Burden, cost of disease and optimization of clinical practice of human cystic echinococcosis in Mongolia

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Prof. Dr. Martin Spiess
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To my beloved parents, Soyolgerel Gochoo and Bold Ereenkhuu.

May your wisdom always lighten my way!

Хайрт ээж аав хоёртоо зориулав.

Та нарын минь мэргэн ухаан замыг минь үргэлж

гэрэлтүүлж байх болтугай!

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Summary

Background: Our goal was to facilitate prevention and control of cystic echinococcosis (CE) in Mongolia by measuring the disease burden and societal cost, investigating the zoonotic linkages, and identifying the key challenges in clinical management of CE with proposed improvement. The disease is caused by the larval stage of *Echinococcus granulosus* sensu lato, and transmitted between dogs and various species of ungulates and also transmitted to humans. In humans, large cystic lesions can occur, mainly in the liver and lungs. Mongolia is one of the areas most affected by CE. The numbers of dogs and livestock are high, and a nomadic herding lifestyle is commonly practiced in most parts of the country. However, existing health services in Mongolia for CE barely reach the targeted populations, and CE cases are only detected at a late stage. For adequate diagnosis and treatment, herders must often travel hundreds of kilometers. Surgical procedures and hospitalization, travel costs, and lifelong disability following complicated surgeries are common for most patients. There is very limited information on infection in livestock populations due to the lack of public slaughterhouses and animal surveillance tools in the country.

Methods: We collected data on human CE cases from hospital records, statistical departments, and ultrasound examination records. Estimates of the reported incidence were used to calculate disability-adjusted life years (DALYs). To estimate the economic cost, we interviewed 65 patients who had CE surgery. The societal cost, including direct medical, direct non-medical and indirect costs, was estimated. We investigated the zoonotic linkages using the data of surgical CE cases and the livestock population of four species, including sheep, goats, cattle, and camels. To support the statistical analysis, samples were collected from CE infected animals in an endemic province. The subspecies identification, genetic diversity and haplotype network analysis were conducted. To understand the current clinical management of CE, we organized Focus Group Discussions (FGD), surveyed health professionals using a questionnaire. The ultrasound cyst images were reviewed by international experts to critically contrast current national practice with WHO-Informal Working Group on Echinococcosis (WHO-IWGE) guideline. Key challenges and further potential improvements were discussed during a workshop with Mongolian and international experts to reach consensus for standardization of clinical practice.

Result: The incidence of surgical cases, diagnosed cases, and total cases including undiagnosed cases was estimated to be 2.2 per 100 000, 15 per 100 000 and 60 per 100 000 person-years, respectively. The DALY was estimated to be 11461 for total cases including undiagnosed cases and 3017 for diagnosed cases.

The total societal cost due to human CE is US$2.7 million which equals 0.024% of total gross domestic product (GDP). The cost decreases to US$0.3million when the productivity loss of undiagnosed and diagnosed cases is excluded. The impact on the household economies is high for surgical cases where 76% of the direct cost is paid by the patients. In total out-of-pocket expense, the cost of albendazole contributed most.

US images of 84 patients were staged and assessed for interrater-agreement. The average raw agreement was 77.2%. Unweighted Kappa coefficient and weighted Kappa was 0.57 and 0.59, respectively. Mean proportion of images judged as stages CE1, CE2, CE3a, CE3b, CE4 and CL were 0.59, 0.01, 0.19, 0.08, 0.03 and 0.11 respectively. 40 cysts met the inclusion criteria of treatment modality analysis. The mean proportion of cases with a single cyst assigned to medical, percutaneous treatment, surgery and watch & wait were 52.5% (95% CI 42-65), 25.8% (95% CI 15-30), 5.1% (95% CI 0-10) and 3.3% (95% CI 0.0-10), respectively. 13.3% (95% CI 5–25) of cysts were staged as CL and therefore assigned to further diagnostic requirement.

The incidence of surgical CE cases increased by a factor of 1.71 for one interquartile range increment in the density of the camel population. No significant association was observed with other livestock species. The samples collected from 96 camels and 15 goats in an endemic region showed a CE prevalence of 19.7% and 6.7%, respectively. All livestock CE were caused by *E.granulosus* s.l. G6/7 (formerly identified as *E.granulosus canadensis* G6/7*)* of the of the *E. granulosus* s.l. complex. Four haplotypes were identified within the livestock samples, two of which had not been previously reported. A common haplotype was identified between humans, camels, goats, and a wolf, all of which were within the same geographical area. A mixed infection of *E. granulosus* s.l. G6/G7 with different haplotypes in the intermediate host was identified first time.

Conclusion: This is the first estimate of the burden and societal cost of human CE in Mongolia. Mongolia has a substantial proportion of the population suffering from cystic echinococcosis. The disease causes a significant amount of loss to society and household economy. Access to fully equipped treatment centers is limited by geographic distance and economic resources. Availability of albendazole is sparse,

and the price is high. WHO-IWGE guidelines are not implemented for allocating patients within the four treatment options based on CE cyst staging, with the result that all CE patients are referred for surgical treatment. This creates an unnecessary high-risk approach for patients who could either be treated with albendazole or percutaneously or observed. Our study revealed evidence that camels play an important role contributing to human CE in Mongolia, which is a critical information for further control and prevention of CE.

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List of Abbreviations

AVSAB	Department of Veterinary and Animal Breeding Government Agency
CE	Cystic echinococcosis
COI	Cost-of-illness
CT	Computer tomography
DALY	Disability-adjusted life years
DW	Disability weight
EKNZ	Ethics Committee of North-Western and Central Switzerland
ERC	Research Ethics Review Committee from WHO
FASE	Focused Assessment of Sonography for Echinococcosis
FCH	First Central Hospital
FGD	Focus Group Discussion
GDP	Gross Domestic Product
GH	General Hospital
ICD	International Classification of Diseases
IQR	Interquartile range
IVM	Institute of Veterinary Medicine
HERACLES	European Registry of Echinococcosis
LIC	Low income-countries
LMIC	Lower middle-income countries
MoH	Ministry of Health
NCCD	National Center for Communicable Diseases
NCMCH	National Center of Mother and Child Health
NCZD	National Center for Zoonotic Diseases
NEMA	National Emergency Management Agency
NSO	National Statistical Office
NTD	Neglected Tropical Disease
PEP	Post-exposure prophylaxis
PHD	Provincial Health Department
PT	Percutaneous Treatment
SCVL	State Central Veterinary Laboratory
SDC	Swiss agency for development and cooperation
SES	Socio-economic status
Swiss TPH	Swiss Tropical and Public Health Institute
TCH	Third Central Hospital
TDR	Special Programme for Research and Training in Tropical Diseases
UB	Ulaanbaatar
US	Ultrasound
WHO	World Health Organization
WHO-CE	Classification of CE stages recommended by WHO-IWGE
WHO-IWGE	Informal Working Group on Echinococosis from WHO
YLD	Years lived with disability
YLL	Years of life lost

1. Introduction

Cystic echinococcosis (CE) caused by the larval stage of *Echinococcosis granulosus* is a zoonotic disease with a substantial economic impact on the human and animal health sectors globally (Torgerson, 2003; Budke et al., 2006; Torgerson et al., 2015). The adult stage of the parasite resides in the intestine of the definitive host` mainly domestic dogs` and parasite eggs are excreted into the environment with host feces. Eggs ingested by intermediate host species mostly livestock then develop into hydatid cysts in the liver and lung (Romig et al., 2017). An endemic situation in the animal host increases the risk of infection in humans` who are considered aberrant intermediate hosts. Progression of symptoms in humans is chronic and can take months to years until diagnosis` depending on the cyst location` size` numbers and host immune reactivity (Romig et al., 1986; Wang et al., 2006) (Figure 1).

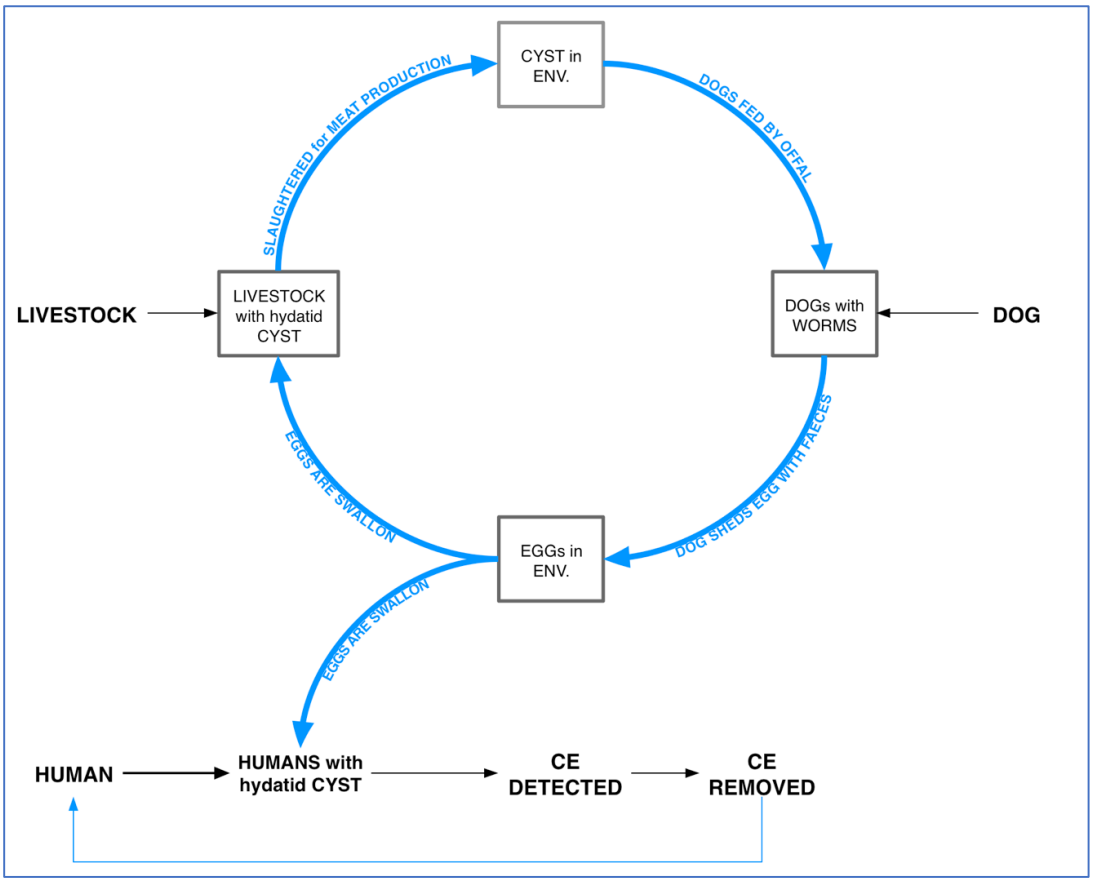

Figure 1. Transmission cycle of cystic echinococcosis. ENV.-environment

Most CE patients are from rural` remote areas where they have close contact with host animals (Li et al., 2015). Especially in semi-arid zones with water scarcity hand hygiene is often poor and contributes to the risk of transmission of *E. granulosus* eggs to humans.

The disease distributed globally. More endemic areas are the eastern part of the Mediterranean region, northern Africa, southern and eastern Europe, at the southern tip of South America, in Central Asia, Siberia and western China (Deplazes et al., 2017). Many countries that are highly potential to be endemic are, however, still not accounted as endemic due to the underreporting (Figure 2).

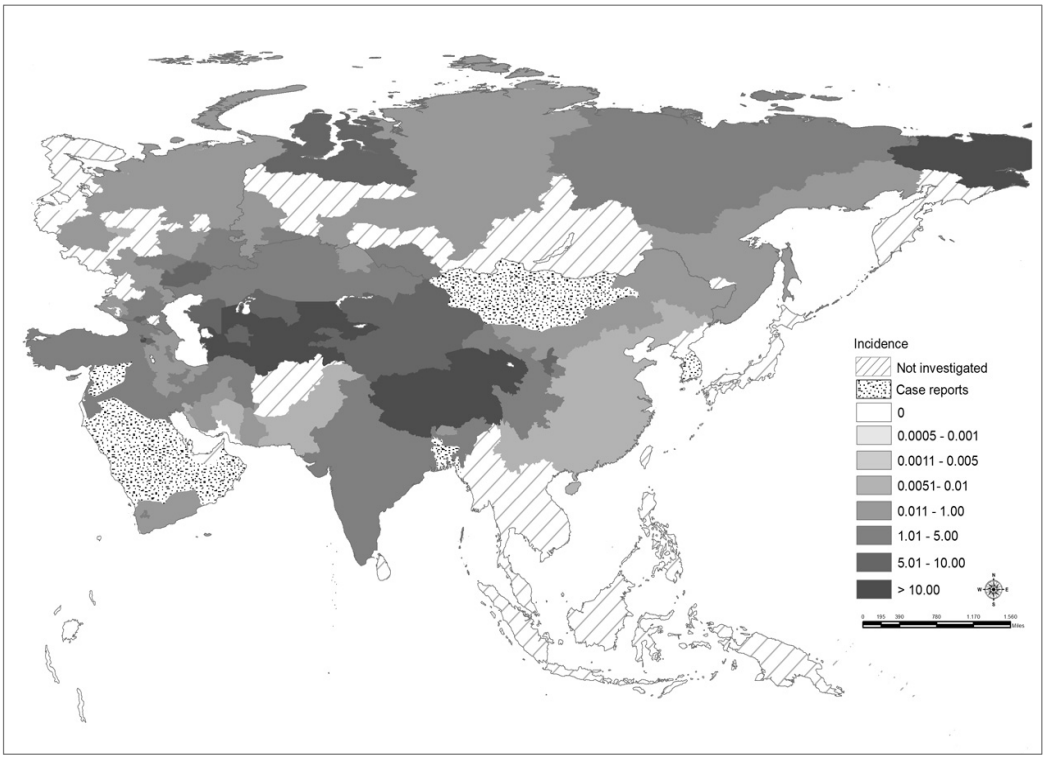

Figure 2. Current incidence of human cystic echinococcosis in Asia (Deplazes et al., 2017)

Disease understanding and effective control strategy is still a challenge for echinococcosis especially in developing countries (Craig et al., 2017). Due to the chronic nature of the symptoms, patient remoteness, absence of local diagnostic capability, and lack of ineffective treatment, the CE burden is largely underestimated (Brunetti et al., 2011; Budke et al., 2017; Tamarozzi et al., 2017).

The current estimated global burden for CE is an annual loss of 184`000 disability-adjusted life years (DALYs) not accounting for the undiagnosed population or 1.77 million DALYs including the undiagnosed proportion (Torgerson et al., 2015).

To fully quantify the burden in both the human and animal sectors, economic loss has been measured in some endemic countries, including Europe, Middle East, South America countries and China (Torgerson et al., 2000; Torgerson et al., 2001; Majorowski et al., 2005; Benner et al., 2010; Fasihi Harandi et al., 2012; Wang et al., 2012; Bingham et al., 2016).

The incubation period could last from months to years depending on the age of the patients, cyst location, number, immunological reaction (Romig et al., 1986). It is not well understood which exact factors affecting the growth and progression of the hydatid cyst (Romig et al., 1986; Frider et al., 1999; Wang et al., 2006). Due to the silent or asymptomatic gradual growth of the hydatid cyst, patients either hospitalized in the advanced stage, or detected due to accidental findings. The organ involvement has a key role in the symptom of the patient (Budke et al., 2013). Recent findings suggesting that organ involvement could be due to genetic subspecies of *E.granulosus* (Cucher et al., 2016). The main organ affected is the liver while around 20% affected the lung with or without liver. A much smaller percentage affects spleen, brain, kidney, bone, peritoneum (Kern et al., 2017). Treatment choice can vary due to cyst stages and activity (Hosch et al., 2007; Hosch et al., 2008).

Ultrasonography has developed into a powerful tool for diagnosing and staging CE (Brunetti et al., 2010; Stojkovic et al., 2012). There two main staging algorithm used in the world: Gharbi et al., (1981) and WHO-CE classification recommended by the WHO – Informal Working Group on Echinococosis (WHO-IWGE) (Gharbi et al., 1981; Brunetti et al., 2010). The updated version from WHO-IWGE has an advantage of using stage specific treatment options and accounts the re-activation of the cyst which can change the whole prognosis of the patient. The core piece of the guidelines is to triage on the basis of ultrasound-defined cyst stages into four groups: medical, percutaneous, surgical treatment (active cyst stage CE1 to CE3b) and 'watch & wait' (inactive cyst stages CE4 and CE5) (Junghanss et al., 2008; Brunetti et al., 2010; Piccoli et al., 2014; Stojković et al., 2014; Stojkovic et al., 2016). The classification is still grossly underused in most epidemic countries (Del Carpio et al., 2012; Tamarozzi et al., 2014; Nabarro et al., 2015).

Based on the global public health challenge faces due to CE, WHO and its collaborating experts' have proposed the global strategy: (i) make a critical assessment on the potential for control of cestode zoonoses focusing on the regions where the populations are at highest risk; (ii) establishing a research and validation agenda on new approaches and tools for study and control of the disease; (iii) developing a work-

plan of action targeting interventions; and (iv) exploiting more resources, favourable public policy, and control options and strategies against echinococcosis (WHO, 2001; Torgerson and Budke, 2003; Xiao et al., 2013).

Mongolia is one of the CE endemic countries. The country has a vast distribution of host animals, strong behavioral risks, and a high prevalence of unregulated slaughtering practice in the absence of control action in last three decades (Ebright et al., 2003). The most vulnerable group for CE are likely to be herder communities who cannot afford the treatment and transport cost. Due to the poor reporting system and late diagnosis, information regarding the epidemiology of CE is scarce. Current prevalence, distribution, algorithm of clinical case management and cost caused by the disease are not known (Gurbadam et al., 2010).

1.1 Background of Mongolia

Mongolia is a land-locked country in the heart of Central Asia with China to the South, and Russia to the North. With a surface area of 1.5 million km²with a population of only 3 million, it is the word's most sparsely populated independent country. The geography is comparatively diverse, including wide areas of desert, mountainous and flat steppe regions. The climate is continental with long cold winters and short summers with temperatures ranging from approximately -30℃ to 30℃. One third of the population is comprised of nomadic herders. Currently, more than 60 million livestock are used for the nomadic livestock husbandry.

1.2 Previous knowledge on CE in Mongolia

In Mongolia, the study of CE started from the 1930s onwards with the collaboration of Russian scientists. In 1938, Mongolia had ranked first in the world in regard to the prevalence of CE in livestock (Polikova, 1939). In 1926-1931, CE detected in livestock was with a prevalence ranging between 20-60% in the slaughterhouses (Polikova, 1939). The prevalence of CE in dogs was between 10-51% among rural dogs and 26% among city dogs (Galbadrakh, 1972). Another study was conducted in 1970 in 9 provinces and cities of Mongolia. The results came as follows: 16% of dogs were positive for CE test in rural areas, 9.7% in Ulaanbaatar (UB) city. Sheep were reported as the highest prevalent among livestock (7.6%). Both livestock and dog prevalence were high in the northern provinces. The study concluded that the interaction

between sheep and dogs is the main component in the transmission of CE (Udev, 1960; Jezek et al., 1971; Jezek et al., 1973).

Between 1950-1980, intensive public health and veterinary measures were taken to strengthen the control of the disease and to improve hygiene and sanitation. At the same time, there has been a huge improvement in the study and practice of diagnosing and surgery of human echinococcosis. In 1970s, human echinococcosis was studied by senior clinicians (Goosh, 1971; Khairulla, 1972; Shagdarsuren et al., 1973; Onkhuudai, 1988). A classification system of echinococcosis was introduced in a retrospective study of complicated cases of echinococcosis (Sodov, 1990; Munkhtogoo, 1991). Surgical cases of echinococcosis among total surgical cases decreased from 7.2% to 3.2% during 1953-1970 (Galbadrakh, 1972).

Due to the economic collapse in 1990, centralized strategic actions of veterinary and public health sector weakened. Diagnosing, reporting of echinococcosis became a great challenge, which eventually led to underreporting. In 1993, it was reported that 18% of the all general surgical cases were caused by echinococcosis in the First Central Hospital (FCH) (Davaatseren et al., 1995; Gurbadam et al., 2010).

Current information regarding the epidemiology of CE in human is scarce. Except a few serological pilot study report, the prevalence, incidence information is very scarce (Watson-Jones et al., 1997; Huh et al., 2006). Molecular genetical investigations identified both *E. granulosus* and *E. multilocularis* in the cystic samples taken from the patients who had surgery. The G1 (*E.granulosus sensu stricto*) and G6-7 (*E.canadensis*) strains of *E. granulosus* were identified from Mongolian patients (Ito et al., 2010; Jabbar et al., 2011; Ito et al., 2014).

1.3 Health system of Mongolia

The current health system functions in a centralized way. Due to geographical isolation, and lack of human resource, the system considered to be most practical. Most diseases, outbreaks reported, managed in this system (Figure 3).

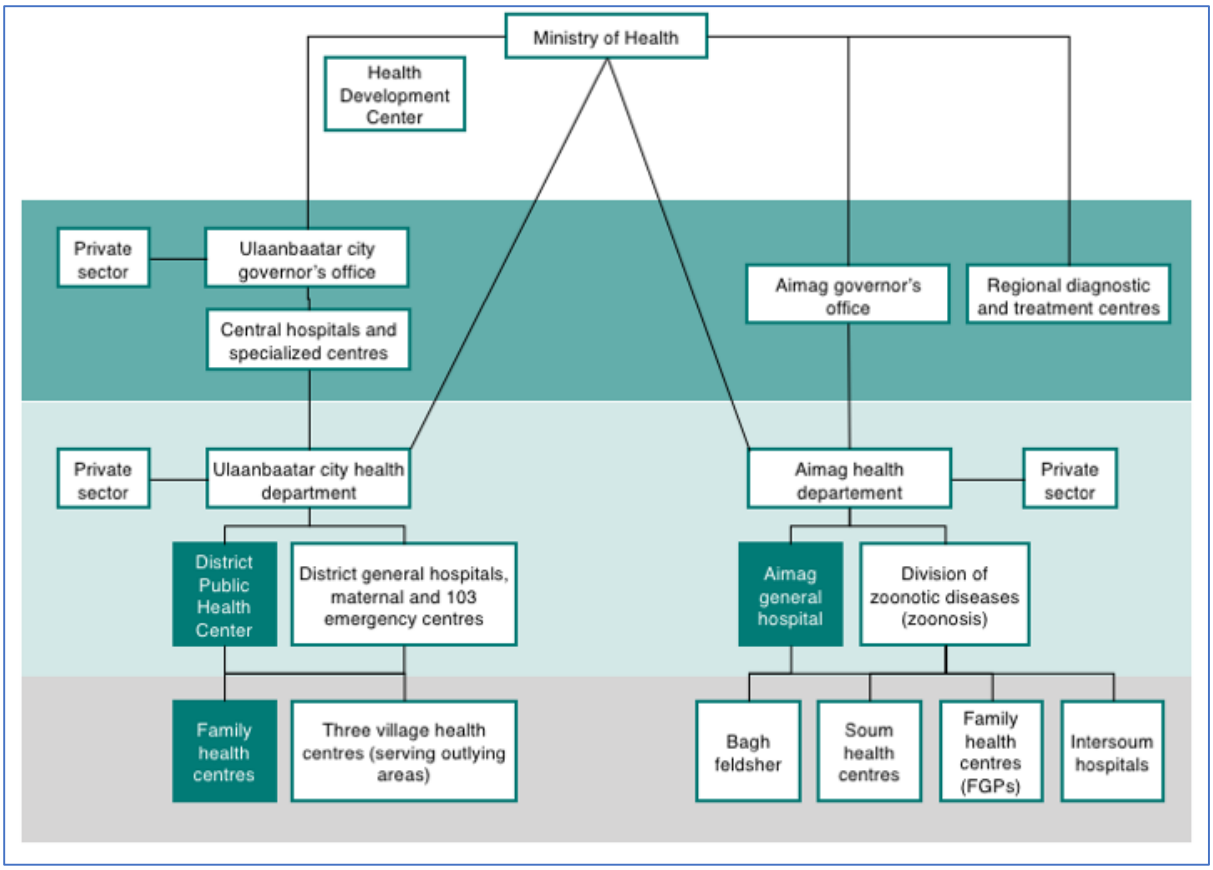

Figure 3. The health system of Mongolia (Tsilaanjav et al., 2013). *Aimag-Province; Soum-subdivision of province; Bagh –smallest administrative unit.*

But for neglected diseases as CE, there is a gap. Because so far there is no official reports while all the signs of endemicity for CE is apparent in a great amount. This could be due to slow growth rate of cysts, the often uneventful clinical course until the cysts have reached a size or complications. On the other hand, technical capacity to provide the required diagnostic and surgical means at the local level is lacking. More so, clinical management provided for CE patient is very limited. In consequense, herders have to travel over hundreds of kilometres. Cost incurring travel, surgery and hospitalization are for many patients out of reach and lifelong disability is common. At central level, neither a national policy nor national guidelines for surveillance, prevention and case management of CE exist. Patients are more likely to be detected by surgical departments and missed out from the surveillance of zoonotic disease. Better knowledge of the burden of disease, social cost and an effective control will contribute to a better approach to reduce the burden of this zoonosis in Mongolia (WHO, 2013). Therefore, the aim of this work is to review the current situation, burden of human CE, its epidemiology and assess the clinical management; and to estimate the public and private cost of CE.

2. Goals and objectives:

Goal of this project was to contribute in the improvement of prevention and control of cystic echinococcosis (CE) in Mongolia by measuring the disease burden, societal cost, investigating zoonotic linkage, and identify the clinical management of CE with proposed improvement.

Objectives:

- Estimate burden, societal cost of CE in Mongolia
- Understand the zoonotic linkage of CE in Mongolia based on the currently available data
- Optimize the clinical algorithm of CE in Mongolia

3. Burden and cost of cystic echinococcosis in Mongolia

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This manuscript is a working paper

3.1 Abstract

Background: Cystic echinococcosis (CE) caused by the larval stage of *Echinococcosis granulosus* is a zoonotic disease with a substantial economic impact on the human and animal health sectors globally. Mongolia is one of the areas most affected by CE. However, the lack of information about disease situation, its implication on the country economy is not well understood which hinders future action on CE control and prevention.

Method: We collected data on human CE cases from statistical departments, and ultrasound examination records. Estimates of the reported incidence were used to calculate disability-adjusted life years (DALYs). To estimate the economic cost, we interviewed patients who had CE surgery. The societal cost, including direct medical, direct non-medical and indirect costs, was estimated.

Result: The total societal cost due to human CE is US$2.7 million which equals 0.024% of total gross domestic product (GDP). The cost decreases to US$0.3million when the productivity loss of undiagnosed and diagnosed cases is excluded. The impact on the household economies is high for surgical cases where 76% of the direct cost is paid by the patients. The cost of albendazole contributed most in total out-of-pocket expense. The DALY was estimated to be 11461 for total cases including undiagnosed cases and 3017 for diagnosed cases.

Conclusion: This is the first estimate of the burden and societal cost of human CE in Mongolia. Mongolia has a substantial proportion of the population suffering from CE. The disease causes a significant amount of loss to society and household economy. Access to fully equipped treatment centers is limited by geographic distance and economic resources. Availability of albendazole is sparse, and the price is high. Further research on cost-effective prevention strategy is needed.

3.2 Introduction

Cystic echinococcosis (CE) caused by the larval stage of *Echinococcosis granulosus* is a zoonotic disease with a substantial economic impact on the human and animal health sectors globally (Torgerson, 2003; Budke et al., 2006; Torgerson et al., 2015). The adult stage of the parasite resides in the intestine of the definitive host, mainly domestic dogs, and parasite eggs are excreted into the environment with host feces. Eggs ingested by intermediate host species, mostly livestock, then develop into hydatid cysts in the liver and lung (Romig et al., 2017). An endemic situation in the animal host increases the risk of infection in humans, who are considered aberrant intermediate hosts. Progression of symptoms in humans is chronic and can take months to years until diagnosis, depending on the cyst location, size, numbers and host immune reactivity (Romig et al., 1986; Wang et al., 2006). Most CE patients are from remote rural areas where they have close contact with host animals (Li et al., 2015). Especially in semi-arid zones with water scarcity hand hygiene is often poor and contributes to the risk of transmission of *E. granulosus* eggs to humans. Due to the chronic nature of the symptoms, patient remoteness, absence of local diagnostic capability and lack of or ineffective treatment the CE burden is largely underestimated (Brunetti et al., 2011; Budke et al., 2017; Tamarozzi et al., 2017).

Currently epidemiological data available for CE are mostly derived from patients who seek health care after a cyst ruptures or becomes large enough to cause severe symptoms which are only a fraction of all infected people (Feng et al., 2015; Counotte et al., 2016; Deplazes et al., 2017). A small number of community surveys conducted in only a few regions were used to extrapolate the undiagnosed population. The current estimated global burden for CE is an annual loss of 184,000 disability-adjusted life years (DALYs) not accounting for the undiagnosed population or 1.77 million DALYs including the undiagnosed proportion (Torgerson et al., 2015). To fully quantify the burden in both the human and animal sectors economic loss has been measured in some endemic countries` including Europe, Middle East, South American countries and China(Torgerson et al., 2000; Torgerson et al., 2001; Majorowski et al., 2005; Benner et al., 2010; Fasihi Harandi et al., 2012; Wang et al., 2012; Bingham et al., 2016). The estimation of the economic loss in humans is based on the cost-of-illness (COI) method whereas the economic loss for animal sectors is based on measuring animal productivity (Torgerson et al., 2001; Narrod et al., 2012).

CE is endemic in Mongolia. The country has a large and widely distributed host animal population, as well as strong behavioral risks, while a high degree of

unregulated slaughtering is ongoing with no control actions over the last three decades (Ebright et al., 2003). A crucial detrimental factor for the control of CE was the sudden privatization of the veterinary sector following the economic collapse of the Soviet Union (Ebright et al., 2003). Currently, reporting on CE prevalence in the animal population is absent, while there are still many surgical CE cases, especially in the children, which indicates ongoing transmission (Bold et al., 2018a). Recent statistical analysis and molecular genetic studies, however, suggest the importance of camels in causing human CE (Bold et al., 2019). In humans, the numbers of surgical cases are the only available data. There is no report on non-surgical cases detected through ultrasound. Rural populations have limited access to CE management because the only tertiary hospital for surgical treatment is located in Ulaanbaatar (Bold et al., 2018a). The secondary level hospitals in rural areas are capable of detecting CE by ultrasound, depending on the radiologists experience, but have no trained personnel for CE surgery. Hospitalizations due to CE are, therefore, rare in secondary hospitals.

Measurement of the epidemiologic burden in DALYs and the economic burden as monetary losses in the human and animal health sectors from available data could show the magnitude of the societal burden and provide valuable information for decision makers (Torgerson, 2003; Torgerson et al., 2015). A lack of available data in many endemic countries obscures the real magnitude of CE and challenges prevention and control efforts nationally and internationally (Torgerson and Budke, 2003). This study aimed to measure the CE burden in Mongolia for the first time by comprehensively assessing the available data to measure DALYs and estimate the cost of disease in humans. It was not possible to estimate the livestock sector burden due to an absence of data on animal prevalence.

3.3 Materials and methods

Ethical statement

The study was approved by the Medical Ethics committee of Mongolia, the World Health Organization (WHO) Research Ethics Review Committee (ERC) and the Ethics Committee of North-Western and Central Switzerland (EKNZ 2014-240). Permission to access hospital and statistical data was obtained. Verbal and written informed consent was given by each interviewed patient. Collected data were only available to the study team. All patient data were rendered anonymous prior to further analysis.

