC-headache patients presenting with tension-type headache	Beta(α=7, β=8)	0.467 (0.230–0.711)	questionnaire analysis
DW for epilepsy, severe (seizures once per month or more)	Beta(α=18, β=14)	0.552 (0.375–0.710)	Salomon et al. 2015
DW for epilepsy, less severe (seizures less than once per month)	Beta(α=20, β=57)	0.263 (0.173–0.367)	Salomon et al. 2015
DW for headache, migraine	Beta(α=19, β=24)	0.441 (0.294–0.588)	Salomon et al. 2015
DW for headache, tension-type	Beta(α=16, β=419)	0.037 (0.022–0.057)	Salomon et al. 2015

DW: Disability Weight*;* UI: Uncertainty interval; Beta distribution is based on continuous probability distribution depending on value distribution of each variable; • symbol for multiplication

12.16 **Table 16: Cost-of-illness parameters: hospitalization due to neurocysticercosis-associated epilepsy**

Parameter	Distribution	Mean (95%UI)	Source
Cost per km, bus	*See Table 21*	0.03 (0.01–0.06)	*Expert elicitation*
Cost per km, boda	*See Table 21*	0.59 (0.31–1.12)	*Expert elicitation*
Cost per km, taxi	*See Table 21*	1.83 (0.69–2.94)	*Expert elicitation*
Probability hospitalization	Beta(α=57, β=243)	0.191 (0.148–0.237)	questionnaire analysis
Hospitalization events per year	Gamma(μ=0.407, σ=0.036)	0.406 (0.341–0.481)	questionnaire analysis
Hospitalization days per event	Gamma(μ=5.63, σ=0.524)	5.63 (4.76–6.70)	questionnaire analysis
Hospitalization cost per day, patient	*See Table 21*	67 (6–322)	*Expert elicitation*
Hospitalization cost per day, relative	*See Table 21*	4.4 (3.1–5.7)	*Expert elicitation*
Probability of undergoing EEG	Pert(min=0.02, mode=0.10, max=0.13)	0.09 (0.05–0.12)	*Expert elicitation*
Cost per EEG	*See Table 21*	49 (19–129)	*Expert elicitation*
Distance to hospital	2 • Gamma(μ=10.7, σ=2.04)	21.39 (14.52–30.46)	questionnaire analysis
Probability travelling by boda	Beta(α=15, β=45)	0.252 (0.150–0.373)	questionnaire analysis
Probability travelling by taxi	Beta(α=9, β=51)	0.152 (0.0752–0.252)	questionnaire analysis

UI: Uncertainty interval; EEG: Electroencephalography; Greek letters: fitted parameters for corresponding distribution within the population; Beta and Gamma distributions are based on continuous probability distribution depending on value distribution of each variable-

12.17 Table 17: Cost-of-illness parameters: healthcare seeking due to neurocysticercosis-associated epilepsy

Parameter	Distribution	Mean (95%UI)	Source
Probability healthcare seeking	Beta(α=290, β=10)	0.967 (0.945–0.985)	questionnaire analysis
Probability of visiting a physician	Beta(α=8, β=282)	0.027 (0.012–0.048)	questionnaire analysis
Probability of visiting a nurse	Beta(α=143, β=147)	0.492 (0.435–0.552)	questionnaire analysis
Probability of visiting a health officer	Beta(α=135, β=155)	0.467 (0.409–0.525)	questionnaire analysis
Probability of visiting a traditional healer	Beta(α=22, β=268)	0.080 (0.049–0.111)	questionnaire analysis
Number of visits per year to a physician	Gamma(μ=0.375, σ=0.070)	0.376 (0.242–0.530)	questionnaire analysis
Number of visits per year to a nurse	Gamma(μ=0.607, σ=0.079)	0.603 (0.462–0.753)	questionnaire analysis
Number of visits per year to a health officer	Gamma(μ=0.409, σ=0.049)	0.408 (0.318–0.502)	questionnaire analysis
Number of visits per year to a traditional healer	Gamma(μ=0.489, σ=0.133)	0.484 (0.261–0.755)	questionnaire analysis
Cost per visit, physician	*See Table 21*	11 (0.7–2)	*Expert elicitation*
Cost per visit, nurse	*See Table 21*	1.4 (0.1–2.9)	*Expert elicitation*
Cost per visit, health officer	*See Table 21*	5.1 (1.6–14)	*Expert elicitation*
Cost per visit, traditional healer	*See Table 21*	10 (1.7–37)	*Expert elicitation*
Distance to physician	2 • Gamma(μ=10.7, σ=2.04)	21.64 (14.69–29.86)	questionnaire analysis
Distance to nurse	2 • Gamma(μ=10.9, σ=0.63)	21.83 (19.59–24.27)	questionnaire analysis
Distance to health officer	2 • Gamma(μ=9.9, σ=0.59)	19.87 (17.70–22.20)	questionnaire analysis

Distance to traditional healer	2 • Gamma(μ=10.9, σ=1.47)	22.01 (16.84–27.77)	questionnaire analysis
Probability of using boda to visit a physician	Beta(α=2, β=7)	0.222 (0.032–0.527)	questionnaire analysis
Probability of using taxi to visit a physician	Beta(α=3, β=6)	0.336 (0.080–0.660)	questionnaire analysis
Probability of using boda to visit a nurse	Beta(α=25, β=115)	0.180 (0.122–0.246)	questionnaire analysis
Probability of using taxi to visit a nurse	Beta(α=7, β=133)	0.050 (0.021–0.092)	questionnaire analysis
Probability of using boda to visit a health officer	Beta(α=27, β=106)	0.204 (0.141–0.279)	questionnaire analysis
Probability of using taxi to visit a health officer	Beta(α=3, β=130)	0.0231 (0.005–0.058)	questionnaire analysis
Probability of using bus to visit a traditional healer	Beta(α=1, β=17)	0.057 (0.002–0.202)	questionnaire analysis

UI: Uncertainty interval; Greek letters: fitted parameters for corresponding distribution within the population; Beta and Gamma distributions are based on continuous probability distribution depending on value distribution of each variable; • symbol for multiplication

12.18 **Table 18: Cost-of-illness parameters—treatment for neurocysticercosis-associated epilepsy and headache**

Parameter	Distribution	Mean (95%UI)	Source
Compliance of anti-epileptic drug treatment	Beta(α=225, β=74)	0.753 (0.702–0.800)	questionnaire analysis
Probability of carbamazepine treatment for epilepsy	Dirichlet(α_1=30, α_2=141, α_3=53)	0.134 (0.093–0.181)	questionnaire analysis
Probability of phenytoin treatment for epilepsy	Dirichlet(α_1=30, α_2=141, α_3=53)	0.629 (0.656–0.691)	questionnaire analysis
Probability of phenobarbitone treatment for epilepsy	Dirichlet(α_1=30, α_2=141, α_3=53)	0.237 (0.183–0.294)	questionnaire analysis
Probability of scarification treatment for epilepsy	Beta(α=12, β=288)	0.040 (0.021–0.063)	questionnaire analysis
Cost carbamazepine per month	*See Table 21*	4.4 (1.3–10)	*Expert elicitation*
Cost phenytoin per month	*See Table 21*	1.2 (0.3–2.8)	*Expert elicitation*
Cost phenobarbitone per month	*See Table 21*	2.9 (0.4–7.4)	*Expert elicitation*
Cost scarification per event	*See Table 21*	9.5 (0.6–37)	*Expert elicitation*
Cost paracetamol per month for headache treatment	*See Table 21*	1.2 (0.4–2.4)	*Expert elicitation*

UI: Uncertainty interval; scarification is a traditional healing method for epilepsy in Uganda; Greek letters: fitted parameters for corresponding distribution within the population; Beta and Dirichlet distributions are based on continuous probability distribution depending on value distribution of each variable

12.19 **Table 19: Estimated annual number of neurocysticercosis: associated incident cases and deaths Uganda, 2010**

