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Article

The Diagnostic Challenge of Cystic Echinococcosis in Humans: First Assessment of Underreporting Rates in Mongolia

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Abstract: Cystic echinococcosis (CE), caused by the larval stage of *Echinococcus granulosus*, is significantly underreported in Mongolia due to geographical remoteness, lack of early diagnostics, and poor clinical management. This study aimed to provide a more accurate estimate of CE in Mongolia by comparing data of surgical (reported) and diagnosed (unreported) cases, and assessing the challenges faced by rural doctors in disease management and surveillance. We collected data on surgical cases hospitalized between 2006-2016 and newly diagnosed CE cases in 2016 from eight provinces. Using a quasi-Poisson regression model of the collected data, we used extrapolation to estimate the number of diagnosed cases for the entire country. Additionally, forty health professionals from all 21 provinces rated local clinical management for CE through a questionnaire. Results reveal that surgical cases (2.2 per year) represent only one-eighth of diagnosed cases (15.9 per year). The laboratory facilities, disease reporting, and cyst classification usage scored below 2. These results highlight the significant underreporting of CE in Mongolia and urges human and animal health experts, along with policymakers, to invest into combating CE, particularly in remote provincial areas. It also emphasizes the need for standard clinical management involving cyst classification according to WHO-IWGE, seamless integration of CE reporting and monitoring mechanisms, which can significantly contribute to the national and global burden estimation of CE.

Keywords: cystic echinococcosis 1; Mongolia 2; clinical guideline 5; burden of disease 6; *Echinococcus granulosus* 6

1. Introduction

Cystic echinococcosis (CE) caused by the larval stage of *Echinococcus granulosus* is a zoonotic disease with a substantial global impact on the human and animal health sectors [1,2]. Humans and intermediate host animals can get the infection by ingesting parasite eggs that are excreted with feces of dogs or other canine species, as they harbor the adult stage of the parasite in their intestines [3]. The ingested eggs can develop into cysts filled with parasite larvae, primarily affecting the liver and lungs, leading to the main clinical symptoms. 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 [4,5].

Ultrasound is a gold standard for diagnosing, staging, and monitoring CE cysts, especially in abdominal sites 6,7. Cyst staging of CE based on ultrasound is pivotal for clinical decision-making

for uncomplicated liver CE cysts [5,8]. Gharbi et al., introduced the initial widely accepted cyst classification of CE in 1981 [9]. Although several classifications emerged thereafter, their adoption was limited. In 1994, due to the introduction of new potential treatments of CE including albendazole and percutaneous treatment, the World Health Organization - Informal Working Group on Echinococcosis (WHO-IWGE) started to develop an internationally standardized ultrasound classification, to establish universal application replacing the diverse range of classifications previously used and to guide the clinical decision making in treating the CE patient [7,10–12]. The four treatment modalities that are specified in WHO-IWGE are: medical (albendazole alone), percutaneous treatment such as Puncture, Aspiration, Injection, Re-aspiration (PAIR), surgical treatment for active cyst stage CE1 to CE3b and 'watch & wait' for inactive cyst stages CE4 and CE5 [13–16]. However, ultrasound can miss small cysts, lung cysts, and access to high-quality devices and expertise in recognizing CE characteristics is limited, especially in remote low- and middle-income countries [12,17].

Serology serves as a complementary method in addition to imaging. While the sensitivity and specificity of various antigens have been established, current assays still face challenges in standardization and accuracy [18]. Debates persist regarding their clinical diagnostic and screening utility, with serodiagnostic performance influenced by factors like cyst location, stage, and size, while these variables remain inadequately assessed to date [19,20]. A recent review confirmed that cyst staging significantly influences the sensitivity of ELISA tests, with sensitivity ranging from 60-90% for CE1-CE3 stages, but dropping below 50% for CE4, CE5, and inactive cysts [8].

Disease affects mostly the rural, farmer communities due to their closeness to the host animal population [21,22]. In remote settings, expertise in ultrasound diagnosis and management is limited, and conventional serology techniques are lacking due to inadequate laboratory facilities and personnel in remote areas [17,23]. These conditions lead to underdiagnosis, underreporting and a large number of individuals with CE remaining undetected until the disease progresses to an advanced stage, resulting in significant underestimation of the disease's global prevalence [24–26].

