Epidemic cystic and alveolar echinococcosis in Kyrgyzstan: an analysis of national surveillance data

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Summary

Background Human cystic and alveolar echinococcosis are among the priority neglected zoonotic diseases for which WHO advocates control. The incidence of both cystic echinococcosis and alveolar echinococcosis has increased substantially in the past 30 years in Kyrgyzstan. Given the scarcity of adequate data on the local geographical variation of these focal diseases, we aimed to investigate within-country incidence and geographical variation of cystic echinococcosis and alveolar echinococcosis at a high spatial resolution in Kyrgyzstan.

Methods We mapped all confirmed surgical cases of cystic echinococcosis and alveolar echinococcosis reported through the national echinococcosis surveillance system in Kyrgyzstan between Jan 1, 2014, and Dec 31, 2016, from nine regional databases. We then estimated crude surgical incidence, standardised incidence, and standardised incidence ratios (SIRs) of primary cases (ie, excluding relapses) based on age and sex at country, region, district, and local community levels. Finally, we tested the SIRs for global and local spatial autocorrelation to identify disease hotspots at the local community level. All incidence estimates were calculated per 100 000 population and averaged across the 3-year study period to obtain annual estimates.

Findings The surveillance system reported 2359 primary surgical cases of cystic echinococcosis and 546 primary surgical cases of alveolar echinococcosis. Country-level crude surgical incidence was 13·1 per 100 000 population per year for cystic echinococcosis and 3·02 per 100 000 population per year for alveolar echinococcosis. At the local community level, we found annual crude surgical incidences up to 176 per 100 000 population in Sary-Kamysh (Jalal-Abad region) for cystic echinococcosis and 246 per 100 000 population in Uch-Dobo (Alay district, Osh region) for alveolar echinococcosis. Significant hotspots of cystic echinococcosis were found in four regions: Osh (five local communities in Uzgen district and four in Alay district), Naryn (three local communities in Jumgal district and one in Naryn district), Talas (three local communities in Talas district), and Chuy (one local community in Jayyl district). Significant alveolar echinococcosis hotspots were detected in the Osh region (11 communities in Alay district, including the local community of Sary Mogol, and one in Chong-Alay district) and in the Naryn region (five communities in Jumgal district and three in At-Bashy district), in the southwest and centre of the country.

Interpretation Our analyses reveal remarkable within-country variation in the surgical incidence of cystic echinococcosis and alveolar echinococcosis in Kyrgyzstan. These high-resolution maps identify precise locations where interventions and epidemiological research should be targeted to reduce the burden of human cystic echinococcosis and alveolar echinococcosis.

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Introduction

Human cystic and alveolar echinococcosis are two severe zoonoses caused by the larval stage of *Echinococcus granulosus* sensu lato and of *Echinococcus multilocularis*, respectively. Domestic and wild canids harbour adult stages of the parasites in the small intestine and release parasite eggs in the environment through their faeces.[1] Human infection occurs through the ingestion of parasite eggs in contaminated food and water, hand-to-mouth contact after exposure to contaminated soil and objects, and direct contact with canid hosts. Infectious larvae (oncospheres) from ingested eggs penetrate the intestinal mucosa, reach the blood circulation, and further develop

into the metacestode stage, forming cysts (cystic echinococcosis) or infiltrative metacestode lesions (alveolar echinococcosis) in the liver and other organs. After an incubation period lasting from months to years, clinical symptoms can result from the growth of the parasitic lesions. In cystic echinococcosis, clinical symptoms are due to space-occupying lesions that can obstruct ducts, impair organ function, and rupture, causing anaphylactic shock or secondary bacterial infections. By contrast, in alveolar echinococcosis, infiltrating protrusions of the metacestode can cause tumour-like lesions in the liver, including metastases to distant organs. Both diseases are chronic, with cystic