Indicator	Absolute number (95%UI)	Rate per 100,000 people (95%UI)
Incident cases, NCC-epilepsy	9,344 (7,685–11,071)	28 (23–33)
Incident cases, NCC-headache	1,426 (0–3,254)	4.3 (0.0–9.8)
Deaths, NCC-epilepsy	2,749 (2,346–3,167)	8.3 (7.1–9.6)

UI: Uncertainty interval; NCC: Neurocysticercosis

12.20 **Table 20: Estimated incidence-based years lived with disability, years of life lost and disability-adjusted life years of neurocysticercosis, Uganda, 2010**

Indicator	Absolute number (95%UI)	Rate per 1,000 person-years (95%UI)	Rate per incident case (95%UI)
YLDs, NCC-epilepsy, receiving proper treatment	51,462 (35,244–71,076)	1.6 (1.1–2.1)	5.5 (4.1–7.1)
YLDs, NCC-epilepsy, not receiving proper treatment	62,415 (39,264–89,707)	1.9 (1.2–2.7)	6.7 (4.5–9)
YLDs, NCC-headache	10,167 (0–26,248)	0.3 (0.0–0.8)	7.1 (3.9–11.1)
YLLs, NCC-epilepsy	58,569 (49,043–68,579)	1.8 (1.5–2.1)	6.3 (4.9–8.1)
DALYs	**182,614 (142,547–228,459)**	**5.5 (4.3–6.9)**	**17 (14–20)**

UI: Uncertainty interval; YLD: Years lived with disease; YLL: year of life lost; DALY: Disability adjusted life years

12.21 Table 21: Estimated incident cost-of-illness of neurocysticercosis

Indicator	Mean (in US-Dollars) (95%UI)	Relative contribution (95%UI)
Hospitalization	11,871,872 (3,810,642–41,892,447)	0.15 (0.06–0.40)
—DHC	*7,791,415 (741,697–37,589,660)*	*0.09 (0.01–0.36)*
—DNHC	*3,734,121 (1,737,844–7,053,030)*	*0.05 (0.02–0.09)*
—INHC	*346,336 (221,504–507,754)*	*0.00 (0.00–0.01)*
Healthcare seeking	1,217,845 (691,774–1,984,607)	0.02 (0.01–0.03)
—DHC	*485,576 (172,080–1,037,388)*	*0.01 (0.00–0.01)*
—DNHC	*525,683 (243,398–976,048)*	*0.01 (0.00–0.01)*
—INHC	*206,586 (150,159–273,484)*	*0.00 (0.00–0.00)*
Treatment and consequences		
Drugs, epilepsy (DHC)	4,861,675 (2,173,501–8,932,231)	0.06 (0.03–0.11)
Drugs, headache (DHC)	555,318 (0–1,701,736)	0.01 (0.00–0.02)
Production losses due to severe epilepsy (INHC)	51,587,633 (39,590,561–64,613,736)	0.69 (0.49–0.78)
Production losses due to premature death (INHC)	5,375,711 (3,921,188–6,979,108)	0.07 (0.05–0.10)
TOTAL	**75,470,055 (56,386,713–108,895,694)**	**1.00 (1.00–1.00)**
—DHC	***13,693,984 (5,124,107–43,593,850)***	***0.17 (0.08–0.41)***
—DNHC	***4,259,804 (2,050,394–7,851,802)***	***0.06 (0.03–0.10)***
—INHC	***57,516,267 (45,341,603–70,751,565)***	***0.77 (0.54–0.87)***
TOTAL, PER CASE	**8,068 (6,825–11,323)**	**1.00 (1.00–1.00)**
—DHC	***1,463 (572–4,660)***	***0.17 (0.08–0.41)***
—DNHC	***455 (230–811)***	***0.06 (0.03–0.10)***
—INHC	***6,150 (5,567–6,761)***	***0.77 (0.54–0.87)***

DHC: Direct healthcare costs, DNHC: Direct non-healthcare costs, INHC: Indirect non-healthcare cost. UI: uncertainty interval All data for Uganda, 2010

DHC at the hospital include costs for medical diagnostics, intervention and treatment at the hospital, whereas outpatient treatment with a doctor/nurse/clinical officer etc. will fall under DHC healthcare seeking. This distinction applieBoths for DNHC and INHC. Regardless of whether inpatient or outpatient treatment, there might be long term treatment and work force loss due to NCC symptoms. This is included in the third category: Treatment and consequences. The total per case costs refer to accumulated life time costs for the average life time affected by NCC.

12.22 **Table 22: Expert elicitation questionnaire results on costs of various neurocysticercosis associated consult, diagnostics and treatment aspects in northern Uganda**

	Richard Idro		Ben Green		Shirley Crawford	
Questionnaire Item	**min**	**max**	**min**	**max**	**min**	**max**
Physician visit	1000	50000	20000	100000	20000	80000
Neurologist visit	25000	100000	50000	250000	60000	150000
Nurse visit	200	5000	2000	10000	5000	10000
Health officer visit			10000	50000	5000	10000
Traditional healer visit	20000	150000	5000	50000	5000	20000
Carbamazepine treatment for epilepsy	3845	24000	4000	40000	5000	30000
Phenobarbitone treatment for epilepsy	780	18000	2500	30000	3000	20000
Phenytoin treatment for epilepsy	921	6000	1500	10000	1000	10000
Scarification treatment for epilepsy	20000	150000	5000	25000	5000	30000
Paracetamol treatment for headache	1273	9000	2000	8000	1000	5000
Herbs/house remedies for headache	20000	150000	1000	10000	1000	10000
One day of hospitalization for epilepsy	15000	1500000	25000	300000	20000	300000
Additional diagnostic done for hospitalized epilepsy patients: EEG	50000	200000	100000	500000	80000	150000
Additional diagnostic done for hospitalized epilepsy patients: Brain CT Scan	120000	250000	100000	500000	150000	300000
Additional diagnostic done for hospitalized epilepsy patients: Brain MRI	500000	750000	250000	1000000	600000	1500000

Average number of days hospitalized for epilepsy (per year)	2 days	5 days	1 day	14 days	5 days	10 days
Relatives necessary?	yes		yes		yes	
Travel:/km traveled						
Bus	45	100	100	200	30	100
Boda (motortaxi)	1000	2000	2000	4000	1000	2000
Taxi	2000	5000	4000	8000	8000	10000

All values given in Ugandan Shilling (UGX); EEG: Electroencephalography; CT: Computed tomography; MRI: Magnetic resonance imaging; km: Kilometres; Relatives present has an influence on the costs of travel (DNHC) and on the workforce loss (INHC); if not indicated differently. For better results minimum (min) and maximum (max) estimates are given; A (weighted) mean was used (see Tables: 12.15-18 Tables 15-18) to assess average costs for patients;

13 Appendix

13.1 Epilepsy screening questionnaire

Inspired by (Placencia et al. 1992, Birbeck et al. 2004); adapted by Prof. Dr. Dr. Winkler

Screening Questionnaire

N°	Question	Answer
SECTION ONE: NCC Screening questionnaire for epileptic seizures		
1.	Have you ever lost consciousness? Or fallen due to lost consciousness?	1= YES 2= NO
2.	Have you ever been told that while you were unconscious your arms and legs shake or stretch out?	1= YES 2= NO
3.	Have you ever had attacks in which you fall and bite your tongue or lost control of your bladder or bowels?	1= YES 2= NO
4.	Have you ever had uncontrollable attacks of shaking or trembling in one arm or leg or in the face without losing consciousness?	1= YES 2= NO
5.	Have you ever experienced attacks of numbness, tingling in one arm or leg without losing consciousness?	1= YES 2= NO
6.	Have you ever had attacks in which you lose contact with the surroundings without losing consciousness?	1= YES 2= NO
7.	Have you ever had attacks of losing awareness that was associated with a feeling of vagueness, unreality or dreaminess or experience of abnormal smells, sounds, or vision without losing or before loss of consciousness?	1= YES 2= NO
8.	Have you ever been told that you had episodes of strange behavior without remembering it?	1= YES 2= NO

N°	Question	Answer
9.	Have you ever been told that you have or had epilepsy or epileptic fits?	1= YES 2= NO
10.	Do you eat barbeque meat from Cows Chickens, goats, **pigs**?	1= YES 2= NO
11.	**SECTION TWO: NCC Screening questionnaire for Children below 7 years Questions to the Parent/Guardian**	
12.	If your child has screened positive for any of the question 1-9, was there fever with any of the attacks? **Note if question 11 is YES then proceed up to question 14**	1= YES 2= NO
13.	Has your child ever had any episode of falling or dropping down?	1= YES 2= NO
14.	Has your child ever dropped things without any obvious reason?	1= YES 2= NO
15.	**SECTION THREE: RLS Questions:**	
16.	Have you experienced the urge to or need to move your legs or other body parts?	
17.	Were the urges to move accompanied by unpleasant sensations in the legs or other body parts?	
18.	Do the urges to move or the unpleasant sensations occur only/mainly at rest and are they partially relieved by movement?	
19.	Are/were urges or unpleasant sensations worse in the evening or night than during the day?	