The current global disease burden of CE is estimated to be 184,000 disability-adjusted life years (DALYs), and this number can rise to more than 1 million if underreporting rates are adjusted based on a few available population surveys [1,2,25,26]. The complex challenge of quantifying the prevalence of CE has been prominently discussed in the recent WHO Neglected Tropical Disease roadmap 2021-2030 [27]. To overcome this challenge, there is a strong emphasis on establishing efficient diagnostic tools that are easily applicable in remote settings, and on successfully implementing standardized guidelines for clinical management. This will greatly impact our understanding of the true disease distribution [17,24].

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 [28–30]. 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 [29,31]. Due to the lack of reporting, the current prevalence estimate of CE is based on the number of cases that received surgical treatment, almost exclusively provided by the three national hospitals located in Ulaanbaatar city, the capital of Mongolia [32,33]. In the current situation, rural populations have very limited access to health service for CE. The challenge of finding reliable data on cases having been diagnosed but not yet referred to these national hospitals is the main cause of the huge underreporting [28,30,34]. Our study aims to provide a more accurate estimate of CE by establishing the underreporting rate from comparison of data of surgical (reported) and diagnosed (unreported cases), and to understand the challenges in clinical management that contribute to this lack of reporting through health professional's questionnaire.

2. Materials and Methods

2.1. 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.

2.2. Data Collection

In Mongolia, each province has one secondary level hospital, the Provincial General Hospital (PGH), where radiologists initially detect, or suspect CE cases based on ultrasonography imaging [34]. These patients are then referred to tertiary hospitals, located exclusively in the capital city of Ulaanbaatar. Examinations of patients that are not hospitalized at PGH often go unreported in electronic registries, and paper-based records of ultrasonography lack consistent information. Therefore, those who reach tertiary level hospitals are reported to the health system as surgical hospitalizations, but most of the cases diagnosed at the PGH get unreported or unregistered.

To estimate the underreporting rate, we divided the CE cases into two different categories, depending on their level of health service received and the situation of their registration

2.2.1. Surgical Cases

Patients hospitalized between 2006 and 2016 in the surgical department of national hospitals with a diagnosis at the discharge of ICD 10 code for CE, which is 67.1-67.9. These data were retrieved from the digital database archive of the Center for Health Development, Ministry of Health, Mongolia. Information extracted included patient age, sex, registration number, residential province, admission date, hospital name, and treatment category of the patients.

2.2.2. Diagnosed Cases

The cases diagnosed by the ultrasonography at the PGH (secondary health care center at the province), but which have not yet received any service at a tertiary hospital, are termed diagnosed cases. Obtaining data records of these cases is highly challenging due to inconsistencies in reporting and the lack of maintenance of paper-based records. Therefore, we collaborated with radiologists at the PGH in eight provinces to enter the newly diagnosed cases for one year (2016) into our online data collection tool developed only for this study. To reduce misdiagnoses, all participating radiologists had a minimum of 2 years of radiology training background, and only those with over 10 years of experience were recruited. In the online system, anonymized patient information was recorded, including age, sex, cyst location, features in the imaging, and treatment recommendation. Moreover, radiologists created a paper version of the record for the later double entry by the local epidemiologists. Since fully calcified cases do not need treatment and are not referred, we excluded all cases diagnosed as full calcification.

2.3. One Round Delphi Survey of Healthcare Professionals

The survey was conducted adjunct to the national stakeholder seminar on CE, held 18 September 2016. Participants were invited to complete the survey following their attendance at the seminar, with the aim of gathering expert opinions on clinical management and diagnostic challenge of CE in provincial hospitals. We invited one radiologist from each PGH and one epidemiologist from the local zoonotic center in each province (infection specialists at the PGH were invited for the provinces that had no local zoonotic center) to answer the questionnaire. A total of 17 radiologists from 17 provinces, 21 epidemiologists from 21 provinces and 2 epidemiologists from the city participated in this survey.