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Research in context

Evidence before this study

In Kyrgyzstan, cystic echinococcosis and alveolar echinococcosis are highly endemic, and they are considered to be a public health emergency. Hence, cystic echinococcosis and alveolar echinococcosis are mandatory notifiable diseases, and the national surveillance system routinely collects data on confirmed surgical cases. We searched PubMed using the search string ("echinococcus"[Title]) OR ("echinococcoses"[Title]) OR ("echinococcosis"[Title]) OR ("human echinococcosis"[Title]) OR ("hydatidosis"[Title]) OR ("hydatid disease"[Title]) AND ("spatial") OR ("spatial analysis") OR ("mapping") OR ("map") OR ("local variation") OR ("local variations") on Jan 19, 2018, for countrywide, English-language studies providing subnational estimates of cystic echinococcosis or alveolar echinococcosis incidence at a high spatial resolution. Additionally, we searched for publications using English and Russian terms for cystic echinococcosis or alveolar echinococcosis in Kyrgyzstan. Al-Jawabreh and colleagues investigated the burden of surgically confirmed cystic echinococcosis cases in Palestine using hospital records, but their study was restricted to the second administrative level (district). Other studies have relied on hospital discharge forms of patients with either cystic echinococcosis or alveolar echinococcosis to estimate countrywide local disease patterns at a low subnational resolution or in countries where the disease is sporadic. Including Kyrgyzstan, no published countrywide studies at a finer spatial resolution on subnational cystic echinococcosis and alveolar echinococcosis variations using official surveillance data were available. Therefore, we investigated within-country variations of both diseases' surgical incidence and identified disease hotspots at the third administrative level—local community—using Kyrgyzstan's national surveillance data.

Added value of this study

We geolocated 3161 confirmed cystic echinococcosis or alveolar echinococcosis cases reported in Kyrgyzstan between 2014 and 2016. To our knowledge, we provide the first countrywide, high spatial resolution incidence estimates and hotspot identification of cystic echinococcosis and alveolar echinococcosis based on national surveillance data at the local community level. Notably high local incidences and hotspots of diseases were concealed by estimates and spatial analyses we previously did at the district level, highlighting the importance of high-resolution data in exploring within-country disease variations.

Implications of all the available evidence

Cystic echinococcosis and alveolar echinococcosis cause a substantial health burden, especially in economically disadvantaged societies. Although WHO prioritises echinococcosis control, cystic echinococcosis and alveolar echinococcosis are often not notifiable and continue to be neglected. Countrywide burden estimates, where present, are often limited to the first administrative level because of inadequate surveillance data. Our high spatial resolution results identify specific locations where epidemiological research should be prioritised to better understand transmission of the diseases to humans, and where scarce resources for control could be more cost-effective. Furthermore, the spatial epidemiology methods used in this study can be used in other settings to improve surveillance and control of cystic echinococcosis, alveolar echinococcosis, and other similar infections.

echinococcosis considered to be a disabling disease, whereas alveolar echinococcosis is lethal if untreated. Cystic echinococcosis treatment options include a watch-and-wait approach, albendazole treatment, surgical intervention (general or percutaneous), and combinations thereof depending on the stage, number, size, and location of the cysts.[2] Alveolar echinococcosis treatment can be achieved by radical surgery followed by albendazole treatment in case of early detection; otherwise, lifelong albendazole treatment remains the only approach.[2]

Cystic echinococcosis is found in all continents except Antarctica,[3] with an estimated 188 000 new cases per year resulting in a burden of 183 500 disability-adjusted life-years (DALYs) globally.[4] Annual surgical incidence of cystic echinococcosis ranges between 2·3 per 100 000 population and 18·0 per 100 000 population in highly endemic countries, with foci where incidence can exceed 30·0 per 100 000 population per year.[5] By contrast, alveolar echinococcosis is confined to the northern hemisphere,[3] primarily in China, central Asia, Russia, Europe, and North America, with an estimated 18 400 new cases per year resulting in 687 800 DALYs.[4]