3.3.1 Data collection

Epidemiological data

Surgical cases: There is no official report on the number of surgical cases. Data from CE cases reported from 2006-2016 were extracted from the database of Center for Health Development next to Ministry of Health, Mongolia. Diagnoses recorded as ICD code 67.1-67.9 were compiled, along with patient age, sex, registration number, residential province, admission date, hospital name, and category of treatment given.

Non-surgical cases: Each Mongolian province has a single secondary level hospital (Provincial General Hospital). In each secondary hospital, two or three radiologists conduct ultrasound examinations on patients with abdominal symptoms. Pathognomonic hydatid cysts are generally identified initially at this level and subsequently referred to tertiary hospitals if necessary (e.g., for advanced diagnostics or surgery). There is currently no algorithm utilized to identify or stage CE hydatid cysts in Mongolia. Diagnostic methods including the Gharbi classification or WHO Informal Working Group on Echinococcosis (IWGE) classifications are not implemented in the provinces, which allows for uncertainty in the clinical management (Bold et al.; Brunetti et al., 2010). Hydatid cysts located extra-abdominally are highly likely to be misdiagnosed or sent directly to a tertiary hospital for further diagnostics without specifying any diagnosis at the secondary level. The retrospective data collection of ultrasound examination failed to give information of consistent data due to paper-based archive maintenance. Therefore, we collaborated with radiologists from eight provincial hospitals and recorded new ultrasonographically diagnosed cases for one year (2016) using an online data collection tool developed for this study. To reduce misdiagnosing, radiologists who had been working for more than 10 years were recruited for the study. Anonymized patient information was recorded, including age, sex, cyst location, features in the imaging, and treatment recommendation. A paper copy of the online form was sent to personnel at the local center for zoonotic disease and entered a second time. Since fully calcified cases do not need treatment and are not referred, we excluded all cases diagnosed with full calcification.

Undiagnosed/non-healthcare seeking cases: Due to the geographical limitation and asymptomatic nature of the disease, a large fraction of all infected patients are not detected by the health system. Previous studies in other endemic areas used

community surveys to estimate the number of infected people. The ratio between the numbers of undiagnosed and diagnosed cases may range between 2 and10, based on the large scale community survey in China (Li et al., 2013; Osman et al., 2014; Feng et al., 2015; Deplazes et al., 2017). In Mongolia, however, there was only one survey conducted 14 years ago in a single "soum" (subdivision of province) which was not representative for extrapolation to country level (Wang et al., 2005). Therefore, extrapolation of undiagnosed cases was based on the proportion of clinical cases and the information in the literature on the average length of the incubation period of CE.

Cost

Patient interviews were conducted to record the amount of money and time spent to get health care due to CE. Patients who were hospitalized for CE surgery at the tertiary hospitals from 2010-2016 were contacted by local clinicians and invited to participate in the study. Patients who agreed to participate received a verbal and written explanation of the consent form by a member study team. If the patient was a child, a parent was asked for permission and gave consent. Patients who gave consent were interviewed at their nearest health facility. 75% of the patients who agreed to participate were hospitalized during 2013-2016. Patient interviews were conducted from 2014 to 2016. The interview questions included age, year of hospitalization, accompanying caretaker, number of visits to the hospital, travel and accommodation costs, and payments for diagnostic tests and treatments. To calculate the income loss, we asked about patients` and family members, income from salary or welfare and coping mechanisms during the health-care seeking period (Table S1).

In Mongolia, CE surgery only conducted in public hospitals. Patients have to pay 10-15% of the medical charges in public hospitals, except for emergency care, or during mass outbreak of infectious diseases. People with disabilities, pensioners, and children under 16 are exempt from these user-fees. In addition, most diagnostic costs above US$ 20 are paid by the patients (Tsilaanjav et al., 2013). In general, due to the long waiting time and overloaded queue for diagnostics in the public hospitals, patients from rural areas often go to private hospitals for diagnostics, to reduce the waiting time. Therefore, we divided direct medical costs, into direct medical public cost and direct medical private cost. In addition, direct non-medical costs and income loss were calculated (WHO, 2016). Patient interviews were the main source of the cost information for surgical and non-surgical patients, with a few exceptions. Fixed values were used for the unit daily costs of accommodation in the city and of a hospital

stay (Table S1). For undiagnosed cases, a loss of productivity, as based on the literature values, was applied (Benner et al., 2010).

Direct medical public cost: Direct public costs consist of the cost of the hospital stay, cost of diagnostics under US$ 20 including ultrasonography, radiography, blood tests. The cost was calculated for both surgical and non-surgical patients.

Direct medical private cost (out-of-pocket expense): Direct private costs include the cost of albendazole treatment, an admission fee which includes a 10-15% user-charge and surgical materials (drainage, bandages), the informal fee for surgeons, informal fee for nurses, physiotherapy during the hospitalization (acupuncture, UV therapy, massage) and diagnostics above US$20 (computed tomography scans, cancer markers). The direct private cost was calculated for both surgical and non-surgical patients. The information on cost of albendazole for non-surgical cases could not be obtained. Albendazole is used as a complementary to surgery not as a separate treatment option, mainly due to unavailability at the rural hospitals. The cost of albendazole of surgical patients was applied to non-surgical patients assuming them all to need treatment with albendazole .

Direct non-medical cost: Depending on the patient's health status and distance from the tertiary hospital, different modes of transport were used including train, car, public bus, and airplane. We included the proportion of caretakers in the computation of average transportation cost. In addition, the meal and accommodation costs for stays in the capital city for CE surgery were included in this category. For non-surgical cases, the meal and accommodation costs were assumed to be zero and travel costs were limited to primary and secondary health care centers.

Indirect cost: Time spent in the capital city for CE surgery for patients with salary and accompanying caretakers with salary were calculated as income loss. To determine the household income loss, the daily income was calculated based on income from welfare, salary and private business. We asked about coping mechanisms during the hospitalization for CE when patients had insufficient money. For those who received bank loans discounted, interest payments were calculated as losses. We did not measure productivity loss for surgical and non-surgical cases, or undiagnosed cases.

Therefore, previously reported productivity loss estimate of 0.015 for undiagnosed cases was used for all cases and reported separately (Benner et al., 2010).

3.3.2 Data analysis

Estimating the human cases

Our calculations were restricted to patients without calcifications as these do not need treatment. Moreover, we first disregarded pulmonary cases. The number of diagnosed non-pulmonary cases could be retrieved for 8 provinces in 2016. The number of diagnosed but not surgically treated non-pulmonary cases in 2016 was calculated as the difference between the number of reported non-pulmonary cases and the number of non-pulmonary surgical cases which were not accidentally detected at the surgical clinic. These differences were fitted by a Quasi-Poisson regression model including the natural logarithm of the average annual count of non-pulmonary surgical cases over the period 2012-2016 in the respective province as independent variable. The model was used to predict the number of diagnosed non-surgical and non-pulmonary cases in 2016 across the other provinces. For the respective numbers in the 8 provinces with existing data, we did not just use the reported figures but computed empirical Bayes estimates according to the formula.

$$\hat{y}^{EB}{}_i = w_i \hat{y}_i + (1 - w_i) y_i$$

where y_i and $\hat{y}_i$ denote the recorded and fitted numbers, respectively, of non-surgical non-pulmonary cases in province i and $w_i = {}^{y_i}/_{y_i + SE(\hat{y}_i)^2}$.

In a similar way, an empirical Bayes estimate was computed for the average annual number of non-pulmonary surgical cases in 2016 using the prediction provided by a Quasi-Poisson regression model with a linear time trend variable having been fitted to the annual numbers of surgical cases between 2006 and 2016.

The numbers of non-pulmonary surgical and non-surgical cases in 2018 were then estimated by multiplying their estimates for 2016 by the factor $\exp(2\hat{\beta})$, with $\hat{\beta}$ denoting the coefficient of the variable year in the aforementioned model.

95%-confidence intervals were computed for the estimated numbers of non-pulmonary cases in 2018 by simulating the uncertainty around the point estimates. For this purpose, we distinguished the number n_1 of surgical cases, the number n_2 of

non-surgical cases in the provinces without data on non-surgical cases, and the number n_3 of non-surgical cases in the eight provinces which provided data on these cases in 2016. The simulation consisted in first adding a random term $SE(\hat{y}) \cdot z_1$ to the respective point estimate $\hat{y}$ with z_1 being sampled from the standard normal distribution, and then multiplying this sum by $\exp(2\hat{\beta}) \cdot (1 + 2SE(\hat{\beta})z_2)$ with z_2 being another standard normal random number. The standard error of the estimate of n_2 included two components, the first one relating to the uncertainty of the regression model and the second one to the uncertainty associated with the over-dispersion of provincial counts.

In a further step, the estimated counts of non-pulmonary surgical and non-surgical cases were divided by the proportion p_{NP} of non-pulmonary surgical cases to obtain estimates of all clinical cases. To take into account the statistical uncertainty introduced by this factor, these estimates were multiplied by the factor $1 - \frac{SE(p_{NP})}{p_{NP}} z_3$, with $SE(p_{NP})$ denoting the standard error of p_{NP} and z_3 a further standard normal random number.

After iterating these simulation steps 1000,000 times, the 95%-confidence limits were estimated by the 2.5th and the 97.5th percentiles of simulated values.

For the estimation of the number of undiagnosed cases, we assumed the average time from infection to diagnosis to be 5 years in adults and 2 years in children. Accordingly, the number of undiagnosed adult cases was estimated to be 4 times the number of diagnosed cases, and the respective number in children was assumed to equal the one for the diagnosed children.

Cost estimates

Different types of costs and frequencies were assessed in an interview among the surgical cases in 2016, enabling estimating mean individual values for these variables along with their standard errors.

To obtain confidence intervals for the mean individual amounts of different types of costs, point estimates $\hat{c}$ from the cost survey were replaced by $\hat{c} + SE(\hat{c}) \cdot t(k-1)$ in the respective formulas, with k denoting the number of reports of the respective cost item in the survey and $t(k-1)$ a random number sampled from the t-distribution with k-1 degrees of freedom. Frequencies were treated in the same way. After 1000,000 iterations of adding random terms to the point estimates of case

numbers, costs and frequencies across cost formulas, 95%-confidence limits were determined as described above for the case numbers.

Based on the data from surgical cases, the proportion of adult cases was estimated to be 60%. If mean costs or frequencies could not be estimated from the survey, estimates were derived from published data. Uncertainties were ignored for these quantities.

DALY estimates

The DALY is the summary measure of public health used to quantify the burden of disease and it is the key measure for Global Burden of Disease estimate. The main components of DALYs are the years lived with disability (YLD) and the years of life lost due to premature mortality (YLL). In DALY estimation, disability is measured from 0 to 1, with 0 representing perfect health and 1 death. The proportion of reduced health due to illness is defined as Disability Weight (DW). The formula for the calculations are the following (Devleesschauwer et al., 2014b):

DALY=YLL+YLD
YLD= Number of cases * duration till remission or death * DW
YLL= Number of deaths * life expectancy at the age of death

We estimated DALY for all persons having been infected with the disease irrespective of whether they were diagnosed or not. The duration of illness was assumed to be lifelong for all categories and approximated by the life expectancy at the mean age of diagnosis (i.e., 23 years), differentiating between men and women (Torgerson et al., 2015). A DW of 0.123 was assumed for all categories. YLL were not accounted for due to the lack of mortality data for the disease.
Simulations were performed using SAS Software, version 9.4

3.4 Results

A total of 446 surgical CE cases were reported between 2006-2016 in Mongolia. The mean age of cases was 28.3 (95%CI 26.4-30.3). The percentages of males and females were 44% and 56%, respectively. For the non-surgical cases, a total of 185 cases were detected with CE in the abdominal organs from 8 provinces during 2016. The mean age of non-surgical cases was 57.9 (95%CI 55.3-60.6). The percentages of males and

females were 30% and 70%, respectively. The estimated number of diagnosed (surgical and non-surgical) cases for 2018 is 476.4 (95%CI 386.8-569.7) and of total cases is 1810.3 (95%CI 1463.3-2171.8) (Table 1). The incidence (per 100'000 person years) based on the estimated number is 2.2 (95%CI 1.8-2.7), for surgical cases, 15.9 (95%CI 12.9-19.0), for diagnosed cases, and 60.3 (95%CI 48.8-72.4) for diagnosed and undiagnosed cases.

A total of 65 surgical cases agreed to participate in the cost interview. The median age of patients interviewed was 37 (IQR: 16 to 53). 75% of the patients agreed to participate were hospitalized during 2013-2016. The percentage of female and male were 49% and 51%, respectively. 83% were from rural areas. The percentages of herder, student, retired, employed, unemployed and disabled patients were 24.9%, 24.9%, 16.9%, 16.9%, 12.3% and 4.6%, respectively. The average monthly family income was US$ 150-300 for 63%, below US$ 150 for 18.5% and above US$ 300 for 18.5%. 32% of the families had a member who was employed. 30% of the patients, family income source was from welfare support (i.e child support, pensions). The percentage of patients accompanied by the caretaker was 70% (Table S2, Table S3). 52% of the patients received a bank loan (i.e salary, retirement, herders loan) for health care seeking for CE surgery.

Table 1.Predicted number of cases of CE, for 2018

Categories	Cases		Incidence*	
	mean	95% CI	mean	95% CI
Surgical cases	67.3	55.0-80.1	2.2	1.8-2.7
Non-surgical cases	409.1	321.4-499.8	13.6	10.7-16.6
Undiagnosed cases	1334	1076-1604	44.5	35.8-53.5
Total diagnosed cases	476.4	386.8-569.7	15.9	12.9-19.0
Total cases*	1810	1463-2172	60.3	48.8-72.4

* number of cases per 100,000 person years

Estimated individual cost due to CE. The average estimated cost per surgical case is US$ 3020 (95%CI US$ 2650-3420) and for non-surgical cases it is US$ 350 (95%CI US$ 290-400). The estimated direct medical public cost for surgical patients is US$270 (95%CI 240 - 310) and for non-surgical patients US$80 (95%CI US$50-110). The estimated direct medical private cost for surgical patients is US$910 (95%CI US$700-

1140) and for non-surgical patients US$ 50 (95%CI US$ 30-70). The estimated direct non-medical cost for surgical patients is US$ 1090 (95%CI US$ 860-1350) and for non-surgical patients US$ 160 (95%CI US$ 120-210). Estimated income loss for surgical patients is US$ 580 (95%CI US$ 460-700) and for non-surgical cases US$ 80 (95%CI US$ 70-90).

Estimated total cost in human. The estimated total cost due to human CE was US$ 2'741'580 (95%CI US$ 2'238'900- 3'266'280), when accounting for the undiagnosed cases and for productivity loss. The respective estimate was US$ 346'130 (95%CI US$ 284'860- 413'240) when accounting only for the diagnosed cases and disregarding productivity loss. Among the total cost without productivity loss, 39%, were attributed to direct medical costs, 40% to direct non-medical costs, and 20% to indirect costs. Total estimated cost of surgical cases was US$ 203'600 (95%CI US$ 159'680-251'890). Of the total cost for surgery, 39% were attributed to direct non-medical cost, 30% to direct medical cost covered by patients and 9% to direct medical cost covered by insurance and 22% to indirect costs. Thus, 91% of cost was covered by the patients for receiving the CE surgery. Loan interest payments accounted for about 5% of these costs. The total cost for non-surgical cases was estimated to be US$ 142`770 (95%CI US$ 106'200-183'670), and 70% of it was attributed to direct medical costs, 15% to direct non-medical costs and 15% to indirect costs.

The estimated productivity loss including undiagnosed cases was US$ 2'395'460 (95%CI US$ 1'935'440-2'875'820). Of the total cost, 87% was attributed to the productivity loss. Beside productivity loss, the item with the highest contribution was chemotherapy, assuming non-surgical cases to be treated with albendazole as well. Among the parameters in the direct medical cost, the informal fee for surgeon is the second most influential. The most influential item for the direct non-medical cost is purchase of food during the stay in Ulaanbaatar city. For the indirect cost, monthly income of the patient has high influence (Figure 1).

DALY estimates. The total estimated DALY for diagnosed cases are 11`461 (95%CI 9`264-13`752) when including the undiagnosed cases. The corresponding estimates are , 3017 (95%CI 2449-3607) for diagnosed cases, 426 (95%CI 348-507) for surgical cases and 2590 (95%CI 2033-2588) for nonsurgical cases.

Table 2. The cost of human CE in Mongolia.

Categories	cost (USD*)		
	Mean	LCL	UCL
Surgical			
Direct medical cost (public)	$18,530	$14,490	$22,970
Direct medical cost (private)	$61,650	$43,910	$81,830
Direct non-medical cost	$73,250	$53,540	$96,440
Indirect cost**	$38,560	$28,730	$49,750
Loan cost	$11,360	$7,330	$16,250
Total cost (surgical)	**$203,360**	**$159,680**	**$251,890**
Non-surgical cases			
Direct medical cost (public)	$33,220	$20,690	$47,610
Direct medical cost (private)	$67,760	$46,090	$92,840
Direct non-medical cost	$21,660	$12,930	$31,620
Indirect cost**	$20,130	$15,220	$25,540
Total cost (non-surgical)	**$142,770**	**$106,200**	**$183,670**
Total medical cost (public)	$51,750	$36,970	$68,440
Total medical cost (private)	$83,310	$63,010	$106,000
Total non-medical cost	$141,010	$110,370	$175,340
Total indirect cost**	$70,060	$55,990	$85,730
Total societal medical cost**	$346,130	$284,860	$413,240
Total productivity loss	$2,395,460	$1,934,440	$2,875,820
Total indirect cost***	$2,465,510	$1,997,560	$2,953,300
Total cost***	**$2,741,580**	**$2,238,900**	**$3,266,280**

*- 1USD= 2000 Mongolian currency (Tugrik), 2016

**- Without productivity loss

***- Including productivity loss for all cases (diagnosed + undiagnosed).

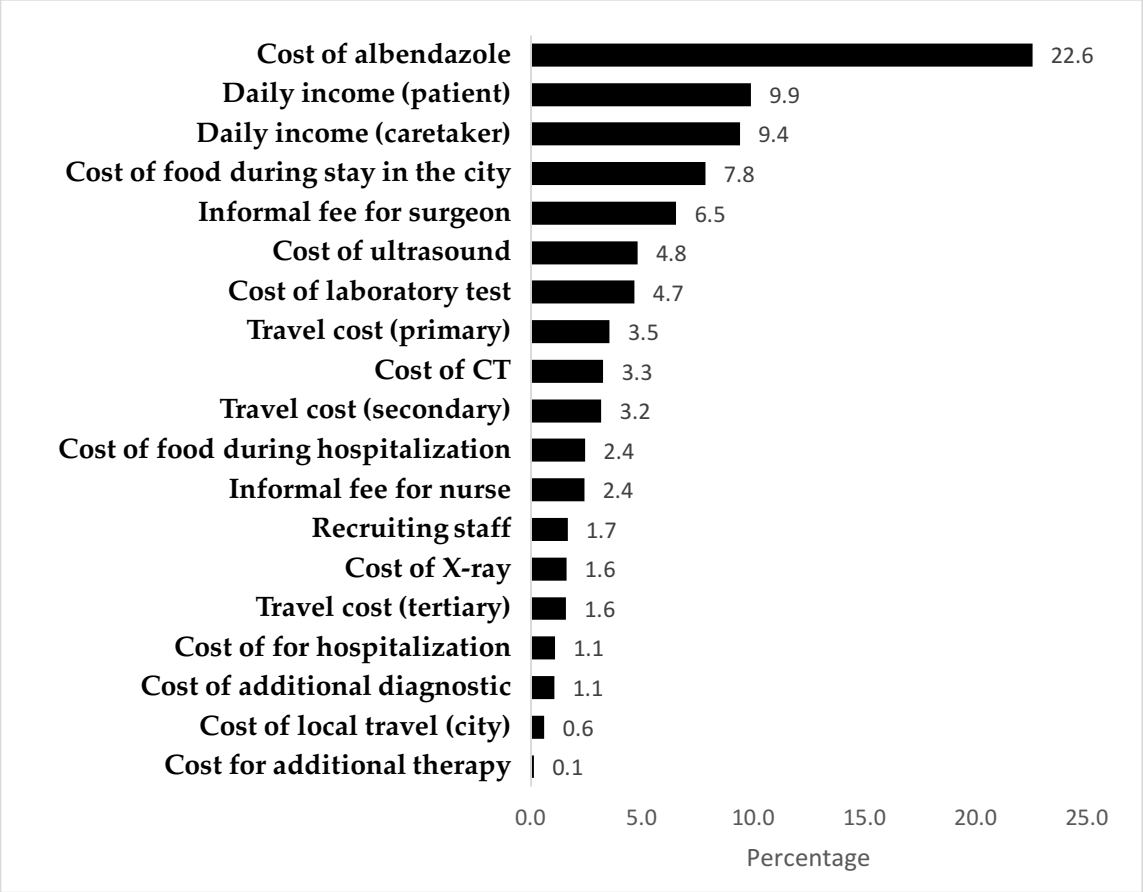

Figure 1. Contribution of different cost items to the total cost

3.5 Discussion

This is the first estimation of the societal cost of human CE in Mongolia. CE is a neglected disease that affects the marginalized population. The disease causes a significant amount of loss to society and household economy. Our results inform decision makers to further develop a strategy to control the disease and prevent the future cost of CE.

The economic loss due to human CE was US$ 2.7 million when accounting the productivity loss, which is equal to 0.024% of the Gross Domestic Product (GDP) of Mongolia. This estimate is slightly smaller than previous estimates in other CE endemic countries which ranged between 0.03-1.5% of GDP (Torgerson et al., 2000; Torgerson et al., 2001; Bingham et al., 2016). One reason may be that the production loss of animals could not be accounted for due to an absence of prevalence data. In

our study, almost 87% of total cost is attributed to the human productivity loss, which is similar to a study in Argentina 77%(Bingham et al., 2016). In the most extreme case, a study in Spain calculated a loss of 133 million when including lost productivity and only 0.9 million otherwise (Benner et al., 2010).

The impact on the household economies is high for surgical cases where an estimated 76% of the direct cost is paid by the patients. A recent report from Mongolia found that 70% of the medical cost for health care in chronic disease was from out-of-pocket and that this proportion increased to 80% for diagnostics (Dugee et al., 2018). Our study provides an example of a catastrophic-health-care-expenditure exceeding the resources of households, which is a major issue in Mongolia and discussed extensively in the public health reports currently (Dugee et al., 2017). According to our estimates, only 10% percent of costs among surgical cases is covered by the public health system. The remaining 90% (US$ 2575) correspond to 70% of the average annual family income. This explains why about half of the patients interviewed reported that they had to take a bank loan while seeking health care. As CE is mostly affecting marginalized populations in rural areas, it contributes to the poverty of Mongolia.

The cost of albendazole had the highest impact on total cost (without productivity loss) (Figure 1). However, in current practice, albendazole is mainly administered to surgical cases so that surgery is the main treatment option at present, offered only by tertiary hospitals. There are two main factors impeding the implementation of albendazole treatment, 1) the lack of a diagnostic algorithm of CE bringing uncertainty to choose the right management, and 2) the high price and limited supply of albendazole. Similar challenges are present in other low-middle-income countries (Bold et al.; Junghanss et al., 2008; Del Carpio et al., 2012; Tamarozzi et al., 2014; Becker et al., 2016). According to our survey, the price of one pill of albendazole equals approximately 20% of the patients' daily income. Also, the availability of albendazole shows large regional differences.

The total case number including undiagnosed cases per year is 1810 which are 60 cases per 100'000 while diagnosed cases are 15 per 100'000. The estimation of the undiagnosed cases was the most challenging part. One strong reason to believe that there are many undiagnosed cases is the high percentage of young children who are hospitalized for CE surgery. On the other hand, among non-surgical cases, older patients were over-represented. While some of the infected persons may be asymptomatic or have only slight symptoms, others may prefer not to seek health care

in order to prevent income and workday loss. One solution would be to invest in percutaneous treatment for CE, which requires shorter hospital stays than open surgery (Junghanss et al., 2008; Brunetti et al., 2010). Moreover, there are promising and implementable tools of telemedicine supporting the decision of patients' referral. There is a great need to conduct community-based surveys to understand the true burden of the disease across all age groups.

The total estimated DALY when including the undiagnosed cases was 11461 as opposed to 3017 for the diagnosed cases only. The studies before 2015 used mainly disability weights (DW's) of liver cancer which are not comparable (Budke et al., 2006; Wang et al., 2012). The most recent studies used different DW's depending on the clinical severity (Counotte et al., 2016). In Kyrgyzstan, for untreated and undiagnosed cases a DW of 0.012 (for hepatic), 0.015 (for pulmonary) and 0.054 (for CNS) was given. For our study, we assumed a lifelong duration of the disease and a DW of 0.123 for all cases, assuming that patients with latent diseases or not seeking health care may suffer the same level of disability. Further studies are needed to estimate the DW's and durations for each CE stage.

We could not estimate YLL due to the unavailability of mortality data for CE. The hospital data in other countries reported fatality rate of 1-2% due to echinococcosis, mostly to surgical complication (Herrador et al., 2016). Number of death due to echinococcosis in Mongolia would be 5-10 if the percentage from previous study was employed. But fatality rate of people going under treatment can be dependent from hospital performance and surgical capacity. We assumed that capacity of surgery and hospital situation in Mongolia is different than other countries mainly due to its low resource. Thus, the mortality estimate from previous studies were not incorporated in our calculation.

An important limitation of the study is that the cost associated with animal loss due to CE is not accounted for. Studies in other countries having considered livestock production loss quantified the percentage of total cost associated with livestock loss to range between 10 and 88% (Moro et al., 2011; Carabin et al., 2014; Singh et al., 2014; Bingham et al., 2016). In Mongolia, livestock agriculture is an important economic source. However, the lack of public slaughterhouses in the country makes it difficult to collect data on animal disease. The inclusion of livestock cost must be one of the next steps.

This study is based on primary data on surgical and non-surgical cases of CE and the related cost. The statistical simulations used should provide a valid estimates within the ranges of uncertainty.

Our result highlights the need for cost-effective control action for CE to prevent high societal cost and burden. Currently, there is no control, and preventive action is taking place in Mongolia regarding CE. There are many preventive strategies potential to be implemented including health education, dog deworming, slaughterhouse improvement and the sheep vaccine which is currently under trial in Argentina and China (Torgerson and Heath, 2003; Gauci et al., 2005; Larrieu et al., 2013). The sheep vaccination combined with dog deworming is estimated to be the most cost-effective on a global scale (Torgerson and Heath, 2003). However, the challenge remains in understanding the transmission dynamics of CE in Mongolia due to lack of information in the animal population.

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3.7 Supplementary material

Table S1. Summary statistics of each parameters used for cost estimation (US$ 1=2000 MNT-Mongolia currency, Tugrik)

	Categories	Mean	SE
Surgical cases			
1	**Direct medical public cost**		
1.1	Unit cost of laboratory test	MNT33,947	MNT2,522
1.2	No. of laboratory tests	2.0	0.3
1.3	Unit cost ultrasound	MNT21,089	MNT861
1.4	No. of ultrasound	3.1	1.0
1.5	Unit cost of X-ray	MNT15,838	MNT411
1.6	No. of X-ray	1.4	0.3
1.7	Unit cost for hospital stay (secondary)	MNT10,000	
1.8	No. of hospital stay (secondary)	7.0	
1.9	Number of hospitalization (secondary)	1.8	0.1
1.10	Unit cost for hospital stay (tertiary)	MNT15,000	
1.11	No. of hospital stay (tertiary)	14.8	0.8
1.12	Number of hospitalization (tertiary)	1.1	0.1
2	**Direct medical private cost**		
2.1	Unit cost of CT	MNT322,057	MNT6,490
2.2	No. of CT	1.0	0.0
2.3	Additional diagnostics	MNT105,625	MNT32,437
2.4	Unit cost of albendazole	MNT4,304	MNT214
2.5	No. of days of albendazole treatment	73.9	8.9
2.6	Cost Supportive drugs/materials	MNT94,286	MNT16,043
2.7	Cost Informal fee for surgeon	MNT572,029	MNT153,494
2.8	Cost Informal fee for nurse	MNT211,429	MNT30,034
2.9	Cost Supportive treatment	MNT263,804	MNT82,783
3	**Non medical out-of-pocket cost (Surgical)**		
3.1	Unit cost of transport (secondary)	MNT15,539	MNT2,892

3.2	No. of hospitalization (secondary)	1.8	0.1
3.3	Unit cost of transport (tertiary)	MNT77,246	MNT9,913
3.4	No. of hospitalization (tertiary)	1.1	0.1
3.5	Unit cost of local transport (city)	MNT5,163	MNT316
3.6	No. of local transport (city)	3.7	0.2
3.7	Unit meal cost (UB stay)	MNT10,065	MNT1,356
3.8	No. of days of stay in UB before surgery	29.6	3.5
3.9	No. of days of stay in UB after surgery	13.9	1.4
3.10	Unit cost of accommodation	MNT15,000	
3.11	Unit cost for meal (in hospital)	MNT8,484	MNT997
3.12	No. of hospital stay	14.8	0.8
4	**Indirect cost**		
4.1	Unit income	MNT19,923	MNT1,158
4.2	No. of stay in UB (patient)	35.9	4.2
4.3	Unit income of caregiver	MNT19,418	MNT2,102
4.4	No. of stay in UB (caregiver)	28.5	2.9
4.5	People recruited for the farm	175000	35355.34
Non-surgical cases			
5	**Direct medical public cost**		
5.1	Unit cost of ultrasound	MNT21,089	MNT861
5.2	No. of ultrasounds	3.1	1.0
5.3	Unit cost X-ray	MNT15,838	MNT411
5.4	No. of X-ray	1.4	0.3
5.5	Unit cost of laboratory test	MNT33,947	MNT2,522
5.6	No. of laboratory tests	2.0	0.3
6	**Direct medical private cost**		
6.1	Unit cost of albendazole	MNT4,304	MNT214
6.2	No. of days albendazole taken	73.9	8.9
7	**Direct non-medical cost**		
7.1	Unit cost of transport (secondary)	MNT15,539	MNT2,892

7.2	No. of hospitalization (secondary)	5.0	1.1
7.3	Unit cost of transport (primary)	MNT3,594	MNT872
7.4	No. of hospitalization (primary)	10.0	
8	**Indirect cost**		
8.1	Unit income (patient)	MNT19,923	MNT1,158
8.2	No. of days of absent from work (patient)	5.0	1.1
8.3	Unit income (caregiver)	MNT19,418	MNT2,102
8.4	No. of days of absent from work (caregiver)	5.0	1.1

Table S2. Background information of the participants (surgical patients)

	n=65	%
Age		
5--15	15	23.10%
16-59	40	61.50%
60<	10	15.40%
Sex		
Female	32	49.20%
Male	33	50.80%
Occupation		
Student	16	24.60%
Herder	16	24.60%
Retired	11	16.90%
Employed	11	16.90%
Unemployed	8	12.30%
Disability	3	4.60%
Education		
Primary	6	9.20%
Middle school	11	16.90%
High school	25	38.50%
University	5	7.70%
Children under 16	16	24.60%

NA	2	3.10%
Hospital of admission		
First National Hospital	40	61.50%
Childrens` Hospital	17	26.20%
Third National Hospital	8	12.30%
Most recent CE surgery		
2016	4	6.20%
2015	20	30.80%
2014	15	23.10%
2013	10	15.40%
2012	8	12.30%
2011	5	7.70%
2010	3	4.50%

Table S3. Socio-Economic-Status of patients`family

SES background	**n=65**	%
Number of members in family		
1--2	9	13.80%
3--5	39	60.00%
6<	17	26.20%
Number of children (under 16 yr old)		
1--2	32	49.20%
3--5	21	32.30%
0	12	18.50%
Number of elderly (over 60 yr old)		
1	17	26.20%
2	5	7.70%
0	43	66.20%
Number of people working		
1	13	20.00%
2	7	10.80%
3	1	1.50%

0	44	67.70%
Number of herders in the family		
1	6	9.20%
2	20	30.80%
0	39	60.00%
Number of people with disability		
1	5	7.70%
2	1	1.50%
0	59	90.80%
Income		
<US$ 150	12	18.50%
US$ 150 - US$ 300	41	63.10%
> US$ 300	12	18.50%
Income source from welfare		
30%	22	33.80%
100%	19	29.20%
10%	12	18.50%
60%	8	12.30%
0%	4	6.20%
Caretaker of the patient		
Parent	20	30.80%
Spouse	12	18.50%
Children	8	12.30%
Siblings	6	9.20%
NA	19	29.20%

4. Evidence for camels *(Camelus bactrianus)* as intermediate host of *Echinococcus granulosus* sensu lato G6/7 in Mongolia

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HELMINTHOLOGY - ORIGINAL PAPER

Evidence for camels (*Camelus bactrianus*) as the main intermediate host of *Echinococcus granulosus* sensu lato G6/G7 in Mongolia

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Abstract

Cystic echinococcosis (CE), the parasitic disease caused by the larval stage of *Echinococcus granulosus* sensu lato (s.l.), is a global public health problem. In Mongolia, despite wide distribution of human CE, not enough information is available on the prevalence and molecular characterization of CE in livestock and its zoonotic linkage with human cases. We investigated the distribution of human CE cases and livestock population using statistical models to get insight into the zoonotic linkage. The incidence of human CE cases increased by a factor of 1.71 for one interquartile range increment in the density of the camel population. No significant association was observed with other livestock species. The samples collected from 96 camels and 15 goats in an endemic region showed a CE prevalence of 19.7% and 6.7%, respectively. All livestock CE were *E. granulosus* s.l. G6/G7 species of the *E. granulosus* s.l. complex. The genetic diversity was investigated using the haplotype network based on full *cox*1 gene analysis of the samples collected from livestock CE and nucleotide sequences previously reported from human CE and wild canids infection in Mongolia. Four haplotypes were identified within the livestock samples, two of which had not been previously reported. A common haplotype was identified among humans, camels, goats, and a wolf, all of which were within the same geographical area. A mixed infection of *E. granulosus* s.l. G6/G7 with different haplotypes in the intermediate host was identified. To the best of our knowledge, this is the most comprehensive description of the current epidemiological situation of CE in Mongolia with substantial evidence that camels might be the main intermediate host of *E. granulosus* s.l. G6/G7 in Mongolia. Moreover, our result presents the first report in the country to provide insight into the prevalence of *E. granulosus* s.l. G6/G7 in livestock.