A questionnaire comprising 20 questions assessed the clinical management of CE at PGH, focusing on diagnosis, treatment, and reporting. Participants rated each indicator on a scale from 0 to 6, with 0 indicating the worst and 6 indicating the best score. The full questionnaire is provided in the supplementary document (S1). We categorized the questions into three sections according to their related topic: diagnosis, treatment, and surveillance. Here we provide the main contents of these three sections (full version is in Supplementary document 1): i) Diagnosis: 1.1 Availability of Ultrasonography, 1.2 Adequacy of Imaging Doctors (2 years training), 1.3 Adequacy of Imaging Doctors (3 months training), 1.4 Use of Clinical Guidelines, 1.5 Doctor's Ability to Identify CE, 1.6 Availability of Serological Kits, 1.7 Availability of Parasitological Lab, 1.8 Availability of Parasitologists, 1.9 Availability of Histological Lab, 1.10 Availability of Histologists; ii) Treatment: 2.1 Use of Cyst Classification, 2.2 Availability of Albendazole, 2.3 Knowledge of Albendazole Treatment, 2.4 Frequency of Monitoring Check-ups, 2.5 Frequency of Follow-up Visits; iii) Surveillance: 3.1 Use of Digital Registration, 3.2 Consistency of Referrals Registration, 3.3 Consistency of Treatment Registration, 3.4 Consistency of Notifiable Disease Reporting (NDR), 3.5 Consistency of Reporting to Zoonotic Center.

2.4. Data Analysis

2.4.1. Estimating the Underreporting Rate of CE

We first removed all calcified cases from our registry of diagnosed cases, as these do not require treatment, only monitoring. Pulmonary cases mostly cannot be identified through ultrasonography, so we also disregarded them from the registry of surgical cases. The number of diagnosed but not surgically treated (non-surgical) cases in 2016 was calculated as the difference between the number of diagnosed cases and the number of surgical cases. These differences were fitted using a Quasi-Poisson regression model, which included the natural logarithm of the average annual count of surgical cases over the period 2012-2016 in the respective province as an independent variable. The model was used to predict the number of diagnosed non-surgical cases in 2016 across other provinces

For the eight provinces with recorded numbers y_i of diagnosed non-surgical cases, the following empirical Bayes estimate was used instead of the observed number y_i :

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

where y_i and \hat{y}_i denote the recorded and fitted numbers of non-surgical cases in province i , respectively, and

$$w_i = \frac{y_i}{y_i + [SE(\hat{y}_i)]^2} \quad (2)$$

In the other provinces, the number was predicted by \hat{y}_i . Similarly, an empirical Bayes estimate was computed for the average annual number of surgical cases in 2016 using the prediction provided by a Quasi-Poisson regression model with a linear time trend variable fitted to the annual numbers of surgical cases between 2006 and 2016.

The numbers of surgical and non-surgical cases in 2018 were then estimated by multiplying their estimates for 2016 by the factor

$$\exp(2\hat{\beta}) \quad (3)$$

with $\hat{\beta}$ denoting the coefficient of the variable year in the aforementioned model.

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

$$SE(\hat{y}) \cdot z_1 \quad (4)$$

to the respective point estimate \hat{y} , with z_1 being sampled from the standard normal distribution, and then multiplying this sum by

$$\exp(2\hat{\beta}) \cdot (1 + 2SE(\hat{\beta}) \cdot z_2) \tag{5}$$

with z_2 being another standard normal random number. The standard error of the estimate of n_2 included two components: the uncertainty of the regression model and the uncertainty associated with the over-dispersion of provincial counts.

In a further step, the estimated counts of 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 account for the statistical uncertainty introduced by this factor, these estimates were multiplied by the factor

$$1 - \frac{SE(p_{NP})}{p_{NP}} \cdot z_3 \tag{6}$$

with $SE(p_{NP})$ denoting the standard error of p_{NP} and z_3 being another standard normal random number.

After iterating these simulation steps 1,000,000 times, the 95% confidence limits were estimated by the 2.5th and the 97.5th percentiles of the simulated values.

2.4.2. Summarizing the Healthcare Professionals Survey

The survey results, rated on a Likert scale from 0 to 6, were aggregated and averaged to rank results from high to low scores, to identify the most significant challenges in clinical management of CE at provincial (secondary) level.

3. Results

3.1. Estimated Cases of CE

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 10 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 (95%CI 387-570) (Table 1). The prevalence (per 100'000 person) 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 (Table 1).

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

Categories	Cases		Prevalence*	
	mean	95% CI	mean	95% CI
Surgical cases	67	55-80	2.2	1.8-2.7
Non-surgical cases	409	321-500	13.6	10.7-16.6
Total diagnosed cases	476	387-570	15.9	12.9-19.0

* Number of cases per 100,000 persons.

