Intense Focus of Alveolar Echinococcosis, South Kyrgyzstan

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Human alveolar echinococcosis (AE) is a highly pathogenic zoonotic parasitic disease caused by *Echinococcus multilocularis*. An ultrasound study in southern Kyrgyzstan during 2012 revealed a prevalence of 4.2% probable or confirmed AE and an additional 2.2% possible AE, representing an emerging situation. The risk for probable or confirmed AE was significantly higher in dog owners.

Human alveolar echinococcosis (AE), caused by the larval stage of *Echinococcus multilocularis*, is a lethal parasitic zoonosis if untreated (*1*,*2*). In China, hyperendemic foci of disease have been described (*3*) with prevalences >5%. AE incidence recently has increased in Europe (*4*). In Kyrgyzstan, the disease incidence has increased rapidly since 2000; a total of 148 AE cases were reported in 2013 (*5*).

Hospital records for AE notifications identified a cluster of cases in the Alay Valley in southern Kyrgyzstan. Therefore, in 2012, we conducted an ultrasound study of the population of Sary Mogol (location 39.66°N, 72.88°E) to determine the extent of infection and to investigate the epidemiology of the disease in this district.

The Study

The study was a census type of design. We obtained informed consent from each study participant or, for children, consent from parents. Participants were interviewed using a questionnaire in Kyrgyz and given an abdominal ultrasound examination. For participants with hepatic lesions suspected to be AE or cystic echinococcosis (CE) or who reported previous treatment for echinococcosis, a venous blood sample was taken for further analysis. The Ministry of Health of the Kyrgyz Republic provided ethics approval for this study.

We detected specific IgG from collected serum in 3 genus-specific ELISAs based on *E. granulosus* hydatid fluid, native protoscolex antigens, and antigen B (*6*). Specific antibodies against *E. multilocularis* were demonstrated using affinity purified Em2G11 antigen (*6*) and the recombinant Em18 antigen (*7*). We further investigated persons who were negative in these ELISAs with a commercial Western blot (*Echinococcus* western blot IgG; LDBio Diagnostics, Lyon, France).

Where possible, we followed participants to treatment. For some patients we obtained samples from resected lesions. DNA was isolated, followed by amplification of part of the *E. multilocularis* mitochondrial 12S rRNA gene (*8*). Confirmation of diagnosis was also achieved by histologic examination of the resected lesions. Possible AE cases were those with ultrasound lesions and no follow-up. Probable cases additionally had positive serologic results, and confirmed cases were positive by histology, PCR, or both.

We analyzed data with all AE cases and with probable or confirmed AE as the dependent variable using a relative risk generalized linear model (GLM). We analyzed differences in lesion sizes between seropositive and seronegative groups by the Wilcoxon test and used Fisher exact test to examine differences in seroprevalence between persons with confirmed AE and persons with only an ultrasound diagnosis.

We examined 1,617 persons (Figure 1) (48% of the population of the district; online Technical Appendix, https://wwwnc.cdc.gov/EID/article/24/6/16-1641-Techapp1.pdf). Of these, 106 persons had ultrasound findings consistent with AE (including 1 concomitantly infected with CE). Probable or confirmed cases (online Technical Appendix) with ≥2 diagnostic criteria (Figure 1) were subsequently diagnosed in 68 (4.2%) persons leaving 36 (2.2%) with possible AE. Three (0.2%) additional persons had lesions suggestive of CE. For 9 persons, images were recorded as inconclusive.

The GLM demonstrated an increase in the risk for possible infection with AE in dog owners, male patients, and persons who practiced home slaughter of livestock. Only dog ownership increased the risk for probable AE infection (Table 1).

Of the 106 persons in whom AE was diagnosed, we detected specific antibodies in 40 (42.1%) of the 95 available serum samples by 3 different ELISAs (Table 2). Western blot analysis of negative serum identified specific antibodies on *Echinococcus* genus level in 9 additional patients. Thus, 49 of the 95 persons had serologic evidence of infection. Lesions, measured in 53 patients, ranged from

