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Taenia solium neurocysticercosis:

Evidence-based treatment recommendations and its surveillance in Europe

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Surname, first name

I hereby declare, that the submitted thesis entitled

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Evidence-based treatment recommendations and its surveillance in Europe

is my own work. I have only used the sources indicated and have not made unauthorised use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given.

I further declare that the dissertation presented here has not been submitted in the same or similar form to any other institution for the purpose of obtaining an academic degree.

Munich, 06.10.2023
Place, Date

Annette Abraham
Signature doctoral candidate

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List of abbreviations

ASM	Anti-seizure medication
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CIR	Cumulative Incidence Ratio
COST	European Cooperation in Science & Technology
CYSTINET	European Network on Taeniosis/Cysticercosis, COST Action TD 1302
DALYs	Disability Adjusted Life Years
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EMMa	ECDC Map Maker tool
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICD	International Statistical Classification of Diseases and Related Health Problems
LMU	Ludwig-Maximilians-Universität München
NCC	Neurocysticercosis[1]
NTDs	Neglected tropical diseases
OIE	World Organisation for Animal Health
PICO	Patient, Intervention, Comparison, Outcome
SDGs	Sustainable development goals
SEL NCC	Single enhancing lesion-NCC
UNEP	United Nations Environment Programme
WHO	World Health Organization

[1] The term neurocysticercosis (abbreviated NCC) is used only for cysticercosis affecting the central nervous system. The term (neuro)cysticercosis is applied when both NCC cases as well as cysticercosis cases are referred to. Compared to the general term cysticercosis including all different forms of cysticercosis (central nervous system, muscles, eyes etc.), the author when applying the term (neuro)cysticercosis wants to highlight the relevance of NCC besides all the other forms of cysticercosis.

Summary

Introduction

Tania solium neurocysticercosis (NCC) is a neglected tropical disease listed by the World Health Organization (WHO). However, this disease is not confined to the tropics and is also existent in Europe. Its treatment can be challenging and is controversially discussed by experts.

Objectives

The aim of this doctoral thesis is to contribute a) to evidence-based treatment guidelines on diagnosis and treatment of NCC, in particular to anti-seizure medication (ASM) and anti-inflammatory treatment of individuals with single enhancing lesion-NCC (SEL NCC) and b) to a better understanding of the epidemiology and surveillance of (neuro)cysticercosis in Europe. The first project was part of the WHO guideline development for diagnosis and treatment of NCC, whereas the second project was embedded in the "European Network on Taeniosis/Cysticercosis" (CYSTINET).

Methods

Project a) is a meta-analysis using standard literature search procedures, a risk assessment employing the Cochrane risk of bias tool, random effects model analysis, the assessment of the body of evidence via GRADE as the basis for evidence-based guidelines.

Project b) is a search for data from various sources for the assessment of the epidemiological situation of (neuro)cysticercosis in Europe such as identification of national reporting systems for cysticercosis with respective notified cysticercosis cases, published and unpublished NCC cases and "International Statistical Classification of Diseases and Related Health Problems" (ICD) based cases.

Results

Regarding project a), few treatment studies were identified: concerning ASM, withdrawal of the medication after complete cyst resolution seems advisable. However, individuals whose cysts calcified post treatment seem to require prolonged ASM compared to those whose cysts

did not calcify (cumulative incidence ratio (CIR) 1.79, 95% CI [1.00, 3.20]). Concerning anti-inflammatory treatment, a beneficial effect of corticosteroids plus ASM compared to ASM alone on epileptic seizure recurrence (CIR 0.44, 95% CI [0.23, 0.85]) was found.

Concerning project b) (neuro)cysticercosis cases were identified through various sources for the period of 2000-2016: ten cysticercosis cases through mandatory notification (Hungary, Iceland and Poland), 263 individual and 721 aggregated NCC cases through a literature search and personal contacts to clinicians and 3,489 cysticercosis cases based on ICD data (from Italy (832), Latvia (8), Portugal (357), Spain (2,116) and Sweden (176).

Discussion

Data limitations in this field of a neglected tropical disease from epidemiology to treatment have to be taken into account:

regarding project a), limitations of the included studies in the meta-analysis were addressed by the Cochrane risk of bias tool. Despite all limitations, the evidence and expert opinion-based treatment recommendations indicate a positive effect of symptomatic treatment on reduction of epileptic seizure recurrence in individuals with SEL NCC.

Concerning project b), the full epidemiological picture of (neuro)cysticercosis in Europe remains fragmented due to unavailability of data and access problems. However, data from various sources indicate that NCC is still occurring in Europe, mostly due to migration and travelling.

Conclusion

The epidemiology and control of (neuro)cysticercosis as well as treatment of NCC deserve further attention in order to successfully reduce the burden caused by this potentially eradicable disease.

Zusammenfassung

Einleitung

Taenia solium Neurozystizerkose (NCC) wird von der Weltgesundheitsorganisation (WHO) als vernachlässigte Tropenkrankheit aufgeführt. Allerdings ist das Vorkommen dieser Erkrankung nicht auf die Tropen beschränkt, sie kommt auch in Europa vor. Die Behandlung kann komplex sein und wird unter Experten kontrovers diskutiert.

Zielsetzung

Das Ziel dieser Doktorarbeit ist einen Beitrag zu den folgenden beiden Punkten zu leisten: a) evidenzbasierte Behandlungsempfehlungen zur Diagnose und Behandlung der NCC, insbesondere zur anti-epileptischen und anti-inflammatorischen Behandlung von NCC-Patienten mit einer einzelnen NCC-Läsion (SEL NCC) und b) Epidemiologie und Krankheitsüberwachung der (Neuro)zystizerkose in Europa. Das erste Projekt war Teil der Diagnose- und Behandlungsleitlinienentwicklung zur NCC unter Leitung der WHO, während das zweite Projekt Teil des „Europäischen Netzwerkes zur Täniose/Zystizerkose“ (CYSTINET) war.

Methoden

Projekt a) ist eine Meta-Analyse basierend auf einer Standard-Literatursuche, einer Beurteilung des Verzerrungspotentials mit dem entsprechenden Cochrane-Instrument, einer „random-effects“ Modellanalyse und der Beurteilung der Gesamt-Evidenz mittels GRADE, die der Leitlinienentwicklung als Evidenzgrundlage diente.

In Projekt b) wurden zur Beurteilung der epidemiologischen Situation der (Neuro)zystizerkose in Europa Daten aus verschiedenen Quellen zusammengetragen, wie etwa der Identifikation einer Meldepflicht der Zystizerkose auf nationaler Ebene mit entsprechend gemeldeten Fällen, publizierte und unpublizierten NCC-Fälle and Fälle basierend auf der “Internationalen statistischen Klassifikation der Krankheiten und verwandten Gesundheitsprobleme“(ICD).

Ergebnisse

Projekt a) betreffend, wurden nur wenige Behandlungsstudien gefunden: hinsichtlich einer Behandlung mit Antiepileptika scheint ein Absetzen der Medikation nach vollständiger

Auflösung der Zyste ratsam zu sein. Bei Personen mit einer kalzifizierten Zyste scheint jedoch eine längere Behandlung erforderlich zu sein verglichen mit Patienten, deren Zysten nicht kalzifizierten (CIR 1.79, 95% CI [1.00, 3.20]). Bezüglich einer Behandlung mit anti-inflamatorischen Medikamenten, wurde eine positive Wirkung von Kortikosteroiden und Antiepileptika verglichen mit alleiniger Gabe von Antiepileptika hinsichtlich geringerem Wiederauftreten von epileptischen Anfällen gefunden (CIR 0.44, 95% CI [0.23, 0.85]).