3.2. Survey Result from Healthcare Professionals

Results from the health professionals survey are shown in Figure 1. It shows that in the Diagnosis category, the highest score was for the Availability of Ultrasonography, which received a rating of 3.97. The lowest score in this category was for the Availability of Parasitologists, with a rating of 1.09. All the scores related to laboratory capacities are low, ranging between 1.31 and 1.83. The next lowest score is for the Use of Clinical Guidelines, which has a rating of 2.05. In the Treatment category, the highest score was for the Frequency of Follow-up Visits, rated at 2.13, while the lowest score was for the Availability of Albendazole, with a rating of 1.33. Except for the Frequency of Follow-up Visits,

all scores in the Treatment category are below 2. For the Surveillance category, the highest score was for the Use of Digital Registration, which had a rating of 2.68, and the lowest score was for the Consistency of Notifiable Disease Reporting (NDR), with a rating of 1.32.

Overall, the top three scores were for the Availability of Ultrasonography (3.97), Adequacy of Imaging Doctors (2 years) (3.67), and Doctor's Ability to Identify CE (3.60). The lowest three scores were for the Availability of Parasitologists (1.09), Availability of Parasitological Lab (1.31), and Consistency of Notifiable Disease Reporting (1.32).

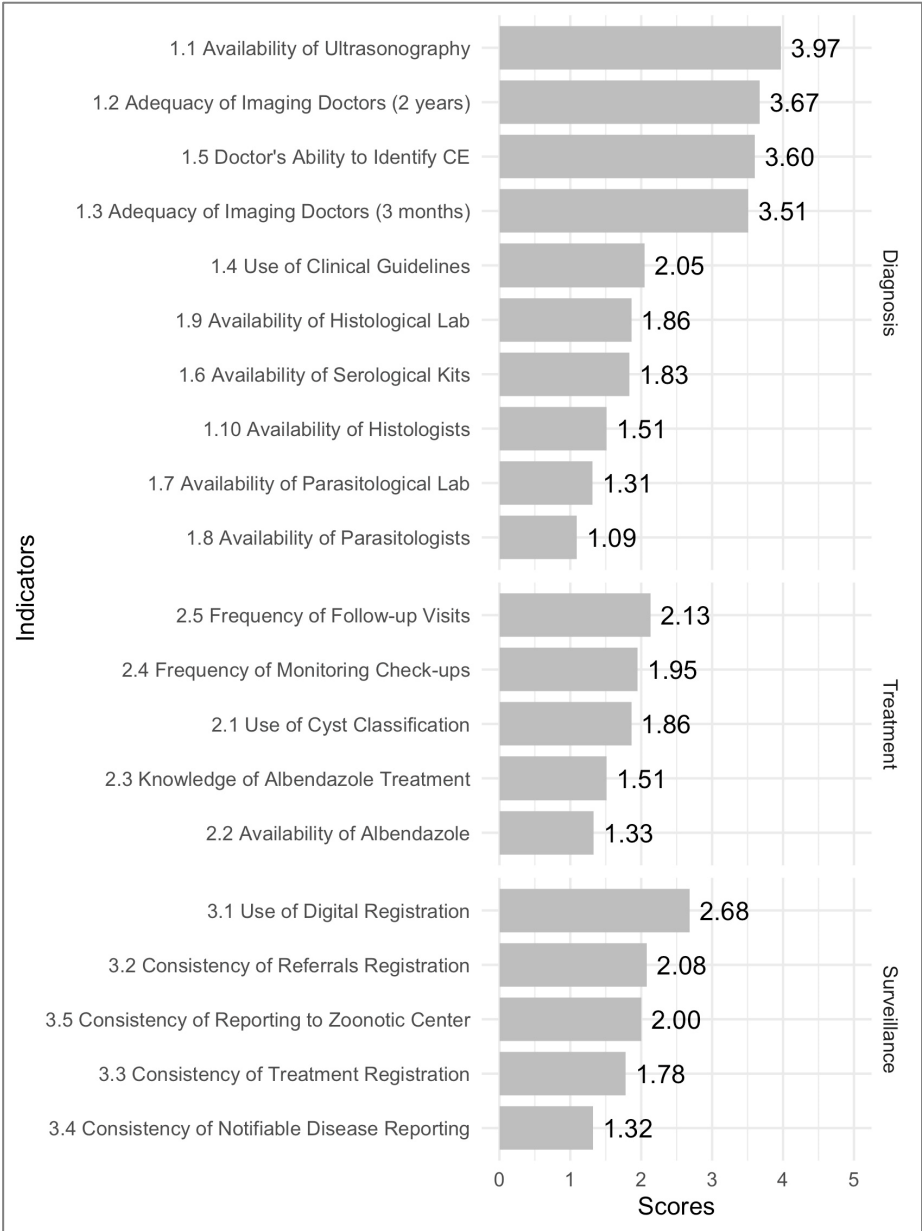


Figure 1. Average adequacy scores for the clinical management of CE at PGH by healthcare professionals across the 21 provinces of Mongolia.