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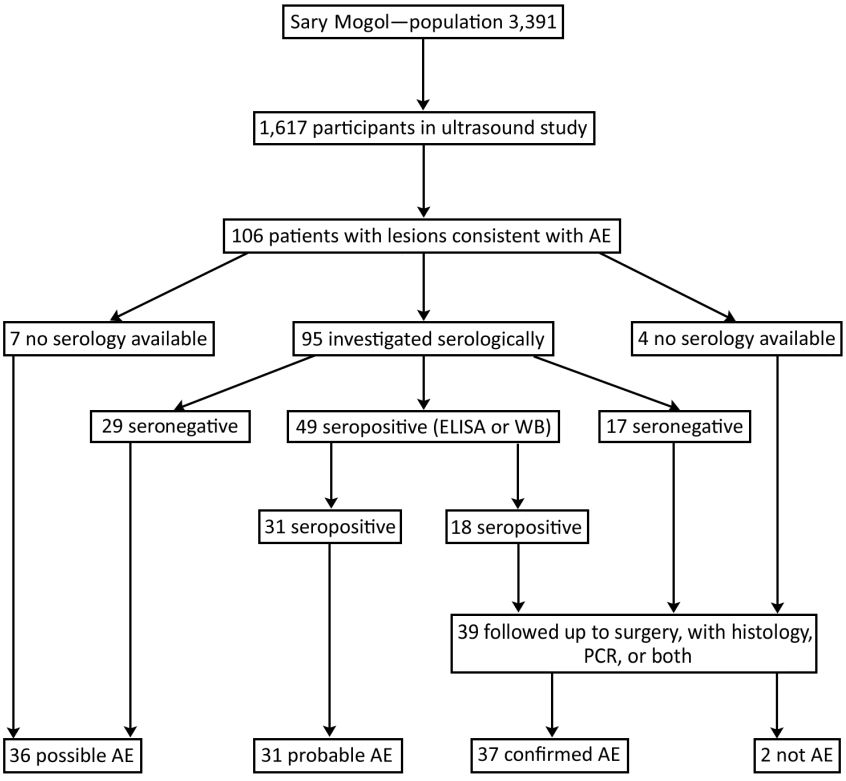

Figure 1. Flowchart of patient selection, ultrasound investigation, serologic testing, and case definitions in a study of AE, southern Kyrgyzstan, 2012. AE, alveolar echinococcosis; WB, Western blot.

5 to 197 mm (mean 28 mm). The mean size of lesions in the 22 ELISA- or Western blot–seropositive persons was 46.1 mm, significantly larger than the mean size of 11.0 mm for lesions from the 27 seronegative patients (p = 0.01; Figure 2).

By September 2017, a total of 39 persons were known to have been treated by hepatic surgery. Among them, AE was confirmed in 37 (94.7%) by histology, PCR, or both. From these 37 persons, 35 serum samples were available; 18 (51.4%) showed serologic evidence of infection. This finding did not differ significantly from the proportion of persons without follow-up data who had serologic evidence of infection (31/61) (Figure 1).

The decreasing risk for possible AE with increasing age, contrasting with findings in areas of China where AE is highly endemic (*9*), indicates different dynamics and hence reflect an emerging epidemic of human AE in Kyrgyzstan. Consequently, this observation supports the hypothesis that the epidemic could be linked to the dissolution of the Soviet Union in 1991 (*5*). In our study, the higher risk for possible AE in male than in female patients contrasts with risk in areas of western China where AE is endemic. The reasons for this difference are unclear but might reflect behavioral (e.g., rates of dog contact) or cultural reasons that result in a greater risk for exposure for female persons in China (*9*) and for male persons in Kyrgyzstan. However, both risk factors disappear if only probable or confirmed AE is used as the case definition for AE.

The poorer sensitivity (≈50%–60%) of the serologic tests as compared with the validations in Switzerland (*6*) might result from cases in Switzerland being

Table 1. Relative risk from multivariable analysis of persons with an ultrasound diagnosis of AE and persons with a probable or a confirmed diagnosis of AE, southern Kyrgyzstan, 2012*

Dependent variable, risk factor	Relative risk (95% CI)	p value
Ultrasound diagnosis of AE		
Patient age†	0.982 (0.969–0.995)	0.0074
Male sex	1.56 (1.07–2.29)	0.021
Dog ownership	1.82 (1.24–2.72)	0.0025
Home slaughter of livestock	1.60 (1.03–2.56)	0.043
Dog ownership among persons with probable and confirmed AE‡	2.81 (1.64–5.09)	0.00033

*Probable diagnosis: ultrasound and serology; confirmed diagnosis: ultrasound and histology/PCR. AE, alveolar echinococcosis.
†Median age of persons with possible AE was 24 y; median age of AE-negative persons was 28 y.
‡Dog ownership was the only risk factor remaining as significant when only probable and confirmed AE were analyzed as the dependent variables.