Alveolar echinococcosis seems to be an emerging public health threat in Europe and potentially in North America.[6,7] In European endemic countries, annual incidences of alveolar echinococcosis range between 0·26 per 100 000 population (Switzerland in 2001–05) and 0·74 per 100 000 population (Lithuania in 2012).[3] However, alveolar echinococcosis is a focal zoonotic disease, with a local prevalence of more than 8% in some communities in China.[3]

Cystic echinococcosis and alveolar echinococcosis are notifiable in Kyrgyzstan (figure 1). The annual surgical incidence of cystic echinococcosis has increased from 5·4 per 100 000 population in 1991[8] to 15·8 per 100 000 population in 2013.[9] The first alveolar echinococcosis case was recorded in 1996, and 0–3 cases per year were reported until 2003.[10] Since 2004, the incidence has increased considerably, reaching 148 cases in 2013 (2·6 per 100 000 population per year).[9]

Cystic echinococcosis and alveolar echinococcosis are among the neglected zoonotic diseases prioritised by WHO. Inadequate data on the number of cystic echinococcosis and alveolar echinococcosis cases at
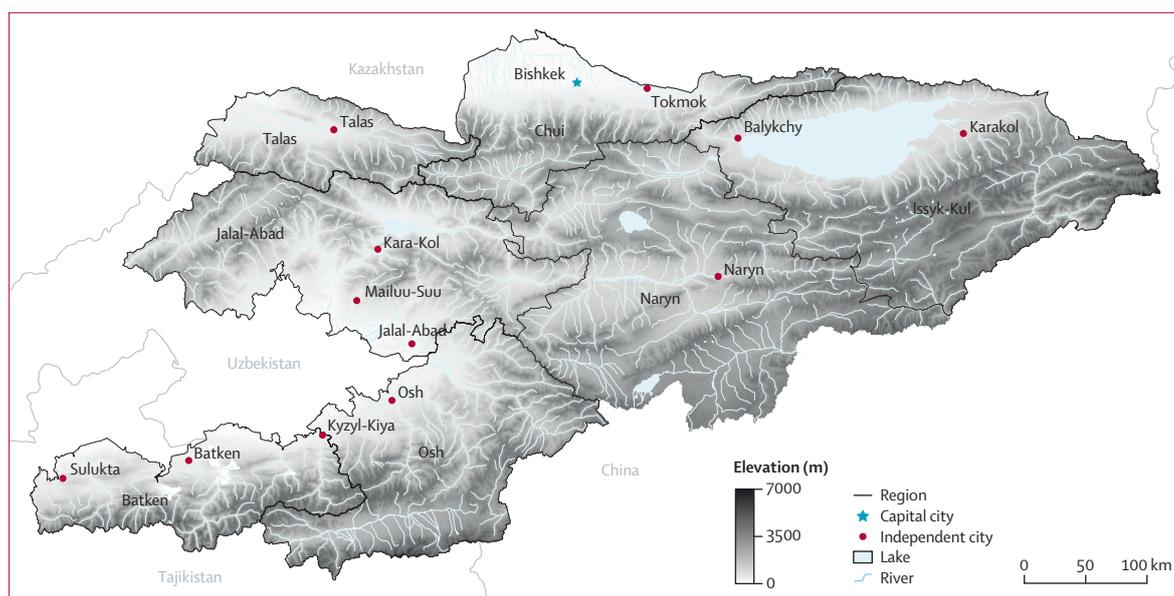
Figure 1: **Regions and independent cities in Kyrgyzstan**