Bezüglich Projekt b) wurden durch verschiedene Quellen (Neuro)zystizerkose Fälle für den Zeitraum von 2000-2006 identifiziert: zehn Zystizerkose-Fälle durch eine Meldepflicht (Ungarn, Island und Polen), 263 Einzel- und 721 aggregierte NCC-Fälle basierend auf einer Literatursuche und persönlichem Kontakt zu Ärzten sowie 3.489 Zystizerkose-Fälle basierend auf ICD-Daten (aus Italien (832), Lettland (8), Portugal (357), Spanien (2.116) und Schweden (176)).

Diskussion

Im Bereich der vernachlässigten Tropenkrankheiten sind Einschränkungen hinsichtlich Daten und Datenqualität zu beachten: Projekt a) betreffend, wurden Qualitätseinschränkungen der in die Meta-Analyse eingeschlossenen Studien mit Hilfe des von Cochrane entwickelten „risk of bias tool“ beurteilt. Trotz der Einschränkungen weisen die auf Evidenz und Expertenmeinung gestützten Behandlungsempfehlungen auf einen positiven Effekt von symptomatischer Behandlung zur Reduzierung des Wiederauftretens von epileptischen Anfällen bei Personen mit SEL NCC hin.

Bezüglich Projekt b) bleibt die Datenlage zur Epidemiologie der (Neuro)zystizerkose in Europa unvollständig, da Daten nicht vorhanden sind oder Zugangsschwierigkeiten bestehen. Die Ergebnisse aus verschiedenen Quellen deuten jedoch darauf hin, dass die NCC in Europa immer noch auftritt und hauptsächlich auf Migration und Auslandsreisen zurückzuführen ist.

Schlussfolgerung

Die Epidemiologie und Kontrolle der (Neuro)zystizerkose, sowie die Behandlung der NCC verdienen weitere Aufmerksamkeit, damit die mit dieser potentiell ausrottbaren Erkrankung einhergehende Krankheitslast erfolgreich reduziert werden kann.

I. Introduction

I.1. Neglected tropical diseases

The term “neglected tropical diseases (NTDs)” describes a diverse group of mainly infectious diseases affecting more than one billion people in 149 countries and territories worldwide (1). They include protozoan, helminthic, viral, bacterial, fungal and ectoparasitic infections as well as envenoming (e.g. snakebite envenoming). Currently, 20 different diseases are listed as NTDs by the World Health Organization (WHO), and around twice as many by the journal PLOS Neglected Tropical Diseases (1, 2). Control as well as elimination strategies may be challenging as NTDs are rather diverse (3-5). Reservoirs are ranging from human to zoonotic - with zoonotic tropical diseases being particularly neglected - thus requiring different One Health control strategies, where the disease in humans and animals and its transmission through their shared environment is considered (6).

NTDs are highly prevalent in low- and middle-income countries, but not exclusively (7). Cysticercosis, as an example, was highly endemic in Germany at the end of the 19th century and is also today not solely confined to the tropics (8-12). Due to climate change, migration and poverty amongst other reasons, NTDs (re)emerge in Europe (e.g. 2012/2013, dengue fever re-emergence in Portugal; Chikungunya outbreak in Italy, France and Spain; occurrence of West Nile virus in southeastern Europe and Germany; autochthonous cases of vivax malaria in Greece, 2009 etc.) (13-19). Taking into account that this group of diseases is not geographically restricted to the tropics, the term “diseases of poverty”, which reflects more the association with a low socio-economic status of the patients, might be more appropriate (20). The term “chronic pandemic” has also been employed for NTDs, highlighting the disabling character of these diseases as well as the large populations affected by it (21). The term neglected, which in its historical context mainly refers to 1) limited attention from policymakers, 2) low priority within health strategies as well as financing and 3) insufficient research due to limited investments, however, points out very well some of the challenges in this research field (22). In recent times, strong commitments to overcome the disease burden caused by NTDs were made giving hope to the affected populations (London declaration, WHO roadmap on NTDs, German G7 summit and G20 meeting, Bill & Melinda Gates foundation etc.) (4, 23-28).

I.2. *Taenia solium* (neuro)cysticercosis

I.2.1. Life cycle

There are several neglected zoonotic diseases prioritised by WHO: the taeniasis/cysticercosis disease complex is one of them as well as rabies, echinococcosis, foodborne trematodiases, human African trypanosomiasis, leishmaniasis and schistosomiasis (29). Zoonotic diseases, that is any disease/infection where transmission occurs between vertebrates and humans, have complex life cycles: in the case of the zoonotic tapeworm *Taenia solium,* humans and pigs are infected by it, causing two distinct diseases in humans, taeniasis and cysticercosis, and cysticercosis in pigs (30-32). The intestinal infection with the adult *T. solium* tapeworm is called taeniasis, while the metacestode larval stage is named cysticercosis. Commonly, the central nervous system is affected by the larval cysts, which is then referred to as neurocysticercosis (NCC) (31, 33).

A detailed overview of the life cycle of *T. solium* is illustrated in the graphic below (Figure 1) (34). Human *T. solium* tapeworm carriers release gravid proglottids, detaching from the distal end of the parasite, and excreted with the faeces (31, 35). The gravid proglottids contain the fertile eggs, which through oral ingestion can cause porcine (intermediate host) and human (accidental/aberrant intermediate host) cysticercosis (31, 36-39). Once humans eat raw or undercooked pork meat infected with cysticerci, they might develop taeniasis and the life cycle begins de novo (40).

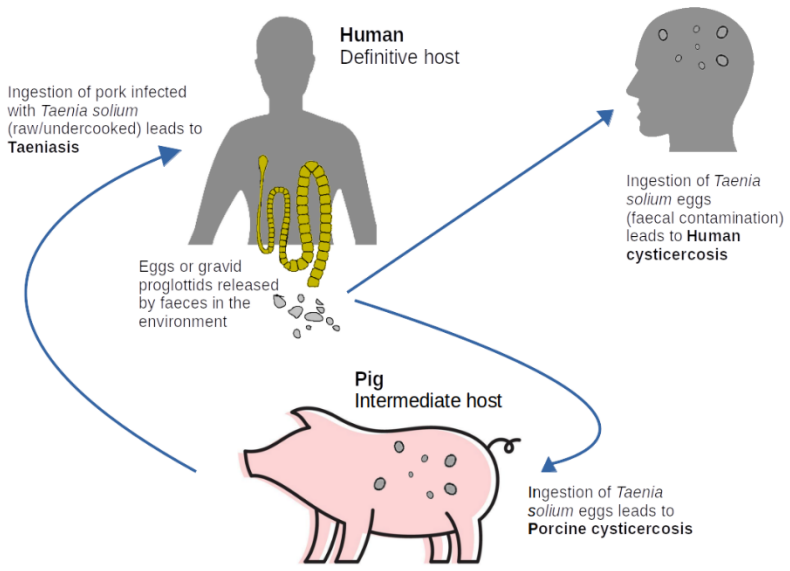

Figure 1: Life cycle of Taenia solium; own work

I.2.2. Epidemiology and public health aspects

T. solium is endemic in all continents (Figure 2), but particularly affecting rural, poor and pig-raising communities (41, 42). *T. solium* NCC is one of the leading cause of preventable epilepsy worldwide and affects around 2.56 – 8.30 million people (36), especially in low- and middle-income countries. With an estimated 2.78 million Disability Adjusted Life Years (DALYs, sum of number of years of life lost due to mortality and the number of years lived with disability due to morbidity) in 2010 and 28,000 deaths, *T. solium* was classified as "the food-borne parasite of greatest global concern" by the Food and Agriculture Organization of the United Nations (FAO)/WHO (43-45). Besides the health burden, the disease impacts health(care) systems, economies, societies, communities and individuals due to treatment costs, lost productivity and other indirect costs as well as socio-psychological factors (such as stigmatization of epilepsy patients).