Table 2. Ultrasound results partially confirmed with PCR/histology for AE or CE in relation to serology, southern Kyrgyzstan, 2012*

	ELISA				WB†				
Ultrasound results	No. available samples‡	Neg	AE/CE§	AE¶	No. available samples‡	Neg	AE/CE	CE	AE
AE, n = 106	95	55	25	15	43	34	6	3	0
Confirmed AE,# n = 37	33	18	10	5	13	10	3	0	0
Inconclusive, n = 9	6	5	1	0	4	4	0	0	0
CE, n = 3	3	2	1	0	0	0	0	0	0
CE and AE, n = 1	1	0	1	0	0	0	0	0	0
Negative but with history of CE/AE, n = 13	6	1	3	2	1	1	0	0	0

*AE/CE indicates the test is specific only to genus level. AE, alveolar echinococcosis; CE, cystic echinococcosis; neg, negative; WB, Western blot.
†ELISA-negative serum only.
‡Not every patient for whom echinococcosis was diagnosed by ultrasound had inconclusive results or a history of echinococcosis provided a blood sample. For some of these patients, insufficient serum was available from the blood sample to undertake both ELISA and WB.
§*E. granulosus* hydatid fluid and/or native protoscolex antigens and/or antigen B positive but Em18 and EmG11 negative.
¶Em18 and/or EmG11 positive (*E. granulosus* hydatid fluid and/or native protoscolex antigens and/or antigen B positive or negative).
#Diagnosis confirmed by PCR and/or histology of resected lesion.

at a more advanced stage of clinical disease. The fact that persons with larger lesions were more likely to be seropositive indicates that seroconversion might not occur either during the early stages of the disease or when only abortive lesions are present. Similar patterns of low seroreactivity were observed in the AE endemic focus in south Gansu (China) (*10*) and included persons with possible abortive forms of the disease. In addition, the mean age of ultrasound-positive persons in our study is 9 years younger than those receiving surgical treatment resulting from clinical disease, indicating that our study has detected an early stage of the disease in these persons. In the patients followed up, the seropositivity rate for those with AE confirmed by histopathology did not differ significantly from the rate for those with only an ultrasound diagnosis. Thus, we can conclude that the same proportion of patients without histologic or PCR confirmation (to date) are likely to have AE. Although the diagnostic efficiency of ultrasound should be estimated with caution, these results might indicate a specificity as high as 99.7% (online Technical Appendix). However, including only probable or confirmed cases in the regression analysis increased the association with dog ownership while eliminating other risk factors. This finding might indicate that some of the possible AE cases are not AE. Nevertheless, specificity of ultrasound in this scenario remains at 97.4%.

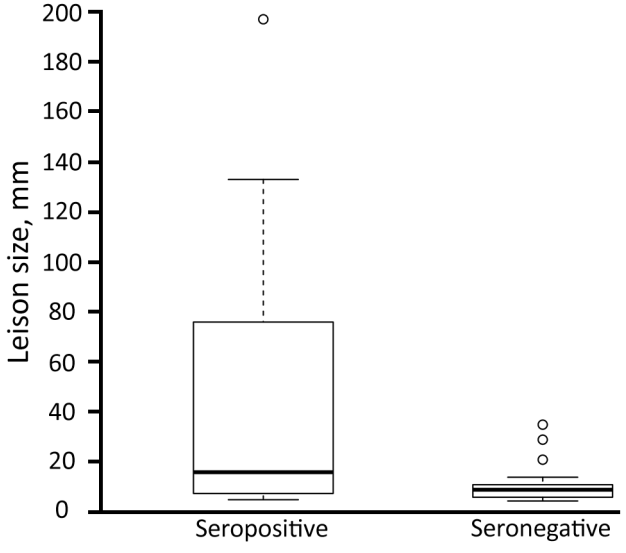

Figure 2. Differences in sizes of lesions (n = 49 serum samples available from 57 patients with measured lesions) diagnosed in persons seropositive by ELISA, Western blot, or both (n = 27) or seronegative (n = 22) in a study of alveolar echinococcosis, southern Kyrgyzstan, 2012. Box plots indicate interquartile range (box top and bottom), median (black horizontal line), 1.5 times interquartile range (error bars), and extreme values (circles).