13.2 Epilepsy in-depth study questionnaire

Inspired by (Placencia et al. 1992, Birbeck et al. 2004); adapted by Prof. Dr. Dr. Winkler

IDENTIFICATION **DATE**_____

SERIAL NUMBER OF PARTICIPANT_____

VILLAGE_____PARISH_____

SUB-COUNTY _____COUNTY _____

DISTRICT_____

HEAD OF HOUSEHOLD_____TEL_____

Distance to Health facility: _____means of transport: _____

Time:_____

	Question	**Answer**
	ONE: DEMOGRAPHICS	
1.	Name of respondent	
2.	Age (In completed years)	
3.	Sex of the respondent:	0= Male 1= Female
4.	What is your religion?	1=Catholic 2=Protestant 3=Muslim 4=African traditional 5= Other (specify): _____
5.	Which of the following tribes do you belong to?	1= Madi 2= Acholi 3= Lango 4= Lubgara 5= Kuku 6 = Kakua 7= Alur 8= Sudanese 9= Aringa 10= Congolese 11=Others (specify): _____

	Question	Answer
6.	What is your occupation?	1= Peasant farmer 2= School child 3= Street trader 4= Market trader 5= Professional 6= In private sector 7= Teacher 8= Administrator 9= Others _____
7.	What is your current marital status?	1= Married 2=Single 3=Divorced 4=Separated 5=Widowed 5= Not applicable 6=Co-habiting (living with a spouse)
8.	Age at marriage:	
9.	Number of children:	
	TWO: DESCRIPTION OF SEIZURE(S):	
10.	In the course of seizure, was there any loss of consciousness ?	1. = From the beginning 2. = After motor signs start 3. = No loss of consciousness
11.	In the course of a seizure what sort of motor activity took place?	1. = Tonic 2. = Clonic 3. = Both 4. = No movements of limbs, but rolling of eyes and grinding of teeth 5. =No movements 6. Myoclonic (short jerky movement) 7. Just falling down (“drop attack”)
12.	On which side of the body are movement of limbs observed?	1. = Only left side 2. = Only right side 3. = Both sides 4. = Not applicable
13.	Fitting; for how long?	1. = Few minutes 2. = 10 minutes 3. = 15 minutes 4. = 30 minutes or more

	Question	Answer
14.	Apart from physical movements, what other signs are observed?	1. = Froth from mouth 2. = Tongue/lip bite 3. = Urine/faecal incontinence 4. = None
15.	Have you ever experienced any injuries during fits?	0 = No 1= Yes
16.	If yes, what kind of injury?	1. = Burn 2. = Bruise 3 = Others
17.	Where was the injury?	
18.	What was the size of the injury in centimetres?	
19.	When did you suffer the injury/injuries?	
20.	Did you receive any treatment for the injury?	0= No 1= Yes
21.	If yes, which treatment was given?	1. = Operation 2. = Dressing 3. = Drugs(specify)_____ 4. = Others (specify)_____
22.	Where was the treatment performed?	1. = Hospital 2. = Health centre 3. = Dispensary 4. = Traditional healer 5. = Others (specify)_____
23.	Reorientation phase present? (post-ictal confusion)	0= No 1= Yes
24.	How long was the reorientation phase present (minutes)	
25.	Description of Reorientation phase (what happens during post-ictal confusion?)	
26.	Are seizures always the same?	0= No 1= Yes

	Question	Answer
27.	If different, please describe to make clear to which type of seizure(s) the aforementioned seizures refer to (e.g. simple partial or complex partial)	
	THREE: FREQUENCY:	
28.	What year did you first experience fits?	
29.	How old were you when the fits started? (Age in years)	
30.	When was the last fit?	
31.	What was the average frequency of fit before treatment?(If only a few seizures ask: Date? If all within one day?->What was patient doing just before seizure?)	Average frequency_____ Date_____ Day_____ What was patient doing_____
32.	What was the average frequency of fit after treatment?(If only a few seizures ask: Date? If all within one day? What was pt doing just before seizure?)	Average frequency_____ Date_____ Day_____ What was patient doing_____
33.	When do the fits normally occur? waking or the hour thereafter = morning = afternoon = during day time = evening = night	

	Question	Answer
	= night while asleep = anytime at day or night	
FOUR: AURA:		
34.	Just before you experience the seizure, are there any unusually feelings you get? e.g. strange smell, insect crawling on the skin, seeing strange things.	0= No aura 1= Aura present
35.	Describe the sensation **(aura)**	
36.	Were there focal signs like jerking of arm/leg or twitching of the face before losing consciousness?	0= No 1= Yes
37.	If yes, for how long were the focal signs present before loosing consciousness?	
FIVE: ASSOCIATION OF OTHER ILLNESSES IN RELATION TO FIRST FIT:		
38.	Any illness prior to first fit?	0= No 1= Yes
39.	If yes what illness prior to the fit	
40.	How long was the illness before the first fit	
SIX: PRECIPITANTS		
41.	Were there any precipitants that brought the seizures on?	0= No 1= Yes
42.	If yes which precipitants?	1= Fever 2 = alcohol 3= menstruation 4 = sleep 5= emotional stimuli 6= hunger 7= flicker lights 8= other:_____

	Question	Answer
	SEVEN: PAST MEDICAL HISTORY:	
43.	Have you ever experienced any severe/chronic illness in the past?	0= No 1= Yes
44.	If yes, describe the illness (type, date, treatment and complications)	Type_____ Date_____ Treatment_____ Complications_____
45.	Have ever been admitted to a hospital or health centre?	0= No 1= Yes
46.	If yes (which hospital or health centre, reason, date, time of stay)	Hosp/HC_____ Reason_____ Treatment_____ Complications_____
47.	When and where was the diagnosis of epilepsy made for the first time?	
	ALCOHOL HISTORY	
48.	Do you currently use or have you ever used alcohol on regular basis?	0= No 1= Yes
49.	If yes describe age when started:	
50.	If yes describe age when stopped:	
51.	If yes describe how many days per week:	
52.	how much did/do you drink?	
53.	how often did/do you get drunk?	

	Question	Answer
	FEBRILE FITS	
54.	Have you ever experienced fits during fever when you were a child from approx 1 month to 7 years of age? (You may have to ask your mother, even if the patient is old enough.)	0= No 1= Yes
55.	If yes, at that age was there fever with all the fits or did you experience fits without fever as well?	
56.	If yes, did you regain consciousness within 6 hours after the last seizure:	
57.	If yes describe how many episodes of fever and seizures did you have during that age range:	
58.	If yes what was the age you first experienced febrile fits:	
59.	If yes describe number of maximum febrile fits in a day:	
60.	If yes describe the localization of fits – one-sided or bilateral:	
61.	If yes describe average time of fits:	
62.	If yes describe any complications:	
	TRAUMA HISTORY	
63.	Have you ever experienced any accident, injuries or trauma?	0= No 1= Yes
64.	If yes describe type of accident, injuries or trauma?	
65.	If yes describe date of accident, injuries or trauma?	
66.	If yes describe the treatment received?	