Keywords *Echinococcus granulosus* s.l. *G6/G7* · Cystic echinococcosis · Camel · Goat · Mongolia

Introduction

Cystic echinococcosis (CE) is the parasitic disease caused by the larval stage of *Echinococcus granulosus* sensu lato (s.l.). The disease burden worldwide is estimated to be 184,000 disability-adjusted life years (DALYs), most of which are from pastoral communities due to their close contact with host animals (Budke et al. 2004; Torgerson et al. 2015). The main

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definitive host of the parasite is the dog when other canids as wolves but also in a lesser extent some felids in Africa may harbor the worms in their intestines (Romig et al. 2017). A wide range of livestock species including sheep, cattle, goats, camels, and pigs may act as intermediate hosts with the presence of hydatid cysts in the liver and/or lungs (Nakao et al. 2013a; Romig et al. 2015).

In Mongolia, nomadic pastoral farmers make up approximately one-third of the population raising more than 60 million livestock including sheep, goats, cattle, and camels, all of which are potential intermediate hosts (NSO 2017; Romig et al. 2017). Dogs are expected to be the predominant definitive host since all farmer family has more than one watch-dog (Gurbadam et al. 2010). Historically, CE prevalence was high in all parts of the country since the early twentieth century (Jezek et al. 1973; Jezek et al. 1971), but with an intensive control program supported by the former Soviet Union, the number of surgical cases decreased from 13% in 1946 to 2% in 1988 in the state hospital (Davaatseren et al. 1995; Ito and Budke 2015). The economic collapse in the 1990s followed by the privatization of veterinary sector hugely influenced the decline of control and prevention of zoonotic diseases in Mongolia (Ebright et al. 2003; Torgerson et al. 2006). In parallel, unregulated private slaughtering practices dramatically increased in rural areas of Mongolia (Gurbadam et al. 2010; McFadden et al. 2016). In slaughterhouses, infected offal is often available and consumed by free-roaming dogs, which is a major factor in perpetuating the CE transmission cycle (Craig et al. 2017). Currently, human CE cases are reported as aggregated data with other surgical diseases; therefore, official data is not available. More recent retrospective studies investigating surgical CE cases, however, reveal that almost half of all cases were children less than 15 years of age, strongly suggesting active transmission in the animal population (Bold et al. 2018).

E. granulosus s.l. is defined as a complex of five cryptic species: *E. granulosus* sensu stricto (s.s.), *Echinococcus felidis* (exclusively in Africa), *Echinococcus equinus*, *Echinococcus ortleppi*, and *Echinococcus canadensis* (Nakao et al. 2013a; Nakao et al. 2013b; Romig et al. 2017; Romig et al. 2015). The taxonomy concerning the latter species is still disputed, as it groups the previous four genotypes and strains: G6 (camel strain), G7 (pig strain), and the two cervid strains G8 and G10. Genetic analyses from mitochondrial genes and some nuclear genes have grouped genotypes G6 and G7 together in the same clade, with differentiation from the other two genotypes (Addy et al. 2017b; Yanagida et al. 2017) potentially regarding these genotypes as two different species (Laurimae et al. 2018a). Thus, the genotypes G6/G7 of *E. canadensis* will be designed here as *E. granulosus* s.l. G6/G7. Worldwide, most human cases (99.5%) are caused by *E. granulosus* s.s. and *E. granulosus* s.l. G6/G7 (Alvarez Rojas et al. 2014), while the species found in human CE cases in Mongolia are *E. granulosus* s.s. and *E. canadensis* (G6/G7 and G10) (Ito et al. 2014; Jabbar et al. 2011; Shirmen et al. 2018). One of the few investigations on the definitive host of *Echinococcus* spp. in Mongolia found wolves infected with *E. canadensis* (G6/G7 and G10) from southern region through wild animal carcass surveys (Ito et al. 2013). There is, however, very limited information for the livestock populations due to the lack of public slaughterhouses and animal surveillance tools in the country (Chinchuluun et al. 2018; Deplazes et al. 2017). To date, there is not enough information on the molecular characterization of *Echinococcus* species causing CE in livestock (Yanagida et al. 2017). As a result, the transmission cycle of CE in Mongolia is largely unknown despite wide distribution of CE in the country. In our study, we provide the first investigation into the zoonotic linkage of CE between humans and animals in Mongolia using epidemiological and molecular approach.

Materials and methods

Data collection of human and animal population

Mongolia has 331 "soums" (smaller administrative unit of province) in 21 provinces and 1 city, Ulaanbaatar. Data on the human population was collected from the National Statistical Office (NSO) for adjustment of CE cases. We collected population data on sheep, camels, goats, and cattle as potential intermediate hosts of CE from the NSO (NSO 2017; Romig et al. 2017). Data were aggregated by livestock species by soum and year with a unit of 1000 heads. For the statistical analysis, the population density of each livestock species (expressed as number of animals per square km) was used as the exposure measure.

Data collection of human cases of CE

Data regarding patients recorded with the diagnosis of CE (ICD code 67.1–67.9) between 2006 and 2016 were extracted from the digital archive of Health Development Center of MoH. We collected information regarding age, sex, registration number, residential province, admission date, hospital name, and received treatment modalities. The analysis was restricted to surgical cases from tertiary-level hospitals, which represent approximately 98% of all surgical CE cases in Mongolia. Human cases of CE subsection were anonymized. The data was aggregated by year and province for further statistical analysis.

Data collection of molecular genetic information of human CE and definitive host

Forty-three CE cases were confirmed previously by histopathology at the National Center of Pathology in Ulaanbaatar (Ito et al. 2014). Among them, 29 cases including 17 children

were caused by *E. granulosus* s.l. G6/G7. Infections by *E. granulosus* s.l. G6/G7 were also diagnosed previously in one wolf each from both Gobi-Altai and Zavkhan provinces, which are in the southwestern part of the country (Ito et al. 2013). As the entire mitochondrial cytochrome c oxidase subunit 1 (*cox*1) was available in GenBank for these human and wolf cases, the corresponding haplotypes were included in the present study in order to obtain a more complete overview of the genetic diversity of *E. granulosus* s.l. G6/G7 in Mongolia.

Biological sample collection from intermediate host

Animal samples from camels and goats were collected from Khurmen and Khankhongor soums of Omnogobi province, which has distance of 330 km from each other. The animals were being processed as part of the normal work of the slaughterhouse. Omnogobi province is located in the Gobi Desert toward the southern part of the country, with a climate ranging from − 20 to − 30 °C in winter and + 30 to + 38 °C in summer. The province has approximately 60,000 people in an area measuring 165,000 km^2. The majority of this area is used for nomadic pastoral farming. The province has 2%, 6%, 0.5%, and 30% of the total sheep, goat, cattle, and camel populations in the country, respectively (Appendix 2) (NSO 2017). Omnogobi was selected for the sampling in this research because according to the previous report, it had the highest number of surgical CE cases (Bold et al. 2018).

Samples were collected from a site in Khankhongor soum and three sites in Khurmen soum in December 2016. November to December is the winter meat preparation period in Mongolia. The camels and goats included in this study were to be used as winter meat storage for the local military. A total of 96 camels and 15 goats from 9 farms were slaughtered under the supervision of a local veterinarian for the meat preparation in winter. All organs of the pleural and abdominal cavities were inspected to determine the presence of hydatid cysts. When cystic lesions were detected, the cyst contents and wall were kept in a tube containing 96% alcohol. Sampling site, animal species, and organ affected were recorded for each sample. The samples were transported to the central laboratory in a portable freezer where it was stored at − 20 °C. After thawing, cyst material was incised with a scalpel. The internal layer of the cyst was applied to an FTA® card for 20 s to impregnate the paper with parasite cells (Boue et al. 2017). The FTA® cards were dried at room temperature for 24 h before shipment to the laboratory (Anses, Malzéville, France) for genetic analysis. One to four hydatid cysts per animal was sampled using the FTA card (Appendix 1).

Statistical analysis

Quantitative variables were described using mean and interquartile range (IQR) and qualitative variables using absolute and relative frequencies. To investigate the link between human CE cases and livestock population, we developed multivariable mixed negative binomial regression models for the total number of cases and the number of cases among children under 15 years of age per province and year. As sheep, goats, cattle, and camels are all potential intermediate hosts, their population densities by province and year were included as predictor variables in the full model. The human population was used as the offset variable to adjust for differences in population size. Random intercepts at the level of provinces were also included in the models to adjust for potential geographic clustering. A potential effect of hospital accessibility on observed counts of CE cases was assessed using an indicator variable for provinces along the railroad. Significant relations were illustrated by a map showing mean surgical incidence at the province level and animal population density at the "soum" level between 2006 and 2016. All analyses and maps were done using the statistical package R v 3.4.0.

Molecular analyses and haplotype network

DNA extraction was performed as previously described using approximately 1 cm square of each impregnated FTA card (Boue et al. 2017). After lysis, the iPrep Charge Switch gDNATissue kit (Invitrogen) was used with the iPrep purification instrument to extract DNA. The entire *cox*1 gene (1608 bp) was sequenced with a nested PCR using two pairs of primers to amplify the gene in one piece (Addy et al. 2017a). The nucleotide sequences were analyzed and aligned using the Vector NTI software program (Invitrogen). A network of the *cox*1 haplotypes was drawn using statistical parsimony with TCS 1.2 software (Clement et al. 2000) and online tcsBU software (Murias dos Santos et al. 2016) to highlight the diversity and relationships among the different haplotypes. The *E. granulosus* s.l. G6/G7 haplotypes of the complete *cox*1 gene from the humans ($n = 29$) and wolves ($n = 2$) identified in Mongolia were added to the haplotype network (Ito et al. 2013; Ito et al. 2014). In order to increase the number of sequences in the haplotype network and to place the Mongolian sequences in a broader geographical context, sequences from 94 samples from 6 intermediate host species originating from 15 different countries obtained by Laurimae et al. (2018b) were added.

Results

Statistical analysis

A total of 446 surgical cases were reported from 2006 to 2016 in Mongolia. The median age of CE cases was 23.0 years (IQR = 10.0–44.7). The percentages of males and females were 44% and 56%, respectively (p value = 0.01). The incidence of surgical cases was 1.4 per 100,000 person years. The

median densities of livestock for sheep, goats, cattle, and camels were 15.3 (IQR 9.36–24.48), 15.0 (IQR 10.76 - 19.92), 1.96 (IQR 1.00–3.76), and 0.10 (IQR 0.04–0.23) per 1 km^2, respectively. Human CE cases were significantly related to camel density in the model with all animal species (Table 1). CE incidence across all ages increased by a factor of 1.71 (1.42–2.04) for an IQR increment in camel density (i.e., 1 camel per 1 km^2) and the respective increase was 2.08 (1.66–2.61), among children under 15 years of age. There were no significant associations between human CE cases and other animal species densities in the first model. In the second model with an indicator variable for provinces with railroad stations, the incidence rate ratio associated with camel density was 1.78 (1.55–2.05) and the negative association with cattle density became statistically significant. Living close to a railroad increased human CE incidence significantly by a factor of 1.6 (1.2–2.1) compared to living farther away from railroads. In provinces without railroad connections, the incidence rate ratio associated with camel density increased to 1.88 (1.61–2.20) while no significant associations were observed with other animal densities.

We also estimated and plotted marginal CE incidence rate as a function of camel population density. The positive association between camel density and human CE cases is illustrated in Fig. 1.

The highest incidences of CE were reported from southern provinces including Omnogobi, Dornogobi, Dundgobi, and Bayankhongor with 7, 3, 4, and 3 cases per 100,000 person years, respectively (Fig. 2). Northern provinces including Arkhangai, Orkhon (a former city), Dornod, and Ulaanbaatar city had the lowest case numbers per 100,000 person years. In parallel, camel population densities were also higher in southern as compared to northern provinces. The highest CE incidence and the highest camel population density were both observed in the province of Omnogobi.

Table 1 Model prediction of human CE cases and livestock density population

Covariates	Estimate[a]	95%LCL	95%UCL	*P* value
Camel density	1.71	1.42	2.04	< 0.0 01
Sheep density	1.13	0.71	1.8	0.61
Cattle density	0.91	0.8	1.03	0.14
Goat density	0.91	0.7	1.18	0.46
Covariates	Estimate[a]	95%LCL	95%UCL	*P* value
Camel density	1.71	1.42	2.04	< 0.0 01
Sheep density	1.13	0.71	1.8	0.61
Cattle density	0.91	0.8	1.03	0.14
Goat density	0.91	0.7	1.18	0.46

LCL lower confidence level, *UCL* upper confidence level

[a] The estimate for the IQR increment in the density of the respective animal population

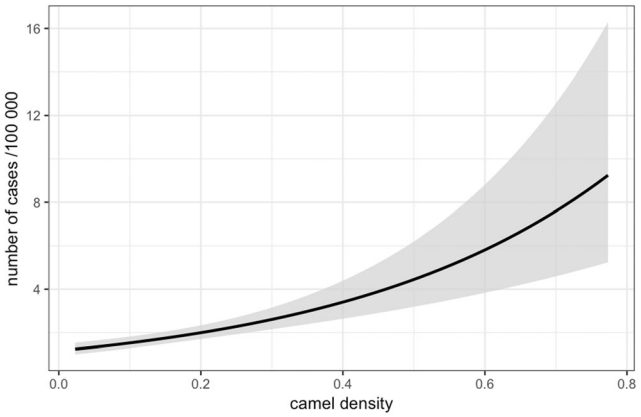

Fig. 1 The predicted incidence of surgical CE cases in humans by camel population density, 2006–2016 (number of camels per 1 km^2)

Molecular genetic analysis

The species *E. granulosus* s.l. G6/G7 was identified in all the 33 FTA samples isolated from 19 camels and 1 goat. The CE prevalence was estimated as 19.7% (CI95% 12.4–29.2%) in camels and 6.7% (CI95% 1.7–32.0%) in goats. The nucleic sequence of the entire *cox1* gene was obtained from 32 samples as only partial results were obtained for one camel sample despite successive assays. Four haplotypes (numbered 1 to 4) were identified with one to four point-mutations (only substitutions) within each other (Appendix 1). Haplotypes 1 and 3 were reported previously in GenBank from the human samples collected in Mongolia (Ito et al. 2014). The haplotypes 2 and 4 had not been reported before. The haplotype 2 is identified as 99% (1607/1608 bp) with haplotypes EcMGL6 from Mongolia and Ec01 from African countries, while haplotype 4 is identified as 99% (1607/1608 bp) with EcMGL15 from Mongolia (Addy et al. 2017b; Ito et al. 2014). As identified in 9 of the 20 infected animals, haplotypes 1 and 2 were the most represented ones, whereas haplotypes 3 and 4 were identified in only three and one animal(s), respectively. The presence of two different haplotypes was observed in two camels with presence of haplotypes 1 and 2 in both cases. The haplotype network reveals a double star-like configuration (Fig. 3), where haplotypes designed as genotype G6 are around haplotype 1 when the haplotypes designed as G7 are hap3, hap4, haplotype 3 and haplotype 4 and those around them. Haplotype 1 identified in this study was previously described in the same species of intermediate hosts (camels, goats, human) from Iran, Argentina, Kenya, Sudan, and Mauritania but also including the haplotype Gmon from a human case of CE in Mongolia. No other correspondence with haplotypes from Laurimae et al. (2018b) was found with haplotypes 2 to 4 described in this study as well as for the haplotypes from human CE cases described by Ito et al. (2014). Concerning only Mongolia, haplotype 1 appears

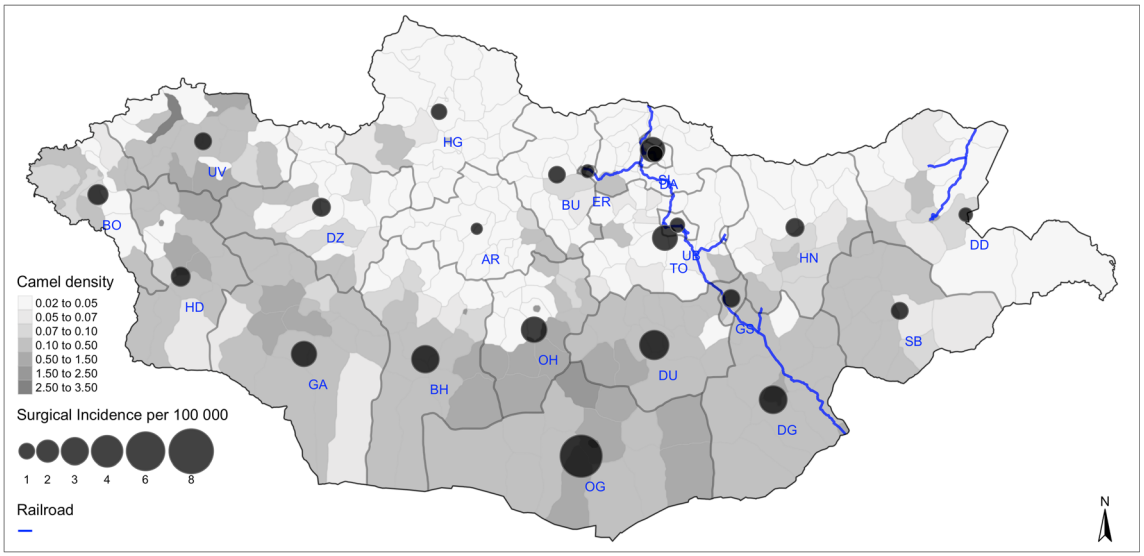

Fig. 2 Geographical distribution of camel density (in number of camels per 1 km^2) and incidence (in number of cases per 100,000 person years). The average camel density between 2006 and 2016 is plotted as base-layer for each soum (gray choropleth). The mean annual incidence of surgical CE cases per 100,000 between 2006 and 2016 is plotted for each province (black circle). Abbreviations of provinces: BO Bayan-Olgii, UV Uvs, HD Khovd, DZ Zavkhan, GA Gobi-Altai, BH Bayankhongor, OH Ovorkhangai, AR Arkhangai, HG Khubsgul, BU Bulgan, DA Darkhan, SL Selenge, ER Orkhon, UB Ulaanbaatar, DU Dundgobi, OG Omnogobi, TO Tov, DG Dornogobi, HN Khentii, DD Dornod, GS Gobisumber, SB Sukhbaatar

to be predominant in Mongolia with identification in camels and humans (corresponding to haplotype EcMGL2 (Ito et al. 2014)), when one of the two wolves as definitive hosts also harbors this haplotype. There are generally few mutations between the different haplotypes from Mongolia (with a maximum of seven), independent of the species and the origin areas of the samples. The haplotype 2 was the most prevalent in camels, along with haplotype 1 which was also found in humans. Haplotype 3 was

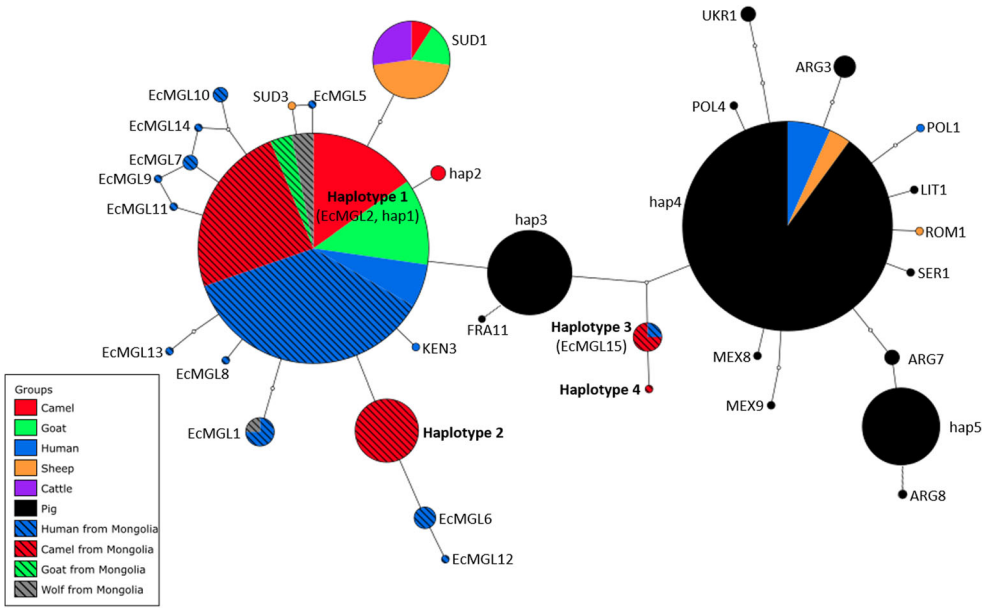

Fig. 3 Haplotype network is based on the full cox1 gene (1608 bp) using statistical parsimony of the *E. canadensis* G6/G7 samples from camels and goats (this study), humans and wolves (Ito et al. 2013; Ito et al. 2014), and 94 samples from 15 countries described by Laurimae et al. 2018b. The worldwide collection composed by G6 samples ($n = 27$) originated from Africa (Sudan, $n = 14$; Kenya, $n = 3$; Mauritania, $n = 2$), Middle East (Iran, $n = 4$), Asia (Mongolia, $n = 1$), and South America (Argentina, $n = 3$). Genotype G7 samples ($n = 67$) originated from Europe (Spain, $n = 1$; France, $n = 27$; Italy, $n = 2$; Serbia, $n = 1$; Romania, $n = 2$; Ukraine, $n = 2$; Poland, $n = 5$; Lithuania, $n = 1$), Central America (Mexico, $n = 10$), and South America (Argentina, $n = 16$). For camels, only one sample per animal was included with the exception of two camels, which harbored two haplotypes. So, one of both haplotypes was retained. Size of the circle is proportional to the number of samples. The smaller white points represent each mutational steps/hypothetical haplotypes

found in camels and in one human case (EcMGL15). The haplotype 4 was identified only in one camel, but it differs from haplotype 3 by only one mutation. In the southern Omnogobi province, where the camels originated, haplotype 1 was identified in camels, goat, and humans (Fig. 4).

Discussion

To the best of our knowledge, the current research provides the most comprehensive description of the current epidemiological situation of both human and livestock CE in Mongolia. An important finding of our study is that we identified the common haplotype among *E. granulosus s.l.* G6/G7 in humans, camels, goats, and a wolf in the same region. This haplotype also corresponds to the main haplotype for G6 identified worldwide by Laurimae et al. (2018b). Our results provide substantial evidence indicating that camels are the main intermediate host of the *E. granulosus s.l.* G6/G7 species of the *E. granulosus* s.l. complex in Mongolia. Moreover, this is the first report from Mongolia that provides insight into the prevalence of *E. granulosus s.l.* G6/G7 in goats and camels, with confirmation of molecular species diagnostic, though the sample size and number of sampling locations needs to be increased. Interestingly, the haplotypes 3 and 4 appear to be more designed as G7 rather than G6 which was more expected. It highlights the interest to analyze additional genes or even the entire mitochondrial genomes as complete *cox1* gene has proved to potentially not correctly differentiate between G6 and G7 genotypes (Laurimae et al. 2018b). In this context, it will be relevant to obtain more genetic information about haplotypes found in Mongolia when the only one sample from this country in the study of Laurimae et al. (2018b) resulted to be highly divergent while it correspond to the main haplotype described in this study using only cox1.

All cases of camel CE were caused by *E. granulosus s.l.* G6/G7. Even more importantly, a common haplotype exists between camels and humans, which is notably the main representative haplotype for both the species and is found in the same geographic area. A maximum of two mutations was identified between the haplotypes from human and animal samples. The two haplotypes M2 and M3 identified in human cases of *E. granulosus* s.l. G6/G7 using short *cox1* sequences from Jabbar et al. (2011) correspond to haplotypes 1 and 2 and haplotypes 3 and 4, respectively, as both pairs are identical for the 363 bp concerned. A higher genetic diversity may be expected in this regard if camels comprised a larger sample, including additional areas, possibly leading to the identification of other shared haplotypes from previously identified human cases, since camels appear to be the main intermediate hosts for *E. granulosus s.l.* G6/G7 in Mongolia. The molecular investigation conducted on human CE cases in Mongolia found that most children cases were caused by the *E. granulosus s.l.* G6/G7 species, while those of adults were caused by both *E. granulosus s.l.* G6/G7 and *E. granulosus* s.s. (Ito et al. 2014; Shirmen et al. 2018). Therefore, our results indicate the importance of camel role in current burden of echinococcosis in Mongolia. However, further research is required to assess the prevalence of CE in sheep and goats, in order to confirm this observation.

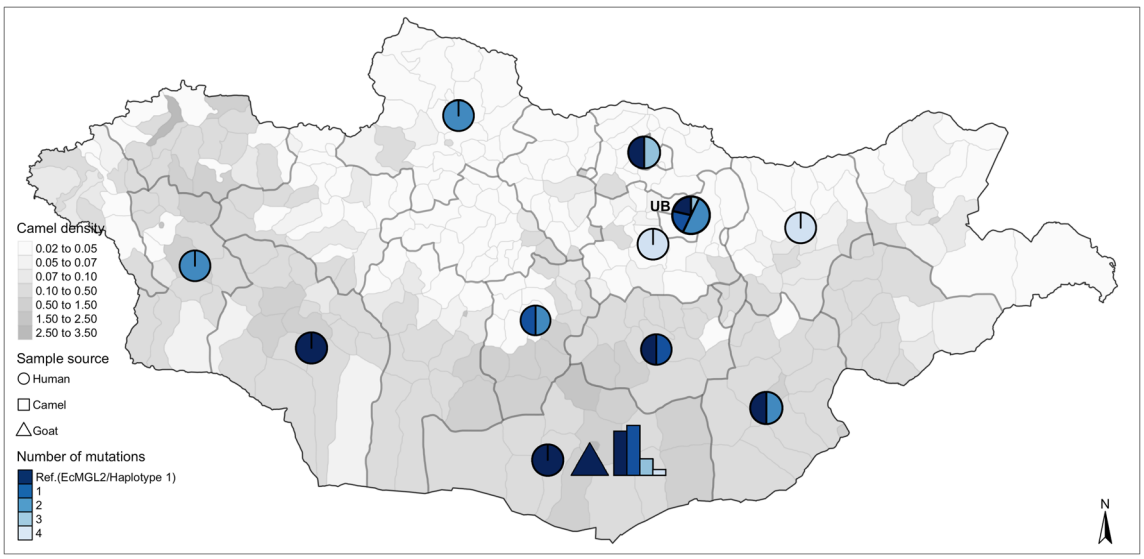

Fig. 4 Geographical distribution of haplotypes of *E. granulosus s.l.* G6/G7 in Mongolia. The average camel density between 2006 and 2016 is plotted as a base-layer for each "soum" (gray choropleth). Distributions of *E. canadensis* G6/G7 from human, camel, and goat cases are presented by pie chart, bar graph (square), and triangle point, respectively. The genetic differences in both human and animal samples are presented by number of mutations (blue color scale) compared to haplotype EcMGL2 (Ito et al. 2014) (haplotype 1 in current study) as a reference. UB Ulaanbaatar, the capital city of Mongolia

This study provides the first report on *E. granulosus s.l.* G6/G7 infection of goats in Mongolia (Deplazes et al. 2017). Goats are the main animals that share pasture with camels in Mongolia (Appendix 2). Our statistical analysis, however, did not find an association between human CE cases and goat population density. Although our results might be suggesting that goats are more of a spillover host for *E. granulosus s.l.* G6/G7, we cannot draw firm conclusions without additional parasite data of CE-infected goats from other southern provinces with a high prevalence of human CE. Further investigation is required to clarify the role of goats in the transmission of CE and *E. granulosus s.l.* G6/G7, including comparisons of the grazing and/or drinking behavior of and ecology among these livestock (Lawson and Gemmell 1983).

Interestingly, in the liver cysts of two camels included in the sample, two different *cox*1 haplotypes (1 and 2) were identified, indicating mixed infections. This could be explained by successive infections, simultaneous infection with eggs from a definitive host harboring worms with both haplotypes, or possibly even contamination of the same area by two definitive hosts harboring worms with different haplotypes. Mixed infection was previously reported for *E. granulosus* s.s. in studies that tested multiple cysts from the same intermediate host, but this occurs infrequently (Boufana et al. 2014; Casulli et al. 2012; Umhang et al. 2014; Umhang et al. 2013). To the best of our knowledge, this is the first time that the presence of mixed infections of *E. granulosus s.l.* G6/G7 with different haplotypes has been confirmed in the intermediate host. These mixed infections involve the two most frequent haplotypes identified in the camels described here (Appendix 1).

We identified the common haplotype in one of the two wolves which were previously described (Ito et al. 2013). There might be marked differences concerning the accessibility of intermediate hosts' offal, for definitive hosts to be infected. Camel offal is more likely to be left in the field during the slaughtering process owing to its large volume and can become accessible to wild canids and stray dogs, whereas offal from small ruminants would be collected by the herders to feed their own dogs. Another consideration is that the previously reported human CE samples were collected in 2009, while our field survey was conducted in 2016, which might also highlight consistency regarding the source of infection in the same geographic region.