Conclusions

We documented a highly endemic focus of human AE in which the prevalence of confirmed or probable AE was ≈4.2% in southern Kyrgyzstan. A characteristic of communities with high levels of human AE are concomitant high prevalences of *E. multilocularis* in the dog population, such as western Sichuan Province (*11*). The mole vole (*Ellobius tancrei*) has recently been confirmed as a natural intermediate host of *E. multilocularis* in Sary Mogol and has identical DNA sequence for the *E. multilocularis* haplotype described in feces of local domestic dogs (*12*). In Kyrgyzstan, prevalences in dogs of 20% have been observed (*13*). In our study, dog owners had 1.8 times higher risk for infection than non–dog owners, increasing to 3.3 times for confirmed or probable infection, thus providing evidence that dogs are involved in transmission to humans.

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Technical Appendix

Study Population

This study was conducted in the community of Sary Mogul in southern Kyrgyzstan (Technical Appendix Figure 1). The expected age distribution if ultrasound participants were precisely representative of census data are in Technical Appendix Table 1. The actual proportions by age and sex is in Technical Appendix Table 2. The differences between the expected proportions and actual population investigated is significant ($p<0.0001$, χ^2 test) Thus, there is an overrepresentation of adult females in the ultrasound surveillance group compared to the expected population according to the census. This may be due to men working (either locally or even abroad—a large number of Kyrgyz men of working age work in Russia ([*1*]) and send remittances back to Kyrgyzstan). Thus, they may not have been available. There was also some underrepresentation of very young children <4 years) and underrepresentation of elderly persons >70 years.

Details of Generalized Linear Model

Variables examined in the generalized linear model (GLM): Age, sex, size of household, length of time resident in Sary Mogul, occupation, dog ownership: if yes—type of dog (hunting or other), dog allowed to roam; visit to summer pastures, living standard, disposal of dog feces, children playing with dog, dog treated with antihelmintics, water supply (stream, well, pipe), wash fruit and vegetables, wash hands before eating, slaughter livestock, feed infected organs from slaughtered livestock to dogs, know about echinococcosis, previous infection with echinococcosis.

The GLM was a binomial model with a log link with ultrasound positive for alveolar echinococcosis (AE) as the dependent variable. The log link (rather than logit) gives an

interpretation in terms of significant variable as relative risk of infection associated with that variable (as opposed to the logit, which gives the odds ratio). All computations were undertaken in R (https://www.r-project.org). A backward selection method was used with all variables initially included; with each iteration, the least significant variable was removed until only variables with $p<0.15$ remained in the model. Variables with $p<0.05$ in the final model were reported as significantly associated with the presence of an AE lesion diagnosed by ultrasound.

The adequacy of the model was addressed by a sensitivity analysis using R. Briefly the data were repeatedly and randomly split in subsets to address the predictive value of the model. Thus, parameters were derived from part of the data and used to predict the accuracy of the model on the remainder of the data. From these, an estimate of the sensitivity and specificity of the model can be made, as well as the overall accuracy (area under the curve in a Receiver Operating Characteristic Curve plot). The Area Under the Curve was 0.64 for the binomial model, which indicates the model had a modest predictive power, despite the significant parameters (Technical Appendix Figure 2). In addition the pseudoR^2 was 0.046 indicating that the final model parameters: dog ownership, sex, age and slaughter of livestock could only predict ≈4.6% of the variation in infection with AE. Variable importance analysis indicated that dog ownership (3.02) had the greatest influence, followed by age of participant (2.68), sex (2.30), and home slaughter (2.02).

Patient Details

Of the 1,617 study participants examined by ultrasound, suspected AE was diagnosed in 106; in 1, cystic echinococcosis (CE) was concomitantly diagnosed. CE was diagnosed in 3 additional participants. Of these, 53 patients with AE had the lesions measured. The mean age of those with measured lesions was 28 years, and 49% were male; mean of those with unmeasured lesions was 20 years and 61% were male. Of the 37 patients who had follow up and lesions confirmed as AE by histopathology, 13 had been measured at the initial ultrasound scan. These had a mean size of 40.1 mm (range 7–133 mm). Of the remaining 70 who were lost to follow up, 40 had their lesions measured during the original ultrasound scan and had a mean lesion size of 25.5 mm (range 5–197 mm). There was some statistical evidence that the group with follow up had larger lesions (Wilcoxen test, $p = 0.02$).