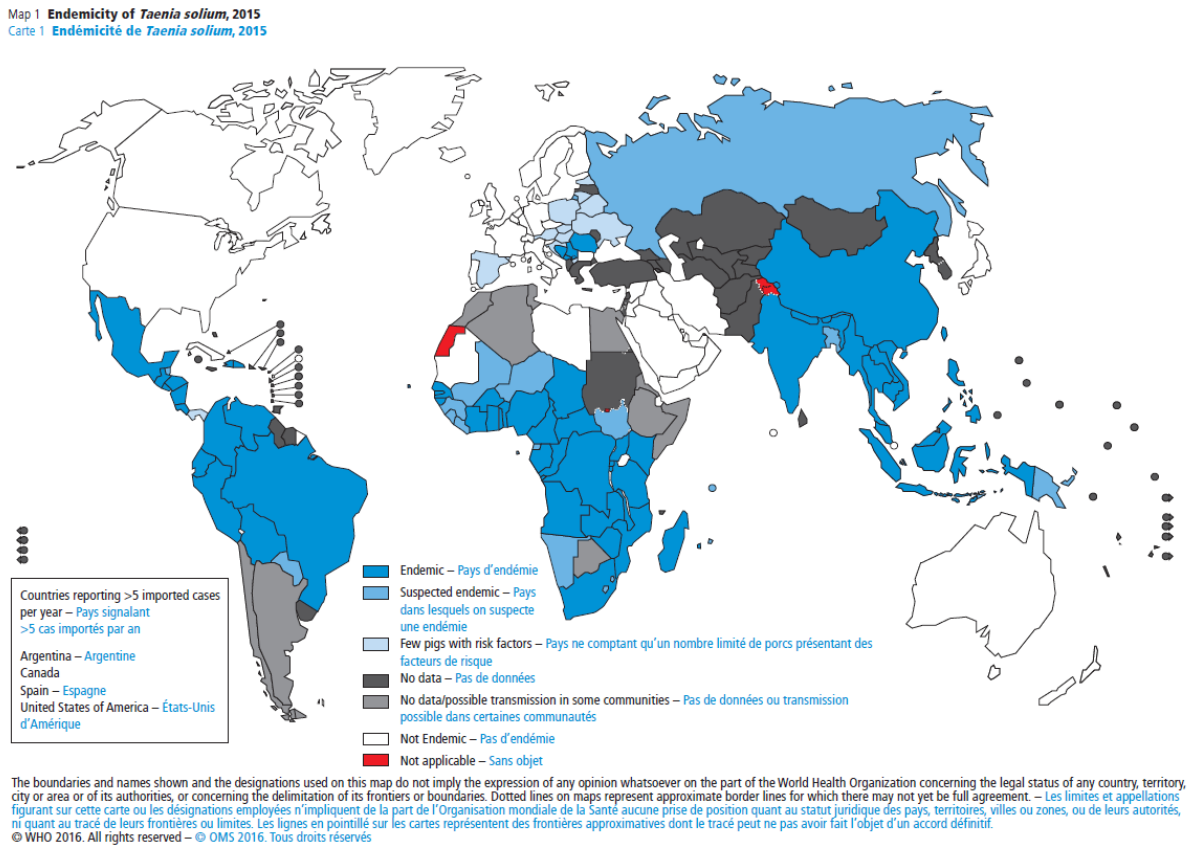

Figure 2: Endemicity of Taenia solium, WHO 2015 (41)

I.2.3. Clinical presentations of neurocysticercosis

Pathophysiological manifestations of NCC mainly include cysts, with and without perifocal edema, granulomas and calcifications. They can be symptomatic with a variety of different neurological and psychiatric signs/symptoms or present completely asymptomatic. Clinically asymptomatic cases can make up to 54% of the NCC cases as shown by a post-mortem study (46). The clinical manifestations range from epileptic seizures (acute symptomatic epileptic seizures or "chronic epilepsy") to headaches (acute or chronic, tension-type or migraine like episodes), focal neurological deficits, signs/symptoms of increased intracranial pressure, meningitic signs/symptoms, gait abnormalities, psychiatric signs/symptoms and others. NCC can be lethal, mainly due to acutely raised intracranial pressure (37, 40, 47-49). The pleomorphic signs/symptoms caused by NCC depend on the number (there may be single or multiple cysts), size, location, stage of the cyst, genotype of the parasite as well as the host immune response (37, 50-53).

Depending on the localisation of the cysts and/or granulomas and/or calcifications, NCC can be differentiated into intraparenchymal and extraparenchymal NCC. Both forms differ in several aspects like signs/symptoms, diagnosis, treatment and prognosis of the disease (37, 40, 54). Extraparenchymal NCC can be further sub-divided into four groups: ventricular NCC, subarachnoid NCC of the brain convexity, subarachnoid NCC of the Sylvian fissure and basal subarachnoid NCC. The main signs/symptoms are mass effects, hydrocephalus, headache, visual problems, cranial nerve lesions and stroke. Individuals with intraparenchymal NCC mostly present with epileptic seizures, headache and focal neurological signs/symptoms (40, 53, 55, 56).

I.2.4. Treatment options for neurocysticercosis

The treatment options need to be tailored to the acuteness and severity of the clinical signs/symptoms, cysts characteristics (location, size, number and developmental stage of the cysts), inflammation as well as other potential risk factors for complications. The interventions range from no treatment at all to symptomatic and/or anthelminthic treatment as well as neurosurgical procedures (37, 40). Concerning medication, there are different options, most importantly anthelminthic drugs that kill the parasite (for example, albendazole and

praziquantel), corticosteroids for inflammation control and anti-seizure medication (ASM) for control of epileptic seizures and/or their prevention (57-66):

Anthelminthic therapy in combination with corticosteroids should be given to individuals with viable parenchymal brain cysts who are presenting with symptoms (strong recommendation) and to individuals with a single enhancing lesion (SEL) to enhance cyst resolution and to reduce seizure recurrence (conditional recommendation). The usual dosage for albendazole is 15 mg/ kg per day and for praziquantel 50 mg/kg per day (67). In a study by Garcia et al. the study authors compared albendazole and praziquantel with albendazole treatment alone in individuals with multiple parenchymal cysts receiving anti-inflammatory drugs and ASM. The dual therapy was found to enhance cyst resolution compared to albendazol treatment alone in this patient group (87). Based on clinical experience, for patients with numerous parenchymal cysts causing inflammation with raised intracranial pressure, anthelminthic drugs should not be used. Instead, inflammation should be controlled with corticosteroid (67).

In individuals with SEL NCC and epileptic seizures treated with ASM, corticosteroid treatment was found to be beneficial both regarding seizure reduction and cyst resolution. Evidence for anti-inflammatory treatment only compared with anthelminthic and/or ASM for NCC patients with parenchymal viable lesions was not identified (67).

ASM is recommended for all patients with epileptic seizures according to respective guidelines (68). Their withdrawel should be considered according to the WHO guidelines 6 months after the last seizure in individuals with a SEL suffering from epileptic seizures with low risk of seizure recurrence. An observational study by Rajshekhar et al. researched the risk factors for seizure recurrence. They found having had more than two seizures or breakthrough seizures and a calcific residue of the granuloma shown on a CT scan to increase the risk of seizure recurrence. The authors concluded that those patients might thus benefit from prolonged ASM (88). In individuals with single or multiple calcified NCC presenting with epileptic seizures ASM is recommended for at least two years (67).

Further detailed information on diagnosis and treatment is compiled in two guidelines: the "Diagnosis and Treatment of Neurocysticercosis: 2017 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Society of Tropical Medicine and Hygiene" and the "WHO Diagnosis and Treatment Guidelines for *Taenia solium*

Neurocysticercosis (NCC)" (67, 68). The current thesis contributed in parts to the latter through compilation of the available evidence on which the treatment recommendations were based on.

I.3. Control of *Taenia solium* taeniasis/cysticercosis

The treatment and control of *T. solium* taeniasis is key to disrupt the life cycle of *T. solium* and to prevent (neuro)cysticercosis. However, as many taeniasis cases are asymptomatic or present with mild symptoms (e.g. abdominal pain, nausea, diarrhoea which are thought to be associated to the tapeworm infestation), case detection is difficult (31).