4. Discussion

In this study, we aimed to address the underreporting of CE in Mongolia by comparing surgical and diagnosed cases and to understand the challenges in the clinical management of CE patients in rural provinces through a survey of health professionals. Our results suggest that the current prevalence of CE based on surgical cases, which is 2.2 per year, might represent only one-eighth of the total number of diagnosed cases, estimated to be 15.9 per year. Additionally, healthcare professionals rated laboratory facilities, disease reporting, and the usage of cyst classification in

clinical practice as poorly performing, with all aspects scoring below 2 out of 6. These results emphasize the need for the standardization of clinical management systems with cyst classification such as WHO-IWGE [10], with seamless integration of CE reporting and monitoring mechanisms, which can significantly improve the underreporting situation of CE.

Estimating the global burden of CE is highly challenging, particularly as the disease primarily affects rural pastoral communities where residents live far from healthcare facilities [24–26]. In such settings, advanced diagnostic capacity is often limited. This is reflected in our health professionals' survey, where parasitological, histological, and serological laboratory facilities all scored below 2. The remoteness and diagnostic challenge are an inherent aspect of the disease that is difficult to change [17,35]. In contrast, clinical management and surveillance systems can indeed be improved just with better communication and governance [7,12,27]. In our survey, CE reporting to the NDR system in Mongolia got the second lowest average score, while such reporting should be mandatory for most infectious and zoonotic diseases. This is because CE cases are predominantly encountered by clinicians, particularly surgeons and radiologists, who often do not have direct contacts to infection specialists or epidemiologists. In 2017, the Ministry of Health mandated CE reporting in the NDR, which eventually failed to yield results due to the absence of clear guidance on communication between clinicians and epidemiologists [34]. This experience underlines the importance of the communication and dialogue between and within the sectors for handling such complex diseases as CE [7].

Our survey indicates that Mongolian health specialists do not view a lack of ultrasound machines or technical ability to identify CE by ultrasound as the main issues; these scored highest in adequacy with 3.60–3.97. Instead, they identify poor usage of cyst classification and inadequate disease monitoring as significant obstacles to effective clinical decision-making, both scoring lowest with 1.86–1.95. Implementing the current clinical guidelines from WHO-IWGE, which include cyst classification and stage-specific treatment algorithms, can significantly improve the situation [12,28,34]. In 2016, the National Center for Zoonotic Disease and the Mongolian Society of Diagnostic Ultrasound introduced the WHO-IWGE guidelines to Mongolian doctors. This initiative was implemented through multisectoral dialogue [34]. However, its effectiveness raises questions, given the country's lack of the four treatment modalities outlined in the guidelines. Percutaneous treatments such as PAIR are not performed due to a lack of interventional radiologists in the country. Furthermore, albendazole supply is not sufficient and costly [34]. This leaves surgery as the only remaining treatment option. In consequence, the utility of WHO-IWGE guideline and its cyst classification is still limited. In fact, many endemic countries, face similar challenges to Mongolia due to the absence of a standardized cyst classification system [24,36]. A current review revealed that only 50% of 173 studies selected for review used the cyst staging in their report, highlighting the global challenges in implementing cyst staging in clinical settings [8,37]. Significant progress has been made with the recent introduction of free albendazole distribution organized by WHO. Such progress is crucial for the effective global implementation of the WHO-IWGE guideline, as it ensures non-surgical treatment at remote, local healthcare facilities, reducing the need to refer patients to advanced facilities and the economic burden of patients [27].

Resources for serological tests at provincial level, scoring 1.83, were another challenge addressed by health professionals. Although currently available conventional serological methods, such as the ELISA test, are not yet fully reliable for diagnostic purposes, significant progress in their sensitivity and specificity has been made in recent years [18–20]. However, in Mongolia, where maintaining lab facilities and resources in remote areas is difficult, easily applicable tests such as Rapid Diagnostic Tests (RDTs) might be more practical at the provincial level. Recent reviews have shown that RDTs for active cysts demonstrate a sensitivity of 74% and a specificity of 96%, which are comparable to the ELISA test results of 69% sensitivity and 96% specificity [28,38]. Furthermore, current evaluations of serological analyses indicate that cyst staging was the only statistically significant factor for the accuracy of serological results, emphasizing the importance of cyst classification [28,34].