	Question	Answer
67.	If yes describe the complication?	
	EIGHT: PPH (PAST PSYCHIATRIC HISTORY)	
68.	Did you experience any psychiatric illness?	0= No 1= Yes
69.	If yes describe the problems in the past	1= Depression 2= Mental retardation 3=Behavioural problems 4=Dementia 5=Psychotic episodes 6=Suicide attempt 7=Other_____
70.	How severe were this problem?	1= mild 2= moderate 3= severe
71.	Describe the psychiatric problems at present	1= Depression 2= Mental retardation 3=Behavioural problems 4=Dementia 5=Psychotic episodes 6=Suicide attempt 7=Other_____
72.	Are this problems enough to interfere with your life	1= mild 2= moderate 3= severe
73.	For how long have you suffered from this problem?	
74.	Did you receive any treatment?	0= No 1= Yes
75.	If yes what treatment was given?	

	Question	Answer
	NINE: DH (DRUG HISTORY)	
76.	Is the patient currently on Anti Epileptic Drug (AED)?	0= No 1= Yes
77.	Which AED is the patient taking? Phenobarbitone Dose:_____ started when:_____ where:_____ Carbamazepine Dose:_____ started when:_____ where:_____ Valproate Dose:_____ started when:_____ where:_____ Phenotoin Dose:_____ __ started when:_____ where:_____	
78.	Is there fits on the current drug?	0= No 1= Yes
79.	If yes what is the frequency of fits on current drug	
80.	Are there side effects	0= No 1= Yes
81.	If yes what are the side effects	1= Dizziness 2= Tiredness 3= Headache 4= Nausea 5= Skin rash 6=other:_____

	Question	Answer
82.	What was the severity of the side effect?	1= Mild 2= Moderate 3= Severe
83.	Have you tried other Anti Epileptic Drugs **(AED)**?	0= No 1= Yes
84.	Which **AED** have you tried? Phenobarbitone Dose:_____ started when:_____ where:_____ **a)** Carbamazepine Dose:_____ started when:_____ where:_____ **b)** Valproate Dose:_____ started when:_____ where:_____ **c)** Phenotoin Dose:_____ started when:_____ where:_____	
85.	When did you stop this drug?	
86.	Were there fits on this drug?	0= No 1= Yes
87.	If yes what was the frequency of fits on this drug	
88.	Were there side effects	0= No 1= Yes
89.	If yes what were the side effects	1= Dizziness 2= Tiredness 3= Headache 4= Nausea 5= Skin rash 6=other:_____
90.	What was the severity of the side effect?	1= Mild 2= Moderate 3= Severe

	Question	Answer
91.	What were the reasons for changing the AED	1= Side effects 2= No response 3= Other_____
92.	Are you currently on other treatment besides anti epileptic drugs (AED)	0= No 1= Yes
93.	If yes, give the details of the treatment:	
94.	Have you ever tried herbal treatment?	0= No 1= Yes
95.	If yes, describe (the ingredient, route, when started, for how long taken, any help, side effects)	
96.	Has Scarification been ever performed on you?	0= 0= No 1= Yes
97.	If yes describe (when, where, manipulation of wound, any help, side effects)	When_____ Where_____ Manipulation of wound: _____ Any help _____ Side effects_____
	TEN: FH (FAMILY HISTORY)	
98.	Is there any one else in the family who suffers from epileptic seizures?	0= No 1= Yes
99.	How are you related to this person?	1= uncle 2= aunt 3=brother 4= sister 5= cousin 6= other_____

	Question	Answer
100.	Describe the seizure(s) in terms of (age at first, last fit, frequency, precipitant(s).	Age at first fit_____ Last fit_____ Frequency_____ Precipitant(s)_____
101.	Are there other family members/relatives who suffer from neurological/mental illness (brain problems)?	0= No 1= Yes
102.	If yes, how are you related to this person?	1= uncle 2= aunt 3=brother 4= sister 5= cousin 6= other_____
	ELEVEN: BIRTH HISTORY AND PRENATAL HISTORY	
103.	Was your **mother** healthy during pregnancy?	0= No 1= Yes
104.	If no. what type of illness did she suffer from and what treatment did she receive?	
105.	Describe where you were born.	1= Hospital 2= Health centre 3= Dispensary 4= Home
106.	Was the delivery at term or preterm?	1= Term 2= Preterm
107.	Describe the mode of delivery:	1= SVD 2= Caesarean section 3= Assisted delivery (forceps etc.) 4= Breech delivery

	Question	Answer
108.	Labour:	1= prolonged 2= precipitated 3= normal 4= duration in hour :_____
109.	Did your mother say that you cried immediately?	0= No 1= Yes
110.	Did your mother say that you breastfed well after delivery?	0= No 1= Yes
111.	Did your mother say she was worried about you because you turned blue after birth?	0= No 1= Yes
112.	Did your mother say you turned yellow within the first 3 days you were born?	0= No 1= Yes
113.	Other problems	= None = Resuscitation = Incubator = Oxygen supply = Neonatal fits = Other_____
114.	Milestones: Head control:	0= Delayed 1= Normal
115.	If delayed, since when:	1= Birth 2= Special event Describe_____
116.	Milestones: Smile:	0= Delayed 1= Normal

	Question	Answer
117.	If delayed, since when	1= Birth 2= Special event Describe_____
118.	Milestones: turning:	0= delayed 1= normal
119.	If delayed, since when:	1= Birth 2= Special event Describe_____
120.	Milestones: sitting:	0= Delayed 1= Mormal
121.	If delayed, since when:	1= Birth 2= Special event Describe_____
122.	Milestones: crawling	0= Delayed 1= Normal
123.	If delayed, since when	1= Birth 2= Special event Describe_____
124.	Milestones: Standing	0= Delayed 1= Normal
125.	If delayed, since when:	1= Birth 2= Special event Describe_____
126.	Milestones: Walking:	

	Question	Answer
127.	If delayed, since when	1= Birth 2= Special event Describe_____
128.	Milestones: Saying the first word:	0= Delayed 1= Normal
129.	If delayed, since when:	1= Birth 2= Special event Describe_____
130.	Did your mother say you had neonatal seizures?	0= No 1= Yes
131.	If yes, then describe in terms of (age, frequency, any associated symptoms/signs)	Age_____ Frequency_____ Associated symptom/signs_____
	TWELVE: SCHOOL	
132.	Did/does patient go to school?	0= No 1= Yes
133.	If no, give reason	
134.	At what age did you start school?	
135.	Did you attend school regularly?	0= No 1= Yes
136.	If no, give reasons	1= Epilepsy 2= Financial 3= Social 4=Other_____
137.	Have you ever dropped out of school	0= No 1= Yes
138.	If yes, give reasons	1= Epilepsy 2= Financial 3= Social 4=Other_____

	Question	Answer
139.	What level did you finish at school?	
	THIRTEEN: WORK	
140.	Before first fit:	Type of work? _____ Hours of work _____
141.	Since fits started:	Type of work? _____ Hours of work _____
142.	Since Treatment started:	Type of work? _____ Hours of work _____
143.	If there is a difference, give reason:	
144.	After fit:	Days lost due to fits: _____ Days with impaired work: _____
	On days with impaired work, how much does the pt work?	1= 0 2= <50% 3= > 50%
Comments: Do you have any other comments?		Comments:

Neurological examination

Note: if patient has an altered state of consciousness (sleepy/drowsy – coma), assess immediately the Glasgow Coma Scale **TOTAL (3–15): _____/15**