There are different drugs for the treatment of *T. solium* taeniasis described in the literature and applied for treatment such as albendazole, praziquantel and niclosamide (69-78). Due to the side effects of praziquantel and albendazole (crossing the blood-brain barrier and thus having the potential of provoking neurological signs/symptoms in patients with latent viable NCC), niclosamide is considered by experts as the treatment of choice (31, 37).

In 1993 the international Task Force for Disease Eradication, a group of scientists supported by the Centers for Disease Control and Prevention (CDC) who evaluated diseases that could potentially be eradicated, concluded that taeniasis/cysticercosis is a potentially eradicable disease (79).

Some reasons for its eradicability are: a) humans are the only definitive host of *T. solium*, b) infection with the adult tapeworm occurs through eating raw or undercooked contaminated pork meat, thus control of pigs can interrupt the life cycle, c) (human) tapeworm carriers are the only source of infection for porcine and human cysticercosis and no other relevant natural reservoir is known, d) interventions are available for humans and pigs, and e) historical examples indicate that elimination is possible (e.g. Germany) (8, 79-81).

In a recent landscape analysis published by WHO the available tools for the control of *T. solium* were reviewed and the following intervention components were identified for the control of *T. solium* (80):

- Humans: preventative chemotherapy (e.g. mass drug administration, focus-orientated chemotherapy or identification and treatment of taeniasis cases) and health knowledge sharing
- Animals (in this case pigs)/meat processing: improved sanitation, vaccination and anthelminthic treatment of pigs, improved inspection and processing of meat
- Environment: better sanitation, hygiene and potential vector control

In addition to the above mentioned, a combined One Health approach, recognizing that health of humans, animals and ecosystems is interconnected, is warranted for the control of *T. solium* and to synergistically enhance human-animal-environmental health. Recently, a new definition of One Health by the One Health High-Level Expert Panel was published (see Figure 3) (89):

> "One Health is an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals and ecosystems. It recognizes the health of humans, domestic and wild animals, plants, and the wider environment (including ecosystems) are closely linked and inter-dependent. The approach mobilizes multiple sectors, disciplines and communities at varying levels of society to work together to foster well-being and tackle threats to health and ecosystems, while addressing the collective need for clean water, energy and air, safe and nutritious food, taking action on climate change, and contributing to sustainable development."

This definition is supported by the in April 2022 established Quadripartite formed by the four international organisations: FAO, the World Organisation for Animal Health (OIE), the United Nations Environment Programme (UNEP) and the WHO (89).

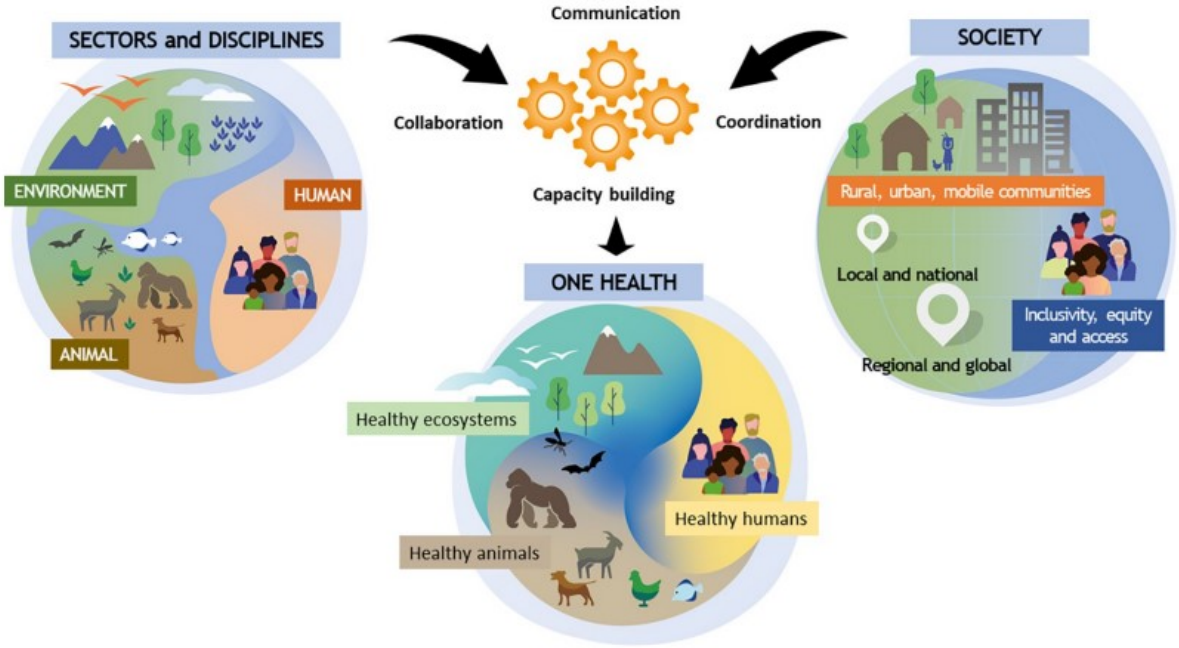

Figure 3: Definition of One Health by WHO's "One Health High-Level Expert Panel" (89)

Climate change leads to geographical spread of vectors, deforestation and agricultural intensification entailing closer human-wildlife contact and thus facilitating spill-over events. In addition, increased travel and trade, urbanisation, conflicts and other factors contribute to the risk of re-emergence and emergence of zoonotic diseases worldwide.

Effective One Health control programs can prevent and control disease and increase human and animal health in a cost-effective way.

II. Research objectives

Treatment of NCC is controversially discussed in the literature. Reliable high-quality and up-to-date meta-analyses as well as diagnosis and treatment guidelines from national or international organisations were lacking at the beginning of the doctorate. At the same time little was known about the epidemiology and surveillance of NCC in Europe.

The aim of these research projects was to contribute to the generation of evidence to inform experts on the current best available treatment options on the one hand (as part of the WHO guideline development) and on the other hand, to improve knowledge on epidemiology and surveillance of (neuro)cysticercosis in Europe (as part of CYSTINET Europe).

To this end, the overarching research questions of the dissertation were:

- What is the best available treatment for individuals with NCC, in particular single enhancing lesion NCC (SEL NCC)? : a) in individuals with SEL NCC and associated epileptic seizure(s)/epilepsy, is the use of prolonged administration (12-24 months) of ASM compared to shorter regimes (6-12 months) associated with a reduction in epileptic seizure recurrence? And b) in individuals with SEL NCC and associated epileptic seizure(s)/epilepsy, is the use of oral anti-inflammatory therapy (e.g. prednisolone) and ASM associated with a reduction in epileptic seizure recurrence and cyst resolution compared to anti-epileptic treatment alone?

- What are the epidemiological characteristics of (neuro)cysticercosis patients in Europe? How is the surveillance and control of this disease complex addressed; are there relevant national surveillance systems in the EU/EEA (European Union/European Economic Area)?

In the following, the two publications of the doctorate candidate are presented along with a description of the first author's contribution to those projects.

II.1. Summary of publication I

The effectiveness of anti-inflammatory treatment and anti-seizure medication for individuals with single enhancing lesion neurocysticercosis: a meta-analysis and expert group-based consensus recommendations

Project information:

These meta-analyses were part of the systematic reviews commissioned by WHO for the guideline development for diagnosis and treatment of *T. solium* (parenchymal) NCC. The guideline development was a collaborative project of the WHO Department of Neglected Tropical Diseases (Neglected Zoonotic Diseases Unit) and of the Department of Mental Health and Substance Abuse with the aim of improving evidence-based patient care in low and middle-income countries. During a face-to-face meeting at WHO Headquarters in Geneva (25-26 September 2017) the retrieved evidence was assessed by the guideline development group, a panel of renowned international experts, and recommendations were formulated.