We were unable to consider infections in dogs due to the absence of existing data. Every rural family has at least one to two watch-dogs. In particular, the children in these rural areas are highly exposed to dogs, as discussed in the national stakeholder meetings (Gurbadam et al. 2010). A nationwide surveying of dogs and livestock remains an urgent task to gain an overview of the current CE endemicity in Mongolia. While *E. granulosus* s.s. is a still an important agent in Mongolia, in areas with high camel density, the presence of *E. granulosus s.l.* G6/G7 needs to be considered as an equally significant threat to public health, especially for children. The insights provided by this paper suggest that priority interventions should aim at affecting behavioral change by improving hand hygiene, proper disposal of offal at home, private slaughtering, and deworming of dogs.

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Compliance with ethical standards

Ethics statement This work presented here was approved by the Medical Ethics committee of Mongolia (July 2014) and WHO ERC (27 Nov 2015).

Ethical approval The animals were being processed as part of the normal work of the abattoir. The routine investigation of local veterinary office on animal carcass do not require ethical approval in Mongolia.

Conflict of interest The authors declare that there is no conflict of interest.

Research data Statistical data of hospital discharge is available upon request from the National Center for Zoonotic Disease (NCZD). The director of NCZD, Dr. Tsogbadrakh Nyamdorj, is the point of contact. Email address is: tsogbadrakh@nczd.gov.mn.

All relevant data regarding animal sample is within the manuscript and its Supporting Information files.

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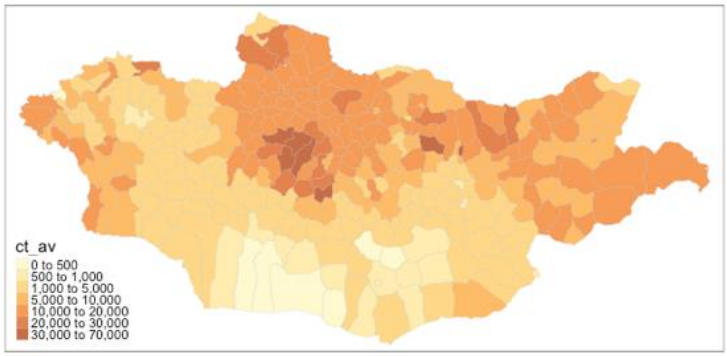
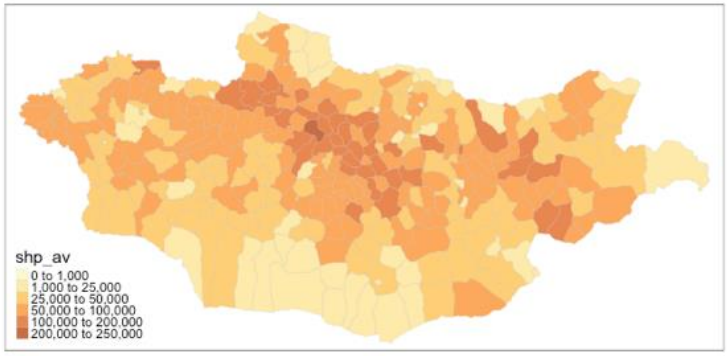
Appendix 1. List of samples according to animal species, organ and geographical origin. The complete *cox1* haplotype of *E. granulosus* s.l. G6-7 is indicated with detail for each cyst sampled when two different haplotypes were identified.

N	Animal species	geographical origin		number of cysts sampled	organ infected	complete *cox1* haplotype
		Province	Soum*			
1	Camel	Khurmen	Khuren zaw	1	liver	4
2	Camel	Khurmen	Khuren zaw	1	liver	2
3	Camel	Khurmen	Khuren zaw	2	liver	2
4	Camel	Khurmen	Khadan us	1	liver	2
5	Camel	Khurmen	Khadan us	3	liver	2
6	Camel	Khurmen	Khadan us	4	liver	1 (n=1), 2 (n=3)
7	Camel	Khurmen	Khadan us	2	liver	1 (n=1),2 (n=1)
8	Camel	Khurmen	Khadan us	2	lungs	1
9	Camel	Khurmen	Khadan us	1	liver	2
10	Camel	Khurmen	Khadan us	1	lungs	2
11	Camel	Khurmen	Khadan us	2	lungs	3
12	Camel	Khurmen	1r bag	1	liver	1
13	Camel	Khurmen	1r bag	1	liver	2
14	Camel	Khurmen	1r bag	2	liver	3
15	Camel	Khurmen	1r bag	1	liver	1
16	Camel	Khurmen	1r bag	1	liver	1
17	Camel	Khurmen	1r bag	2	lungs	1
19	Camel	Khurmen	NA	1	liver	3
20	Camel	Khurmen	NA	1	liver	1
18	Goat	Khankhongor	Bumbat	2	liver	1

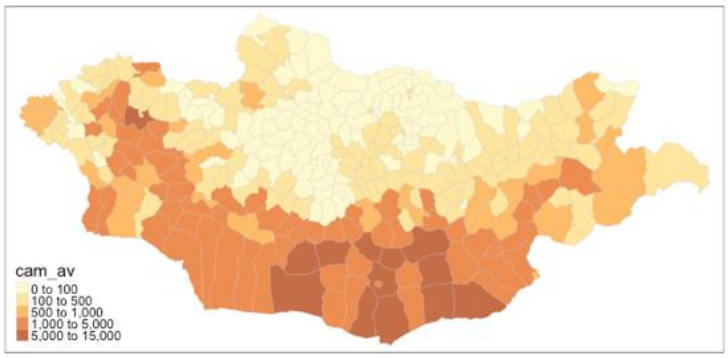
Appendix 2. Geographical distribution of cattle, sheep, camel, goat in Mongolia (average between 2006-2016)



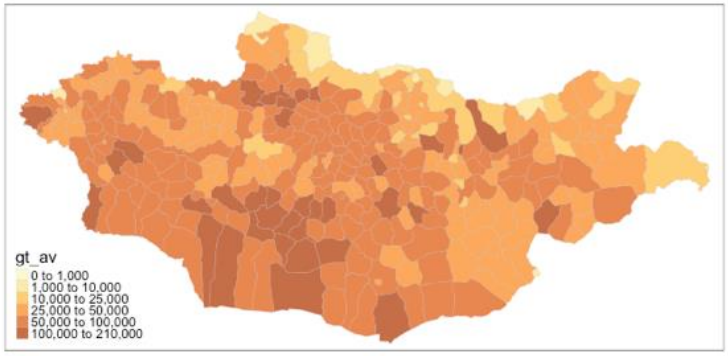
Cattle



Sheep



Camel



Goat

5. Patients with cystic echinococcosis in the three national referral centers of Mongolia: a model for CE management assessment

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RESEARCH ARTICLE

Patients with cystic echinococcosis in the three national referral centers of Mongolia: A model for CE management assessment

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Abstract

Background

Mongolia is one of the endemic countries for cystic echinococcosis (CE), a zoonotic disease caused by the larval stage of *Echinococcus granulosus*. The goal of this study is to describe the current clinical management of CE in Mongolia, to capture the distribution of cyst stages of patients treated, and to contrast current practice with WHO-IWGE expert consensus.

Methods

Hospital records of CE patients treated between 2008 and 2015 at the three state hospitals and fulfilling the inclusion criterion 'discharge diagnosis CE' (ICD 10 code B.67.0–67.9) were reviewed. Demographical, geographical, clinical and ultrasonography (US) data were extracted and analyzed. The annual surgical incidence was estimated. The digital copies of US cyst images were independently staged by three international experts following the WHO CE cyst classification to determine the proportions of patients which ideally would have been assigned to the WHO recommended treatment modalities surgery, percutaneous, medical (benzimidazole) treatment and watch & wait.

Results

A total of 290 patient records fulfilled the inclusion criteria of the study. 45.7% of patients were below 15 years of age. 73.7% of CE cysts were located in abdominal organs, predominantly liver. US images of 84 patients were staged and assessed for interrater-agreement. The average raw agreement was 77.2%. Unweighted Kappa coefficient and weighted Kappa was 0.57 and 0.59, respectively. Mean proportions of images judged as stages CE1, CE2, CE3a, CE3b, CE4 and CL were 0.59, 0.01, 0.19, 0.08, 0.03 and 0.11, respectively. 40 cysts met the inclusion criteria of treatment modality analysis. The mean proportions of

Tropical Diseases (WHO/TDR), Impact Grant 2014-B4013, http://www.who.int/tdr/news/2015/impact-grant/en/. Initial part of data collection received financial support from the World Bank/Capacity Building for Emerging Infectious Disease Preparedness Project which implemented in Mongolia (project ID: P131204), http://projects.worldbank.org/P131204/capacity-builiding-emerging-infectious-disease-preparedness?lang=en&tab=overview. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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cases with a single cyst assigned to medical, percutaneous treatment, surgery and watch & wait were 52.5% (95% CI 42–65), 25.8% (95% CI 15–30), 5.1% (95% CI 0–10) and 3.3% (95% CI 0–10), respectively. 13.3% (95% CI 5–25) of cysts were staged as CL and therefore assigned to further diagnostic requirement.

Conclusion

WHO CE cyst classification and WHO-IWGE expert consensus on clinical CE management is not implemented in Mongolia. This results in exclusively surgical treatment, an unnecessary high risk approach for the majority of patients who could receive medical, percutaneous treatment or observation (watch & wait). Introduction of WHO-IWGE expert consensus and training in ultrasound CE cyst staging would be highly beneficial for patients and the health care services.

Author summary

Cystic Echinococcosis (CE) is a zoonotic disease, commonly known as dog tapeworm. The disease is distributed globally and predominantly affects rural populations with limited access to health care. Following the expert consensus of the WHO-Informal Working Group on Echinococcosis (WHO—IWGE) patients with uncomplicated cysts are assigned on the basis of WHO cyst classification to four treatment modalities: medical (benzimidazoles), percutaneous, surgical treatment, and 'watch & wait'. In Mongolia, one third of the population practices nomadic farming. These populations are heavily affected by CE. However, cyst staging and WHO-IWGE recommendations are not implemented and patients referred to the three national treatment centres receive surgical treatment. This exposes a large proportion of patients to an unnecessary high risk approach who could be treated–depending on cyst stage—with benzimidazoles, percutaneously or observed (watch & wait). We reviewed the hospital records of patients with CE and admitted between 2008 and 2015 to the three national CE treatment centres, retrospectively staged the cysts and assigned the patients to the four WHO-IWGE recommended treatment modalities. We found a high proportion of patients in the study population who would have most likely benefitted from non-surgical treatment options.

Introduction

Cystic echinococcosis (CE) is a zoonotic disease caused by the larval stage of *Echinococcus granulosus*. The life cycle of *E. granulosus* is maintained between the dog as the definitive host and various livestock as the intermediate host. Humans are considered as an aberrant intermediate host. Ingested larvae develop into cystic lesions, mostly in the liver and lung [1]. The disease is globally distributed including Central Asian countries and China [2–4]. The annual global burden of disease is estimated at 184,000 Disability Adjusted Life Years (DALYs) [5, 6]. Due to a large proportion of asymptomatic cases and underreporting the disease burden is widely underestimated. Pastoral communities in countries with limited resources bear the greatest burden [3, 5, 7].

In Mongolia, one-third of the population is engaged in extensive pastoral farming. The presence of a large livestock population accompanied by watchdogs, a big number of stray

dogs, unregulated private slaughtering, and lack of health education are the main reasons for the heavy human CE exposure [8, 9]. Historically, due to strong public and veterinary action, the surgical cases decreased from 13% in 1946 to 2% in 1988 in the state hospital [10, 11]. After the Soviet Union collapsed in 1990, the veterinary and public health sectors weakened and many control programs for zoonotic disease, including CE, collapsed [12]. Currently, CE is not included in the national surveillance system, and official statistics are, therefore, unavailable [8, 9, 13]. There are few reports on the current transmission of CE in Mongolia including small scale serological surveys, hampered, however, by the sensitivity and specificity problems of serological CE testing [11, 14–18].

CE predominantly affects rural populations with very limited access to health care [19]. Diagnosis, cyst staging, treatment and follow-up depend on imaging [20, 21]. Ultrasonography, however, is only recently introduced in low and lower middle income countries (LICs and LMICs)[22–24]. Thus most endemic countries, including Mongolia, have not yet implemented the WHO Informal Working Group on Echinococcosis (WHO-IWGE) expert consensus [25, 26]. The core piece of the WHO-IWGE expert consensus is to triage on the basis of ultrasound-defined cyst stages into four groups: medical, percutaneous, surgical treatment (active cyst stage CE1 to CE3b) and 'watch & wait' (inactive cyst stages CE4 and CE5) [20, 27–30].

The goal of this study is to describe the current clinical management of CE in Mongolia, to capture the distribution of cyst stages retrospectively from stored ultrasound images, to critically contrast current practice in Mongolia with WHO-IWGE expert consensus and to suggest a LIC / LMICs-adapted implementation strategy for WHO-IWGE expert consensus.

Materials and method

Ethics statement

This work presented here was approved by the Medical Ethics committee of Mongolia (July 2014) and WHO ERC (27 Nov 2015).

Study area and data collection

We reviewed the hospital records of patients diagnosed with CE and admitted between 2008 and 2015 to the three state hospitals conducting CE surgery in Mongolia: First Central Hospital (FCH), Third Central Hospital (TCH), National Center for Maternal and Child Health (NCMCH). Patients identified as probable CE cases in the peripheral or secondary hospitals are, as a rule, referred to the three state hospitals for confirmation and surgery. In the archives of the state hospitals, the medical records are chronologically stored in bundles of 150–200 reports. On the front page of each record the discharge diagnosis is recorded by the surgeon, based on histopathology which is done as a routine in the national hospitals. The 'discharge diagnosis CE' (ICD 10 code B.67.0–67.9) was the inclusion criteria for our study.

The following data were extracted from the patient records on data extraction sheets: demographic and geographic data (specified in Table 1), clinical symptoms and signs, ultrasonography (US) reports including number and size of cysts, US images, surgical reports and final diagnosis. US images (photos) were digitalized and stored. The data collected on data extraction sheets were double entered into a data base.

Data analysis

The demographic information including age, sex, occupation, type of home, and distance from health care was presented with the relevant percentage. The distance between secondary

Table 1. Demography, socio-economic status (SES) and geographical data of the patients.

Patient characteristics	Frequency	
	n	%
Age		
<14	113	45.7
15–59	116	47.0
>60	18	7.3
Total	***247***	***100***
Sex		
Male	116	47.0
Female	131	53.0
Total	***247***	***100***
Occupation		
Paid employee	42	34.4
Self-employed	16	13.1
Employed in animal husbandry	12	9.8
Unemployed/retired/disabled	52	42.6
Total	***122****	***100***
Distance from secondary level hospital		
<100 km	107	62.2
100 km-200 km	53	30.8
>200 km	12	6.9
Total	***172****	***100***
Type of home		
Apartment	47	19.0
Yurt	200	81.0
Total	***247***	***100***

*- 60 pediatric cases and 65 cases without information on employment were excluded from calculating the percentage of occupation.

**- 60 cases from Ulaanbaatar city and 15 cases without an exact address were excluded from calculating the percentage of distance

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hospital (provincial general hospital) and current address of the patient was calculated. The levels of the clinical care in Mongolia are provided in Fig A in S1 Appendix.

The socio-economic status (SES) in the adult patients was stratified according to the labour force category of the National Statistical Office [31]. The current address of the patient was used to plot the geographical distribution by employing the ArcGIS 10.0 (ESRI 2011. ArcGIS Desktop: Release 10. Redlands, CA: Environmental Systems Research Institute). The annual surgical incidence was estimated based on the hospital records. The frequency of the clinical signs & symptoms was calculated. The size and number of CE cysts were presented in three different categories, <5 cm, 5–10 cm, and >10 cm and single cyst, 1–3 cysts, and multiple cysts, respectively.

The digital copies of US cyst images were independently reviewed by three international experts (reviewers) to estimate the frequency distribution of cyst stages according to WHO cyst classification (CL, CE1, CE2, CE3a, CE3b, CE4, CE5) in the patient population referred to the state hospitals for confirmatory assessment and treatment. The exercise was performed on the US images of abdominal lesions. The experts received no further information about the patients. Duplicate images of cysts were provided when available. If the reviewer felt unable to

stage a cyst, e.g. because of poor quality of an image, the cyst was classified 'not identifiable' (NI). After the assessment, exclusions were made on the double images. If a double image of a cyst was assessed identical by the reviewers, we selected randomly one of the images. If a double image was assessed not identical by the reviewers, the one with fewer "NI" votes was selected to represent the cyst. Interrater-agreement was calculated using the Kappa statistic. Raw agreement was calculated as the proportion of cysts where the raters noted the same stage and kappa statistics for ordered categories (CL, CE1, CE2, CE3a, CE3b, CE4, CE5). We report both, unweighted and weighted kappa statistics with weights calculated as the square of the distance between the two ordinal groups. We judged agreement as poor if $\kappa < 0.2$; fair if $0.2 \leq \kappa < 0.4$; moderate if $0.4 \leq \kappa < 0.6$; substantial if $0.6 \leq \kappa < 0.8$; and good if $\kappa \geq 0.8$. The estimates represent the arithmetic mean of the 3 pair-wise comparisons. "NI" judgements were considered as missing values which have been excluded pair-wise for raw agreement and kappa estimation.

Allocation of the cysts to WHO recommended treatment modalities was performed on the basis of cyst staging by the 3 reviewers and cyst size. Cases with images assessed as "NI" by all three reviewers were excluded; equally, cases with more than one cyst since completeness and ascertainment of US images was difficult retrospectively. The double images were excluded using the same algorithm as in the analysis of interrater-agreement. We calculated combinations of CE stage and cyst size for all three reviewer assessments separately and calculated the mean percentage. Based on this combination, the probability of assignment of cases to the treatment modalities as defined by the WHO-IWGE expert consensus were estimated for each case. Assignment of cysts to WHO recommended treatment modalities was performed as if all cysts were uncomplicated since the retrospective data did not allow to reliably differentiate complicated from uncomplicated cysts. Bootstrap resampling with 10,000 replicates was used for estimating the 95% confidence intervals for the treatment options. The analysis was conducted using the statistical package R v 3.4.0.

Results

A total of 290 medical records fulfilled the inclusion criterion 'discharge diagnosis CE' (ICD 10 code B.67.0–67.9) of the patients admitted to the three state hospitals between 2008 and 2015, 43 records were excluded. For details see Fig 1.

The demographic data are presented in Table 1.

During the period 2008–2015, the average annual CE surgical incidence per 100 000 was 1.06 (95% CI 0.7–1.4) based on the current data collection. On average 30.8 (95% CI 20.4–41.3) cases per annum underwent CE surgery in the central hospitals between 2008 and 2015 (Fig B in S1 Appendix).

The patients originated from 20 provinces corresponding to 95% (20/21) of all provinces (Fig 2). The southern provinces Omnogobi (OG), Dundgobi (DU), and Bayankhongor (BH) have the highest number of cases. Average CE surgical incidence for the survey period in these provinces was 2.7–6.1 per 100 000 inhabitants based on the medical records in the three state hospitals.

The frequency of symptoms & signs in CE patients at admission to the three state hospitals are provided in Fig C in S1 Appendix. The location of CE cysts of the surgically treated patients at the three state hospitals between 2008 and 2015 are provided in Fig D in S1 Appendix.

Preoperative ultrasound reports were available in 83.5% (152/182) of patients who had undergone abdominal surgery for CE. 26.3% (40/152) were explicitly recorded as hydatid cysts, 54.6% (83/152) as cystic lesions, and 19% (29/152) as other space occupying lesions. 99.3% (151/152) of the abdominal cases had the information on the cyst number in the US

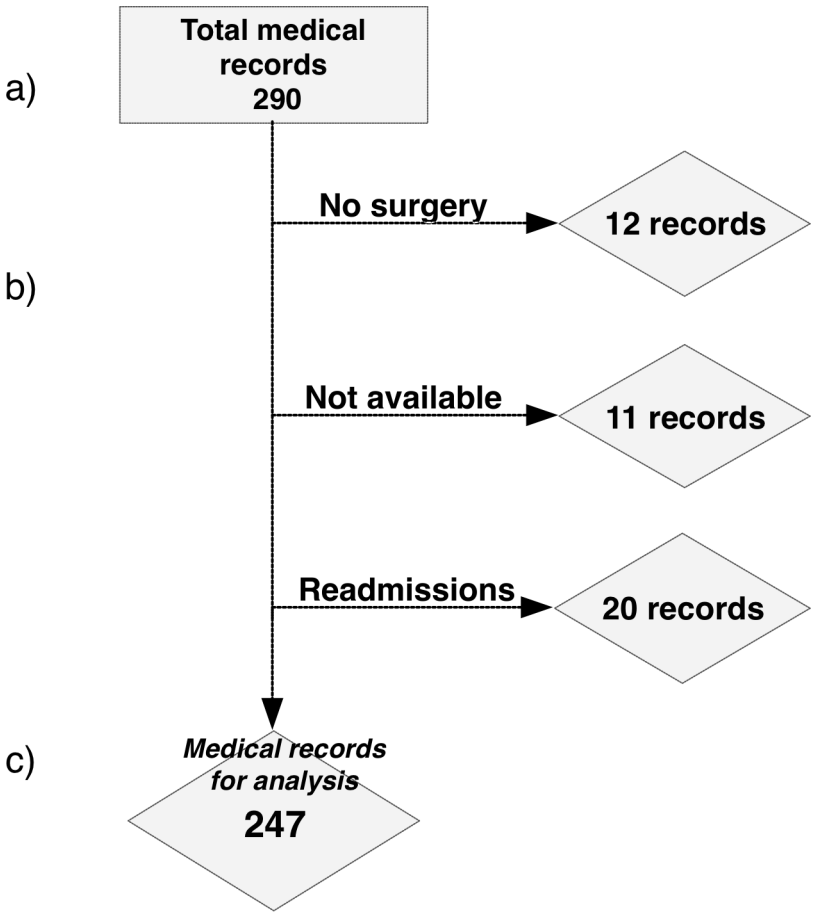

Fig 1. Selection of CE surgical case records. (a) 290 records (patients) in the 3 state hospitals in Mongolia fulfilled the inclusion criterion 'discharge diagnosis CE' (ICD 10 code B.67.0–67.9); (b) 12 records (patients) were excluded because the patients have not been operated on (4 surgeries postponed, 3 post-surgical conditions, 4 calcified cysts not needing surgery, 1 no information), 11 because of missing surgical information, 20 records belonged to 15 patients who were re-admitted once or twice; (c) 247 cases were analyzed.

https://doi.org/10.1371/journal.pntd.0006686.g001

record. Among them, 78.1% (118/151) had single cysts, 20% (31/151) had 1–3 cysts and 1.3% (2/151) had more than 3 cysts. The information on size was available for 90.1% (137/152) of the abdominal cases. Among them, 48.9% (67/137) had cysts smaller than 5 cm, 35.0% (48/137) of 5–10 cm and 16.1% (22/137) were bigger than 10 cm.

138 US imaging photos of 84 cases with liver and abdominal cysts were available for review and CE cyst staging based on the WHO CE cyst classification by three international reviewers. Following the inclusion / exclusion procedures described in the method section images of 84 unique cysts were assessed for interrater-agreement analysis. The raw agreement was 77.2%. We observed substantial agreement with an average unweighted Kappa coefficient of 0.57 and an average weighted Kappa coefficient of 0.59 (squared weights). The proportions of CE cyst stages are shown in Fig 3. Mean proportion for CE stages including CE1, CE2, CE3a, CE3b, CE4, and CL were 0.59, 0.01, 0.19, 0.08, 0.03 and 0.11, respectively. No CE5 cysts were identified.

Of the cysts staged by the three reviewers, 40 met the inclusion criteria for the treatment modality analysis (selection process see methodology section). The mean proportion of cases assigned to medical treatment, percutaneous treatment, surgery and watch & wait was

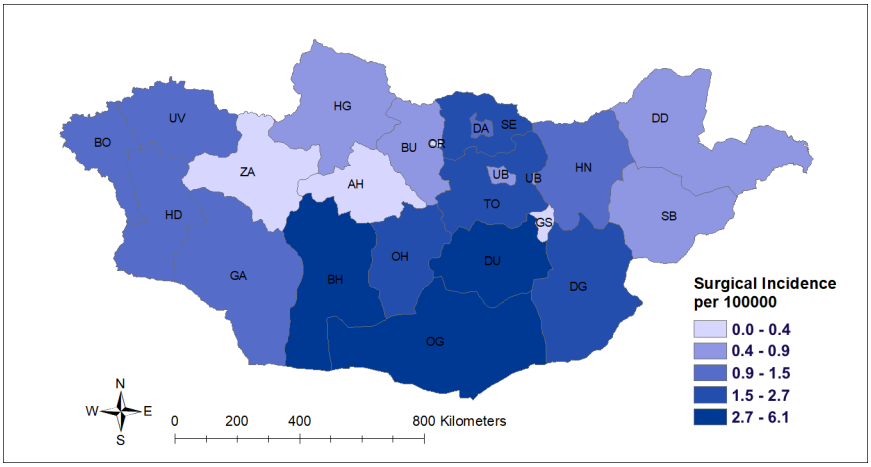

Fig 2. Average CE surgical incidence in each province for the period 2008–2015. Abbreviations: BO-Bayan-Olgii, UV-Uvs, HD-Khovd, ZA-Zavkhan, GA-Gobi-Altai, BH-Bayankhongor, OH-Ovorkhangai, AH- Arkhangai, HG-Khubsgul, BU-Bulgan, DA-Darkhan, SE-Selenge, ER- Orkhon, UB-Ulaanbaatar, DU-Dundgobi, OG-Omnogobi, TO- Tov, DG-Dornogobi, HN-Khentii, DD-Dornod, GS-Gobisumber., SB-Sukhbaatar.

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calculated as 52.5% (95% CI 42–65), 25.8% (95% CI 15–30), 5.1% (95% CI 0–10) and 3.3% (95% CI 0–10), respectively. 13.3% (95% CI 5–25) of the cysts were staged as CL in need for further diagnostic work up (Fig 4).

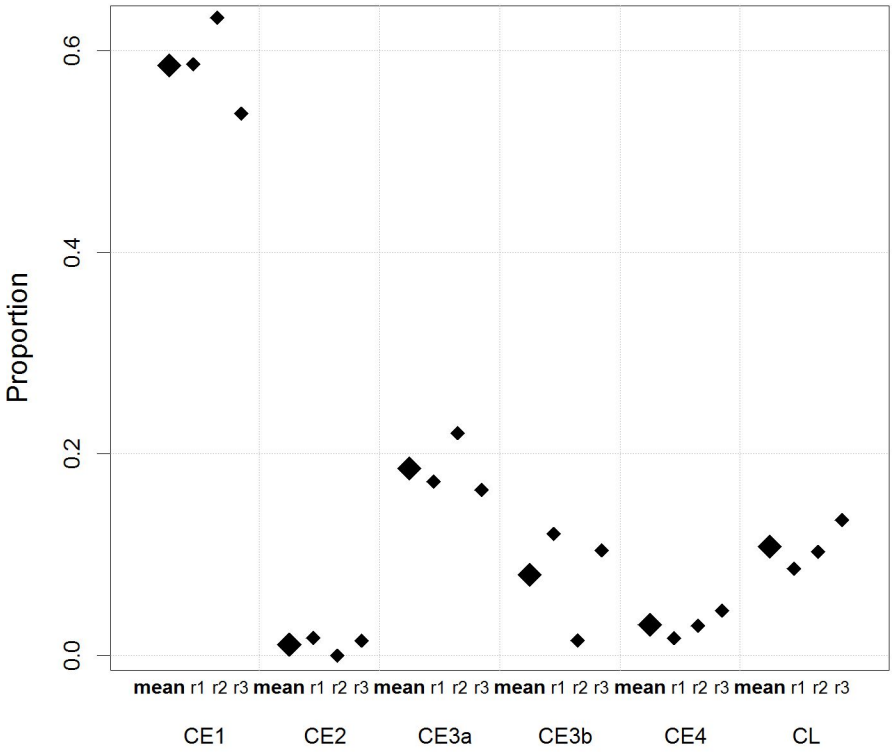

Fig 3. Distribution of CE cyst stages on the basis of the WHO CE cyst classification. The average proportions (big diamond) of CE cyst stages staged on the basis of the WHO CE cyst classification by the three experts. r1, r2, r3 are the proportions (small diamonds) of CE cyst stages classified by the expert 1, 2, and 3, respectively.

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A

CE stage	Size <5cm	5-10cm	>10cm
CE1	45.0%	18.3%	1.7%
CE3a	5.0%	7.5%	0.0%
CE3b	2.5%	1.7%	1.7%
CE4	2.5%	0.0%	0.8%
CL	10.8%	2.5%	0.0%

B

Treatment	N	% (95% CI)
Surgery	2.0	5.1(0-10)
Percutaneous treatment	10.3	25.8(15-30)
Albendazole	21.0	52.5(42-65)
Watch&Wait	1.3	3.3(0-10)
Further	5.3	13.3(5-25)

Fig 4. Assignment of CE cysts of the study population to WHO-IWGE recommended treatment modalities on the basis of retrospective cyst staging by three international experts. In uncomplicated CE cysts WHO-IWGE recommended assignment of patients to the four treatment modalities surgery, percutaneous methods, drug treatment (albendazole, mebendazole) and watch & wait is based on cysts stage and size (three groups). **A** Three size groups and the average percentages of WHO cysts stages in the study population as retrospectively staged by three international reviewers. Although there was a small percentage (1%) of CE2 identified by the three reviewers (Fig 3) this stage could not be included into the analysis because the information on cyst size was lacking. CE5 was excluded since none of the reviewers attributed one of the cysts presented for retrospective staging to CE5. **B** Based on the matrix in A, the probability of assignment of patients to the WHO-IWGE recommended treatment modalities is presented. The grey shading of the cells in A and B matrices correspond to each other. Cysts staged as CL would have needed further diagnostic work up.

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Discussion

To the best of our knowledge this is the first description of the clinical management of CE patients in LICs / LMICs with an attempt to critically contrast current national practice with the WHO-IWGE expert consensus [20] on the basis of interrater-agreement calculated from the retrospective cyst staging by three independent experts. Mongolia offers the unique opportunity for this exercise for two reasons. CE patients identified on the peripheral level of the health care services are exclusively referred for confirmation and treatment to the three state hospitals where patient records are carefully stored in archives with a discharge diagnosis on the front page of each patient file. The data of 290 patients with the 'discharge diagnosis CE' (ICD 10 code B.67.0–67.9) admitted between 2008 and 2015 were available to characterize the CE patients who currently receive treatment in Mongolia. Ultrasound photos of 46% (84/182) of patients with abdominal cysts were available for retrospective cyst staging on the basis of WHO CE cyst classification by three international experts. Based on the retrospective staging result and size, proportions of assignment to WHO-IWGE recommended treatment modalities were estimated.

The socio-demographic characteristics of the study population receiving treatment at the three state hospitals show some interesting features. Around 50% of the patients are below 15 years of age. In Kazakhstan and Kyrgyzstan, countries in the same region as Mongolia and with a similar pastoral lifestyle, also reported high proportion of children among the surgical cases [3]. Equal proportions of male and female patients suggest that, understandably, the infection risk is equal with CE transmitted in a food borne dog faecal-human oral cycle. Distance to the secondary hospital is a relevant factor for access to specialized health care in all LICs and most MICs [32, 33]. About 40% of the surgical patients had to travel at least 100 km to reach the secondary hospitals. Besides the geographic barrier other factors might contribute to underreporting but currently no data are available. 80% of the patients are living in a "yurt"

which suggest that these patients are exposed to the combination of poor infrastructure, poor water and sanitation and frequent contact with watch-dogs and their faeces [34, 35].