- **EYE OPENING**

None 1 = Even to supra-orbital pressure

To pain 2 = Pain from sternum/limb/supra-orbital pressure

To speech 3 = Non-specific response, not necessarily to command

Spontaneous 4 = Eyes open, not necessarily aware _____

- **MOTOR RESPONSE**

None 1 = To any pain; limbs remain flaccid

Extension 2 = Shoulder adducted and shoulder and forearm internally rotated

Flexor response 3 = Withdrawal response or assumption of hemiplegic posture

Withdrawal 4 = Arm withdraws to pain, shoulder abducts

Localizes pain 5 = Arm attempts to remove supra-orbital/chest pressure

Obeys commands 6 = Follows simple commands

- **VERBAL RESPONSE**

None 1 = No verbalization of any type

Incomprehensible 2 = Moans/groans, no speech

Inappropriate 3 = Intelligible, no sustained sentences

Confused 4 = Converses but confused, disoriented

Oriented 5 = Converses and oriented _____

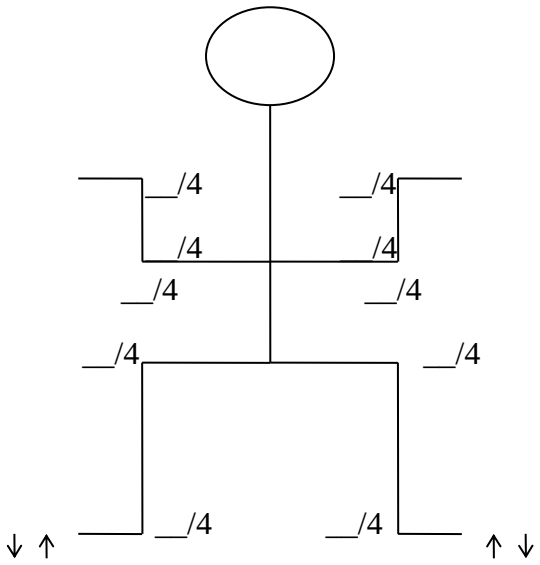
NEUROLOGICAL SIGN(S)			
Higher functions			**If abnormal, detail**
Level of consciousness	Awake ☐	Sleepy ☐	GCS:/15
Orientation (time, place, person)	Normal ☐	Abnormal ☐	Time☐ Place☐ Person☐
Behaviour and talking/acting	Normal ☐	Abnormal ☐	Detail:
Cognitive: simple arithmetics	Normal ☐	Abnormal ☐	
Cognitive: remote memory	Normal ☐	Abnormal ☐	
Cognitive: recent memory	Normal ☐	Abnormal ☐	
Head and neck exam			
Neck stiffness flexion/extension	Absent ☐	Present ☐	Distance chin-chest: __ cm:
Neck stiffness rotation	Full☐	Reduced☐	Left ☐ Right ☐
Cranial nerve exam			
Visual acuity	Normal ☐	Abnormal ☐	Left ☐ Right ☐ Detail:
Visual fields	Normal ☐	Abnormal ☐	Left ☐ Right ☐ Detail:
Eye movements: nerve palsy (III, IV, VI)	No ☐	Yes☐	Left ☐ Right ☐ III ☐ IV ☐ VI☐
Eye movements: gaze palsy (up, down, lateral)	No ☐	Yes☐	Up ☐ down☐ Lateral L ☐ Lateral R ☐

Eye movements: smooth pursuit	Normal☐	Abnormal☐	Detail:
Pupils equal size?	Yes☐	No☐	R-Size (___mm) L-Size (___mm)
Pupils reactive to light (direct)?	Yes☐	No☐	Left ☐ Right ☐ Myosis☐Mydriasis☐
Pupils reactive to light (indirect)?	Yes☐	No☐	Left ☐ Right ☐ Myosis☐Mydriasis☐
Pupils accommodate?	Yes☐	No☐	Left ☐ Right ☐
Ptosis	Absent ☐	Present ☐	Left ☐ Right ☐
Facial hypoaesthesia	Absent☐	Present☐	Left ☐ Right ☐
Masseter reflex	Normal☐	Abnormal☐	Left ☐ Right ☐
Facial palsy (upper, central)	Absent ☐	Present ☐	Left ☐ Right ☐ Partial ☐ Complete☐
Facial palsy (lower, peripheral)	Absent ☐	Present ☐	Left ☐ Right ☐ Partial ☐ Complete☐
Hearing impairment	Absent ☐	Present ☐	Left ☐ Right ☐
Nystagmus (spontaneous):	Absent ☐	Present ☐	Left ☐ Right ☐
Nystagmus (provoked):	Absent ☐	Present ☐	Left ☐ Right ☐
Dysarthria	Absent ☐	Present ☐	Detail:
Dysphonia	Absent ☐	Present ☐	Detail:
Dysphagia	Absent ☐	Present ☐	Detail:
Gag reflex	Normal☐	Abnormal☐	Detail:

Tongue movement	Normal☐	Abnormal☐	Left ☐ Right ☐:
Motor exam			
Muscle atrophy	Absent ☐	Present ☐	Left ☐ Right ☐ Location:
Hemiparesis/hemiplegia	Absent ☐	Present ☐	Left ☐ Right ☐ Partial ☐ Complete ☐
Quadriparesis/quadriplegia	Absent ☐	Present ☐	Partial ☐ Complete ☐
Localized motor deficits	Absent ☐	Present ☐	Left ☐ Right ☐ Partial ☐ Complete ☐ Location:
Primitive reflex exam			
palmomental	Absent ☐	Present ☐	
Snout	Absent ☐	Present ☐	
Deep tendon/plantar reflex			See Fig below
Triceps reflex			
Biceps reflex			
Brachioradialis reflex			
Patellar reflex			
Achilles reflex			
Plantar response	Down☐	Up☐	Equivocal ☐
Fanning of toes	Absent☐	Present☐	Detail:

Tone			
Hypotonia	Absent ☐	Present ☐	Left ☐ Right ☐ Location:
Hypertonia (spasticity, rigidity)	Absent ☐	Present ☐	Left ☐ Right ☐ Location:
Coordination and gait exam			
Gait	Normal ☐	Abnormal ☐	Left ☐ Right ☐
Finger-nose test	Normal ☐	Abnormal ☐	Left ☐ Right ☐
Knee-heel test	Normal ☐	Abnormal ☐	Left ☐ Right ☐
Tremor	Absent ☐	Present ☐	Left ☐ Right ☐ Location: Resting tremor: Action tremor: Intention tremor:
Sensory exam			
Localized hypo/anesthesia	Absent ☐	Present ☐	Left ☐ Right ☐ Partial ☐ Complete ☐ Face ☐ Arms ☐ Legs ☐

Deep tendon and plantar reflexes



Deep Tendon Reflex Grading Scale	
Grade	Description
0	Absent
1+	Hypoactive
2+	"Normal"
3+	Hyperactive without clonus
4+	Hyperactive with clonus

Motor Strength (rate each 0 – 5 as described below):

	Finger spread	Finger extension	Finger flexion	Wrist extension	Biceps	Triceps	Deltoid	Shoulder shrug	Hip flexion	Knee flexion	Knee extension
R											
L											

	Dorsi-flexion	Plantar-flexion
R		
L		

Muscle strength	
Grade	Description
0/5	No muscle movement
1/5	Visible muscle movement, but no movement at the joint
2/5	Movement at the joint, but not against gravity
3/5	Movement against gravity, but not against added resistance
4/5	Movement against resistance, but less than normal
5/5	Normal strength

13.3 Headache screening questionnaire

With friendly permission of Hélène Carabin (Carabin 2010b)

GULU UNIVERSITY

NEUOROCYSTICERCOSIS STUDY IN SUB SAHARAN AFRICA

Screening questionnaire prevalence of headache

1. **Have you ever had bad headaches that did not go away and that got worse over time?**

☐ Yes, currently has ☐ Yes, in the past year, but not currently

☐ Yes, one year or more ago, but not currently ☐ No

☐ Cannot remember, do not know

1.1 Were these headaches bad enough to keep you from doing your daily chores, work or going to school?

☐ Yes ☐No ☐Cannot remember, do not know

[*If any 'yes' to question 1 and 'yes' or 'can't remember/don't know' to question 1.1 – NOTE that this person should be examined by the field doctor*]