Based on our estimates, the prevalence could be approximately 16 cases per 100,000 persons, which is eight times higher than the number of reported surgical cases. This does not imply that this is the true prevalence, but rather a more accurate estimate if passive surveillance was included the

CE. To make our two data sources as comparable as possible, we did not account for non-abdominal and calcified cases in our estimation. Non-abdominal cases are unlikely to be detected at the PGH, and calcified cases would not be reported as surgical cases. Thus, the actual number of diagnosed cases is likely higher. In terms of the number of cases, regional differences may exist, as evidenced by a recent ultrasonographic survey in four Mongolian provinces showing prevalence variations from 2% to 13% [33]. We did not compare regional differences, focusing instead on underreporting due to issues in the clinical management and surveillance systems. The robustness of our data collection is supported by the high qualifications of participating radiologists, who had a minimum of 2 years of radiology training and over 10 years of professional experience, ensuring accurate identification of CE.

Our study highlights the significant underreporting of CE in Mongolia, urging human and animal health experts, along with policymakers, to invest into combating CE, particularly in remote provincial areas. It emphasizes the need for further investigation at the population level within the One Health framework to determine the true extent of the disease burden and to obtain more accurate infection rates for control measures. While the remoteness of affected communities, chronic latent symptoms, and lack of early detection methods pose inherent challenges that are difficult to overcome, improvements in clinical guidelines, cyst classification, and better communication between healthcare specialists can significantly enhance disease management and surveillance. Our study provides valuable insights that are helpful to understand the challenges in implementing the WHO-IWGE guidelines and in disease reporting in low- and middle-income countries.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. For the full version of the questions in the survey of healthcare professionals, please refer to Supplementary Document.

Author Contributions: Conceptualization, Bolor Bold, Christian Schindler, Uranshagai Narankhuu, Agiimaa Shagj, Sonin Sodov, Tsogbadrakh Nyamdorj and Jakob Zinsstag; Data curation, Bolor Bold, Christian Schindler, Uranshagai Narankhuu, Erdenebileg Bavuujav, Sonin Sodov, Tsogbadrakh Nyamdorj and Jakob Zinsstag; Formal analysis, Bolor Bold, Christian Schindler, Uranshagai Narankhuu, Agiimaa Shagj and Jakob Zinsstag; Funding acquisition, Bolor Bold, Tsogbadrakh Nyamdorj and Jakob Zinsstag; Investigation, Bolor Bold, Christian Schindler, Uranshagai Narankhuu, Agiimaa Shagj, Erdenebileg Bavuujav, Sonin Sodov, Tsogbadrakh Nyamdorj and Jakob Zinsstag; Methodology, Bolor Bold, Christian Schindler, Sonin Sodov, Tsogbadrakh Nyamdorj and Jakob Zinsstag; Project administration, Bolor Bold, Sonin Sodov, Tsogbadrakh Nyamdorj and Jakob Zinsstag; Resources, Bolor Bold, Sonin Sodov, Tsogbadrakh Nyamdorj and Jakob Zinsstag; Software, Christian Schindler and Uranshagai Narankhuu; Supervision, Christian Schindler, Sonin Sodov, Tsogbadrakh Nyamdorj and Jakob Zinsstag; Validation, Bolor Bold, Christian Schindler, Erdenebileg Bavuujav, Sonin Sodov, Tsogbadrakh Nyamdorj and Jakob Zinsstag; Visualization, Bolor Bold and Uranshagai Narankhuu; Writing – original draft, Bolor Bold, Christian Schindler, Tsogbadrakh Nyamdorj and Jakob Zinsstag; Writing – review & editing, Bolor Bold, Christian Schindler, Erdenebileg Bavuujav, Tsogbadrakh Nyamdorj and Jakob Zinsstag. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and 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.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data supporting the reported results are available from the National Center for Zoonotic Disease of Mongolia (NCZD) for researchers who meet the criteria for access to confidential data. Interested researchers can request access by contacting the director of National Center for Zoonotic Disease of Mongolia at amgalanbayar.bandikhuu@nczd.gov.mn; nczd@nczd.gov.mn. Due to privacy and ethical restrictions, the data are not publicly available.

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