local and global levels make their control challenging and contribute to their neglect.[11] WHO recommends integrated efforts towards echinococcosis control and promotes collection and mapping of epidemiological data.[12] Spatial epidemiology approaches are useful to understand and predict disease risk,[13] especially for zoonoses with focal spatial distribution such as that of cystic echinococcosis and alveolar echinococcosis. However, such approaches should account for the long period between time of infection and onset of clinical signs. Fine-scale mapping of the disease provides useful operational information, which includes the identification of priority areas for resource allocation, tailored public health interventions, and their cost–benefit analyses, helping to make the case for control. This is particularly important in Kyrgyzstan, which is a lower-middle income country, with 65% of the population living in remote and rural areas. Furthermore, geographically referenced disease data can be complemented by environmental, climatic, and socioeconomic data to investigate spatial risk factors that might explain local geographical variations of disease. Al-Jawabreh and colleagues[14] investigated the burden of surgically confirmed cystic echinococcosis cases in Palestine using hospital records, but their study was restricted to the second administrative level (district).

Although cystic echinococcosis and alveolar echinococcosis are serious threats to human health in Kyrgyzstan, no countrywide studies have so far been done for both diseases at a fine spatial resolution.[8–10,15] To fill this knowledge gap, we aimed to explore cystic echinococcosis and alveolar echinococcosis within-country incidence and geographical distribution at high spatial resolution in Kyrgyzstan.

Methods

Retrieving, preprocessing, and mapping surgical cases

We accessed the national human echinococcosis surgical cases surveillance system compiled by the Government Sanito-Epidemiology Unit in Bishkek, Kyrgyzstan (appendix 2 pp 3–4). We extracted all cases of cystic echinococcosis and alveolar echinococcosis that were reported between Jan 1, 2014, and Dec 31, 2016, from the nine regional databases. Case reports included individual residential address, sex, age, occupation, diagnosis (ie, cystic echinococcosis, alveolar echinococcosis, cystic echinococcosis relapse, or alveolar echinococcosis relapse), and lesion localisation. The diagnosis was confirmed through morphological and histological examination of resected lesions. We removed case-report duplicates and case reports without diagnosis information, and standardised attributes on occupation and age. We also standardised residential addresses—village, local community, district, and region names—according to 2009 national census entries (appendix 2 pp 5–6, 11–12). Standardisation of addresses prevented data mismatch due to homonymous villages, typographical errors, or incomplete addresses. We also computed the age at the time of diagnosis using year of birth. When missing, we derived patients' sex information from their names, and imputed missing age information with single imputation based on sex-stratified and diagnosis-stratified mode.

All reported cystic echinococcosis and alveolar echinococcosis cases were manually geocoded according to the patients' residential addresses, which were assumed to be the locations of infection. Residential address coordinates were obtained using the Russian, Kyrgyz, or translated village names on Google Maps, OpenStreetMap, and Wikipedia (GeoHack). When village coordinates were not

See **Online** for appendix 2

For **Google Maps** see https://maps.google.com/

For **OpenStreetMap** see https://www.openstreetmap.org/

For **GeoHack** see https://en.wikipedia.org/wiki/Template:GeoTemplate/sandbox

found on the maps, we used the coordinates of a village belonging to the same local community according to the 2009 national census. Ethical approval for the study was granted by the ethics committee of the Ministry of Health in Kyrgyzstan.

Accessing and preprocessing administrative boundaries and population data

We used the administrative boundaries of Kyrgyzstan as provided by REACH, a joint initiative of IMPACT, ACTED, and the UN Operational Satellite Applications Programme (UNOSAT). We assessed the topology of all 479 original administrative units, and matched them to official place names and identifiers (appendix 2 pp 3, 5–6). We then used the 2009 census maps and the web map of Kyrgyz local community boundaries as a reference to edit the topology of 157 administrative boundaries by removing holes, expanding boundaries to connect adjacent units, and adding missing polygons. After those topological corrections, we obtained administrative boundaries of 476 validated local communities, the 12 independent cities, and the two main cities (Bishkek and Osh), which enabled us to link disease reports and population data at the finest spatial resolution available (appendix 2 pp 6–9).