2. **How old were you when this type of headaches first happened?**

☐ I was a child (less than 15) and I was _____ years old

☐ I was a young adult (15-19) and I was _____ years old

☐ I was an adult and I was (20 or more) and I was _____ years old

☐ Cannot remember, do not know

3. **When you have headaches, do you have any trouble with your vision, such as black spots, or seeing zig-zag or wavy lines or numbness in your fingers, arms or legs?**

☐ Yes ☐No ☐Cannot remember, do not know

4. **When you have headaches, do you also suffer from nausea or vomiting?**

☐ Yes ☐No ☐Cannot remember, do not know

13.4 **Headache in-depth questionnaire**

With friendly permission of Hélène Carabin (Carabin 2010b)

SEVERE PROGRESSIVE HEADACHE

1. **Headache sufficient to interfere with activities of daily life or requires analgesics?**

☐ Yes ☐ No ☐Does not know

2. **Headache frequency?**

☐ Generally constant ☐ Daily ☐ Weekly

☐ Monthly ☐ Less than once per month

☐ Unable to determine

3. **What type of pain are the headaches usually accompanied with?**

☐ Throbbing (pulsating)

☐ Piercing (perforating sensation)

☐ Stabbing or sharp

☐ Pressure

4. **How do the headaches occur?**

☐ They are continuous ☐ Begin suddenly and unexpectedly (paroxysmal)

☐ They occur periodically (episodic)

5. **Have headaches become progressively worse since they started, have they remained at the same level of pain, or have they gotten less painful?**

☐ More severe ☐ About the same ☐Better ☐ Uncertain

6**. When did headaches begin?** ☐ Within past month
☐Within 6 months

☐ Within past year
☐ More than one year ago ☐ Uncertain

7. **How long do the headaches usually last?**

☐ Several minutes but less than 1 hour ☐From 1 to 2 hours ☐ From 3 to 6 hours ☐ Half a day

☐ All day ☐ Other (Specify _____

8. **Are the headaches triggered by any of the following situation?**

☐1 Yes ☐1 No [*Go to question 9*]

8.1 **What are they triggered by?**

☐ Brushing teeth ☐ Shaving

☐ Drinking alcohol ☐ Chewing

☐ Other (Specify _____)

9**. Are the headaches usually accompanied by [Check all that apply]:**

☐ Nausea ☐ Vomiting ☐ Photophobia ☐Phonophobia

☐ Impossible to determine/ does not know

10. **Just before or during headaches does the patient have visual disturbance?**

☐ Yes ☐ No [*Go to question 11*]

10.1 **What are those visual disturbances (check all that apply)**

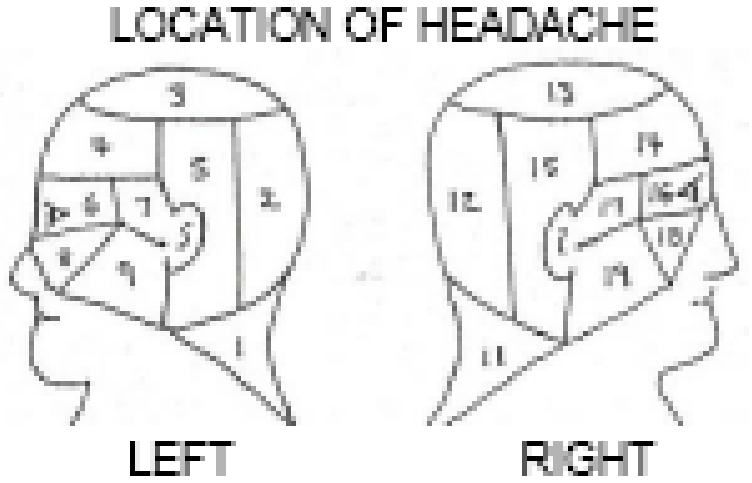
☐ Black spots ☐ Gaps in visual field ☐Zig-zag lines
☐Other evidence of aura

☐ Other visual disturbance (describe) _____
☐Cannot determine

11. **Which picture below best shows how much pain you have when you have headaches?**

0 = VERY HAPPY, NO HURT
1 = HURTS JUST A LITTLE BIT
2 = HURTS A LITTLE MORE
3 = HURTS EVEN MORE
4 = HURTS A WHOLE LOT
5 = HURTS AS MUCH AS YOU CAN IMAGINE
(Don't have to be crying to feel this much pain)

12. **Location of headache:** (*Show the patient the illustration of the cranium and ask them to identify all the places where they feel pain. Mark on the illustration accordingly.)*



12.1 **Do the headaches tend to start on one particular side before moving to the next?**

☐ Yes ☐ No [*Go to Q13*]

12.2 **On which side does the headaches usually start?**

☐ Left ☐ Right

13. Brief description of headaches:

_____

_____

_____

_____

14. **Is this patient's history consistent with a diagnosis of severe, progressively worsening headaches?**

☐ Definite ☐ Probable ☐ No ☐ Uncertain

13.5 CWGESA questionnaire

published by (Mukaratirwa 2010)

Cysticercosis Working Group for Eastern & Southern Africa

CWGESA
Questionnaire on *Taenia solium* cysticercosis/taeniosis

[Interviewer please fill in on the provided lines and circle all appropriate answers]

I. GENERAL INFORMATION

Date of interview: ___ ___/___ ___/___ ___ ___ ___ ***(dd/mm/yyyy)***

Country: _____

District: _____

Sub-County: _____

PARISH _____

Village: _____

Name of interviewer: _____

II. HOUSEHOLD INFORMATION

1. Name of interviewee: _____

2. Age: _____ (years)

3. Sex:

a. Male
b. Female

4. What is the highest schooling grade you have completed?

a. None
b. Primary school
c. Ordinary level school
d. Advanced level school

5. What further education have you completed?

a. None
b. College
c. University
d. Technical/vocational
e. Other (please specify): _____

6. What is your main occupation? _____

III. INFORMATION ON DRINKING WATER AND SANIITATION

7. From where do you usually get your drinking water? Ok

a. River
b. Well
c. Bore-hole
d. Tap
e. Rain catchments
f. Other (please specify): _____

8. Has your drinking water been boiled before you drink it? OK

a. Always
b. Almost always
c. Sometimes
d. Rarely
e. Never

9. Do you have a latrine at home? OK

a. Yes
b. No (please skip to Q. 11)

10. How often do you use a latrine when you have to defecate? Ok

a. Always
b. Sometimes
c. Never

IV. INFORMATION ON PORK CONSUMPTION

11. Do you ever eat pork? ***Have you ever eaten pork?***

a. Yes
b. No (please skip to Q. 14)

12. How often do you eat pork? OK

a. At least once a month

b. Less than once a month but at least once a year

c. Less than once a year

13. How is the pork that you eat prepared? OK

a. Boiled
b. Fried
c. Barbeque
d. Other (please specify): _____

V. INFORMATION ON PIG MANAGEMENT

14. Do you or anyone in your household keep pigs? OK

a. Yes

b. No (please skip to Q. 27)

15. What type of pigs do you keep? Needs modification

a. Foreign

b. Native

c. Both foreign and native

d. Cannot remember, do not know

16. Of the pigs you have, how many are for? Most people keep pigs for income generation

[Interviewer: Read each choice and record the number]

a. Home consumption
b. Trading
c. Reproduction
d. Not decided yet
e. Other (specify)_____

17. Where do you keep your pigs in the different seasons? (Check where appropriate)

Seasons	In pens	Free ranged	Tethering	Other (please specify)
Planting				
Growing				
Harvesting				
Fallowing				

18. Do you or any in your household raise piglets? OK

a. Yes
b. No (please skip to Q. 20)

19. For how long do you leave the piglets to roam freely? OK

a. Not at all
b. Always
c. Less than 1 month
d. Between 1 – 2 months
e. Other (please specify): _____

20. What do you feed your pigs? OK

a. Pasture
b. Kitchen leftovers
c. Commercial feed
d. Commercial waste products (specify) _____
e. Others (please specify)