CE was diagnosed in only 3 participants (a prevalence of just 0.2%), which is too small a sample size to undertake any analysis for this disease. It is also a somewhat lower prevalence than found in similar studies elsewhere in Kyrgyzstan (*2*) or in a neighboring region of Kazakhstan (*3*). The reasons for this are not known, but ongoing research mapping all cases of echinococcosis and analyzing the geographic distribution may give clues to this.

Accuracy of the Diagnostic Procedures

Diagnostic accuracy of the serology and ultrasound examination can be assessed only against proven AE infections. We have examined 3 possible scenarios, all with the assumption that ultrasound has a diagnostic sensitivity of 100% (Technical Appendix Table 3):

1. Of the 39 patients followed up through treatment, 37 were proven to have AE after histopathology and/or PCR of the resected lesion. Of these 37 patients, 33 were examined serologically (4 serum samples were not available). Of the 33 serum samples, 18 had serologic evidence of infection through ELISA or Western blot, indicating sensitivity of serology to be 18/33 or 54.5% (exact binomial 95% CI 36.4%–71.9%). Thus, there are substantial numbers of false negatives suggesting that serology on its own is an insensitive diagnostic technique for this population. It is not possible to estimate the specificity of the serology without serologic data from those patients who were ultrasound negative, and serum samples were not taken for such serologic investigation. For the ultrasound examination, of 39 patients with a diagnosis of AE on ultrasound, 37 patients were proven to have AE by histopathology after lesion resection. If these 37 patients are assumed to be representative of the 106 patients who had a ultrasound diagnosis of AE, then it would be expected that ≈2/39 × 106 would be false positives = 5 false positives. Thus, 101 of the 106 would be true positives. Therefore, of the 1,617 patients examined, 1,516 would not be infected with AE. The ultrasound would have correctly identified 1,516 – 5 = 1,511 as not infected. Thus, the specificity of ultrasound can be estimated to be 1,511/1,516 = 99.7%. The prevalence of infection, assuming this specificity would be 101/1,617 = 6.2%.

2. A lower estimate of the specificity could be made by assuming that the 67 cases without follow up were all AE negative; thus, the false positives would be 69 of the 106 cases. In this instance, the number of patients not infected with AE would be 1,617–37 = 1,580, and the ultrasound correctly diagnoses 1,511 as not infected, giving a specificity of 1,511/1,580 = 95.6%.

The prevalence of infection, assuming this lower specificity, would be 37/1,617 = 2.3%. These all assume that the sensitivity of ultrasound is near 100%. This is reasonable because a case definition is a visible lesion consistent with AE on ultrasound. It is possible that there may have been cases of AE without a primary lesion in the liver, which would have escaped detection by ultrasound, but such cases are rare. Just 9 of 387 AE cases in France had primary extrahepatic lesions (*4*).

3. Alternatively 49 study participants (of 95 with serology) were serologically positive, and so probably had AE. In addition, there were 18 confirmed cases of AE (seronegative or no serum sample, but confirmed by histology), which would suggest 67 cases as confirmed or probable AE. This gives a prevalence of 4.1% and a specificity of the ultrasound as 97.4% (39 false positives in 1,550 not infected)

The sensitivity of the serology varies little between scenario 1 and 2, and we cannot estimate it in scenario 3. The positive predictive values (i.e., the probability of having AE given a positive diagnosis with ultrasound) varies from 34.9% to 94.8% depending on which scenario is adopted. The prevalence also varies, but even with the most conservative estimate, assuming all cases lost to follow up were AE negative, it still gives a high prevalence of 2.3%.