The resulting administrative units were linked to cystic echinococcosis and alveolar echinococcosis case reports, and to 2009 national census population data. We also obtained data on the 2016 Kyrgyz population age and sex distribution at country and regional levels (appendix 2 p 3) from the National Statistical Committee of the Kyrgyz Republic.

Statistical analysis

For both cystic echinococcosis and alveolar echinococcosis cases, we computed descriptive statistics on patients' demographics, including proportion of relapses, lesion localisations, and occupation. We then excluded relapses to compute crude and standardised surgical incidence of primary (ie, new) cystic echinococcosis and alveolar echinococcosis cases at the country, regional, district, and local community levels. All incidence estimates were calculated per 100 000 population and averaged across the 3-year study period to obtain annual estimates.

At the country level, we adjusted the crude surgical incidence of primary cystic echinococcosis and alveolar echinococcosis with direct standardisation by sex and age using the 2017 world reference population (appendix 2 p 3), and we also computed sex-specific and 10-year age group-specific crude surgical incidence of cystic echinococcosis and alveolar echinococcosis. We analysed differences in case numbers by 10-year age-sex groups using the χ^2 test, assuming the age distribution of the Kyrgyz population. We did post-hoc χ^2 tests to assess whether there were significant differences in the number of expected and observed cases in each age-sex group. We used Bonferroni's correction to assess statistical significance in post-hoc analyses (appendix 2 pp 13–15).

At the district level, we adjusted the crude surgical incidence of primary cystic echinococcosis and alveolar echinococcosis with direct standardisation using the 2016 Kyrgyzstan population as a reference (appendix 2 p 3). We also computed annual crude surgical incidence of primary cases of both diseases at regional and district levels (appendix 2 pp 16–22).

At the local community level, including the 12 independent and two main cities, we computed crude surgical incidence as well as standardised incidence ratios (SIRs)—namely, the ratio between observed and expected primary cases at the local community level. When computing the SIRs, we used indirect standardisation because the number of cases at the local community level was small. In addition, we assumed that the age and sex composition at each local community is the same as its parent region, and we used country-level age-sex-specific incidence as a reference. We produced choropleth maps of the spatial distributions of cystic echinococcosis and alveolar echinococcosis crude surgical incidence per 100 000 population aggregated over local communities across Kyrgyzstan.

We then tested the spatial distributions of cystic echinococcosis and alveolar echinococcosis on the basis

	Cystic echinococcosis (n=2563)	Alveolar echinococcosis (n=598)
Sex		
Female	1399 (54·6%)	377 (63·0%)
Male	1164 (45·4%)	221 (37·0%)
Age, years		
<10	293 (11·4%)	38 (6·4%)
10–19	490 (19·1%)	119 (19·9%)
20–29	556 (21·7%)	157 (26·3%)
30–39	442 (17·2%)	107 (17·9%)
40–49	330 (12·9%)	77 (12·9%)
50–59	276 (10·8%)	64 (10·7%)
60–69	143 (5·6%)	28 (4·7%)
≥70	33 (1·3%)	8 (1·3%)
Relapses	204 (8·0%)	52 (8·7%)
Lesion localisation		
Liver	2074 (80·9%)	582 (97·3%)
Lung	313 (12·2%)	6 (1·0%)
Other organ*	94 (3·7%)	1 (0·2%)
Not available	42 (1·6%)	7 (1·2%)
Liver and other organ†	33 (1·3%)	1 (0·2%)
Brain	7 (0·3%)	1 (0·2%)

*Includes, in order of frequency: abdominal cavity, kidney, spleen, pelvis, bones, ovary, spine, abdominal cavity and small pelvis, adrenal glands, bladder, pancreas, soft tissues, stomach, and subscapular cavity. †Includes, in order of frequency: liver and lung, liver and abdominal cavity, liver and spleen, liver and small pelvis, and liver and lung and spleen.