21. Do you or any in your household ever slaughter any of your pigs?
a. Yes
b. No (please skip to Q. 25)

22. How often are pigs slaughtered at your home?

a. At least once a month
b. Less than once a month but at least once a year
c. Less than once a year
d. Cannot remember, do not know (please skip to Q. 25)

23. Have you ever had your home slaughtered pork inspected by a meat inspector?

a. Yes
b. No (please skip to Q. 25)

24. If „yes“, who exactly was the meat inspector?

a. Veterinarian
b. Veterinary assistant
c. Somebody from the village

25. How often is your meat inspected by a meat inspector?

a. Always
b. Almost always
c. Sometimes
d. Rarely
e. Never
f. Cannot remember, do not know

26. What is the value of a pig when it is ready to be slaughtered?

(Please specify the currency used) _____at month⁄age_____

27. What is the value of a piglet aged 4 months or less?

(please specify the currency used)_____

28. Have you or any in your household ever owned pigs?

a. Yes
b. No (please skip to Q. 30)

29. When did you or your household member own pigs?

a. Yes, in the past year
b. Yes, one (1) to five (5) years ago
c. Yes, more than five (5) years ago

30. What kind of pigs were they?

a. Foreign
b. Native
c. Both foreign and native
d. Can not remember, do not know

VI. INFORMATION ON PORCINE CYSTICERCOSIS

31. Have you ever seen or heard of white nodules (rice) in pig carcasses?

a. Yes
b. No (please skip to Q. 34)

32. Do you know where you can find nodules on a live pig?

a. I don't know
b. It is not possible to find them on a live pig
c. Under the skin
d. Under the tongue
e. Somewhere else (please specify) _____

33. Do you know how pigs get these nodules?

a. I don't know
b. By eating human faeces
c. By eating pig faeces
d. From another infected pig
e. Other (please specify)_____

34 What would you do if you discovered that your pig had nodules?

a. I don't know
b. Sell the pig
c. Treat it with herbs, If yes, which ones----------
and how often_____
d. Pierce the nodules
e. Other (please specify) _____

35. Have you ever heard of the disease 'porcine cysticercosis?

a. Yes
b. No (please skip to Q. 38)
c. Can not remember, do not know (please skip to Q. 38)

36. Have you ever seen or been told that your pigs were infected with cysticercosis?

a. Yes
b. No (please skip to Q. 38)
c. Can not remember, do not know (skip to Q. 38)

37. When was the last time you became aware of cyst (cysticercosis) in your pigs?

a. In the past year
b. More than one year ago
c. Can not remember, do not know (skip to Q. 38)

38. When that happened, were you able to sell your pigs?

a. Yes
b. No
c. Can not remember, do not know

39. If "yes", who were they sold to?

a. local market
b. local restaurant/bar
c. other (please specify)_____

40. "At which price was the infected meat sold"?

_____

41. "Were pigs ever dewormed" and if "yes",

"what medication was used, _____

how often was it given to the pigs and _____

at what age of the pigs" _____

VII. INFORMATION ON HUMAN CYSTICERCOSIS/TAENIOSIS

42. How many days of work have you missed because of illness in the past month?

_____ days

43. Have you ever heard of tapeworm infection in humans?

a. Yes
b. No (please skip to Q. 43)

44. How did you learn about it? _____

45. How does one know that he/she has a tapeworm?

_____

46. How do people get tapeworm infection?

_____

47. 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

48. 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

49. Have you ever had sudden loss of consciousness and episodes of incontinence or foaming of the mouth or tongue biting?

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. 48)
e. Can not remember, do not know (please skip to Q. 48)

50. How often have you had these symptoms?

a. Only once
b. More than once
c. Can not remember, do not know

51. How old were you when this first happened? _____ years

52. 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. 51)
e. Can not remember, do not know (please skip to Q. 51)

53. How often have you had these symptoms?

a. Only once
b. More than once
c. Can not remember, do not know

54. How old were you when this first happened? _____ Years

55. 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. 54)
e. Can not remember, do not know (please skip to Q. 54)

56. How often has this happened?

a. Only once
b. More than once
c. Can not remember, do not know

57. How old were you when this first happened? _____ years

58. 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. 57)
e. Can not remember, do not know (please skip to Q. 57)

59. How often has this happened?

a. Only once
b. More than once
c. Can not remember, do not know

60. How old were you when this first happened? _____ years

61. 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. 60)
e. Can not remember, do not know (please skip to Q. 60)

62. How often has this happened?

c. Only once
d. More than once
d. Can not remember, do not know

63. How old were you when this first happened? _____ years

64. 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

*[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 61]

65. Have you had a head injury that made you lose consciousness?

a. Yes
b. No (please skip to Q. 63)

66. When did your seizure symptoms start?

a. Before head injury
b. Soon after head injury
c. Can not remember, do not know

67. Have you had meningitis (brain infection) during childhood?

a. Yes
b. No (please skip to Q. 65)

68. 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

69. Have you had cerebral malaria?

a. Yes
b. No (please skip to Q. 68)

70. 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

71. What happens to you when you have a seizure or a fit?

_____

_____

72. Have you ever hurt yourself when you lose consciousness or during a seizure?

a. Yes
b. No (please skip to Q. 70)
c. I do not lose consciousness or have seizures (please skip to Q. 70)
d. Can not remember (please skip to Q. 70)

73. 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) _____

74. 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. Cannot remember, do not know

[Interviewer: Read the following statement:]

"Now I want to ask you some questions about your treatments for seizure/epilepsy"

75. Have you ever been hospitalized because of seizure/epilepsy?

a. Yes
b. No (please skip to Q. 78)
c. Cannot remember (please skip to Q. 78)

76. How many times have you been hospitalized in the past 5 years? _____times

77. When were you last hospitalized? _____(month)_____(year)

78. How many days did you stay in hospital? _____ (days)

79. How much did it cost? (specify the currency) _____

80. How far is the hospital from your house? _____ km

81. 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) _____

82. Have you ever consulted a health provider because of seizure/epilepsy?

a. Yes
b. No (please skip to Q. 83)
c. Cannot remember (please skip to Q. 83)

83. When was the <u>last</u> 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. Cannot remember, not sure

84. 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. Cannot remember, not sure

85. How much did it cost <u>last</u> 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. Cannot remember, not sure

86. 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. Cannot remember

87. Were you ever tested with a diagnostic test because of this condition?

a. Yes
b. No (please skip to Q. 87)
c. Cannot remember, do not know (please skip to Q. 87)

88. 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. Cannot remember, not sure

89. 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. Cannot remember, not sure

90. 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. Cannot remember, not sure

91. 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)

92. 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. Cannot remember, not sure

93. 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. Cannot remember, not sure

94. How much did it cost <u>last</u> time you bought this medication

a. Phenobarbital _____
b. Dilantin _____
c. Valproic acid _____
d. Traditional medicine _____
e. Other (specify) _____ _____
f. Cannot remember, not sure

THIS IS THE END OF THE INTERVIEW

THANK YOU VERY MUCH FOR YOUR COOPERATION

[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

13.6 Economic calculations in northern Uganda: Expert opinion

Please specify what you believe is the **average cost** of each of the following items. You may specify a minimum and maximum value to define the range within which the average cost may fall.

	USH, MINIMUM	USH, MAXIMUM
Physician visit		
Neurologist visit		
Nurse visit		
Health officer visit		
Traditional healer visit		

Treatment costs (medication)

Please specify what you believe is the **average <u>monthly</u> cost** of each of the following items. You may specify a minimum and maximum value to define the range within which the average cost may fall.

	USH, MINIMUM	USH, MAXIMUM
Carbamazepine treatment for epilepsy		
Phenobarbitol treatment for epilepsy		
Phenytoin treatment for epilepsy		
Scarification treatment for epilepsy		
Paracetamol treatment for headache		
Herbs/house remedies for headache		

Hospitalization

Please specify what you believe is the **average cost** of each of the following items. You may specify a minimum and maximum value to define the range within which the average cost may fall.