A significant proportion of patients presented with non-specific symptoms, around 20% with abdominal pain corresponding to 29% of the patients with abdominal cysts. Around 16.6%, 8.5% and 6.9% of all patients had cough, chest pain and dyspnoea, respectively. This amounts to 50%, 32%, and 14%, respectively, of patients with lung cyst. These results are in line with the clinical experience that most patients present with non-specific symptoms and signs [36]. Fever, observed in 22.3% of all admissions, may, however, indicate that some patients had complication such as a cysto-biliary fistula with secondary bacterial infection of the cyst or cholangitis associated with biliary obstruction due to spillage of cyst content into the biliary tree; the latter also causes abdominal pain [37]. Similarly, patients with lung cysts may have had fever due to pneumonia following bronchial compression caused by expanding cysts or secondary bacterial infection of the residual cavity after the cyst content has been expectorated via a cysto-bronchial fistula. Both complications are associated with cough and dyspnoea [38]. Care should be exercised, however, to not over interpret retrospectively non-specific signs and symptoms such as fever, documented in medical records.

Most patients had only a single cyst in abdominal organs of which almost 50% had a diameter equal or smaller than 5 cm. This alone casts doubts on the indication for major surgery. If uncomplicated, these cysts would—following the WHO-IWGE expert consensus—either fall in the medical treatment group, if active (CE1 to CE3), or the watch & wait group, if inactive (CE4 and 5).

Only 40 reports of the 182 abdominal cysts examined by ultrasound spelled out "hydatid cyst" as the US diagnosis, without, however, mentioning accepted US criteria and without an attempt to stage with the WHO-IWGE or Gharbi classification.

The most exciting part of this data set was the unique opportunity to review and retrospectively stage 138 US imaging photos of 84 patients by three international experts to compare current practice in Mongolia with WHO recommended treatment modalities [20]. The distribution of WHO cyst stages retrospectively analysed from a subset of patients treated between 2008 and 2015 at the three state hospitals in Mongolia showed proportions of 0.59, 0.01, 0.19, 0.08, 0.03 and 0.11 for CE1, CE2, CE3a, CE3b, CE4, and CL, respectively (see Fig 3). Given the relatively high number of categories, the observed raw agreement of about 80% and Kappa coefficients of close to 0.6 indicate that the method appears to be generally valid but with room for improvement. A similar result was found in a recent study assessing interrater-agreement of the WHO cyst classification based on 2-D US images. The authors emphasized that an improvement can be achieved when non-static imaging (video recording etc.) is incorporated in future studies [39].

Assignment of patients to the WHO-IWGE recommended treatment modalities takes into account cyst size in addition to cyst stage. Merging the cyst sizes with the retrospective WHO cyst staging of the study population provides an insight into deviations of current practice in Mongolia from the WHO-IWGE expert consensus. Of particular significance for patients regarding unnecessary treatment risks and for the health care services with respect to avoidable treatment costs is the fact that 3.3% of abdominal cysts would have not warranted any treatment at all since they were already in an inactive stage (CE 4). Following the WHO-IWGE expert consensus they would have been submitted to the watch & wait approach with a very high probability of no need for further treatment [28, 29]. 52.5% of active abdominal cysts (CE1 to CE3) with a diameter of 5 cm or smaller would have been submitted to medical treatment following the WHO-IWGE expert consensus [20, 40]. This draws attention to the fact that availability of albendzole, the preferred benzimidazole for CE therapy, is hugely lacking in Mongolia. Currently, the price of albendazole is very high with approximately USD 2 per

400mg tablet. Albendazole is mostly sold in pharmacies in cities, which also limits access. Access to albendazole is a very much debated issue in the care for the neglected tropical disease echinococcosis in neglected populations [41]. In addition to albendazole cost, 10–15% of the hospital admission fee of public hospital is paid by the patients and the remaining cost is covered by the national health system in Mongolia [42]. However, there are many other costs including informal fees to clinicians and advanced diagnostics increasing the economic burden CE patients have to carry. Almost 26% of the patients assessed would have been allocated to percutaneous treatment (PT). PT options are generally underused and are not carried out in Mongolia for CE management due to a lack of trained personnel. Introducing PT into Mongolia should be considered because it carries less risks for the patients, reduces treatment cost and length of hospital stay. A study in Bulgaria showed similar deviations from best practices as recommended by WHO-IWGE expert consensus[43].

There are several limitations of the study. The data were extracted retrospectively from patient files. The fact that in Mongolia CE patients are being treated exclusively at the three state hospitals with high standards of documentation and archiving compensated partly for this shortcoming. Also, cyst staging was retrospectively performed on the basis of 2-D ultrasound photos. Our interrater-agreement of retrospective cyst staging, however, gives confidence that the staging result provides an acceptable estimate of the distribution of cyst stages seen at the three national hospitals. Identifying complicated cysts is difficult in retrospective studies. In some instances we could suspect that a cyst was complicated by combining various pieces of available retrospective information (e.g. fever, abdominal pain plus US cyst features suspicious of secondary bacterial infection of a cyst). This, however, is all too vague and would be an over interpretation of retrospective data. We thus did the analysis "as if" the cysts of the US images classified were uncomplicated. This may have resulted in an overestimate of the non-surgical treatment modalities.

In conclusion, our study demonstrates

1. Mongolia has a significant section of the population suffering from cystic echinococcosis and is in need of implementing a LMIC-adapted version of the WHO-IWGE expert consensus
2. Access to the privileged treatment centres, the three state hospitals, may be limited by geographic distance and economic resources
3. Ultrasonography is available, but diagnostic CE criteria seem not to be sufficiently well known and cyst staging is not performed
4. WHO-IWGE expert consensus for assigning patients to the four treatment options based on CE cyst staging and cyst size are not implemented resulting in surgical treatment of all CE patients and in an unnecessary high risk approach in patients who could be treated with albendazole or percutaneously or observed (watch & wait).

It is recommended

1. To systematically include CE into the disease surveillance system of Mongolia
2. To make ultrasonography available to the primary / secondary health care level and to train local, physicians in the WHO CE cyst staging. The Focused Assessment with Sonography for Echinococcosis (FASE), a short course for general practitioners, could be a model [26]. In 2016, a pilot training was conducted on WHO-CE cyst classification and staging for primary/secondary ultrasonography doctors by leading experts in the field.

3. To introduce and implement the WHO-IWGE expert consensus at all levels of the health care system to triage patients into the four WHO treatment modalities (a) medical treatment of small active cysts, (b) percutaneous treatment of larger active cysts (CE 1 and CE 3a), (c) surgery for complicated, very large cysts and cysts unresponsive to medical therapy, and (d) watch & wait for inactive cysts (CE4 and 5). Implementation at the primary and secondary health care levels saves transport cost, travel time for patients and allows a substantial proportion of patients to stay near or in their homes during treatment.
4. To apply our strategy of assessing CE clinical epidemiology and management in other CE endemic LICs / LMICs as a basis for planning.

Supporting information

S1 Appendix.
(PDF)

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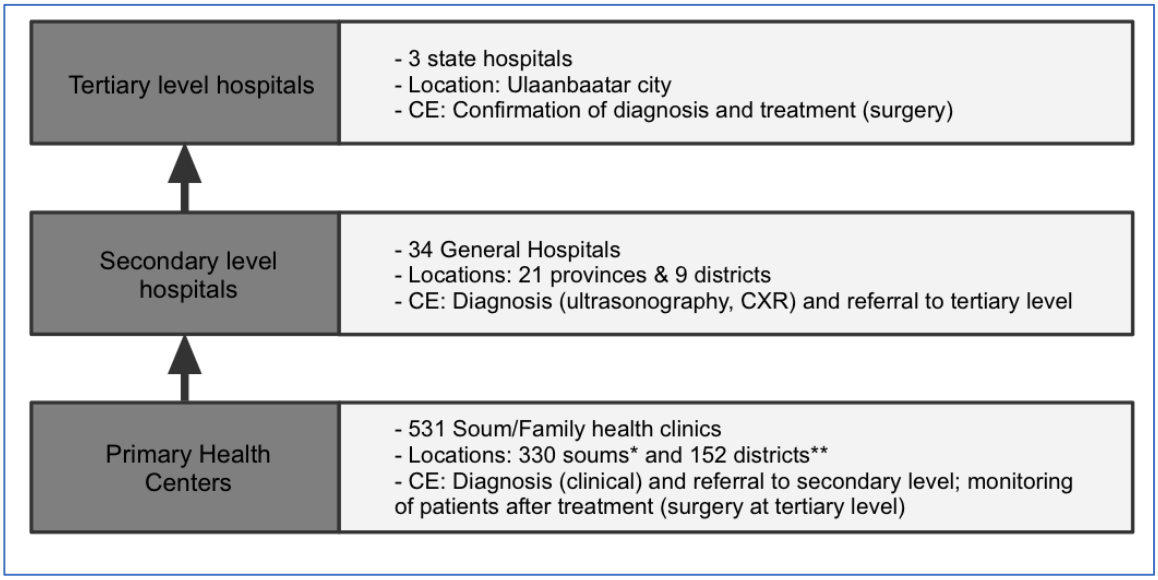
S1 Appendix

Fig A. CE management provided at the three levels of health care in Mongolia



**- smaller administrative unit of province*

***- smaller administrative unit of district*

Fig B. CE surgical cases per year, 2008-2015

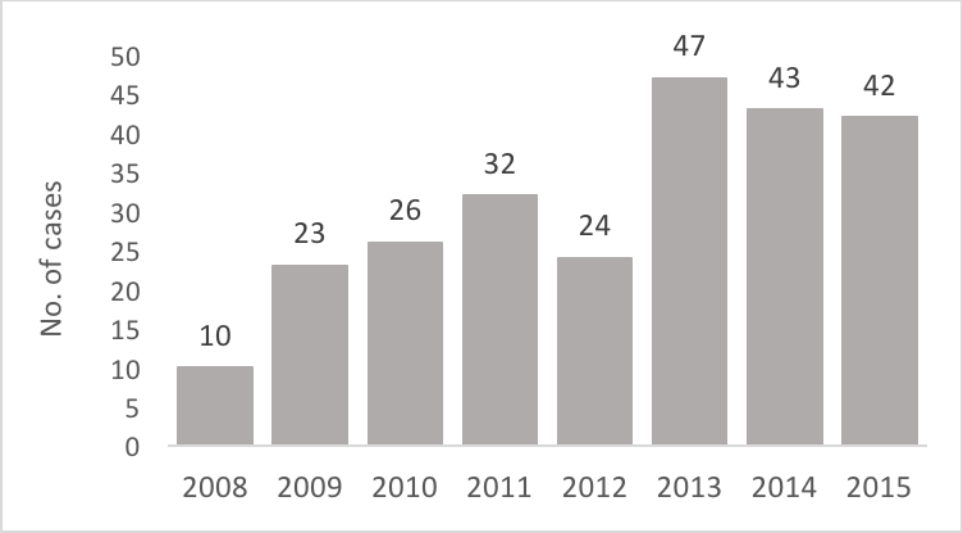
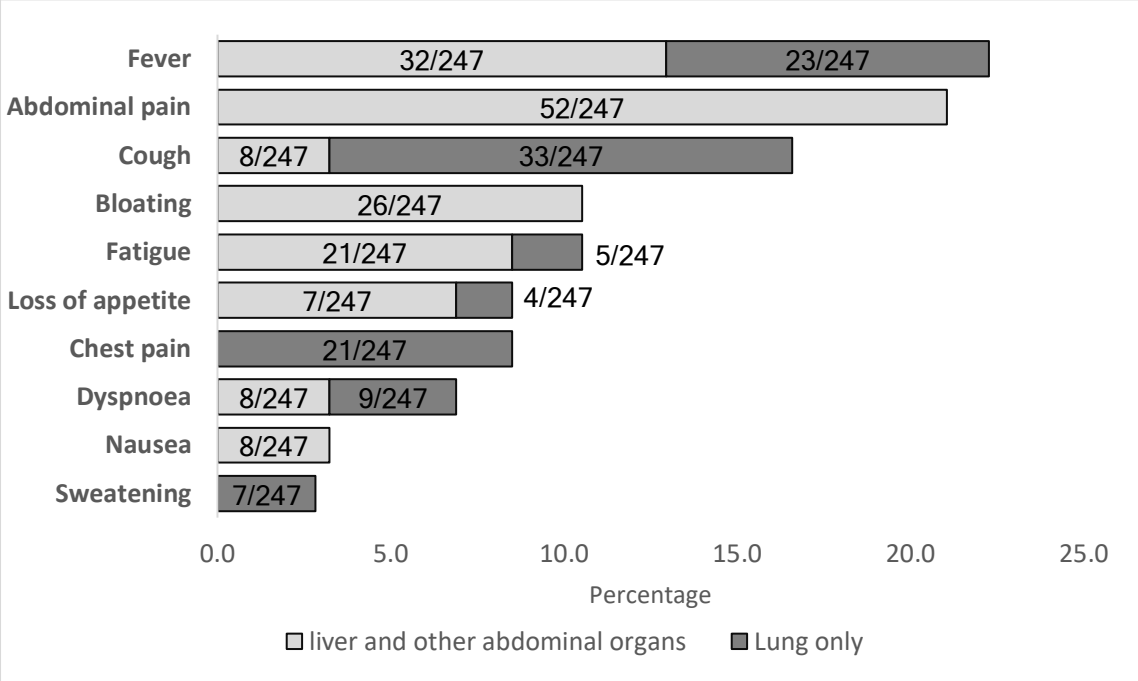
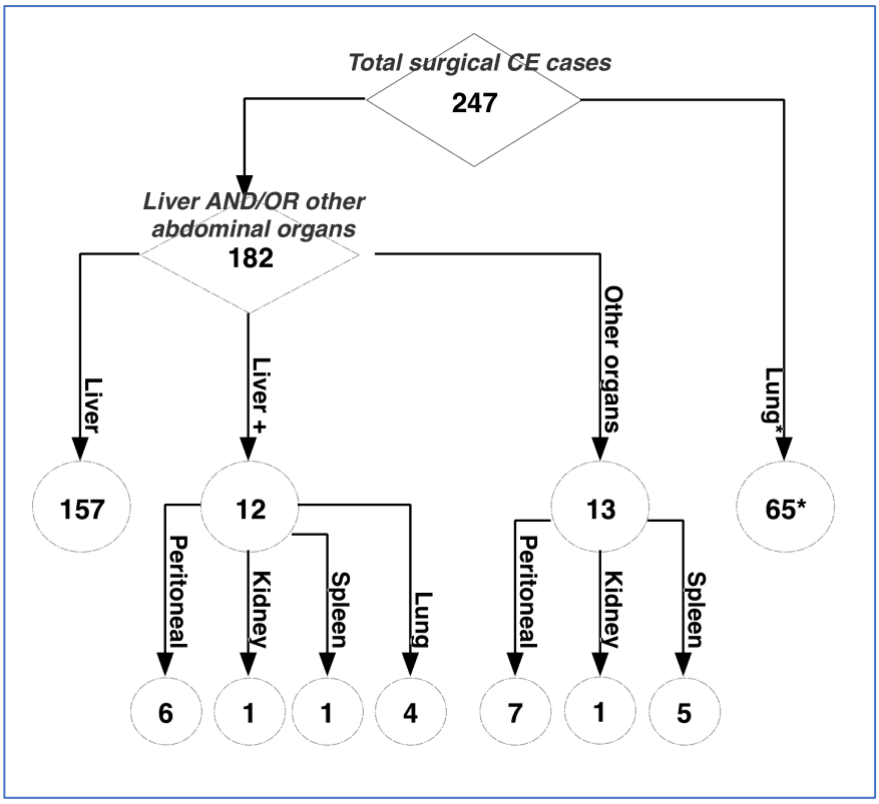


Fig C. Clinical symptoms and signs at admission to the three state hospitals



Numbers in bars represent $N_{reported}/N_{total}$.

Fig D. Locations of CE cysts of the surgically treated patients at the three state hospitals between 2008 and 2015



**Not analyzed for CE cyst stages (WHO CE cyst classification) due to unavailability of the X-ray films or other appropriate imaging*

6. Diagnostic algorithm of cystic echinococcosis in rural setting of Mongolia

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6.1 Abstract

Background: Ultrasonography has developed into a powerful tool for diagnosing and staging CE. WHO-CE cyst classification dividing cysts into active (CE1, 2, 3a, 3b) and inactive (CE4,5) is the basis for tailoring the four treatment options albendazole, surgery, percutaneous methods and watch & wait to patients. The classification is still grossly underused in most epidemic countries including Mongolia. Our objective was to explore the knowledge and use of WHO-CE cyst classification and current clinical management in Mongolia.

Method: A questionnaire on the WHO-CE cyst classification and CE patient management was issued to clinicians of rural health care centres in charge of ultrasound services and a Focus Group Discussion on clinical management of CE conducted with health professionals.

Results: The ultrasonography doctors in rural health centers have a pivotal role in clinical decision making. However, an unstandardized diagnostic approach and an uncertainty of available treatment in local hospitals are the main challenges, leading to a lack of diagnostic confidence. The majority (90%) of the clinicians did not know about the WHO-IWGE algorithm and all willing to participate in the training program.

Conclusion: The majority of the CE patients are from remote, rural areas and have great difficulty in accessing health services. An optimization or standardization of the current CE clinical management in rural hospitals can largely prevent the clinical and financial burden of patients. The training of ultrasonography doctors with WHO-IWGE expert consensus is the key step for standardization of the clinical management.

6.2 Introduction

Ultrasonography has developed into a powerful tool for diagnosing and staging cystic echinococcosis (CE) (Brunetti et al., 2010; Stojkovic et al., 2012). There two main staging algorithm used in the world: Gharbi et al., (1981) and WHO-CE classification recommended by the WHO – Informal Working Group on Echinococosis (WHO-IWGE) (Gharbi et al., 1981; Brunetti et al., 2010). The updated version from WHO-IWGE has an advantage of using stage specific treatment option and accounts the re-activation of the cyst which can change the whole prognosis of the patient. The core piece of the guidelines is to triage on the basis of ultrasound-defined cyst stages into four groups: medical, percutaneous, surgical treatment (active cyst stage CE1 to CE3b) and 'watch & wait' (inactive cyst stages CE4 and CE5) (Junghanss et al., 2008; Brunetti et al., 2010; Piccoli et al., 2014; Stojković et al., 2014; Stojkovic et al., 2016). The classification is still grossly underused in most epidemic countries (Del Carpio et al., 2012; Tamarozzi et al., 2014; Nabarro et al., 2015).

Ultrasonography, however, is only recently introduced in low and lower middle income countries (LMICs)(Groen et al., 2011; Becker et al., 2016; Belard et al., 2016). Thus most endemic countries, including Mongolia, have not yet implemented the WHO Informal Working Group (WHO-IWGE) expert consensus.

6.3 Materials and methods

Our main objective was to identify the key challenges for optimization of clinical algorithm for CE in Mongolia and propose the optimized algorithm. We conducted following activities:

1. Focus Group Discussion (FGD)
2. Questionnaire on WHO-IWGE and stage specific treatment:
3. One round Delphi survey on clinical management of CE

6.3.1 Focus Group Discussion

The main goal of the FGD was to get first insight into a perspective of rural health professionals in CE management.

Study area: General Hospital (GH), of Dalanzadgad city (provincial center) in Omnogobi province.

Participants: Director of the clinical service of GH; Epidemiologist of GH; Senior imaging doctor of GH; Senior doctor for internal medicine of GH; Surgeon at GH;

Chief of statistician at of Provincial Health Department (PHD); Director of Zoonotic Center in Omnogobi; Epidemiologist of Zoonotic Center of Omnogobi; General practitioner in Dalanzadgad city

FGD topic: frequency of CE suspected patients; management provided to CE suspected patients; what algorithm or guideline used for managing CE patients; usage of CE staging; how do you register cases; how to improve reporting; challenges

Discussion output:

1. Although CE patients are rare, it is increasing
2. Most CE suspected patients referred to surgery
3. There are no standard approach for diagnosing CE.
4. Staging does not practiced.
5. The pathognominic signs: "water-lily" shape, "honeycomb like" shape, or "umbrella" are listed in the clinical guideline of chronic diseases.
6. CE does not get listed in the Notifiable disease list

6.3.2 Questionnaire on WHO-IWGE and stage specific treatment

The main objective was to identify applicability of WHO-IWGE cyst classification in General Hospital in provinces (secondary level hospital).

Study area: 12 provinces

Participants: A total of 31 clinicians from general hospitals in 12 provinces participated for the questionnaire

Questionnaire (supplementary material)

Preliminary result:

90% have not heard of the WHO-IWGE consensus during their training or in professional experience. 60% answered that they do not follow any ultrasound diagnostic classification algorithm. The main clinical managements are surgery (37%) and monitoring (50%), while only 8% considered of using benzimidazole. Almost all of the US doctors 94% (17/18) responded that they need additional training to staging the CE. 40 percent answered that patients are followed more than one year and others answered below one year.

6.3.3 One round Delphi survey on clinical management of CE

The main goal was to identify the priority challenges for optimization of CE clinical management by asking from the health professionals who are most familiar with the situation.

Study area: representatives from all 21 provinces

Participants: The Delphi survey took during the Stakeholder meeting in 2016 (Appendix 1). 44 health professionals from 21 provinces and the city. A total of 17 imaging doctors 17 provinces, 21 epidemiologists from 21 provinces and 2 epidemiologists from the city participated in the exercise.

Preliminary result

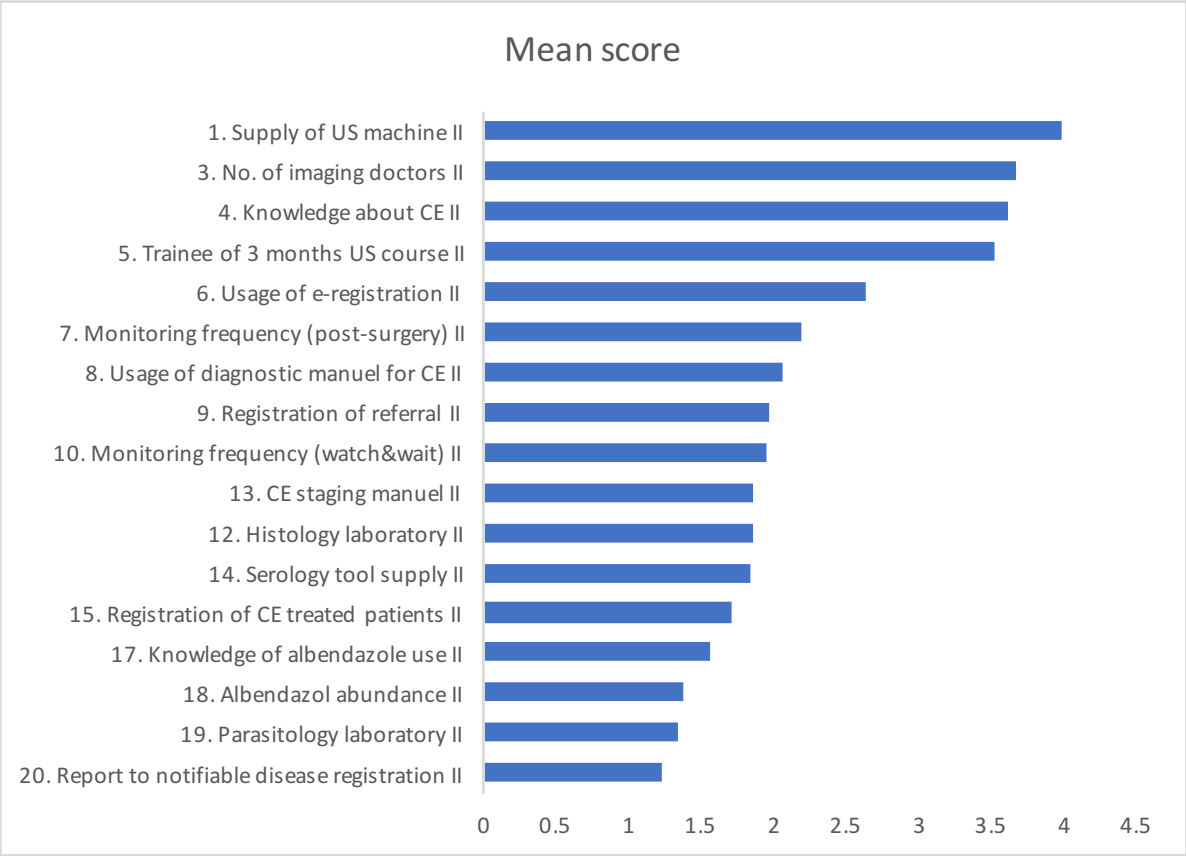

Figure 1. Mean scores of each item in clinical management of CE in secondary level

6.4 Discussion

The inclusion of CE within the notifiable disease registry would not be successful, without clear case definition guided by the standard clinical guideline. All diagnostics of abdominal lesions heavily relied on the radiologists, but not all CE cases are reported in the digital system due to the uncertainty of the case definition. Moreover, all treatment options recommended by WHO-IWGE group except "watch & wait" is not available at the secondary level. There is no albendazole supply in the rural provinces, and its price is high. The surgery of CE does not conduct at the local level and only provided by the few surgeons in tertiary hospitals. Therefore, if the patients diagnosed with CE, they have to go to tertiary center at the city to get the required treatments, and they would not be hospitalized at the secondary level unless they reported with another disease that secondary level could provide service. Such situation puts the radiologists, internal doctors in a difficult situation to report CE, which causes so seldom report of CE in the statistical system of secondary level hospitals.

The CE is highly local disease in Mongolia. Radiological, surgical doctors, have been studied extensively during 1950-1980 to improve the clinical management. We found at least two local proposals for classification of echinococcosis in 1990 (Sodov, 1990; Munkhtogoo, 1991). The pathognomonic features in ultrasound including "water-lily" shape, "honeycomb like" shape, or "umbrella" signs, were familiar, which was also listed in the Clinical Guideline for Diagnostics of Common Disease (MoH, 2008). However, it is still a grey area, especially for young radiologists. Current radiologists graduates from two training system: 1)Medical school for specialized training and 2) Training from Mongolian Society of Diagnostic Ultrasound (MSDU) for primary and secondary health care specialists.

6.4.1 Proposed algorithm flowchart

Based on the information, we developed a proposed diagnostic algorithm which is to be discussed with the national experts (Figure 2, 3).

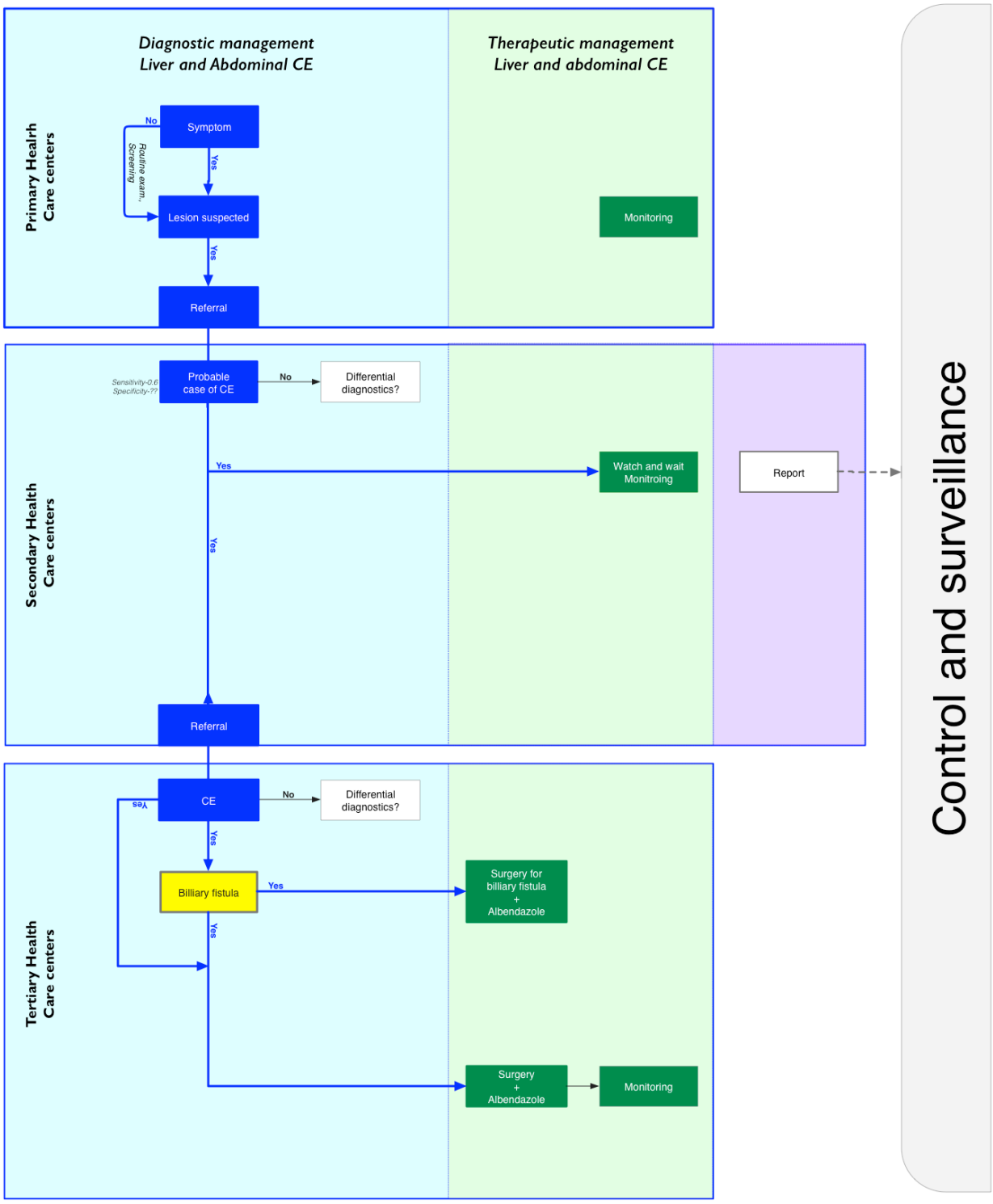

Figure 2. Current clinical algorithm in Mongolia for CE in the abdominal organ

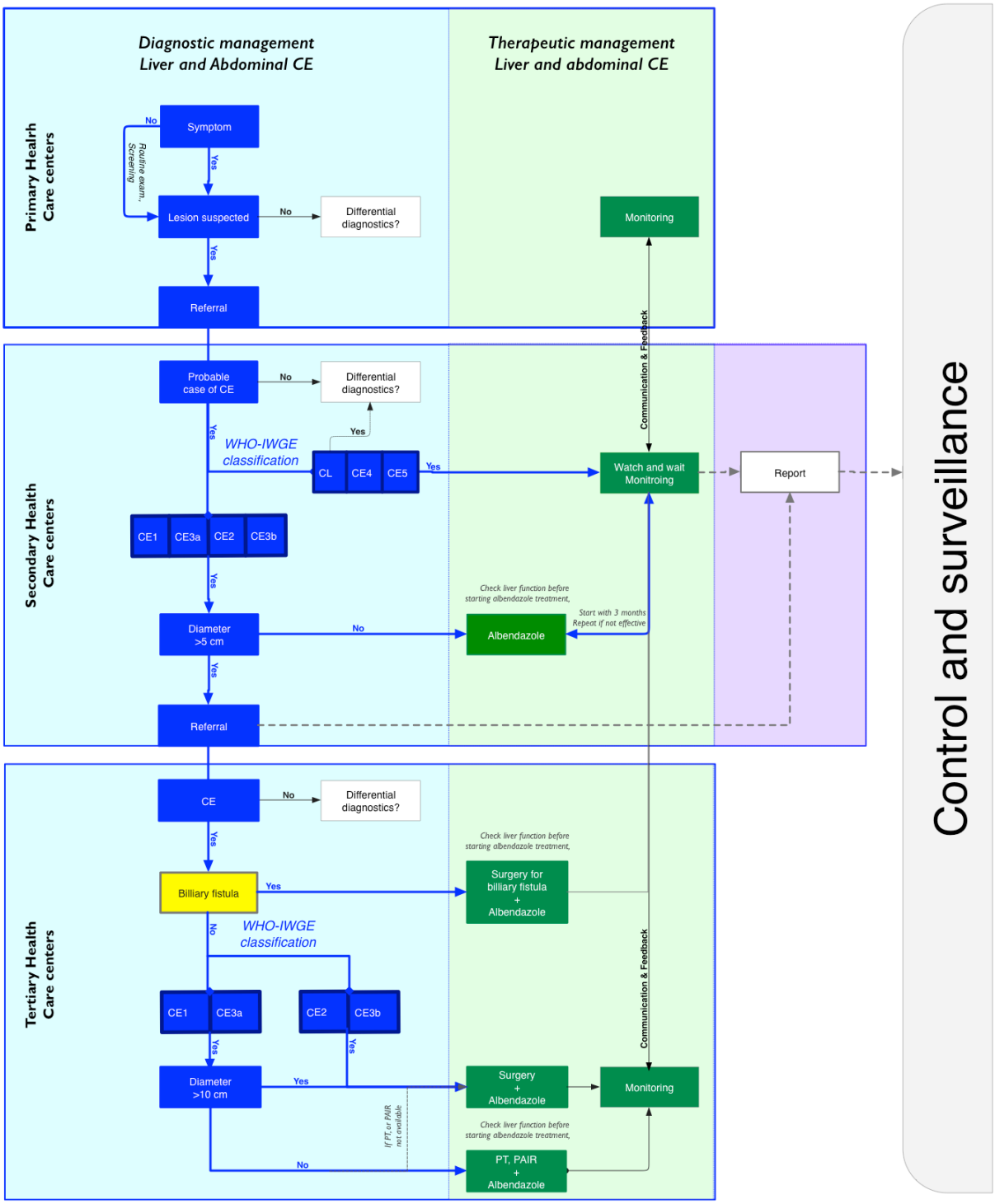

Figure 3. Proposed diagnostic algorithm for CE in abdominal organ (draft). *The draft algorithm will be circulated to the national experts before finalization.*