Table 1: Patients with surgical cystic and alveolar echinococcosis in Kyrgyzstan, 2014–16

of their SIRs for global spatial autocorrelation using the Moran's *I* statistic.[16] This measure tests whether the spatial distributions of cystic echinococcosis and alveolar echinococcosis in terms of SIR were clustered among local communities compared with the null hypothesis of spatial randomness (no clustering). Last, we assessed local spatial autocorrelation using local indicators of spatial association (LISA)[17] in SIRs. The LISA test detects local communities characterised as high-high clusters, indicating areas with high SIR surrounded by areas with high SIR values. Disease hotspots were defined as local clusters of high cystic echinococcosis and alveolar echinococcosis SIRs. We set the significance level at 5% for all tests and used the contiguity method to define spatial structure in both spatial autocorrelation tests (appendix 2 p 29). We produced choropleth maps of significant hotspots and risk for surgical cystic echinococcosis and alveolar echinococcosis aggregated over local communities across Kyrgyzstan. The risk for surgical cystic and alveolar echinococcosis was classified into five categories on the basis of the cystic echinococcosis and alveolar echinococcosis SIR at the local community level. We assigned the risk category high to local communities where the observed incidence was more than seven times higher than the expected incidence; intermediate to local communities where the observed incidence was between 1·5 and seven times higher than

the expected incidence; expected to local communities where the observed incidence was between 0·5 and 1·5 times the expected incidence; low where the observed incidence was higher than zero up to half (0·5) the expected incidence; and negligible to local communities where no cases were reported in the study period, and thus the observed incidence was 0.

Last, we tested the possible correlation of cystic echinococcosis and alveolar echinococcosis with the distance to the nearest health facility and the number of health facilities per local community on the basis of their SIRs using the Spearman's rank correlation coefficient (Spearman's ρ). This measure tests whether the distribution of cystic echinococcosis and alveolar echinococcosis in terms of SIR was correlated to the local presence or distance to health facilities (appendix 2 p 28).

The codes of analyses are available online. Descriptive statistics, incidence computation, mapping, and spatial analyses were carried out using R, version 3.3. Administrative boundaries processing was done in QGIS 3.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, the viewpoints expressed, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

For **codes** see https://git.math.uzh.ch/reinhard.furrer/Echin_kgz/tree/master

	Population			Primary cases				Crude surgical incidence per 100 000 population		
	Total	Female	Proportion female	Total	Female	Male	Proportion female	Total	Female	Male
Cystic echinococcosis										
Age <10 years	1395457	680440	48·8%	275	140	135	50·9%	6·57	6·86	6·29
Age 10–19 years	1025880	503246	49·1%	460	198	262	43·0%	15·0	13·1	16·7
Age 20–29 years	1150820	569613	49·5%	509	273	236	53·6%	14·7	16·0	13·5
Age 30–39 years	835635	416257	49·8%	398	242	156	60·8%	15·9	19·4	12·4
Age 40–49 years	646305	332181	51·4%	301	178	123	59·1%	15·5	17·9	13·1
Age 50–59 years	538539	286241	53·2%	251	163	88	64·9%	15·5	19·0	11·6
Age 60–69 years	267629	151227	56·5%	134	80	54	59·7%	16·7	17·6	15·5
Age ≥70 years	159215	99381	62·4%	31	17	14	54·8%	6·49	5·70	7·80
Total	6019480	3038586	50·5%	2359	1291	1068	54·7%	13·1	14·2	11·9
Alveolar echinococcosis										
Age <10 years	1395457	680440	48·8%	35	21	14	60·0%	0·836	1·03	0·653
Age 10–19 years	1025880	503246	49·1%	105	57	48	54·3%	3·41	3·78	3·06
Age 20–29 years	1150820	569613	49·5%	151	101	50	66·9%	4·37	5·91	2·87
Age 30–39 years	835635	416257	49·8%	96	65	31	67·7%	3·83	5·21	2·46
Age 40–49 years	646305	332181	51·4%	71	47	24	66·2%	3·66	4·72	2·55
Age 50–59 years	538539	286241	53·2%	59	37	22	62·7%	3·65	4·31	2·91
Age 60–69 years	267629	151227	56·5%	23	14	9	60·9%	2·86	3·09	2·58
Age ≥70 years	159215	99381	62·4%	6	4	2	66·7%	1·26	1·34	1·11
Total	6019480	3038586	50·5%	546	346	200	63·4%	3·02	3·80	2·24