Background:

Single enhancing neurocysticercosis (SEL NCC) is a common presentation of NCC lesions observed at imaging, especially in patients from the Indian sub-continent and in travellers returning from disease endemic regions. When the parasite *T. solium* lodged in the cerebral tissue degenerates, radiologically the lesion appears as a single nodular or annular lesion, which enhances after the administration of contrast medium, thus it is usually referred to as single enhancing lesion. Treatment of SEL NCC associated epilepsy, which is a common clinical presentation, however, remains controversial.

Methods:

A search for relevant studies in several international databases was carried out with the objective of assessing the effect of different anti-seizure medication (ASM) and anti-inflammatory treatment options on epileptic seizure reduction post-treatment in individuals

with SEL NCC: the first PICO (patient, intervention, comparison, outcome) question focused on the benefits and harms of different durations of ASM (6-12 versus 24 months and 6 versus 12-24 months) and the second PICO question referred to the potential benefits of oral anti-inflammatory treatment and ASM compared to ASM drugs alone for individuals with symptomatic (NCC-associated epileptic seizure(s)/epilepsy) SEL NCC. Quality assessment of the included studies was conducted according to the Cochrane risk of bias tool. Pooled estimates were calculated by random-effect models and the body of evidence was assessed using GRADE tables. Expert recommendations were reached by applying the GRADE framework for guideline development. The expert panel consisted of 12 gender and geographically balanced members from diverse disciplines.

Results:

Out of a total of 16,969 publications, four studies comparing the effect of different treatment durations of ASM and six studies assessing the effect of corticosteroids plus ASM compared to ASM and placebo or no anti-inflammatory treatment regarding epileptic seizure recurrence were included for the qualitative assessment. Three and four of these studies for the first and second PICO, respectively, were eligible for the meta-analysis. No statistical significant difference was found between the risk of epileptic seizure recurrence with 6 month versus 12-24 month ASM nor 6 month versus 24 months (Cumulative Incidence Ratio (CIR) 1.29; 95% confidence interval (CI) [0.76, 2.18]) and CIR 1.38, 95% CI [0.76, 2.51] respectively). However, when conducting a sub-group analysis in patients whose cysts had calcified a borderline significant result was reached (CIR 1.79, 95% CI [1.00, 3.20]). Regarding anti-inflammatory treatment, corticosteroids compared to no corticosteroids in patients receiving ASM were found to have a beneficial effect on preventing epileptic seizure recurrence (CIR 0.44, 95% CI [0.23, 0.85]).

Discussion:

The sub-group analysis shows that a differentiation between patients whose cysts calcified and those in whom cysts resolved is of clinical importance: patients with resolved cysts do not require prolonged administration of ASM whereas for patients with calcifications this seems to be beneficial to prevent further epileptic seizures. Additional corticosteroid treatment was found to favour both seizure reduction and cyst resolution.

Various research gaps, deserving further attention were identified, namely: optimal drug(s), dose and duration of ASM/ anti-inflammatory treatment. Further high quality randomized controlled trials with an adequately long follow-up time to detect possible events, ideally multicentric to counterbalance the fact that so far studies came from few centres only and were of small sample size, would be required.

Author's contribution:

All steps of the meta-analysis (e.g. study design, literature search, data extraction, quality assessment, analysis, manuscript drafting) were conducted by the first author together with the second shared first author in their role of independent reviewers. A detailed overview and contribution of the first authors as well as co-authors can be found in annex II (Overview of project I) as well as in the publication itself.

II.2. Summary of publication II

Epidemiology and surveillance of human (neuro)cysticercosis in Europe: is enhanced surveillance required?

Project information:

This study was embedded in the work package of CYSTINET, a European Network on Taeniosis/Cysticercosis. The aim of this COST (European Cooperation in Science & Technology) Action was, amongst others, to advance the knowledge and understanding of taeniasis/cysticercosis and the assessment of the disease burden in Europe. CYSTINET was divided in different working groups of which working group II (led by Prof. Andrea Winkler together with Prof. Teresa Garate) was relevant for the current thesis and aimed at providing data on NCC occurrence, amongst others, through inter-European cooperation of scientists.

Background:

Human *T. solium* NCC, a possibly eradicable disease, is one of the leading causes for new-onset epilepsy in endemic areas, and can present with a wide range of signs/symptoms, depending on various factors such as cyst numbers and localisation. In Europe, reliable epidemiological data on this disease is scarce, while travel and migration to/from highly endemic areas is increasing. This leads to the question if an increase in (neuro)cysticercosis cases could be timely detected, prevented and controlled, and if adequate surveillance systems are in place.

Methods:

Therefore, the objective of this study was to gain knowledge on this disease occurrence (from 2000- end 2016) by a comprehensive search including a) data from relevant national reporting systems on cysticercosis, b) a systematic literature search, c) contact with clinicians who had seen relevant cases, and d) "International Statistical Classification of Diseases and Related Health Problems" (ICD) based data. Data was extracted from the respective documents and aggregated when possible. The country information and corresponding number of patients were mapped by means of EMMa (ECDC Map Maker tool).

Results:

Mandatory notification for cysticercosis was found in three EU/EEA countries and respective data was extracted: in Hungary and Iceland no cases were notified, while in Poland ten cases were reported. ICD-based data were available from five countries with a total of 3,489 cases coded from 2000 to 2016 (832 from Italy, 8 from Latvia, 357 from Portugal, 2,116 from Spain and 176 from Sweden). Through information given by clinicians and the systematic literature search, 984 NCC cases from 19 European countries were identified for the same period.

Discussion:

Although, data remains fragmented even though different data sources were taken into account, it shows that cysticercosis is still occurring in Europe. Limitations of diagnostic tools, latency of symptom development and the zoonotic nature of this disease complex challenge its surveillance and control. More work on how to tackle this disease, how to collect reliable epidemiological data and how to ensure its control/surveillance needs to be carried out. To conclude, the question if we would be capable in Europe to timely detect an increased incidence rate of cysticercosis cases cannot be answered comprehensively at present.

Author's contribution:

The first author was responsible for the study design, data collection, analysis and drafting of the manuscript. A detailed project overview can be found in Annex II (Overview of project II).

III. Conclusion

Putting the results gained through the current thesis in the broader context, they align with several international goals/targets: the best known are probably the sustainable development goals (SDGs). In 2015, the 2030 agenda for sustainable development with its 17 SDGs was adopted by all United Nations Member States (82). For this thesis SDG 3 targeting good health and well-being and in particular SDG 3.3 (and more precisely SDG 3.3.5) focusing on NTDs („by 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases...“) are highly relevant (83). The output of the current thesis contributes to epidemiological data and to treatment guidelines for patients suffering from NCC.

Besides the alignment with SDG 3, the WHO guidelines for diagnosis and treatment of *T. solium* NCC, to which the current thesis made a substantial contribution, are in close synergy with the WHO resolution on epilepsy (resolution WHA 68.20 call to reduce the epilepsy treatment gap amongst others,), the WHO roadmap on NTDs (official title: “Ending the neglect to attain the Sustainable Development Goals: a road map for neglected tropical diseases 2021–2030”) and universal health coverage (access to needed health services for individuals and communities without suffering financial hardship) (4, 84, 85). In a practical way, it should serve health care practitioners to adequately diagnose and treat NCC patients.

Regarding the surveillance and control of *T. solium* taeniasis/cysticercosis, a “One Health approach” (including physicians, veterinarians, epidemiolgists, social scientists and other experts at an human-animal-environmental interface) plays a major role (86). Human health, in particular in the case of zoonotic diseases, is closely interlinked with animal health and environmental factors. Urbanization, nutrition, migration, conflict and climate change to name but a few are global challenges favouring the spread of infectious diseases. In particular for *T. solium,* increase in meat production especially in low- and middle-income countries poses additional risks. Last but not least, migration and travelling from/to disease endemic areas increases the risk of infections, showing that effective control measures require cross-border solutions.