6.5 Supplementary material

Questionnaire from health personnel about the current practice of cystic echinococcosis:

General information on interview

- Initials interviewer _____
- Date of interview Day____ Month____ Year_____
- Location of interview _____

- Choose your profession:
  - Surgeon (local/national hospital)
  - Ultrasound imaging doctor (local/ national hospital)
  - General practitioner (local/national hospital)
  - Other _____
- The years that your worked in your hospital?
  - 1-3 years
  - 4-7 years
  - 7 years<
- Is cystic echinococcosis endemic in your area?
  - Yes
  - No
- [if YES to question 3] What risk factors of cystic echinococcosis do you think exist in your province?
  - Most of the people have a 1 or more guard dogs
  - People often feed their dog with sheep or other livestock offal
  - Private slaughter slabs are abundant
  - Water and sanitation situation is poor in some area
  - Other, specify_____
- How many patients with cystic echinococcosis come to seek your help last year?
  - Never
  - 1 or more times daily
  - 1 or more times weekly
  - 1 or more times monthly
  - 1 or more times yearly
- What are the challenges in diagnosing cystic echinococcosis? [multiple choice]
  - Most of the ultrasonographic specialists in our hospital have no training for identifying CE

- We do not organize telemedicine in our hospital to confirm the diagnose of cystic echinococcosis
- Others_____

- How many ultrasound machines run in your hospital
  - 0
  - 1
  - 2-4
  - More_____
- [For ultrasound imaging doctors] Specify the time period of your US training?
  - 1 week-1 month
  - 1 -3 month
  - 4-6 month
  - 6 month – 2 years
  - Other [specify the time period]_____
- [For ultrasound imaging doctors] How long ago you had your last US training (which included training on cystic echinococcosis)?
  - <1 year ago
  - 1-5 year ago
  - 5-10 year ago
  - 10 year ago<
- Which cystic echinococcosis classification do you use?
  - The Gharbi classification
  - The WHO classification
  - None
  - Other_____
- Do you need more training to be confident with recognizing cystic echinococcosis cyst on US?
  - Yes
  - No
  - Don't know
- How many patients do you see in a day?
  - 1-9
  - 10-19
  - 20-29
  - 30-39
  - 40<
- How do you register cystic echinococcosis patients? [multiple choice]

- Registration journal of ultrasound unit
- Registration journal of X-ray unit
- Registration journal of referral
- Hospital statistical department
- Other _____

- Are therapeutic choices for cystic echinococcosis available in your hospital? [multiple choice]
  - Albendazole
  - Surgery
  - PAIR
  - Watch and wait method
- For how long do you follow-up the patients?
  - <1 year
  - 1-5 years
  - 5 years<
- How do you follow up your patient? [multiple choice]
  - Phone (specify the frequency in a year _____)
  - Home visits (specify the frequency in a year _____)
  - Patients visits to hospital (specify the frequency in a year _____)
  - Other_____
- Are you aware that WHO guideline of cystic echinococcosis is available in your hospital?
  - Yes
  - No
- [if YES to question 17] Which edition of WHO guideline of cystic echinococcosis is available in your hospital?
  - 1996
  - 2010

7. Control of cystic echinococcosis in Mongolia and One Health

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Manuscript to be submitted to Mongolian Medical Journal

7.1 What is One Health?

A current definition of One Health is any added value, regarding health of humans and animals, financial savings or environmental services, which is achievable through a closer cooperation of human and veterinary medicine when compared to the two medical sectors working alone *(Chapter 2, (Zinsstag, 2015))*. In other words, dialogue and closer cooperation between human and animal health sectors should lead to a synergistic effect. Earlier disease outbreaks characterized by misdiagnosis and/or delayed detection due to lack of communication between public and animal health sectors have been documented, for example Rift Valley fever in Mauritania (Digoutte, 1999; Zinsstag et al., 2007) and Q-fever in the Netherlands (Enserink, 2010). Examples such as these were instrumental in conceptualizing modern One Health (Zinsstag et al., 2005b). The above mentioned added value of closer cooperation requires new methods for addressing the animal/human interface both qualitatively and quantitatively to demonstrate linkages between human and animal infections, joint estimations of the burden of disease, societal assessment of disease cost and financial savings of intervention and joint health services.

7.2 Examples of One Health approach

A simultaneous cross-sectional serological survey of brucellosis was conducted in human and livestock populations in Kyrgyzstan (Bonfoh et al., 2012). Samples were collected from sheep, goats, cattle, and humans. Serological results were confirmed by molecular typing of bacterial isolates (Kasymbekov et al., 2013). In this way, it could be shown that human brucellosis seropositivity depended mostly on sheep, which were identified as a main reservoir for brucellosis in Kyrgyzstan. Ironically, bacterial *Brucella* isolates from humans could not be investigated at the same time because the public health authorities would not agree to collaborate. This is a classic example of the need for building better communication between sectors beforehand. In the Kyrgyzstan study, an association between human and animal seroprevalence was found, but such relationships are not always demonstrated, as shown by a similar study on brucellosis in Mongolia (Tsend et al., 2014). Demonstrating linkages between human and animal disease frequencies depends, among other factors, on the geographical scale and the mobility of pastoral communities.

The concept of added value of a One Health approach can be clearly shown using the example of economic analysis. Brucellosis, which causes abortion in animals and chronic febrile illness in humans, is one of the top priority zoonotic diseases in Mongolia. The financial aspect of a control strategy was assessed, using a One Health approach, to decide whether mass vaccination of 25 million cattle, goats and sheep was justified in order to prevent human brucellosis. Based on a dynamic livestock-human brucellosis transmission model, a cross-sector economic analysis estimated the public and private costs of health care for brucellosis using statistical information and patient interviews (Zinsstag et al., 2005a). Expenditures on out-of-pocket expenses, transportation, drugs, and informal treatments were recognized as an inseparable aspect in estimating the societal cost since the patients are mostly from remote rural communities . The cost of livestock mass vaccination exceeded the benefits in public health, which would, from a public health perspective, lead to the conclusion that mass vaccination of livestock is not profitable. However, a subsequent cross-sector assessment included private health costs, out-of-pocket expenses and the benefits of reduced abortion to livestock production. The cumulative societal benefits of the livestock mass vaccination exceeded the cost of livestock mass vaccination by a factor of three. This example shows that when a sectoral view is extended to include a societal perspective, interventions which are not profitable for one sector may become profitable for the whole society.

A further compelling example of One Health economics, which is directly analogous to echinococcosis, is dog transmitted rabies. Rabies is an invariably fatal viral disease, transmitted almost exclusively by animal bites. Humans do not contribute to rabies transmission dynamics, and the most common reservoir of rabies in developing countries is the domestic dog. Human post-exposure prophylaxis (PEP) is life-saving when instituted immediately after exposure to a rabid animal. However, this does not interrupt the transmission cycle in dogs, which can only be achieved through mass vaccination of dogs. Recent simulations and mass vaccination campaigns show that the cumulative cost of PEP continues to rise (Zinsstag et al., 2009; Mindekem et al., 2017) . In contrast, the cumulative cost of dog mass vaccination along with human PEP starts at a higher cost because of the cost of dog mass vaccination but reaches a plateau earlier because dog rabies transmission is interrupted. The cumulative cost of dog mass vaccination and PEP eventually breaks even with the cumulative cost of PEP alone. After that point, the cumulative cost of dog rabies mass vaccination is less than human PEP alone.

7.3 The key challenges for control of cystic echinococcosis in Mongolia

Often the long-term control program interrupted mainly due to an financial problem. Despite the necessity for sustainable financial resources, a key problem in Mongolia is human resources. According to national statistics from 2014, a total of only 1609 people worked in 921 private veterinary services in the country. One veterinarian was responsible for 29000 animals, on average. Given the current human resources, providing a dog deworming service over the vast territory of 1.5 million square kilometers with a density of 2 people per square km would require an enormous amount of time, in addition to the financial resources necessary for transport and accommodation. These unique conditions clearly show the challenges of CE control in the veterinary sector, especially in nomadic and semi-nomadic pastoral settings (Huang et al., 2008; Larrieu and Zanini, 2012). Figure 1 summarizes the important factors to consider in choosing effective and sustainable interventions for CE in Mongolia. The transmission cycle is between dogs and livestock, and potential control strategies could be employed at different stages including supervised dog deworming with praziquantel (PZQ), Eg95 vaccination of sheep, slaughterhouse management, and health education. For each of these interventions, there are several underlying questions which are absolutely critical for sustainability.

On a global scale, a major question is the cost-effectiveness of Eg95 vaccination for sheep (Torgerson and Heath, 2003; Gauci et al., 2005; Larrieu et al., 2013). According to a recent trial in China and Argentina, the vaccine is highly effective against cystic echinococcosis caused by sheep strains. Mongolia has over 60 million livestock animals, of which 20 million are sheep. This would lead to a high cost of vaccination. Disease understanding and awareness is still low in rural communities, and therefore the incentive to mobilize and vaccinate these animals is expected to be low. Advocacy of long-term benefit of the vaccines to authorities is essential. The question posed is: Is it less costly to treat humans infected with CE using chemotherapy and surgery, or is it, in the long run, less costly to deworm dogs and vaccinate livestock, with the aim of interrupting transmission? In addition, echinococcosis poses direct animal health losses to livestock (Torgerson, 2003). Livestock production loss estimated to be 10% or more and can cause substantial loss to agriculture. The benefit to both livestock health and human health should be accounted when estimating the cost-effectiveness. Also, the cost can be reduced by integrating Eg95 vaccination campaign with other national program that has the same

target groups. Mongolia is highly resource-limited country with a great geographical challenge. Therefore, adaptable, country-specific strategy to control CE is should be developed.

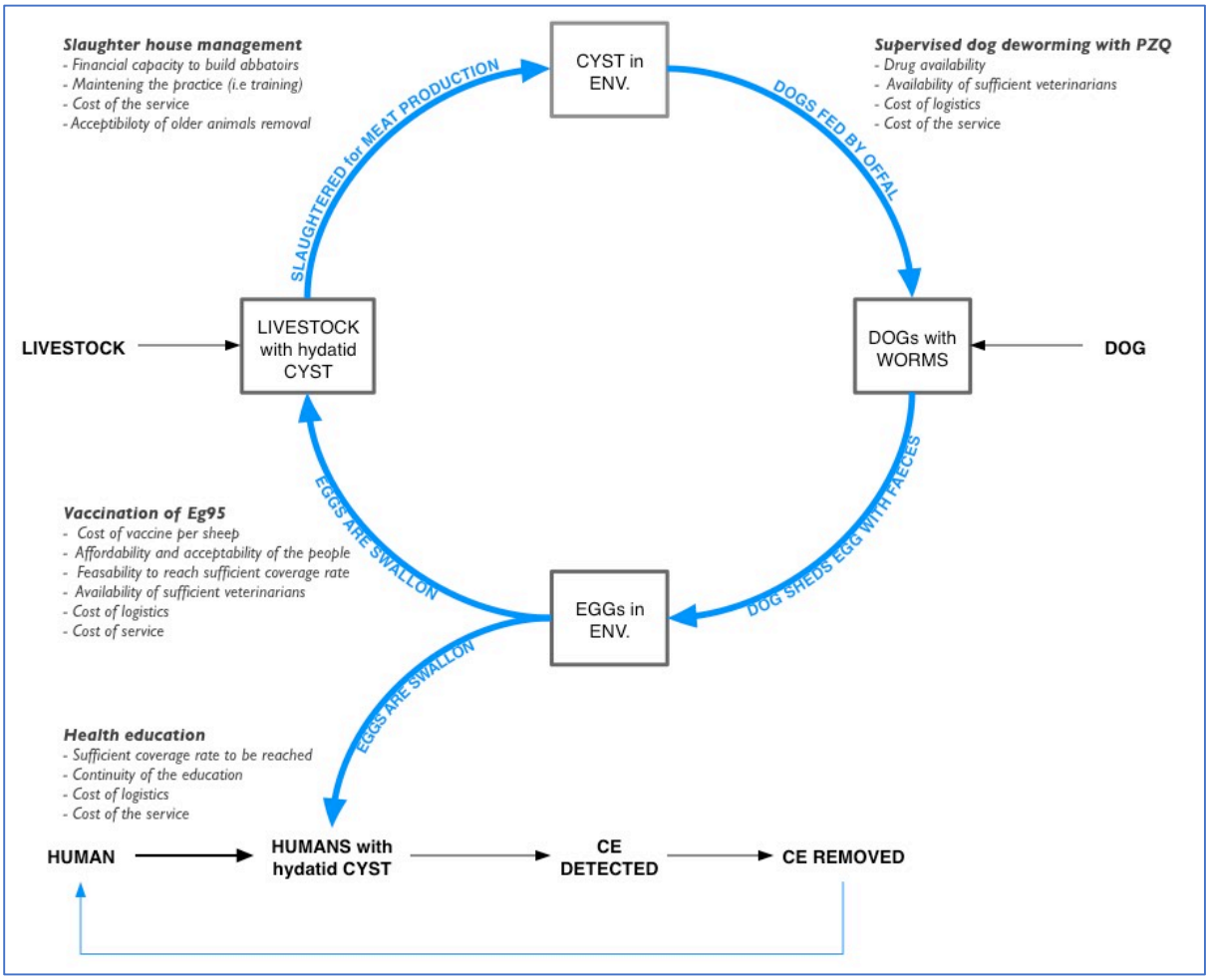


Figure 1. Cystic echinococcosis transmission and intervention choice in Mongolia.

7.4 Emergence of One Health in Mongolia and implication on CE

Due to the frequent zoonotic outbreaks and natural disasters, the inter-sectoral communication was already built in the system. The main organizations in that network are National Center for Communicable Disease (NCCD), and National Center for Zoonotic Disease (NCZD) and State Central Veterinary Laboratory (SCVL), Department of Veterinary and Animal Breeding Government Agency (AVSAB), Institute of Veterinary Medicine (IVM), and National Emergency Management Agency (NEMA). However, it mainly acted on the outbreaks or emergency.

Official inter-sectoral committee for zoonotic and vector-borne disease was established between ministries during the "One Health-One World" project from World Bank which was mainly focused on Avian Influenza, and subsequent project from World Bank "Capacity building on prevention and control of infectious disease" (Figure 2). The latter one supported multiple inter-sectoral research of zoonotic disease including CE and was facilitating the collaboration between the sectors.

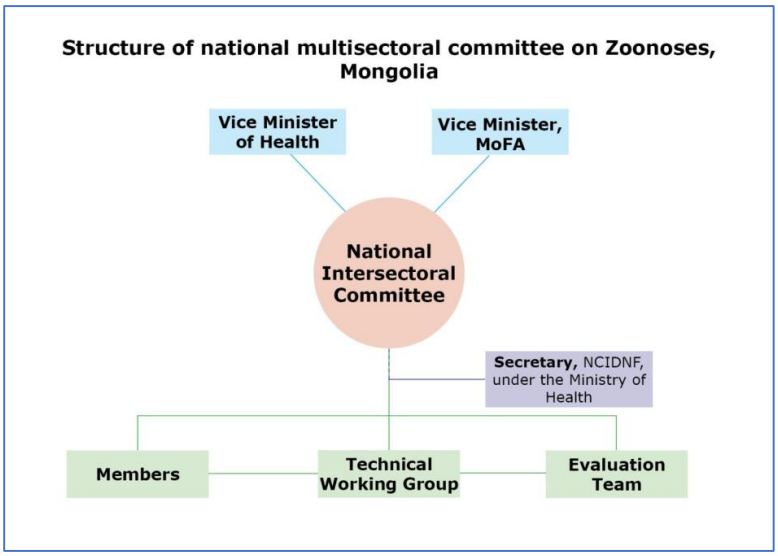


Figure 2. The structure of the inter-sectoral committee. MoFA-Ministry if Food and Agriculture, NCIDNF is former name of National Center of Zoonotic Disease (2011).

At the same time, the long-term inter-sectorial project "Animal Health" to improve intervention in brucellosis funded by Swiss Development Agency (SDA) continuously trained the mixed group of specialists from the organizations mentioned above. Also, the "Strengthen the control of vector-borne disease and lessen the impact of climate change" inter-sectoral project funded by Korean International Agency (KOICA) was ongoing. All these projects hugely contribute to forming the One-Health concept in Mongolia. Also, professional network becomes much stronger, and the understanding of the zoonotic disease became increased dramatically. In the outcome, government specialists raised the issue of investing the zoonotic diseases in Mongolia to WHO. At that time, there was no investment due to lack of evidence. However, this was the first step to get introduced to the Neglected Zoonotic Disease (NTD) framework from WHO. The national reports revealed that evidence of CE emergence in the country and addressed the need for further investigation. WHO in 2013, conducted situation analysis during the mission visit in Mongolia and the main conclusion is that there is great potential to be endemic and effort should be taken to improve surveillance in both sectors and clinical management(NTD/WHO, 2013).

8. Discussion

Cystic echinococcosis (CE) is one of the neglected diseases in Mongolia. Although, the key components and infrastructure for surveillance and control of CE exist within the human and animal health system (Figure 1), the period of critical shortcomings for the surveillance and control of many zoonotic disease occurred when the animal health sector was privatized after the end of the socialist period, at the beginning of the 1990s as a result of an abrupt political shift towards a liberal market reform and the reduction of state services (Ebright et al., 2003).

CE is a disease that has multiple host species requiring multiple sectors to collaborate for maintaining an adequate surveillance and response system. In the present work it was essential to establish a dialogue between the public and animal health sectors in the first place about this neglected disease. The magnitude of the problem was not visible due to lack of communication between and within the sectors, lack of technical knowledge, and complex ecology of transmission of the disease. Efforts were made by international scientists to discuss CE and specialists were trained for molecular analysis. Although it was an important step, the results from earlier studies failed to be conveyed to the public health policy makers (Wang et al., 2005; Gurbadam et al., 2010; Ito and Budke, 2015). While the true burden of the CE remains hidden under the "tip of the iceberg" cases, massive animal reservoirs continue to share the parasite load silently until the human cases reach epidemic proportions. For diseases with a long lag period, such as CE, waiting for the transmission to be manifest in humans is too expensive, and makes disease control very difficult. Therefore, immediate actions need to be taken to reveal the true burden through improved surveillance systems in both the human and animal sectors while implementing an effective strategy for case management.

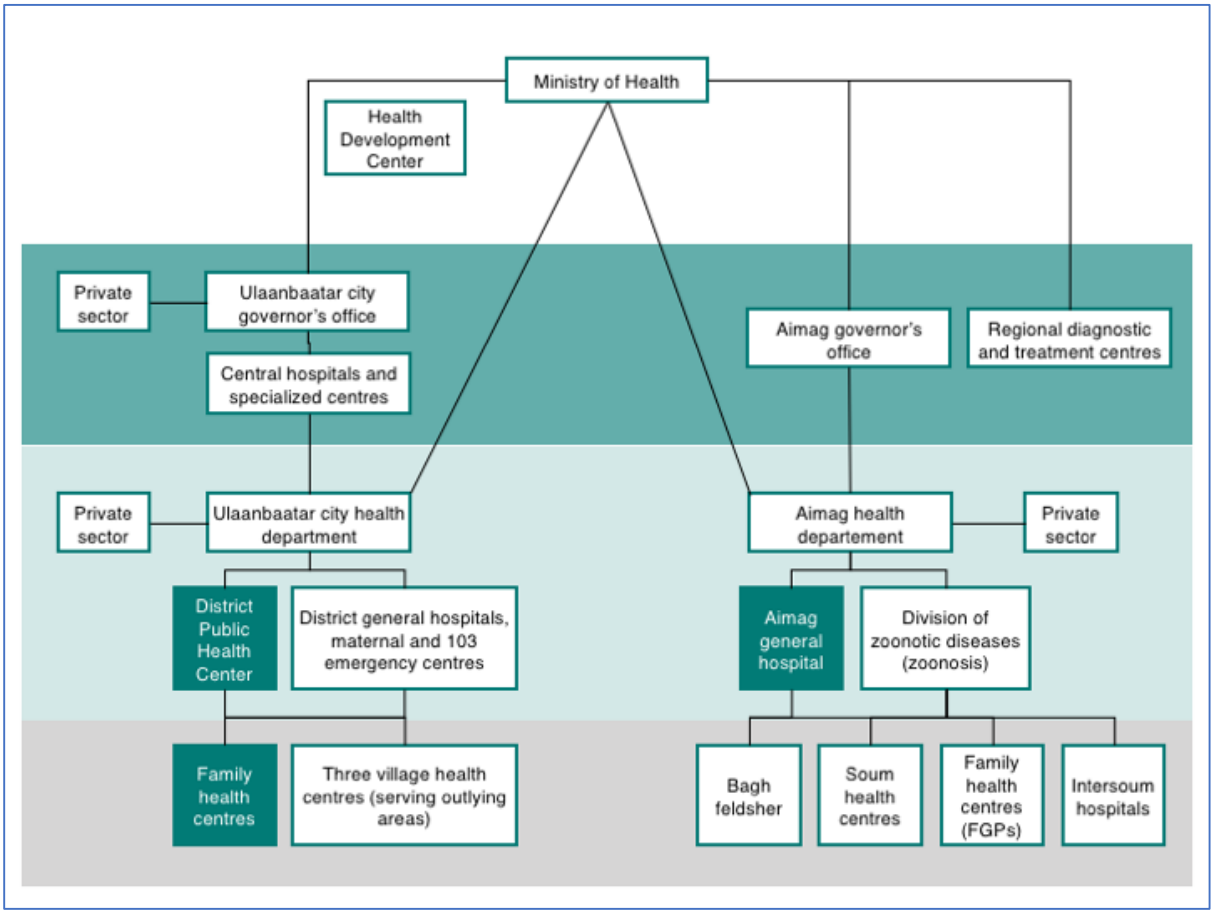
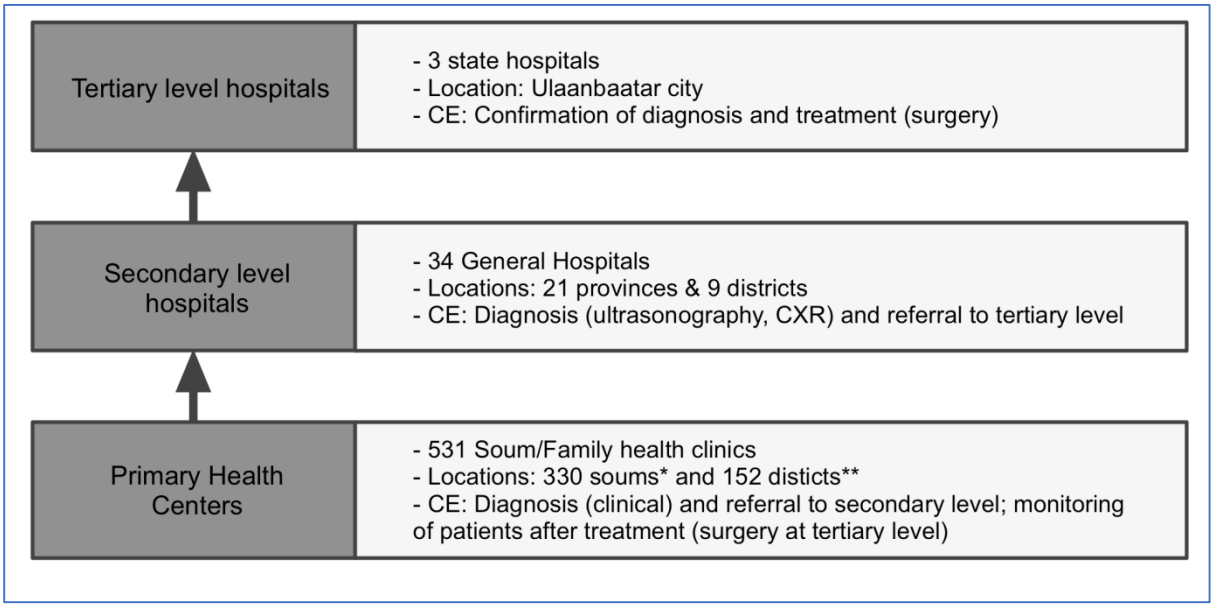


Figure 1. Health system of Mongolia(Tsilaanjav et al., 2013). *Aimag-Province; Soum-subdivision of province; Bagh –smallest administrative unit.*

8.1 Key challenges

8.1.1 Human CE

Surveillance. Both surgical and non-surgical cases are not in the official reports. Active surveillance is currently not conducted. From the structure of the Mongolian Health system regarding passive CE surveillance, it has almost full capacity to provide surveillance of CE (Figure 1). However, we identified critical points that need to be communicated to facilitate smooth CE reporting. There is a good network of primary health care which is also supervised by secondary and tertiary hospitals and eventually belonging to the Ministry of Health (Figure 2).



*- smaller administrative unit of the province

**- smaller administrative unit of the district

Figure 2. CE management provided at the three levels of health care in Mongolia.

This is the main flow of the CE patient. In our data, very few cases cases directly approach the tertiary hospital. This network is well communicated to the notifiable disease system, organized by the National Centre for Communicable Diseases (NCCD) and the National Centre for Zoonotic Diseases (NCZD). But CE is considered as a chronic surgical disease and does not belong to notifiable disease registry while other zoonotic disease including brucellosis, rabies, tick-borne diseases are reported at the notifiable disease center (www.mohs.mn). The number of CE cases usually ends up to be reported together with other surgical diseases in the official reports.

Clinical management. The inclusion of CE within the notifiable disease registry would not be successful without clear a case definition guided by the standard clinical guidelines. All diagnostics of abdominal lesions heavily rely on the radiologists, but not all CE cases are reported in the digital system due to the uncertainty of the case definition. Moreover, all treatment options recommended by WHO-Informal Working Group on Echinococcosis (WHO-IWGE) group except "watch & wait" is not available at the secondary level. There is no regular albendazole supply in the rural provinces, and its price is high. CE surgery is not conducted at the local level and only provided by the few surgeons in tertiary hospitals. Therefore, patients diagnosed with CE, have to go to a tertiary center in Ulaanbaator to receive the required

treatments, and they would not be hospitalized at the secondary level unless they were reported with another disease that the secondary level could provide service for. Such situations puts the radiologists, internists in a difficult situation to report CE, which causes so seldom to report CE in the statistical system of secondary level hospitals.

CE is a highly local disease in Mongolia. Radiologists and surgeons, have extensively studied CE in the period of 1950-1980 to improve the clinical management. We found at least two local proposals for classification of echinococcosis in 1990 (Sodov, 1990; Munkhtogoo, 1991). The pathognomonic features in ultrasound including "water-lily" shape, "honeycomb like" shape, or "umbrella" signs, were familiar, which was also listed in the Clinical Guideline for Diagnostics of Common Disease (MoH, 2008). However, it is still a grey area, especially for young radiologists. Current radiologists graduated from two distinct training systems: 1) the Medical School for specialization for radiology and 2) the Mongolian Society of Diagnostic Ultrasound (MSDU) for primary and secondary health care specialists.

8.1.2 Livestock CE

The available data on the prevalence of CE in animals was too limited for a comprehensive assessment of the situation (NTD/WHO, 2013; Chinchuluun et al., 2014; Yanagida et al., 2017). Public veterinary services inspect all animals that are brought to the public slaughter houses. However, there are only two major public slaughterhouses in Ulaanbaatar, and most of the slaughterhouses outside of Ulaanbaatar are privately owned. Every branch office in the local province has a role to conduct surveys, laboratory analyses and supervise local veterinarians, veterinary pharmacies, control vaccinations and dog deworming. The main challenge is that salaries of state veterinarians much lower than those of private veterinarians. This imbalance affects human resource of the public veterinarians, and the inspection activity of public veterinary sector is very much limited in the rural areas.

8.1.3 Dog management

There is no information of Echinococcus in dogs in Mongolia. It was not well decided whose responsibility it was to control and prevent the disease in dogs. A huge number of stray dogs are now in Ulaanbaatar city and rural areas. Usually, stray dogs are handled by the local governors. There are statistics of dog-owners in Ulaanbaatar city

but not in the rural areas. There was a long discussion between NCZD, Institute of Veterinary Medicine (IVM) and City Governors` office to establish a strategy to control and prevent diseases in dogs and cats. NCZD has more responsibility due to the experience in rabies (Bayar et al., 2016). However, experience on working dog feces surveys, parasitological examination, and conducting laboratory analyses is hugely lacking. There is a huge shortage of parasitologists in all institutes. The laboratory capacity for both human and animal diagnosis is not yet well established. Safer techniques could be implemented to avoid exposure of laboratory personnel, for example, the Kato-Katz technique is used for the analysis of dog feces (NTD/WHO, 2013).

8.2 Research findings

8.2.1 Human CE

8.2.1.1 Burden

Our estimate is the first comprehensive insight into the burden of disease of CE in Mongolia. All currently available data were attempted to be collected from different sources. Four available sources were scrutinized to estimate the burden: 1) Medical records of surgical patients at the major hospitals for 8 years; 2) Un-aggregated hospital discharge statistical information from the Department of Health Development in MoH for 11 years; 3) Digital records (Health-Info) system; 4) Ultrasound examination report from the secondary hospitals. The last two sources failed to give sufficient data. Therefore, we developed an online tool for clinicians to report the diagnosed cases and followed it for one year for the burden estimate. There is a huge difference between the estimated number of surgical, non-surgical and undiagnosed cases. This is mainly caused by disease detection, reporting tool, geographical limitation in accessing health care and lack of disease knowledge in the population. In Mongolia, where exposure to an animal is high in the absence of control action, provision of epidemiological number can give the opportunity to compare and make decisions.