	USH, MINIMUM	USH, MAXIMUM
One day of hospitalization for epilepsy		
Additional diagnostic done for hospitalized epilepsy patients: <please specify which> EEG		
Additional diagnostic done for hospitalized epilepsy patients: <please specify which> Brain CT Scan		
Additional diagnostic done for hospitalized epilepsy patients: <please specify which> Brain MRI		

Please specify what you believe is the **average number of days an epilepsy patient would get hospitalized**, if hospitalization was required. You may specify a minimum and maximum value to define the range within which the average number may fall.

	MINIMUM	MAXIMUM
Average number of days hospitalized for epilepsy		

Please specify whether you believe it is **required to keep a relative closeby when being hospitalized**.

	YES	NO
Required to keep a relative closeby when being hospitalized (Costs?)		

Travel expenses

Please specify what you believe is the **average cost per km travelled** for each of the following items. You may specify a minimum and maximum value to define the range within which the average cost may fall.

	USH, MINIMUM	USH, MAXIMUM
Bus	/= per Km	/= per Km
Boda (motortaxi)	/= per Km	/= per Km
Taxi	/= per Km	/= per Km

13.7 Ethics-approval documents

13.7.1 Figure 18: Ugandan ethics approval (25.09.2008)

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FACULTY OF MEDICINE

25th September 2008

Dr Julius K Kuule
Faculty of Medicine,
Gulu University.

Dear Dr Kuule;

RE: ETHICAL CLEARANCE FOR THE NEUROCYSTICERCOSIS STUDY

The Research and Ethics committee of the Faculty of Medicine, Gulu University sat on the 24th September 2008 after you had presented the consortium proposal on "Neurocysticercosis in sub-Saharan Africa which is an emerging public health problem".

I am pleased to inform you that after thorough scrutiny, the committee has cleared your proposal on the following grounds:

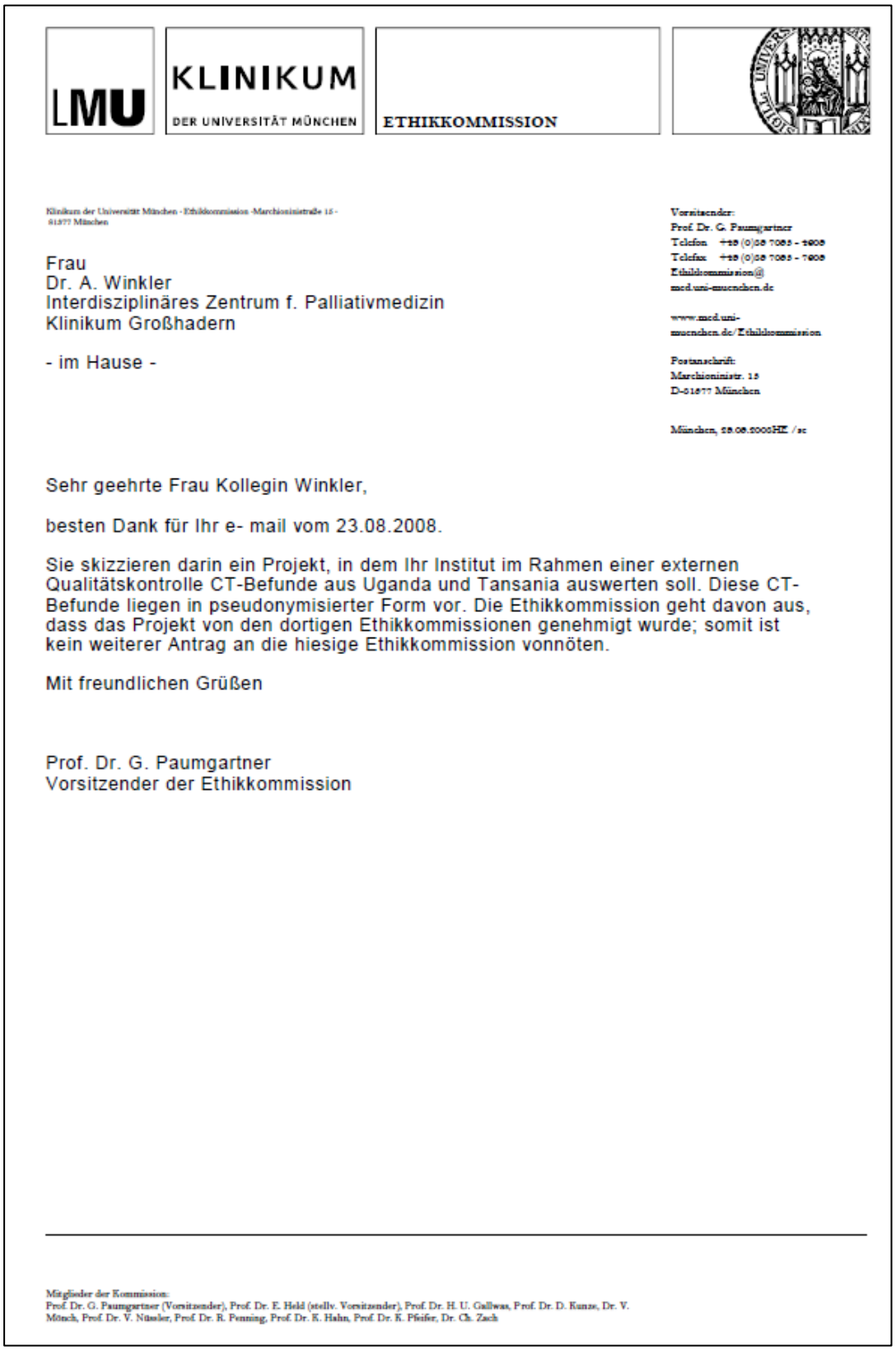
1. The study was deemed original and intended to investigate one of the neglected health problems facing Northern Uganda.
2. The objectives of the study were measurable.
3. The significance of the study was fairly well stated but the committee requested you to rewrite the last sentence as indicated in the text
4. The purpose of the study too needs to be revised as recommended
5. The Methodology for the study was well written with the scientific aspects and ethical considerations governing collection and analysis of human samples were well brought out. The sample size formulation and scientific packages to be used in the analysis were deemed okay.

Good luck.

Dr Emmanuel Odongo-Aginya, (PhD)
Chairman, Research and Ethics committee and
Acting Dean, Faculty of Medicine.

CC. DFB, Germany
„ UNCST
„ Committee file
„ Dean

13.7.2 Figure 19: German statement on ethics approval (29.09.2008)



LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN — ETHIKKOMMISSION

Klinikum der Universität München - Ethikkommission -Marchioninistraße 15 - 81377 München

Frau
Dr. A. Winkler
Interdisziplinäres Zentrum f. Palliativmedizin
Klinikum Großhadern

- im Hause -

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München, 29.09.2008HK /sc

Sehr geehrte Frau Kollegin Winkler,

besten Dank für Ihr e- mail vom 23.08.2008.

Sie skizzieren darin ein Projekt, in dem Ihr Institut im Rahmen einer externen Qualitätskontrolle CT-Befunde aus Uganda und Tansania auswerten soll. Diese CT-Befunde liegen in pseudonymisierter Form vor. Die Ethikkommission geht davon aus, dass das Projekt von den dortigen Ethikkommissionen genehmigt wurde; somit ist kein weiterer Antrag an die hiesige Ethikkommission vonnöten.

Mit freundlichen Grüßen

Prof. Dr. G. Paumgartner
Vorsitzender der Ethikkommission

Mitglieder der Kommission:
Prof. Dr. G. Paumgartner (Vorsitzender), Prof. Dr. E. Held (stellv. Vorsitzender), Prof. Dr. H. U. Gallwas, Prof. Dr. D. Kunze, Dr. V. Mönch, Prof. Dr. V. Nüssler, Prof. Dr. R. Penning, Prof. Dr. K. Hahn, Prof. Dr. K. Pfeifer, Dr. Ch. Zach

14 Acknowledgments

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- Klinikum Rechts der Isar, Germany
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- Gulu University, Uganda
- ICTMM, Australia
- Cystinet Europe

**there is no importance of contribution in the order of appearance*

The end