Crude surgical incidence of primary cases was calculated per 100 000 population and averaged across the 3-year study period to obtain annual estimates.

Table 2: Crude surgical incidence of primary cases of cystic and alveolar echinococcosis in Kyrgyzstan, 2014–16
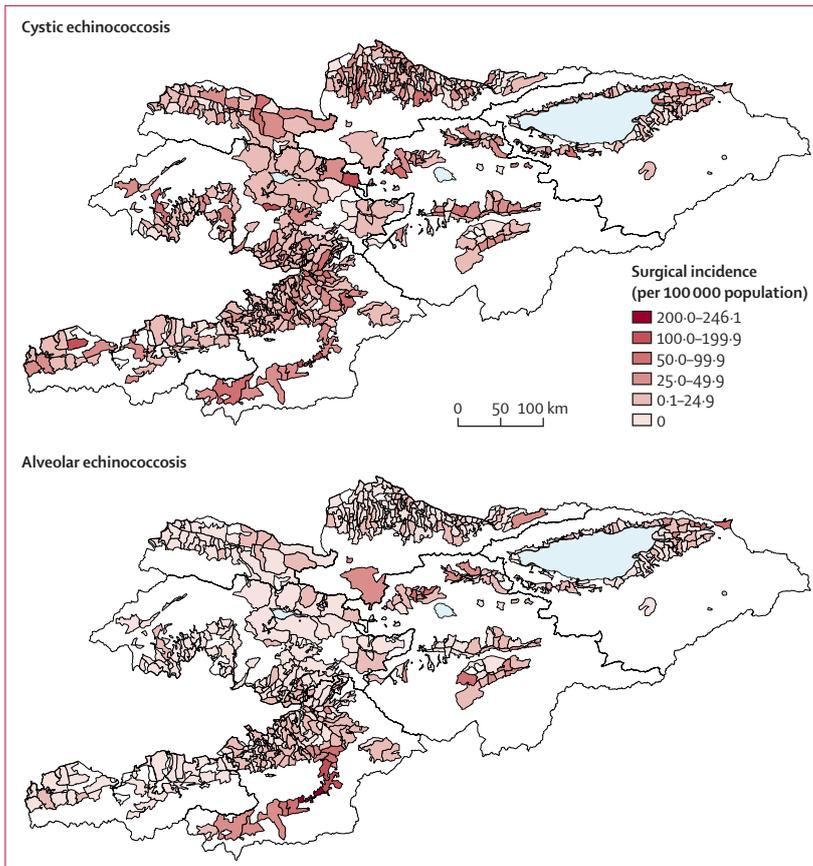
Figure 2: Crude surgical incidence of cystic and alveolar echinococcosis at the local community level in Kyrgyzstan, 2014–16
The local administrative units of Kyrgyzstan do not cover the entire country, but only the settlements and their surroundings. The white spaces are unsettled areas that do not fall within any local administrative unit.