Recommendations and further research:

- Large scale community ultrasound surveys to validate the estimated burden.

- Understanding of the difference between health seeking patients and non-seeking patients would be very useful factor for predicting the proportion of undiagnosed cases.

- The inclusion of CE in the notifiable disease report after conducting the training on the CE staging described by WHO-IWGE and implement the case definition based on WHO-IWGE classification.
- Surveys on the health status of people whose CE stage is known could provide valuable information to further assess the disability weight of CE.
- High societal cost from CE is an important message to invest in the control and prevention strategy in cost-effective way.

8.2.1.2 Cost

We provide the first estimation of the societal cost of human CE in Mongolia. CE is a neglected disease that affects the marginalized population. The disease causes a significant amount of loss to society and household economy. Our results inform decision makers to further develop a strategy to control the disease and prevent the future cost of CE. The economic loss due to human CE was US$ 2.7 million when accounting the productivity loss, which is equal to 0.024% of the Gross Domestic Product (GDP) of Mongolia. This number is an underestimate because in Mongolia there is no animal prevalence data in livestock. The cost of diagnosed cases alone would be 0.3 million which is still a substantial number for only 476 patients. And yet, only 10% of it is supported by the government. Regarding out-of-pocket expenditure, 76% of the total medical cost was borne by CE patients, while Dugee et al., (2018) reported 70% for patients in chronic disease which validates our estimation (Dugee et al., 2018). This is defined as catastrophic-out-of-pocket expense and a major public health issue in Mongolia at the moment(Dugee et al., 2017). Especially, the albendazole price for one pill is about two US$ dollar which is a high price. During the stakeholder meeting in 2016, we had the chance to talk shortly with a patient coming from Ovorkhangai province who had CE surgery one month ago. He just had finished taking one month of albendazole. He described his issue: "*I had 40 sheep. Every time when I finish my drug, I was selling my sheep one by one. Now I have just a few sheep left. And when the sheep are finished, I will stop taking the drug*". Unsurprisingly, this situation reflects for many cases CE patients as the cost of albendazole is the highest proportion of the total cost after productivity loss.

Recommendations and further research:

- Measuring the animal productivity loss supported by the animal prevalence data. This would complete the estimation of full societal cost.

- This was a first estimation on neglected zoonotic and parasitic disease in Mongolia. The burden of parasitic disease is very much neglected in Mongolia and we hope our estimate will raise the issue of re-surging the parasitic disease field in Mongolia. However, the parameters need to be improved in the next cost estimation. Including human productivity loss.
- To our knowledge, prior to our work the cost of brucellosis was the first estimate for both the human and animal sectors conducted in Mongolia The cost of other zoonotic disease must be calculated in a similar way using all available data and should lead to policy recommendations for decision making on zoonoses control (Roth et al., 2003; Zinsstag et al., 2005a).
- Loss of working time is high for both patients and caretakers. One of the solutions would be the implementation of telemedicine for CE referral or Percutaneous Treatment (PT) which requires shorter stays in hospital than surgery. The possibility of implementation and training needs should be explored.

8.2.1.3 Clinical management

WHO-IWGE guidelines for allocating patients to the four treatment options based on CE cyst staging – are not implemented resulting in surgical treatment of all CE patients, in an unnecessary high-risk approach in patients who could be treated with albendazole, percutaneously or who could just be observed (watch and wait). Access to the privileged treatment centers, the three state hospitals, is limited by geographic distance and economic resources. The ultrasonography doctors in rural health centers play a pivotal role in clinical decision making. Ultrasonography is available, but unstandardized diagnostic approach and uncertainty of available treatment including albendazole in local hospitals are the main challenges, leading to a lack of diagnostic confidence. The majority (90%) of the clinicians at the secondary level did not know about the WHO-IWGE algorithm and all were willing to participate in the training program.

Recommendations and further research:

- To systematically include CE into the disease surveillance system of Mongolia
- To make ultrasonography available to the primary / secondary health care level and to train local, rural physicians in the diagnostic features of CE and CE cyst staging. The Focused Assessment with Sonography for Echinococcosis (FASE), a short-term course for general practitioners, could be a model(Tamarozzi et al., 2014). In 2016, the pilot training was conducted to primary/secondary ultrasonography doctors on WHO-IWGE cyst staging by leading experts in the field (1) (Bold, 2016) (Appendix 2).
- To introduce and implement the WHO-IWGE guidelines at all levels of the health care system to triage patients into the four WHO treatment modalities (a) medical treatment of small active cysts, (b) percutaneous treatment of larger active cysts (CE 1 and CE 3a), (c) surgery for complicated, very large cysts and cysts unresponsive to medical therapy, and (d) watch & wait for inactive cysts (CE4 and CE5) (Brunetti et al., 2010).

8.2.2 Livestock CE

New research questions arised while we were investigating the incidence data. The camel population was the only livestock species having a statistically significant association with human cases of CE. Our study is the first report in Mongolia that gives insight into the prevalence of CE in the camels and goat, although the sample size, number of locations needs to be increased. An important finding in our study is that we identified the common haplotype of *E. canadensis* G6-7 in humans, camels, goat, and wolves in the same region, using the previously described genetic information of humans and wild canids. To our knowledge, this is the most comprehensive description of the current epidemiological situation of CE in Mongolia with substantial evidence of camel as an important intermediate host of *E.canadensis* in the country. Mongolia locates right between Central Asia, China, and Russia. However, the area was never explored enough regarding CE. Our survey was a short survey of only one week from 1 province (Table 1). Yet, there are many interesting findings such as the first report of *E.canadensis* from a goat in Mongolia, first mixed infection from *E.canadensis*, two new haplotypes. There is a huge potential in Mongolia for further studies in livestock. Specifically it is surprising that given the large numbers of sheep and goat, they don't seem to play and important role as intermediary hosts?.

Table 1. *Echinococcus spp*. cases in different hosts in Mongolia

Host	G1	Reference	G6-7	Reference	G10	Ref.
Human	**46**	(Jabbar et al., 2011; Ito et al., 2014)	**7**	(Jabbar et al., 2011; Ito et al., 2014)	5	(Ito et al., 2014)
Dog	**5**	(Zhong et al., 2014)				
Fox			**3**	(Ito et al., 2013)	2	(Ito et al., 2013)
Wolf						
Goat			**1**	Current study		
Camel			**18**	Current study, (Yanagida et al., 2017)		
Sheep						
Cattle						

(review was updated from Deplazes et al., 2017);

Recommendations and further research:

- There is a huge research gap untouched in Mongolia concerning CE in the animal population. A main issue is the lack of access to private slaughterhouses. However, our study showed that in collaboration with a local veterinarians and nomadic farmers, a survey would be possible.
- One Health study including multiple host animals in one space and time can give more accurate, faster, and more valid information regarding zoonotic linkage and create a clearly added value compared to separated sectoral studies (Zinsstag, 2015). Further surveys should include larger samples involving more host animals.
- This is the first report of CE prevalence in the animal population, which contributes to developing first transmission model for CE in Mongolia, including camels.
- Our study could not have provided the same information without previously identified genetic information on humans. Therefore, further genetic studies of CE patients is encouraged. There is strong competition between the institutes and researchers on the genetic studies and they are reluctant to collaborate. This leads to a compromised comparability as we witnessed during our study. We realized that only a collaborative approach can facilitate systematic well-designed One Health sample collection and can provide more valuable information(Schelling, 2015).
- Protocols of CE sample collection should be standardized for both human and animal health sectors.

9. Conclusion and Outlook

We provided the first estimate of the burden and cost due to CE in Mongolia and insight into the magnitude of the problem caused by CE in the society and the health system. Our statistical results on camel population and human incidence is a successful example of using already available data to show the zoonotic linkage despite the absence of public slaughterhouses and human resource. It provides a further case example for an added value of a closer cooperation between human and animal health (Zinsstag, 2015) There is a further added value of combining statistical data and genetic data. We also identified key challenges in clinical management. The challenges are solvable. The critical message in the clinical management is that the sequence of action should be 1) improve the supply of albendazole, 2)training ultrasound doctors on stage-specific treatment, 3) implementing the WHO based case definition and staging of cysts, 4)inclusion of CE in the notifiable disease. But not the other way around. Actions one and two can be implemented at the same time. This work is primarily to serve decision making of control and prevention of CE for human and animal health specialist in Mongolia. Two important lessons were learned during our study: 1) Studies on neglected zoonotic disease require special study designs for the provision of evidence of human-animal linkages. Therefore, study designs should be adapted to neglected zoonotic diseases; 2) Better communication, and building networks between all the stakeholders including national and international partners is the key to success.

Better drug supply and better diagnosis and clinical management of human patients are certainly the first steps to better Echinococcosis control in Mongolia. Yet this should not be the end and further efforts should be made to control CE at the source keeping its potential elimination in mind. The control at the source should include 1) the systematic training and implementation of behavior change in slaughter practices to avoid feeding offal to dogs 2) The systematic deworming of dogs and safe disposal of dog feces during the period of worm excretion. 3) the testing of recently developed livestock vaccines in Mongolia. Specifically, it would be very interesting if the could also protect camels. 4) training and implementation of behavior change of hand hygiene would not only prevent exposure to CE but also other diseases. 5) All intervention studies should be accompanied by relevant follow up of intervention effectiveness and barriers of implementation.

Appendix 1

Report of the stakeholder meeting "Multidisciplinary stakeholder meeting on the strengthening surveillance of cystic echinococcosis in Mongolia", Ulaanbaatar, 16-17 September.

Background

Mongolia is one of the countries that have the highest risk of cystic echinococcosis (CE). This is because one third of the population is engaged in extensive pastoral sheep farming. The most vulnerable group for echinococcosis is likely to be herder communities who cannot afford the treatment and transport cost. An existing health service in Mongolia barely reaches the targeted population and cases are detected at a late stage. Due to the poor reporting system and late diagnosis, information regarding the epidemiology of echinococcosis is scarce.

In 2013, WHO experts highly recommended to improve the surveillance system and case management for cystic echinococcosis during their mission in Mongolia to assess situation on echinococcosis. There are several individual studies conducted since 2013 to identify current prevalence, burden and cost of disease. Individual studies from different organizations need to be combined and compared. To implement the knowledge obtained from these studies, an engagement from the national decision makers is essential. The clinical management and possibility to optimize the clinical algorithm is in progress and will be the main evidence for developing Standard Operational Procedure for clinical management of CE. It is a key moment to update the current available information and discuss further plans.

In collaboration with National Center of Zoonotic Disease (NCZD), and Mongolian Society of Diagnostic Ultrasonography (MSDU), we conducted two days of Stakeholder meetings on strengthening control and clinical management of cystic echinococcosis in Mongolia between 16-17, September 2016. All the stakeholders including representative from ministry of health, WHO country office, national centers, hospitals, academics who work on echinococcosis, ultrasonography doctors and epidemiologists from all of the provinces participated. The international leading experts on cystic echinococcosis participated in the meeting and gave insightful recommendations and lectures to the participants.

Working group for the Stakeholders meeting

A working group consisted of specialists from MSDU, NCZD, National Center for Communicable Diseases (NCCD).

Stakeholders:

Ministry of Health and Sport (MoHS), WHO, NCZD, NCCD, MSDU, Mongolian National Association of Surgeons (MNAS), Institute of Veterinary Medicine (IVM), Health Science University of Mongolia (HSUM) and provincial clinicians and epidemiologists.

Facilitators:

- Professor Sonin Sodov, The president of MSDU
- Dr. Bolor Bold, researcher in NCZD
- Dr. Erdenebileg Bavuujav, Ultrasound expert, MSDU
- Dr. Tsogbadralh Nyamkhuu, The director of NCZD

The participants (70 people):

International experts invited:

- Dr. Bernadette Abela-Ridder, Team leader of Neglected Zoonotic Disease in WHO HQ
- Prof. Jakob Zinsstag, Head of Human and Animal Health unit, Swiss Tropical and Public Health Institute (Swiss TPH)
- Prof. Thomas Junghanss, Chief of Section of Tropical Infectious Disease, Heidelberg University Hospital
- Dr. Francesca Tamarozzi, Project manager of HERACLES (European cyst echinococcosis project) in University of Pavia, WHO collaborating center for CE
- Prof. Ning Xiao, Deputy director of National Institute of Parasitic Diseases in Shnaghai, China CDC (NIPD)

National participants:

- Ultrasonography Specialists
- Surgeons from central hospitals (First Central Hospital, Third hospital, National Center of Maternal Child Health)
- 21 Clinicians from the provinces (General Hospitals)
- 21 Epidemiologists from Province (Provincial Zoonotic Centers and General Hospitals)
- Experts from NCZD, NCCD, IVM, HSUM

Opening session:
Dr. Narangerel, Officer in Charge of Emergency Operational Center in Ministry of Health opened the session with an high emphasis of CE an important issue especially for Mongolia because of people have high possibility to expose the infection. Dog deworming, educating of the population, and early detection are the key issues to be addressed to prevent from this disease. Rural, herder communities are exposed to the infection which often goes undetected with consequences of chronic, long-term illness that put them in high burden. She stressed the importance of timelines and collaborative effort of the meeting to control the disease.
Dr. Soe Nyunt-U, WHO representative in Mongolia was very appreciative about the attention from both international and national experts on this disease and collaborating to strengthen the current clinical management and control activities. Currently, an on-going national programme organized by HSUM, with support of WHO focuses on early detection of all adults above 40 years old. The programme

started from the 3 soums of Omnogobi province, and will eventually cover all over Mongolia in coming three years. The main objective is to establish a database from the result of medical examination of all people, which could be further analysed by experts. The examination of ultrasonography can be shared with the experts on CE for to estimate prevalence of cystic echinococcosis. Since the start of the programme, increasing the technical knowledge of the remote doctors is very much needed and this meeting outcome will highly contribute to the primary health care doctors diagnosing and examining skills.

Dr. Bernadette Abela-Ridder, Team Leader of Neglected Tropical Disease(NTD) unit in WHO in Geneva, highlighted the previous mission in 2013 on cystic echinococcosis and appreciated the progress until 2016. She gave an overview of WHO strategy, vision on NTD and how echinococcosis is inclusive within it. The participation of the countries is very important in achieving the goal on NTD by 2020. Just few months ago the WHO initiated the Working group on clinical management and Prof. Thomas Junghanss is the head of the working group, which also joined this stakeholder meeting. Therefore, it is a great opportunity to learn and experience from the national experts about the challenge and problems in control and clinical management of cystic echinococcosis.

Dr. Enkhbayar, Secretary of Mongolian Society of Diagnostic Ultrasound mentioned working on CE project a year ago with Dr. Bolor Bold. Specialized diagnostic and therapeutic skill is in high level in most tertiary hospitals. Futher progress working with the NCZD on CE in the remote areas is planned. He emphasized international expert contributions to strengthening the clinical management of CE in Mongolia. The very fruitful symposium and hands-on training was held on 15 September on WHO-IWGE guideline of diagnosing CE and stage specific treatment organized in First Central Hospital with clinicians and Prof. Junghanss and Dr. Tamarozzi lecturing on this subject.

Discussions

Prof. Thomas Junghanss from Heidelberg University, Dr. Francesca Tamarozzi from University of Pavia, Dr. Bernadette Abela Ridder a from WHO, Prof. Xiao Ning from Shanghai Parasitological Institute, Prof. Jakob Zinsstag from Swiss Tropical and Public Health Institute was invited and gave excellent presentations about current global vision on control of echinococcosis, implementation of classification system from WHO and stage-specific treatment. One of the issues stressed during the meeting was that of insufficient drug distribution. Currently albendazole is not supported by the insurance system. The rough estimate of price of albendazole for monthly usage equals the minimum wage of the country. This has a much bigger effect on the rural people, most of whom hardly have any income.

In 2013, there was an initiation from the Mongolian government and a study was conducted on the epidemiology of echinococcosis. Lack of statistical information and no clinical registration at the provincial level was identified. As a tip of the iceberg- few surgical cases in the central hospital which was about 30-40 in a year

were reviewed. Among them young children have a high percentage. Preliminary estimate showed that at least 5 times higher cases diagnosed as CE in the province after reviewing documents in some provinces. There was absolutely no information about how many patients are infected in the population.

There was small scale focus group discussion and health professional questionnaire on current clinical guidelines. Currently there is no guideline to diagnose in both central and primary health care. Diagnostic algorithm was last updated in 1987. Health professionals do not follow the classification system. Stage-specific –treatment options were not discussed. Patients buy the anti-helminthic drug themselves, which is quite expensive. Technical capacity to conduct CE surgery is very limited in the provincial hospital. A majority of the patients were referred to the central hospital. The CE registration system has conflicts with the health insurance regulation, and therefore statistics are poorly recorded.

We conducted a workshop in 2015 with ultrasonography doctors and epidemiologists from secondary hospitals in the provinces. One of the main objectives of the workshop was to introduce WHO- Informal Working Group Experts Consensus (WHO-IWGE) on classification of CE in ultrasonography. During the workshop, almost all the health professionals answered that they were not aware of the WHO-IWGE classification system.

A hands-on training program for central clinical professionals and provincial clinical professionals on using WHO classification system for diagnosing cystic echinococcosis by ultrasonography. We invited Prof. Thomas Junghanss and Dr. Francesca Tamarozzi to give a lecture on using a WHO-IWGE and stage specific treatment algorithm. The training was highly informative and efficient for the local participants.

Experts recommandations

Dr. Bernadette Abela-Ridder:

- Encouraged integration of control of cystic echinococcosis into the national health system
- Further activities on control action should be focused on reducing risk factors

Prof. Thomas Junghanss:

In terms of optimizing clinical management, the following areas should have priority:

- Early detection
- Clinical management of detected patients. How to report to the system
- Monitoring of the patients in primary, secondary, tertiary level
- Defining the monitoring period
- Integration into the health system

Dr. Francesca Tamarozzi:

- Surgical patients from rural areas are better able to be monitored in the provincial hospitals
- E-registration form for reporting cases is more efficient when there are fewer, but more important questions.

Prof. Jakob Zinsstag:
Further research on primary prevention is an essential part of control. The applicability of any prevention method should be considered in the Mongolian situation. Pilot project should be started on the primary preventive activities:

- Educating people on cooking the dog food before feeding,
- Dog deworming activities in collaboration with different sectors,
- Vaccination of the intermediate host,
- Integration of health system and other programme.

Prof. Ning Xiao: Careful design of projects is crucial for the successful implementation. Especially, all the activities should be conducted in a best applicable way for Mongolia.

- Health system strengthening is the foundation
- Criteria for surveillance system needs to be created
- Baseline research on echinococcosis in national level is important for control strategy.
- But before that small scale pilot study must be held in order to get an efficient result.

Summary of the group work presented by Dr. Buyanjargal, vice director from NCCD.

- On developing the guidelines of clinical management and surveillance of cystic echinococcosis based on WHO recommendation, following issues should be prioritized:
  - Primary prevention
  - Seasonal monitoring
  - Health professionals role should be defined clearly
  - Monitoring the patients at least 5 years after surgery
- Implementation should be in alliance with other programmes in Mongolian health system
- Indicators for programme implementation, baseline surveys needed to initiated.
- Strengthening database, improve the surveillance system
- Developing data registration form
- Training on the approved guideline
- Cost analysis to estimate burden
- Discounting the drug price
- Provision of drug and procurements
- Strengthening the collaborating between different sectors

Figure 1. Stakeholder meeting participants.

The list of the participants from the provincial centers for Stakeholders consultation meeting on the Control and Prevention of Cystic Echinococcosis in Mongolia

September 16-17, Corporate Convention Centre, Ulaanbaatar city

№	Province/City	Name	Organization	Occupation
1	Arkhangai	B.Byambasuren	Center of Zoonotic Disease	epidemiologist
2	Arkhangai	B.Delgerkhangai	General Hospital	US doctor
3	Bayankhongor	S.Baasankhuu	Center of Zoonotic Disease	epidemiologist
4	Bayankhongor	CH.Bayanmonkh	General Hospital	US doctor
5	Govi-Altai	S.Batsaikhan	Center of Zoonotic Disease	epidemiologist
6	Govi-Altai	TS.Sansarmaa	General Hospital	US doctor
7	Darkhan-Uul	L.Olziijragal	Health Department	epidemiologist
8	Darkhan-Uul	Z.Monkhsuvd	General Hospital	US doctor
9	Dornogovi	J.Myagmarsuren	General Hospital	epidemiologist
10	Dornogovi	U.Enkhbayar	General Hospital	US doctor
11	Dundgovi	B.Altantogs	Center of Zoonotic Disease	epidemiologist
12	Dundgovi	Buyandelger	General Hospital	US doctor
13	Dornod	Ch.Odgerel	Health Department	epidemiologist
14	Dornod	S.Yundendorj	General Hospital	US doctor
15	Sukhbaatar	D.Oyunbileg	Health Department	epidemiologist
16	Sukhbaatar	Ts.Uuganmonkh	General Hospital	US doctor
17	Khentii	G.Gantsetseg	Center of Zoonotic Disease	epidemiologist
18	Khentii	Ya.Aюush	Soum clinic	US doctor
19	Bayan-Olgii	J.Balshikyer	Center of Zoonotic Disease	epidemiologist
20	Bayan-Olgii	A.Akjarkhin	General Hospital	US doctor
21	Zavkhan	G.Dashdavaa	Center of Zoonotic Disease	epidemiologist
22	Zavkhan	B.Amarzayaa	General Hospital	US doctor

23	KHovd	J.Mongontsetseg	Center of Zoonotic Disease	epidemiologist
24	KHovd	D.Sarangerel	General Hospital	US doctor
25	Uvs	G.Maralmaa	Center of Zoonotic Disease	epidemiologist
26	Uvs	P.Naranchimeg	General Hospital	US doctor
27	Omnogovi	Uuganjavkhaa	Center of Zoonotic Disease	epidemiologist
28	Omnogovi	L.Myaasuren	General Hospital	US doctor
29	Ovorkhangai	S.KHorolmaa	Center of Zoonotic Disease	epidemiologist
30	Ovorkhangai	V.TSerendemberel	General Hospital	US doctor
31	Bulgan	S.Ariunaa	Health Department	epidemiologist
32	Bulgan	O.Bilguun	General Hospital	US doctor
33	KHovsgol	D.ErdeGHchimeg	Center of Zoonotic Disease	epidemiologist
34	KHovsgol	TS.ErdeGHbolor	General Hospital	US doctor
35	Selenge	E.Saranzayaa	Center of Zoonotic Disease	epidemiologist
36	Selenge	J.Batsuren	General Hospital	US doctor
37	Orkhon	M.Uranchimeg	General Hospital	epidemiologist
38	Orkhon	TS.Mendsaikhan	General Hospital	US doctor
39	Tov	CH.Purevsuren	Health Department	epidemiologist
40	Tov	T.Amarsanaa	General Hospital	US doctor
41	Govisumber	SH.Altantsetseg	Health Department	epidemiologist
42	Govisumber	A.Oюuntsetseg	General Hospital	US doctor
43	Niislel	D. TSegmid	Center of Zoonotic Disease	epidemiologist
44	Niislel	G.Odontuul	General Hospital	US doctor

The list of the speakers and national/international experts for Stakeholders consultation meeting on the Control and Prevention of Cystic Echinococcosis in Mongolia

September 16-17, Corporate Convention Centre, Ulaanbaatar city

№	Name	Organization	Occupation	Resp.
1	D.Narangerel	Ministry of Health	Head of Emergency Operation Center	Chairman/ Speaker
2	N.Tsogbadrakh	National Center of Zoonotic Disease (NCZD)	Director	Chairman/ Speaker
3	S.Sonin	Mongolian Society of Diagnostic Ultrasonography (MSDU)	President	Chairman/ Speaker
4	Ya.Buyanjargal	National Center for Communicable Disease (NCCD)	Deputy Director	Chairman/ Speaker
5	D.Enkhbayar	Mongolian Society of Diagnostic Ultrasonography (MSDU)	Secretary	Chairman/ Speaker
6	Dr.Soe Nyunt-U	World Health Organization, Country Office	Representative	Chairman/ Speaker
7	O.Ariuntuya	World Health Organization, Country Office	Officer	Participant
8	A.Dolgorhand	Ministry of Health	Officer in Emergency Operation Center	Participant
9	D.Abmed	National Center for Communicable Disease (NCCD)	Senior consultant of parasitological	Participant

			laboratory, Head of Research Committee	
10	A.Ambaselmaa	National Center for Communicable Disease (NCCD)	Head of Communicable Disease Surveillance Department	Participant
11	Ts.Selenge	National Center for Communicable Disease (NCCD)	Head of Zoonotic and Emerging Disease Surveillance Unit	Participant
12	M.Narankhajid	Health Science University of Mongolia	Lecturer in Parasitological Department	Participant
13	B.Boldbaatar	Institute of Veterinary Medicine, IVM	Head of Virological Department	Participant
14	J.Erdenebaatar	Institute of Veterinary Medicine, IVM	Head of Infectious disease and Immunological laboratory	Participant
15	Ya.Nomkhon	State Department of Veterinary Medicine	Senior consultant	Participant
16	D.Tserennorov	National Center of Zoonotic Disease (NCZD)	Head of Administrative Unit	Chairman/Speaker
17	D.Ganbold	National Center of Zoonotic Disease (NCZD)	Head of Professional Service Unit	Participant
18	N.Uranshagai	National Center of Zoonotic Disease (NCZD)	Researcher	Coordinator
19	Sh.Agiimaa	National Center of Zoonotic Disease (NCZD)	Officer in Charge of Echinococcosis in Surveillance Department	Coordinator
20	Ts.Bayar	National Center of Zoonotic Disease (NCZD)	Biologist and researcher in Surveillance Department	Presenter
21	B.Bolor	National Center of Zoonotic Disease (NCZD) Swiss Tropical and Public Health Institute	Researcher and PhD candidate	Coordinator
22	D.Amgalan	First Central Hospital of Mongolia	Head of General Surgical Department	Chairman/Speaker
23	B.Chinchuluun	Institute of Veterinary Medicine, IVM	Researcher in Helminthology Laboratory	Presenter
24	D.Temuulen	Health Science University of Mongolia	Lecturer in Parasitological Department	Presenter
25	Ts.Lkhagvatseren	Institute of Veterinary Medicine, IVM	Researcher in Helminthology Laboratory	Presenter

Timetable for Multidisciplinary Stakeholder Meeting on Strengthening The Control and Clinical Practice of Cystic Echinococcosis in Mongolia

3rd National Meeting on Neglected Zoonotic Diseases (NZDs)

Day 1 Timetable **16.09.2016, Ulaanbaatar**

8.30-9.00	**Registration**
9.00-9.30	***Opening remark*** *MoH,* *WHO Representative in Mongolia* *Bernadette Abela-Ridder, Team Leader of Neglected Zoonotic Diseases, WHO* *Prof.Sonin Sodov, President of Mongolian Society of Diagnostic Ultrasound* *N.Tsogbadrakh, National Center for Zoonotic Disease*
9.30-12.30. Session 1. Strengthening the Surveillance System and Clinical Management of Cystic Echinococcosis (CE) in Mongolia: Challenges and Possibilities *Chairperson: Dr.Narangerel D, Head of Emergency Operational Disease,, Ministry of Health*	
9.30-10.00	**Current Situation of Cystic Echinococcosis in Mongolia** *Dr.Tsogbadrakh Nyamdorj, Director of National Center for Zoonotic Diseases*
10.00-10.20	**WHO response on the Global Challenges of Cystic Echinococcosis** Dr.*Bernadette Abela-Ridder, Team Leader of Neglected Zoonotic Diseases, NTD/WHO, Geneva, Switzerland*
10.20-10.50	**Implementing One Health: Theory to Practice and Added Value** *Prof.Jakob Zinsstag, Head of Human and Animal Health Unit, Swiss Tropical and Public Health Institute (Swiss TPH), Basel, Switzerland*
10.50-11.20	**Surveillance System of Echinococcosis in China** *Prof. Ning Xiao, Deputy Director, National Institute of Parasitic Diseases (NIPD), Shanghai, China*
11.20-11.40	Tea break
11.40-12.00	**Current Epidemiological Burden and Societal Cost of Cystic Echinococcosis in Mongolia** *Bolor Bold, PhD candidate of Swiss Tropical and Public Health Institute (Swiss TPH), Basel, Switzerland*
12.00-12.30	Discussion
12.30-13.30	Lunch
13.30-17.00. Session 2. Current Knowledge: The Update from the Recent Researches on CE in Mongolia *Chairperson: Prof.Tsogbadrakh, Director of National Center for Zoonotic Diseases*	
13.30-13.45	**Molecular Genetical Study of Cystic Echinococcosis** *Dr.Temuulen Dorjsuren, Lecturer, Department of Parasitology, Health Science University of Mongolia*

13.45-14.00	**Serological Study of Cystic Echinococcosis in Human** *Dr. Anu, Researcher, Department of Parasitology, National Center for Communicable Diseases*
14.00-14.15	**Echinococcosis Situation in Livestock Population and Challenges** *Dr. Chinchuluun Batbaatar, Researcher, Parasitological Department, National Institute of Veterinary Medicine*
14.15-14.30	**Dog Survey in a Sub-Urban District of Ulaanbaatar** *Bayar Tserendovdon, Biologist, Surveillance Department, National Center for Zoonotic Diseases*
14.30-15.00	**Validation of Molecular Genetic Studies of Cystic Echinococcosis** *Prof. Ning Xiao, Deputy Director, National Institute of Parasitic Diseases (NIPD), Shanghai, China*
15.00-15.30	Discussion
15.30-15.50	Tea break
15.50-16.40	**Group work (Part 1): Towards Integrated Human and Animal Cystic Echinococcosis (CE) Surveillance-and Control (elimination) in Mongolia**
16.40-17.00	Presentation of group work

Day 2 Timetable **17.09.2016, Ulaanbaatar**

8.30-9.00	**Registration**
9.00-9.30	**Summary of sessions on Day 1** *Bolor Bold, PhD candidate of Swiss Tropical and Public Health Institute (Swiss TPH), Basel, Switzerland*
9.30-12.30. Session 1. Strengthening the Surveillance System and Clinical Management of Cystic Echinococcosis (CE) in Mongolia: Further Strategy *Chairperson: Dr. Enkhbayar Dondog, General Secretary of Mongolian Society of Diagnostic Ultrasound*	
9.30-10.20	**Clinical management of CE patients: current guidelines and ways forward** *Prof.Thomas Junghanss, Head of the Section of Tropical Medicine, University Hospital of Heidelberg, Germany*
10.20-11.10	**WHO collaborating center of CE in Italy: Training on WHO classification system and introduction of European registry system of CE** *Dr. Francesca Tamarozzi, Project Coordinator, WHO collaborating center on CE, University of Pavia, Italy*
11.10-11.20	**Tea break**
11.20-11.40	**Implementing the Algorithm for Clinical Management of CE: Feasibility of stage Specific Treatment** *Dr.L.Amgalan, Head of Surgical Department, First State Central Hospital*

11.40-12.00	**The Role of using WHO classification System for CE for Integrated Surveillance/Registration** *Prof. Sonin Sodov, President of Mongolian Society of Diagnostic Ultrasound* *Dr. Enkhbayar Dondog, General Secretary of Mongolian Society of Diagnostic Ultrasound*
12.00-12.30	Discussion
12.30-13.30	Lunch
13.30-17.00. Session 2. Discussion on the Standard Operational Procedure of Clinical Management and Surveillance *Chairperson: Dr. Buyanjargal, Deputy Director of National Center for Communicable Diseases*	
13.30-13.45	**Introduction of the Draft of Guideline for Clinical Management and Surveillance for CE** *Bolor Bold, PhD candidate of Swiss Tropical and Public Health Institute*
13.45-14.00	**Introduction of the Draft of Guideline for Surveillance for CE in Livestock** *Dr. Chinchuluun Batbaatar, Researcher, Parasitological Department, National Institute of Veterinary Medicine*
14.00-14.30	Discussion
14.30-14.40	Tea break
14.40-15.50	**Group work (Part 2): Towards Integrated Human and Animal CE Surveillance-and Control (elimination) in Mongolia**
15.50-16.20	Presentation of group work
16.20-16.40	Summary and Closing

Appendix 2

Report of the training on clinical management of cystic echinococcosis in First Central Hospital of Ulaanbaatar city and Dalanzadgad hospital, Omnogobi province

Background

Cystic echinococcosis (CE) is caused by *Echinococcosis granulosis* (*E.granulosis*) an important zoonotic disease in Mongolia which has been endemic since the early 20th century. An intensive control program was implemented before the 1990s. During that period many improvements in the clinical management came about and echinococcosis was a notable topic in the surgical field. Innovative new techniques on CE surgical procedures for complicated case with variously-affected organs were introduced between 1960 and 1990. Worldwide, surgery was the only treatment available until the 1980s. In some countries, in the early 1980s less invasive or non-invasive treatment options were applied in clinics, including benzimidazole and percutaneous treatment. The choice for optimal therapeutic approaches depends highly on the staging method of CE. In 1981, Gharbi et al., developed the staging system which is most widely used worldwide. In Mongolia Dr.Sonin Sodov applied it for the first time in the field of radiology. However, the therapeutic methods improved and there was a need to update CE staging. In 2011 the WHO-Informal Working Group on Echinococcosis (WHO-IWGE) developed an expert consensus for diagnosing CE. Based on the cyst staging protocol by WHO-IWGE, stage-specific treatment options could be chosen. In Mongolia, the WHO-IWGE guidelines are not yet implemented. The staging of hydatid cysts is not standardized and even often neglected in clinical practice. Training is highly needed for local health professionals on the current standard clinical approach.