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Technical Appendix Table 1. Expected age and sex distribution of the 1,617 participants of the ultrasound surveillance based on the Kyrgyz census data*

Age, y	Female	Male	% Female
0–4	102.706499	106.896314	0.0635167
5–9	92.5792435	88.1877789	0.05725371
10–14	93.4082444	90.9436469	0.05776638
15–19	84.8493695	89.8457808	0.05247333
20–24	77.7020369	81.8918526	0.04805321
25–29	68.4485936	69.5240543	0.04233061
30–34	55.0501455	60.1585839	0.03404462
35–39	45.6174588	51.3980601	0.02821117
40–44	42.3910766	41.6741028	0.02621588
45–49	40.3521823	36.7449079	0.02495497
50–54	29.8888458	27.357032	0.01848413
55–59	22.0021339	18.1259942	0.01360676
60–69	22.786324	20.7698351	0.01409173
≥70	30.6506305	25.0492726	0.01895524
Total	808.432784	808.567216	0.4997

*The total population of Sary Mogul, Kyrgyzstan, is 3,391.

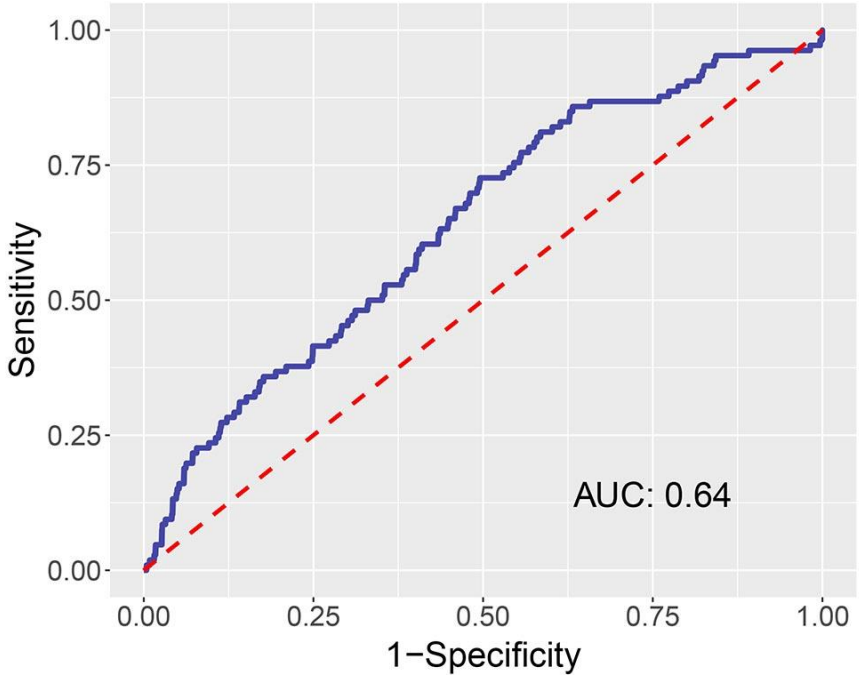
Technical Appendix Table 2. Actual age and sex distribution of the 1,617 participants of the ultrasound surveillance of alveolar echinococcosis, southern Kyrgyzstan, 2012

Age, y	Female	Male	% Female
0–4	25	33	0.01546073
5–9	104	89	0.06431664
10–14	111	112	0.06864564
15–19	94	57	0.05813234
20–24	62	39	0.03834261
25–29	96	68	0.0593692
30–34	97	64	0.05998763
35–39	85	40	0.05256648
40–44	70	38	0.04329004
45–49	58	21	0.03586889
50–54	69	31	0.04267161
55–59	51	22	0.03153989
60–69	32	15	0.01978973
≥70	16	8	0.00989487
Total	970	637	0.5999

Technical Appendix Table 3. Sensitivity and specificity of ultrasound and serology under varying assumptions in a study of alveolar echinococcosis, southern Kyrgyzstan, 2012

	Ultrasound				
Assumption	Sensitivity, %	Specificity, %	Positive predictive value, %	Serology, sensitivity, %	Prevalence, %
Confirmed cases are representative	100	99.7	94.8	54.5	6.2
Nonconfirmed cases are negative	100	95.6	34.9	51.4	2.3
Confirmed and/or seropositive cases are probable alveolar echinococcosis	100	97.4%	63.2		4.1

Technical Appendix Figure 1. Location of study area, Sary Mogul, southern Kyrgyzstan. Map data © 2017 Google.



Technical Appendix Figure 2. Analysis of relative risk regression results indicating the sensitivity and specificity of the predictions given by the model. Purple line indicates Receiver Operating Characteristic Curve; red line indicates line of no-discrimination.