Furthermore, more research, appropriate dissemination and result translation to policymakers, political commitment, and interdisciplinary as well as local/global solutions are needed to

control and eventually eliminate *T. solium* taeniasis/cysticercosis - a truly neglected potentially eradicable disease.

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V. Declaration of autonomy

I, Annette Abraham, hereby confirm that the doctorate thesis entitled "*Taenia solium* neurocysticercosis: Epidemiology, treatment and control" was done by me and that I have used no other sources of information than those mentioned in the reference list. All literal and logical citations have been indicated. I have not submitted this thesis before.

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Date Signature

VI. Acknowledgements

This dissertation could never have been done without the help of many people; now that this work comes to an end I would like to take the opportunity to thank all those who made this work possible.

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In this regard, I would also like to express many thanks to Bernadette Abela-Ridder (Department of Control of Neglected Tropical Diseases, WHO) and Tarun Dua (Department of Mental Health and Substance Abuse, WHO) for their support.

Special thanks go to Javier Bustos for doing all the systematic reviews together with me and sharing the up and downs of this process. The development of the WHO NCC guidelines would never have been possible without this great collaboration, mutual understanding and support!

I also wish to thank Hélène Carabin (Canada Research Chair in the Epidemiology and Control of Parasitic Zoonoses in a Global Context) for methodological advice during the WHO guideline development process and her critical review of our work.

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I am sincerely thankful to Veronika Schmidt, my „co-supervisor“. She helped me during the doctorate time not only with her scientific knowledge, but also with advice and sharing of her own doctorate experience.

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VII. Annex

VII.1. Annex I: Publications

Publication I:

The effectiveness of anti-inflammatory and anti-epileptic medication for individuals with single enhancing lesion neurocysticercosis: a meta-analysis and expert group-based consensus recommendations

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This work was published as:

Abraham A, Bustos JA, Carabin H, de Meijere R, Sahu PS, et al. (2021) The effectiveness of anti-inflammatory and anti-seizure medication for individuals with single enhancing lesion neurocysticercosis: A meta-analysis and expert group-based consensus recommendations. PLOS Neglected Tropical Diseases 15(3): e0009193. https://doi.org/10.1371/journal.pntd.0009193

And can be found under following link:

https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0009193

Publication II:

Epidemiology and surveillance of human (neuro)cysticercosis in Europe: is enhanced surveillance required?

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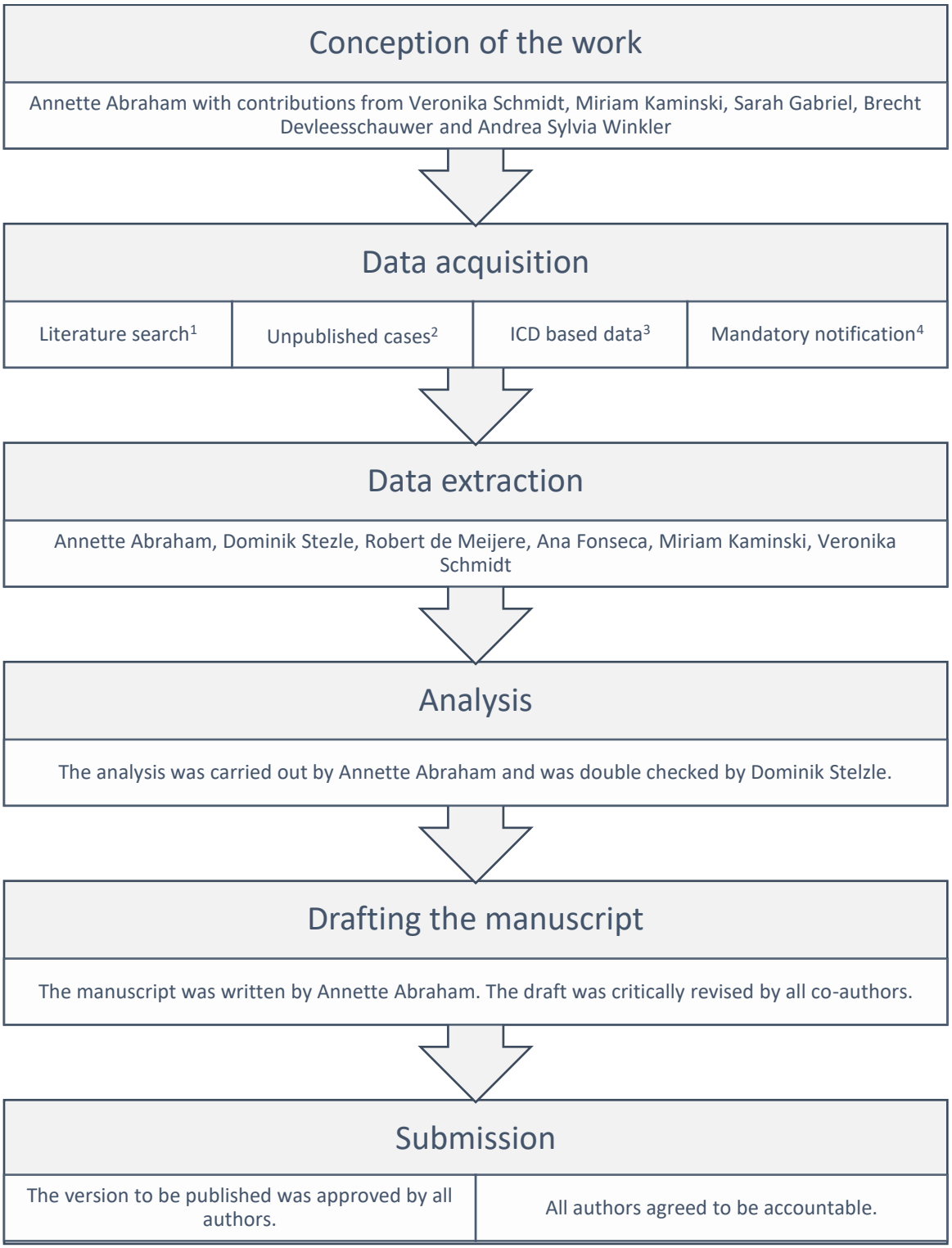
VII.2. Annex II: Project Overview

Overview Project I

1: Peter Chiodini, Christina Coyle, Sarah Gabriel, Hector Garcia, Mamoun Homeida, Theodore Nash, Bernard Ngowi, Gagandeep Singh, Rajshekhar Vedantam, Clinton White, Andrea Winkler, Xiao Nong Zhou

Overview of project II



[1]: Search for published studies: Annette Abraham together with Javier Bustos with support from Priyadarshi Sahu and Cesar Ugarte; cross checking with the search from CYSTINET WG1 (Veronique Dermauw, Brecht Devleesschauwer, Sarah Gabriel, Minerva Laranjo, Chiara Trevisan); Grey literature search: Annette Abraham, Branko Bobic, Maria Ángeles Gómez Morales, Miriam Kaminski, WG1 [2]: Carmen Cretu, Peter Chiodini, Naomi Walker [3]: Gunita Deksne, Ana Fonseca, Manuela Vilhena, Lorenzo Zammarchi [4]: Annette Abraham, István Kucsera

VII.3. Annex III: Conference Participations and Attended Courses

Conference participations

The following conferences were attended during the doctorate period (posters presented are cited in the publication list in the CV):

11/2019 ***CYSTINET-Africa: First cysticercosis/taeniosis conference 2019,*** Arusha (November 26 – 28, 2019); member of the conference organizing support team, oral and poster presentation, conception of student workshop

10/2019 ***World Health Summit*****,** Berlin (October 27 – 29, 2019), meeting attendance

10/2019 ***One Planet, One Health, One Future,*** German Federal Foreign Office, Berlin (October 25, 2019), meeting attendance

10/2019 ***Healthy Planet – Healthy People: Oxford-Berlin-LSHTM Dialogue,*** Berlin (October 24, 2019), meeting attendance