Objective

To pilot the training for the local specialists on CE diagnostics

The working group:

- Bolor Bold, PhD Candidate University of Basel; Swiss Tropical and Public Health Institute (Swiss TPH); National Center for Zoonotic Diseases, Mongolia (NCZD)
- Prof. Sonin Sodov, President of Mongolia Society of Diagnostic Ultrasound (MSDU);
- Dr.Amgalan Luvsanjav, Head of General Surgical Department in First Central Hospital (FCH)
- Dr. Erdenebileg Bavuujav, Secretary of Mongolia Society of Diagnostic Ultrasound and Senior (MSDU); Consultant of First Central Hospital (FCH) of Radiology
- Dr. Tsogbadrakh Nyamdorj, Director of National Center of Zoonotic Disease (NCZD)

- Dr.Agiimaa Shagj, Epidemiologist from National Center of Zoonotic Disease (NCZD)
- Dr. Altanchimeg, Director of Center of Zoonotic Disease in Omnogobi Province (CZD)

For the preparation of workshop, the working group met three times. To introduce the training objective, the role of each member was discussed. The training was organized twice:

- The Symposium of Cystic Echinococcosis and Hands-on training on 15 September in Ulaanbaatar in FCH with doctors, surgeons and district clinicians, radiologist.
- Hands-on training of WHO-IWGE classification and control on 18- 19 of September in Dalanzadgad city of Omnogobi province with local clinicians, radiologists and family doctors from 20 soums.

The speakers and mentors for the workshop on CE clinical management are:

- Dr.Francesca Tamarozzi, Project Manager of HERACLES (European Registry of Echinococcosis); Supervisor in FASE (Focused Assessment of Sonography for Echinococcosis) training in WHO-Collaborating Center in University of Pavia, Italy
- Prof.Thomas Junghanss, Head of Tropical Medicine Section in Heidelbeg University Hospital, Heidelberg, Germany
- Prof. Sonin Sodov, President of Mongolia Society of Diagnostic Ultrasound (MSDU), Ulaanbaatar Mongolia
- Dr. Erdenebileg Bavuujav, Secretary of Mongolia Society of Diagnostic Ultrasound and Senior (MSDU); Consultant of First Central Hospital (FCH) of Radiology, Ulaanbaatar Mongolia
- Dr.Amgalan Luvsanjav, Head of General Surgical Department in First Central Hospital (FCH), Ulaanbaatar Mongolia

The speakers and mentors for the control:

- Ning Xiao, Deputy director of National Institute of Parasitic Disease, Shanghai, China
- Bernadette Abela Ridder, Team leader of Neglected Zoonotic Disease, NTD WHO HQ, Geneva, Switzerland
- Bolor Bold, University of Basel, Swiss TPH
- Chinchuluun Boldbaatar, Institute of Veterinary Medicine, Ulaanbaatar, Mongolia

September 15, 2016:

The Symposium of Cystic Echinococcosis and Hands-on training in Ulaanbaatar in First Central Hospital, Ulaanbaatar

Opening

The first day of the workshop was conducted among clinicians of tertiary and secondary hospitals in FCH, Ulaanbaatar on 15 of September. The seminar was organized in alliance with fourth national symposium of MSDU in the theme of current liver diagnostic approaches. In the full day seminar clinicians from FCH, clinicians from district hospitals, general hospitals, and private hospitals participated. A total of 87 clinicians and specialists participated in the workshop. Prof.Byambadorj, the director of the FCH, and Prof. Sonin Sodov opened the workshop with presentations about the current importance of CE in Mongolia. Prof. Sonin emphasized that standardizing current clinical practice is one of the issues that has not been addressed for many years in Mongolia.

Presentation from Prof. Sonin Sodov

The first presentation was the diagnostic algorithm developed by Prof. Sonin on CE in 1987. It is based on the Gharbi et al., (1981) classification of diagnosing hydatid cyst using ultrasonography. Prof. Sonin was the first to introduce an ultrasonography machine in Mongolia in 1982, an ALOKA SSD 202, and started to use it in FCH (formerly named as The State Central Clinical Hospital). Ultrasonography (US) is a first choice, most accurate diagnostic method. US images are direct visualization of the cyst including: size, location, vascular relations, number of cysts and other associated pathology. It is the least invasive, highly economic and most accessible in remote areas. Prof. Sonin talked about how prevalent CE was in Mongolia before 1990s: *"…There were no week without CE surgery in FCH…".*

The previous classification, proposed by Prof. Sonin in 1987, is the following:

Simple hydatid cyst (wall- sign)
Hydatid cyst with daughter cyst – cysts within the cyst and honeycomb sign
Dead hydatid cyst with daughter cyst-pattern and cyst within the cyst
Dead hydatid cyst- pattern
Partly calcified- striped
Fully calcified- umbrella

Presentation from Dr. Amgalan Luvsanjav

Dr. Amgalan presented the historical development in CE surgical methods in Mongolia. CE was always one of the most challenging and interesting diseases in the surgical field in Mongolia, given the fact that it was one of the most common diseases. The leading clinical professors, including Prof. Dolgor, Prof. Ichinkhorloo, Prof. Davaatseren, were the pioneers in this field. Novel techniques in CE surgery have been patented with their names and implemented until now.

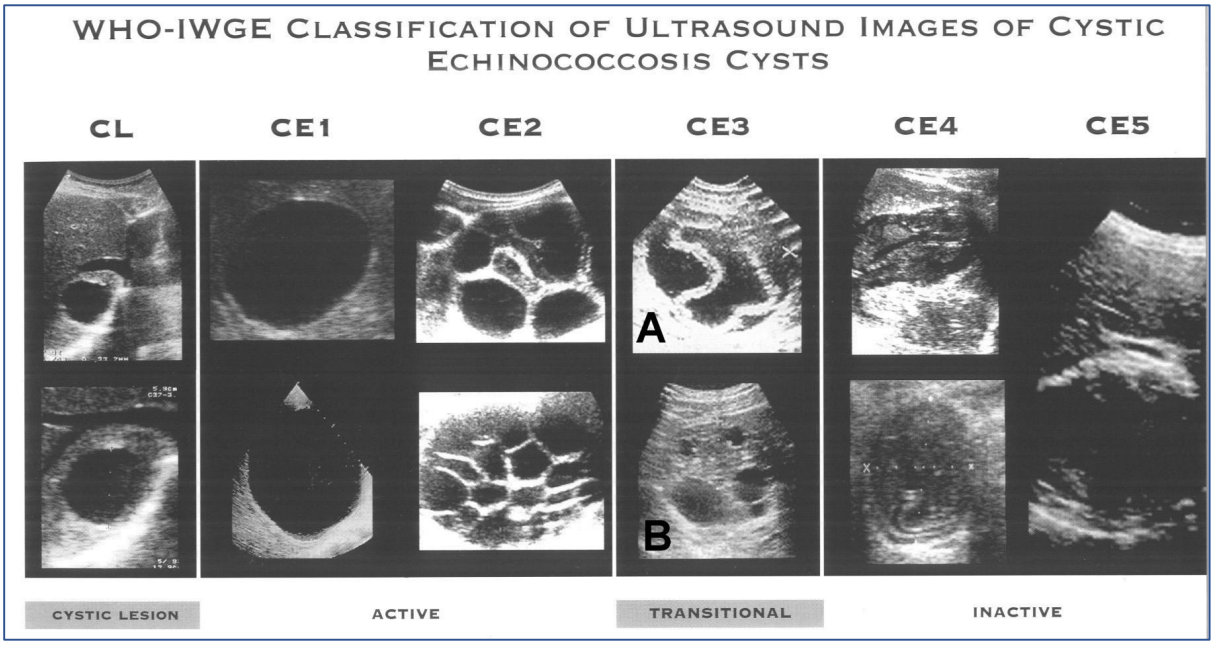
Presentation from Dr. Francesca Tamarozzi

After the Mongolian experts discussed current clinical management of CE, invited international experts gave presentations on clinical management of CE. Dr. Francesca

Tamarozzi from the WHO collaborating center at the University of Pavia presented the current diagnostic classification of CE recommended from WHO which was updated in 2011. The classification was standardized by WHO experts in 1995, in a form that could be applied in all settings to replace numerous previous classifications and allow a natural grouping of the cysts into three relevant groups:

- *active (CE1 and 2),*
- *transitional (CE3)*
- *inactive (CE4 and 5)*

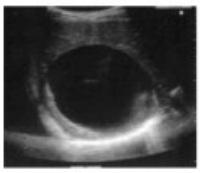
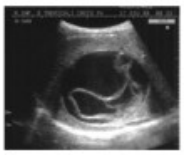
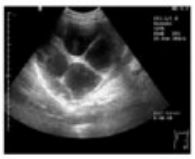
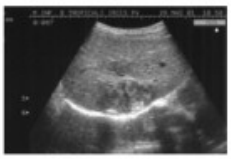
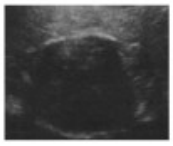
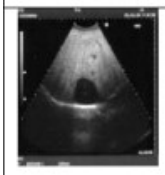
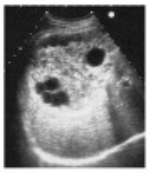
Figure 1. WHO-IWGE classification of ultrasound imagec of cystic echinococcocosis cysts (Brunetti et al., 2010)(WHO-IWGE, 2011).



CL= *Undifferentiated cysts. If the cyst was parasitic or non-parasitic is unknown.*
CE1*= Active stage, unilocular, fluid filled cyst with "double line sign"*
CE2*= Active stage, multiple daughter cysts, multiple septae resembles "honey comb"*
CE3A*= Transitional (active to inactive), filled with fluid and detachment of inner membranes resembles "water-lily-sign".*
CE3B= *Transitional (inactive to active)* ***, viability of parasite still remains,*** *unilocular), composition of solid and daughter cysts.*
CE4= *Inactive stage, different pattern of solid components, non-viable, pathognomonic channel-like pattern is seen.*
CE5*= Inactive, thic cystic wall, and non-viable solid cystic appearance.*

This classification was updated in 2001 and again updated in 2011, with Type 3 further divided into two subgroups (**CE3a-** separated endocysts and **CE3b-** solid type containing daughter vesicle). In addition, all undifferentiated cysts can be classified into CL. Currently, the classification developed by Informal Working Group on Echinococcpsis from WHO (WHO-IWGE) in 2011 is the most recommended. Figure 1 shows the classification algorithm updated by WHO-IWGE classification in 2011.

Figure 2 presents the comparison between Gharbi and WHO-IWGE classification. **Figure 2. Comparison of Gharbi's and WHO-IWGE ultrasound classification(Brunetti et al., 2010). (WHO-IWGE, 2011).**

Gharbi	I	II	III	IV	V
					
WHO	CE1	CE3a	CE2	CE4	CE5
					
CL			CE3b		

CL, as a potentially parasitic cyst, was not included in Gharbi's classification. WHO CE3b was not explicitly described by Gharbi. CE3b might be classified as Type III, although in the original Gharbi paper there was no distinction between multivesiculated (honeycomb-like) cysts and cysts with daughter cysts in solid matrix.

Improvement in the updated classification (WHO-IWGE 2011)

The hydatid cyst should transform into an inactive state at the end of its biological developement and die. Then biological sequence is the following:

- Formation of active stage with filled with clear fluid (CE1)→
- Gradually detachment of endocyst wall (CE3a) →
- Most of the parasitic fluid is absorbed and only solid parts will be left (CE4) →
- Inactive calcified, solid cyst (CE5).

The patients were followed-up for 2 years without any intervention and 20% of them had recovered in a natural process.

Natural detachment of endocyst wall (CE3a) can be interrupted by formation of multiple daughter cyst with septae, filled with highly infective parasitic fluid. In this case cyst is classified as CE2. The reason for CE1 to CE2 transition is not fully understood. However, host immune condition, number and infectivity of pathogen could influence the detachment of endocyst wall. The main reason for re-activation, classifiied as CE3b, is as a result of unsuccessful drug (albendazole) treatment. Albendazole can be prescribed in CE1, CE2, CE3a, CE3b stages of hydatid cyst with the single goal to progress the biological stage to CE4.

If patient is diagnosed at the CE4 stage in the first visit, the probability of inactivation of the cyst is very high. By follow-up study with CE4 patients, only 2% relapsed after 5 years. Therefore, when patients diagnosed with CE4 at the first visit, monitoring without any other management should be sufficient for recovery. However, if the patient transformed into CE4 in the result of albendazole treatment, around 50%

transform back to active stages because the viability of the parasite still remains and some daughter cysts re-formed with fluid. In the result, multiple daughter cysts with fluid are shown in a solid environment. Once the CE3b formed, the effect of albendazole decreases dramatically.

The difference between CE3a and CE3b were studied in terms of viablitiy. Direct assessment of *E. granulosus* and its viability (Microscope examination of protoscoleces after cyst fluid aspiration using vital staining) gives evidence for the parasitic nature and viability of a cyst (WHO/OIE, 2001). In Table 1, the comparison between stages daignosed by US and actual biological viability stages are shown. Among all samples taken during the CE3a stage, 42% were viable by light microscopy and 35% by MR scpetroscopy. Among all samples taken during CE3b, 88% were viable. The result confirms that there is a principle difference between these stages and treatment decisions have to be taken into account differently. The Gharbi and other classification did not account for this difference, and were, therefore, not optimal for determining the best treatment option.

Dr.Tamarozzi gave scietific evidence for each classification. For example since the earlier version of the CE classification, anti-helminthic treatment became an efficient non-invasive method for CE patient. Some major studies showed that 1-2 years after starting albendazole treatment, 50-75% of CE1 reach inactivation, 30-50% of CE2 and CE3 reach inactivation, better response if <6 cm (CE1) and on average 25% reactivate after first inactivation. The relapse in less than 1 year is about 50% of those inactivated. In the study of follow-up 12 months after albedazole treatment 77% of CE1 and CE3a had a response and no response for CE2 and CE3b. These results highly emphasize an important role for the WHO-IWGE classification for clinicians in choosing the right treatment for individual patients.

Table 1. Comparison of cyst stage by US, light microscopy and MR spectroscopy (Hosch et al,, 2007)

Stages by US	Number of samples	Light microscopy		MR spectroscopy	
		Viable	Non-viable	Viable	Non-viable
CE1	7	5	2	6	1
CE2	8	7	1	8	0
CE3A	**14**	**6**	**8**	**5**	**9**
CE3B	**9**	**8**	**1**	**7**	**2**
CE4	8	0	8	1	7
CE5	2	0	2	0	2

Presentation from Prof. Thomas Junghanss:
The main goal of the WHO-IWGE is to find the optimal treatment for patients. Therefore the- stage-specific-treatment-options are the nucleus of the WHO-IWGE guideline. It was introduced by Prof. Thomas Junghanss, a Head of Section of Tropical Medicine in University of Hospital of Heidelberg. Recently Prof. Junghanss appointed for team leader of clinical management of WHO-IWGE (2016). The important message at the beginning of the Prof.Junghass presentation was to bring the marginal disease, marginal populations in another word neglected diseases to the center of health system. However, in many parts of the world proper disease management is simply neglected. Elimination and control of CE can only be achieved using a One Health approach, a collaboration between human and animal health sectors in order to get added value.

In Europe, CE has been eliminated in most of countries, due to industrialization and development. However, prevalence in imported cases are high due to high migrants from endemic region. Therefore clinical management has been progressed in the most advanced conditions. Currently in Heidelberg hospital, CE patients are managed by a multidisciplinary group. Such technical group would consist of ultrasonographist, gastroentereologist, surgeon, anaesthesiologist, nand parasitologist.

Although surgery is considered as the main solution in many countries, the management before and after surgery is key to get successful recovery. A collaboration between clinicians, radiologists and surgeons is highly efficient in treatment and will prevent patient burden substantially. Implementation of stage specific treatment with a WHO-IWGE classification system can solve many of the issues in terms of health care inequality. Stage specicific treatment is about choosing the optimal treatment based on the WHO-IWGE classification. However, there are a few exceptions including rare location of the cyst, complicated cyst and disseminated cys, which are rare. The following figures are the slides from Prof.Junghanss about summary stage specific treatment.

The screening program is often used to decide on initiating a control program and to estimate epidemiologcal burden. It has been implemented extensively in many endemic regions. Prof. Junghanss highly emphasized that a plan for management needs to be available in advance to offer further diagnosis and management to patients in terms of screening.

In case management, national SOP-based diagnosis and treatment should include following essential components:

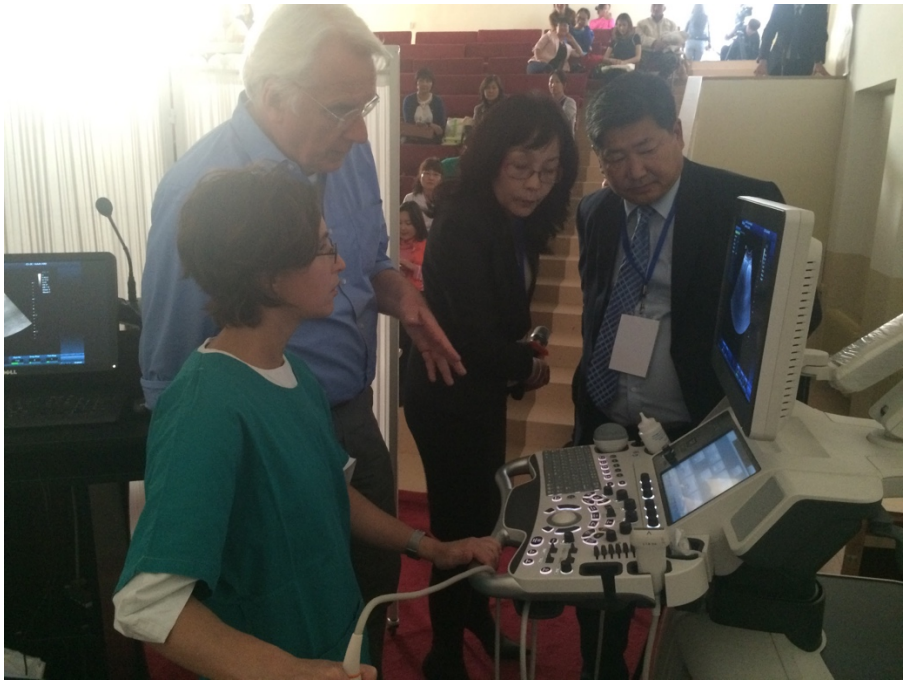
- Ultrasound-based treatment decision (→ regular course for local GPs to optimize case detection and follow-up in local areas including back up through telemedicine / smartphones
- Interdisciplinary management on the basis of agreed and implemented SOPs (→ full integration of CE management into health services
- Good communication between hospital and family physician (including via telemedicine / smartphones)
- Follow-up yearly for 5 years

Presentation from Dr. Bolor Bold

Dr. Bolor Bold, a PhD candidate from University of Basel and Swiss Tropical and Public Health Institute introduced the current project on CE. The local radiologist, clinicians active participation, awareness is crucial point for surveillance, control, and elimination. During the project, registration at the secondary level with the involvement of radiologist could contribute substantially to optimization of clinical management.

Hands-On training

Hands-on training was supervised by Dr. Francesca Tamarozzi and Dr. Erdenebileg Bavuujav from Society of Diagnostic Ultrasound and performed with the volunteer CE patients.



Prof. Thomas Junghanss and Dr. Francesca Tamarozzi and Dr. Erdenebileg confer on the patient image finding while performing US examination

Prof.Thomas Junghanss giving the consultancy on each patients image finding

The CE patients under monitoring of Dr. Amgalan Luvsanjav, a head of surgical department at First Central Hospital, and Dr. Bat-Ireeui, and Dr. Otgonbayar volunteered for examination. In each patient, Dr. Francesca Tamarozzi assisted by Dr. Erdenbileg performed US examination with a big screen and the image findings were discussed by Dr. Thomas Junghanss.

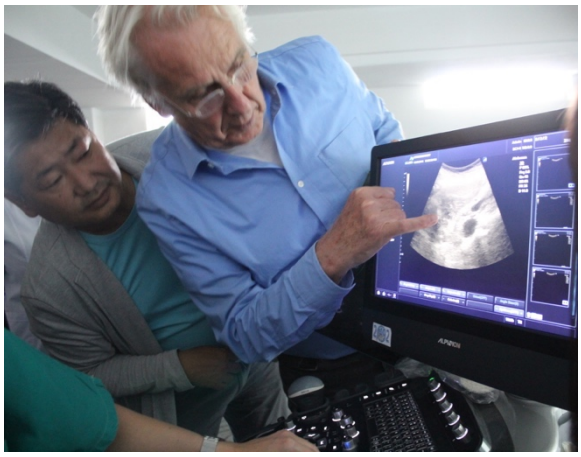
September 18-19, 2016: Hands-on training of WHO-IWGE classification and control in Dalanzadgad city

The team with international experts visited Dalanzadgad city of Omnogobi province to conduct hands-on training and workshop of CE with the local professionals.

In the field trip:

Dr. Erdenebileg Bavuujav, Mongolian Society of Diagnostic Ultrasound,
Dr. Tsogbadrakh Nyamdorj, National Center for Zoonotic Disease,
Dr. Shagj Agiimaa, National Center for Zoonotic Disease,
Dr. Uranshagai Narankhuu, National Center for Zoonotic Disease,
Dr. Chinchuluun Boldbaatar, Institute of Veterinary Medicine,
Dr. Bolor Bold, University of Basel
Dr. Bernadette Abela-Ridder, NTD, World Health Organization
Prof. Ning Xiao, National Institute of Parasitic Institute
Prof. Thomas Junghanss, Heidelberg University Hospital
Prof. Francesca Tamarozzi, Univeristy of Pavia,

From 18-19 of September, the hands-on training of WHO-IWGE and stage-specific-treatment of CE was held in General Hospital of Dalanzadgad city, organized by CZD and NCZD. In the training, the above working group and local health professionals, radiologists and family doctors from 20 soums and suspected and diagnosed CE patients participated.



Dr.Tamarozzi performing US examination

Prof. Junghanss is giving comment on the image findings

Dr. Francesca Tamarozzi and Prof. Thomas Junghanss gave presentations about WHO-IWGE and Stage specific treatment as presented in FCH on 15 September with small modifications for local health professionals. In addition, Prof. Junghanss explained the mechanism of percutaneous treatment (PAIR) in CE, and the principle of albendazole during follow up period and the common complication of CE. All participants received credit hours and certificate.

Dr.Erdenebileg is preparing the patients for examination

Table 2. The list of participants for hands –on training, Dalanzadgad, Omnogobi, 18 September

№	Name of Soums in Omnogobi	Participants` Name	Organization	Occupation
1	Bayan-Ovoo	S.Chuluuntogtoh	Soum clinic	physician
2	Bayandalai	T.Otgonchimeg	Soum clinic	physician
3	Bulgan	B.Dolgormaa	Soum clinic	physician
4	Gurvantes	D.Renchin	Soum clinic	physician
5	Khabogd	J.Narantsetseg	Soum clinic	physician
6	Khurmen	B.Tuul	Soum clinic	physician
7	Mandal-Ovoo	Ts.Narmandakh	Soum clinic	physician
8	Manlai	D.Ulambayar	Soum clinic	physician
9	Nomgon	B.Batchimeg	Soum clinic	physician
10	Noyon	Ts.Burmaa	Soum clinic	pediatrician
11	Sevrei	B.Uyanga	Soum clinic	physician
12	Tsogt-Ovoo	N.Olz	Soum clinic	physician
13	Tsogttsetsii	Amartuvshin	Soum clinic	Surgeon
14	Dalanzadgad	Ravdanjamts	“Khatanzayat” private clinic	US doctor
15	Dalanzadgad	Ch.Bolormaa	“Unu-Orshikh” family clinic	physician
16	Dalanzadgad	Gansuvd	“Shim bileg” family clinic	physician
17	Dalanzadgad	Enkhmaa	General Hospital	physician
18	Dalanzadgad	Solongo	General Hospital	US doctor
19	Dalanzadgad	Tsetsgee	General Hospital	physician
20	Dalanzadgad	Enkhtuya	“Tegsh duuren” private clinic	US doctor
21	Dalanzadgad	Erdenebayar	“Khunleg” private clinic	US doctor

On 19 September, a workshop held among public and veterinary professionals of Dalanzadgad city was organized by Dr. Altanchimeg from CZD and local health department. The list of participants is in Table 3. In the workshop, Dr. Bernadette Abela-Ridder gave a summary of the vision and goals of World Health Organization on Cystic Echinococcosis and Neglected Diseases, Prof. Ning Xiao from NIPD gave a presentation about control programs, especially campaigns to raise awareness of disease prevention of CE in Chinese endemic regions. All participants received credit hours and certificate.

Dr. Enkhjargal, Head of Health Department in Omnogobi province, opened the workshop

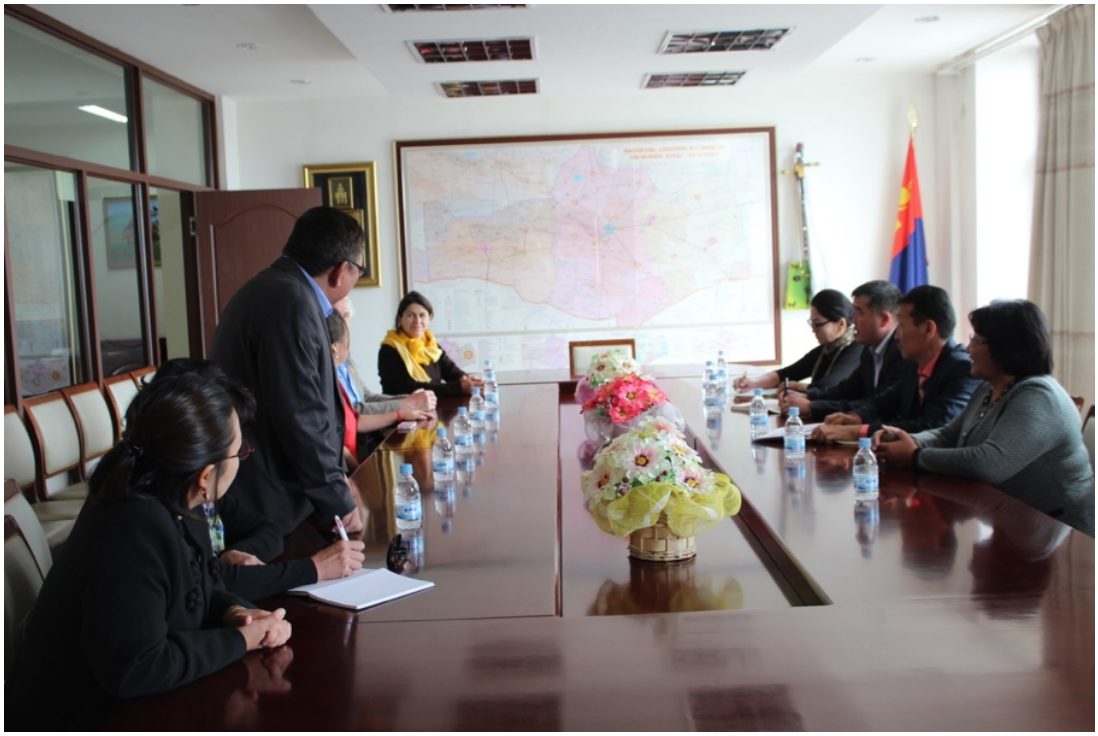
Table 3. Participants of workshop on prevention of CE , Dalanzadgad, Omnogobi province, 19 September

№	Soum* names of Omnogobi	Name	Organization
1	Dalanzadgad	D.Buyanbaatar	Veterinary Department
2	Dalanzadgad	J.Anhbayar	Veterinary Department
3	Khanbogd	B.Nandintsetseg	Soum hospital
4	Khanbogd	Ts.Narantuya	Soum hospital
5	Noyon	B.Javzan	Soum hospital
6	Noyon	Sh.Uyanga	Soum hospital
7	Bulgan	E.Byambadelger	Health Department
8	Bulgan	Kh.Shinekhuu	Health Department
9	Mandal-Ovoo	Duuvee	Health Department
10	Mandal-Ovoo	Tserensuren	Health Department
11	Sevrei	Bayartsengel	Soum hospital
12	Gurvantes	E.Uranchimeg	Health Department

13	Gurvantes	M.Manduukhai	Health Department
14	Dalanzadgad	Shurentsetseg	Center of Zoonotic Disease
15	Dalanzadgad	Sh.Oyuntuya	Center of Zoonotic Disease
16	Dalanzadgad	Chuluundavaa	"Iveeh" private clinic
17	Mandal-Ovoo	Ts.Narmandakh	Clinic at the soum center
18	Khabogd	J.Narantsetseg	Clinic at the soum center
19	Sevrei	B.Uyanga	Clinic at the soum center
20	Dalanzadgad	Ch.Bolormaa	"Unu-Orshikh" family clinic

Dr. Bernadette Abela-Ridder presenting about CE from the WHO perspective.

Prof.Ning Xiao giving presentation about CE awareness raising, IE program in China



The team is meeting the Vice Governer of Omnogobi province.

The vice Governer of Omnogobi province Mr. Batbold and Head of Veterinary department, Dr. Munkhchuluun and Dr Altanchimeg from CZD at the meeting.

Team visited the laboratory of CZD in Omnogobi province

Team visited the laboratories of veterinary health department. The macro specimen at the parasitological laboratory.

The team in front of CZD in Omnogobi province with director Altanchimeg and her team.

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