10/2019 ***CYSTINET Copenhagen meeting 2019,*** Copenhagen (October 9, 2019); oral presentation on working group progress

07/2019 ***Task force meeting: Global Task Force on the Cost Burden of Epilepsy,*** Bangkok (July 29, 2019); oral presentation on systematic reviews

09/2019 ***11th European Congress on Tropical Medicine and International Health,*** Liverpool (September 16 – 20, 2019), poster presentation

04/2019 ***PAHO/WHO guideline development group (GDG) meeting for preventive chemotherapy for Taenia solium taeniasis*** (April 23 – 24, 2019); active participation in the expert discussions and decisions

04/2019 ***Conference on Tropical Medicine and Global Health (CTM),*** Munich (April 4 – 6, 2019); poster prize

12/2018 ***2nd network meeting "Women in Global Health - Germany"***, Munich (December 08, 2018); part of the organizing team

10/2018 ***World Health Summit***, Berlin (October 14 – 16, 2018), meeting attendance

09/2018 ***NEOH (Network for Evaluation of One Health) final conference***, Department of Agricultural and Food Science, University of Bologna, Bologna (September 10 – 12, 2018); meeting attendance

07/2018 ***ISPED Symposium „Enjeux et défis majeurs de la santé collective: horizon 2030"***, Bordeaux (July 2 – 3, 2018), meeting attendance

01/2018 ***Launch of Women in Global Health Chapter: WGH Germany***, Berlin (January 26, 2018), meeting attendance

10/2017 ***CYSTINET final conference***, Pasteur Institute, Athens (October 24 – 25, 2017); attendance of the management meeting and presentation of the work progress

09/2017 ***WHO guideline development group (GDG) meeting for diagnosis and treatment of Taenia solium Neurocysticercosis,*** Geneva (September 25 – 26, 2017); presentation of the evidence for the guideline

06/2017 ***CYSTINET 1st Working Group meeting 2017***, Institute of Food safety, Animal Health and Environment "BIOR", Riga (June 6 – 7, 2017); presentation of the results from the 2nd European guideline development meeting for diagnosis and treatment of neurocysticercosis

04/2017 ***CYSTINET 2nd European guideline development group meeting***, Oslo (April 24 – 26, 2017); presentation of methodological aspects of WHO guideline development

09/2016 ***CYSTINET 2nd Working Group and Management Committee Meeting***, Ljubljana (September 27 – 28, 2016); presentation of the PICO questions for the systematic review for the WHO guideline development on diagnosis and treatment of *T. solium* neurocysticercosis

06/2016 ***CYSTINET 1st Working Group and Management Committee meeting 2016***, Institut Pasteur, Paris (June 2 – 3, 2016); presentation of the activities of working group 2, in particular clinical aspects of neurocysticercosis cases in Germany and surveillance of cysticercosis and taeniasis in Europe

04/2016 ***CYSTINET 1st European guideline development group meeting***, Oslo (April 26 – 27, 2016); presentation on guideline development methodology

04/2016 ***"Polio Eradication: Endgame Challenges, Lessons and Legacy"***, Royal Society in London, London (April 13, 2016)

04 /2016 ***"Polio eradication: Securing the legacy of the global vaccination initiative" meeting***, Houses of Parliament, London (April 12, 2016)

03/2016 ***CIH^{LMU} 5th Public Health Symposium 2016 "Public health challenges of forced migration"***, Munich (March 19, 2016)

02/2016 ***CYSTINET: Working group 3 meeting***, Copenhagen (February 18 – 19, 2016); active participation at the working group meeting on control of cysticercosis and taeniasis

11/2015 ***ESCAIDE (European Scientific Conference on Applied Infectious Disease Epidemiology)***, Stockholm (November 11 – 13, 2015); attendance of the conference as part of the study visit at European Centre for Disease Prevention and Control

10/2015 ***1st CYSTINET International Conference***, Belgrade (October 03 – 04, 2015); distribution of a questionnaire (questions relating to NCC cases in Europe and disease surveillance)

Attended courses

The following courses were attended during the doctorate period:

06/2020 ***1st EUGLOH Innovation Days on One Health Challenges,*** hosted by the Ludwig-Maximilians-Universität (LMU), 25.05. – 27.05.2020

03/2019 ***"Befragen oder Beteiligen? Die Rolle von Stakeholdern in der Gesundheitsforschung",*** Institut für Ethik, Geschichte und Theorie der Medizin (LMU), 28.03.2019

04/2019 ***„Forschungsergebnisse publizieren – Offline-Online-Open Access",*** Munich Graduate Center (LMU), 15.04.2019

12/2017 ***Workshop "Optimizing reading strategies in English"***, Graduate Center (LMU), 11.12. – 13.12.2017

10/2017 ***Workshop "Writing and publishing of papers, reviews and theses"***, Munich Graduate Center (LMU), 16.10. – 17.10.2017

07/2017 ***Workshop "Kompetenzbilanz – Selbstmarketing in der Wissenschaft"***, Graduate Center (LMU), 25.07.2017

07/2017 ***Workshop "Meetings und Diskussionsrunden leiten"***, Graduate Center (LMU), 18.07. – 19.07.2017

07/2017 ***Projektmanagment und KommUNIkation***, Student & Arbeitsmarkt (LMU), 30.06. – 08.07.2017 (32 h)

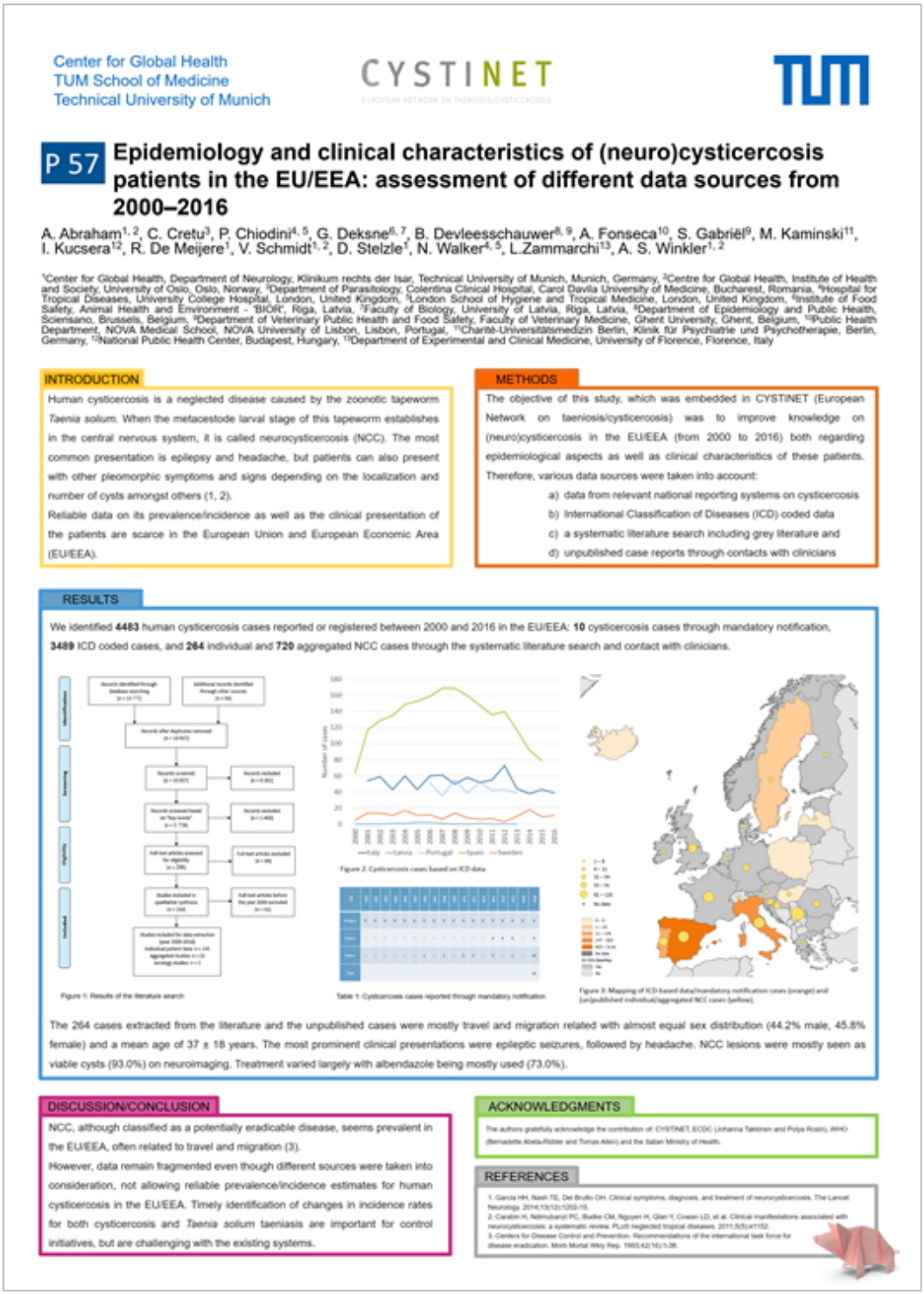
02/2017 ***10. Expertenwerkstatt der Qualitativen Forschung: "Methodenplurale Forschung"***, Medizinische Fakultät: Institut für Ethik, Geschichte und Theorie der Medizin (LMU), 24.02.2017

01/2017 ***Workshop "Presentation skills (natural and life sciences) "***, Graduate Center (LMU), 18.01. – 19.01.2017

07/2016 ***3rd European summer school in evidence-based Public Health (EBPH)***, Pettenkofer School of Public Health (LMU), 04.07. – 08.07.2016

VII.4. Annex IV: Prices and Memberships

First poster prize of the "Conference on Tropical Medicine and Global Health" 2019



Center for Global Health
TUM School of Medicine
Technical University of Munich

CYSTINET

P 57 **Epidemiology and clinical characteristics of (neuro)cysticercosis patients in the EU/EEA: assessment of different data sources from 2000–2016**

A. Abraham[1, 2], C. Cretu[3], P. Chiodini[4, 5], G. Deksne[6, 7], B. Devleesschauwer[8, 9], A. Fonseca[10], S. Gabriël[9], M. Kaminski[11], I. Kucsera[12], R. De Meijere[1], V. Schmidt[1, 2], D. Stelzle[1], N. Walker[4, 5], L.Zammarchi[13], A. S. Winkler[1, 2]

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INTRODUCTION

Human cysticercosis is a neglected disease caused by the zoonotic tapeworm *Taenia solium*. When the metacestode larval stage of this tapeworm establishes in the central nervous system, it is called neurocysticercosis (NCC). The most common presentation is epilepsy and headache, but patients can also present with other pleomorphic symptoms and signs depending on the localization and number of cysts amongst others (1, 2).

Reliable data on its prevalence/incidence as well as the clinical presentation of the patients are scarce in the European Union and European Economic Area (EU/EEA).

METHODS

The objective of this study, which was embedded in CYSTINET (European Network on taeniosis/cysticercosis) was to improve knowledge on (neuro)cysticercosis in the EU/EEA (from 2000 to 2016) both regarding epidemiological aspects as well as clinical characteristics of these patients. Therefore, various data sources were taken into account:

a) data from relevant national reporting systems on cysticercosis
b) International Classification of Diseases (ICD) coded data
c) a systematic literature search including grey literature and
d) unpublished case reports through contacts with clinicians

RESULTS

We identified **4483** human cysticercosis cases reported or registered between 2000 and 2016 in the EU/EEA: **10** cysticercosis cases through mandatory notification, **3489** ICD coded cases, and **264** individual and **720** aggregated NCC cases through the systematic literature search and contact with clinicians.

Figure 1: Results of the literature search

Figure 2: Cysticercosis cases based on ICD data

Table 1: Cysticercosis cases reported through mandatory notification

Figure 3: Mapping of ICD-based data/mandatory notification cases (orange) and (un)published individual/aggregated NCC cases (yellow).

The 264 cases extracted from the literature and the unpublished cases were mostly travel and migration related with almost equal sex distribution (44.2% male, 45.8% female) and a mean age of 37 ± 18 years. The most prominent clinical presentations were epileptic seizures, followed by headache. NCC lesions were mostly seen as viable cysts (93.0%) on neuroimaging. Treatment varied largely with albendazole being mostly used (73.0%).

DISCUSSION/CONCLUSION

NCC, although classified as a potentially eradicable disease, seems prevalent in the EU/EEA, often related to travel and migration (3).

However, data remain fragmented even though different sources were taken into consideration, not allowing reliable prevalence/incidence estimates for human cysticercosis in the EU/EEA. Timely identification of changes in incidence rates for both cysticercosis and *Taenia solium* taeniasis are important for control initiatives, but are challenging with the existing systems.

ACKNOWLEDGMENTS

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2. Carabin H, Ndimubanzi PC, Budke CM, Nguyen H, Qian Y, Cowan LD, et al. Clinical manifestations associated with neurocysticercosis: a systematic review. PLoS Neglected tropical diseases. 2011;5(5):e1152.
3. Centers for Disease Control and Prevention. Recommendations of the international task force for disease eradication. Morb Mortal Wkly Rep. 1993;42(16):1-38.

Figure 4: Poster presented at the "Conference on Tropical Medicine and Global Health" (CTM) in Munich, 2019.

First prize at the EUGLOH One Health Innovation Days 2020

EUGLOH
European University Alliance for Global Health

CERTIFICATE

Annette Abraham

successfully attended the online workshop

1st EUGLOH Innovation Days on One Health Challenges
25 May 2020 — 27 May 2020

hosted by the **Ludwig-Maximilians-Universität München**, Germany (LMU)
as part of the European University Alliance for Global Health (EUGLOH).

Annette Abraham and her team achieved the first place in the final pitch of innovations.

Authentication on behalf of Ludwig-Maximilians-Universität München

Katja Radon

Prof. Dr. Katja Radon
Chairwoman of EUGLOH Academic Board
Ludwig-Maximilians-Universität München

Dr. Sebastian Planck
Head of Qualification
Social Entrepreneurship Akademie

Co-funded by the Erasmus+ Programme of the European Union.

www.eugloh.eu

Figure 5: Certificate of successful attendance of the 1st EUGLOH Innovation Days on One Health Challenges and achievement of the first place in the final pitch.

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Member Gallery

See some examples of how our members contribute to global health

Annette Abraham, Technical University of Munich

"Human and animal health in their shared environment are interconnected. Neurocysticercosis, caused by the pork tapeworm Taenia solium, is one example for this One Health perspective. My colleagues and I are contributing through evidence-based treatment guidelines, diagnostic tool developments, epidemiological and clinical data acquisition and capacity building in Africa to improved diagnosis, treatment and control of this possibly eradicable disease."

On behalf of the Center for Global Health (AG Prof. Winkler), Technical University of Munich, CYSTINET-Africa and The Lancet One Health Commission

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Figure 6: Member Gallery of the German Alliance for Global Health Research with examples of contribution to global health in Germany: https://globalhealth.de/people.html. This contribution won the prize for two tickets to the World Health Summit 2020.

List of Memberships

- ***CYSTINET, European Cooperation in Science and Technology Action TD 1302*** (https://www.cystinet.org/)
- ***Women in Global Health, Germany*** (https://www.womeningh.org/germany-chapte)
- ***Global Cost of Epilepsy Task Force of the International League Against Epilepsy*** (https://www.ilae.org/about-ilae/topical-commissions/yes/commission-on-epidemiology/members)
- ***German Alliance for Global Health Research*** (https://globalhealth.de/people.html)
- ***The Lancet One Health Commission Secretariat*** (https://www.med.uio.no/helsam/english/research/centres/global-health/lancet-commision-one-health/)