Results

3168 cystic echinococcosis and alveolar echinococcosis surgical cases were reported through the human echinococcosis surveillance system in Kyrgyzstan. Data from seven individuals were excluded from the analyses because of missing diagnosis information. Missing age information was imputed for 19 individuals, and sex was assigned to 2504 individuals on the basis of their names. Of the 3161 total cases, 2563 were cystic echinococcosis and 598 were alveolar echinococcosis. The mean age of patients was 31 years (SD 17·4, range 1–86) for cystic echinococcosis and 32 years (16·4, 4–78) for alveolar echinococcosis. Two surgical cases of cystic echinococcosis were reported in patients aged 1 year. The median age was 28 years (IQR 17–44) for cystic echinococcosis and 29 years (19–43) for alveolar echinococcosis. For both diseases, the 20–29 age class was the most represented, accounting for 556 (21·7%) of 2563 cystic echinococcosis cases and 157 (26·3%) of 598 alveolar echinococcosis cases. The demographic distribution of the study population and the proportion of relapses and lesion localisations is detailed in table 1.

The proportions of different patients' occupations by diagnosis and sex are shown in the appendix 2 (pp 11–12).

2359 primary cases of cystic echinococcosis and 546 primary cases of alveolar echinococcosis were analysed. Country-level crude annual surgical incidence of primary cases of cystic echinococcosis was 13·1 per 100 000 population and that of primary cases of alveolar echinococcosis was 3·02 per 100 000 population (table 2). When adjusting for age and sex by direct standardisation, the annual surgical incidence of cystic echinococcosis was 13·3 per 100 000 population and that of alveolar echinococcosis was 3·05 per 100 000 population. The majority of patients with cystic echinococcosis (1291 [54·7%] of 2359 primary cases) and alveolar echinococcosis (346 [63·4%] of 546 primary cases) were female. 522 (22·1%) of 2359 primary cases of cystic echinococcosis and 96 (17·6%) of 546 primary cases of alveolar echinococcosis were in children younger than 15 years (appendix 2 p 14). Sex-specific and 10-year age group-specific crude surgical incidences of alveolar echinococcosis and cystic echinococcosis are detailed in table 2.

For both diseases and in both sexes, we found a significantly lower number of observed surgical cases than expected in children aged younger than 10 years. We also found a significant excess of surgical cases in women aged 20–59 years for cystic echinococcosis, and in women aged 20–49 years for alveolar echinococcosis (appendix 2 pp 13–15).

Averaged and annual regional and district-level estimates of cystic echinococcosis and alveolar echinococcosis incidence are presented in the appendix 2 (pp 16–22, 26–27), as well as district-level standardised surgical incidences and hotspots of cystic echinococcosis and alveolar echinococcosis. Spatial analyses at district level revealed significant cystic echinococcosis hotspots in the Batken district (Batken region), and in the districts of Alay, Chong-Alay, Kara-Kulja, and Uzgen (Osh region). Significant alveolar echinococcosis hotspots were found in Alay and Chong-Alay districts (Osh region; appendix 2 pp 20–23).

Cystic echinococcosis cases were reported in 383 (78·2%) of 490 local communities (figure 2). The highest annual crude surgical incidences of cystic echinococcosis were detected in three local communities located in three distinct regions: 176 per 100 000 population in Sary-Kamysh (Jalal-Abad region), 113 per 100 000 population in Margun (Batken region), and 105 per 100 000 population in Uch-Dobo (Osh region). Alveolar echinococcosis cases were reported in 176 (35·9%) of 490 local communities. The highest annual surgical crude incidences were detected in four local communities located in the Alay district (Osh region): Uch-Dobo (246 per 100 000 population), Sary-Tash (187 per 100 000 population), Alay (186 per 100 000 population), and Lenin (137 per 100 000 population). All data—including the improved administrative boundaries—are available online.

We uncovered significant global spatial autocorrelation in the SIRs of both cystic echinococcosis (Moran's I=0·06, p=0·031) and alveolar echinococcosis (0·63, p<0·0001). Furthermore, LISA revealed significant hotspots of cystic echinococcosis in four regions: Osh (five local communities in Uzgen district and four in Alay district), Naryn (three local communities in Jumgal district and one in Naryn district), Talas (three local communities in Talas district), and Chuy (one local community in Jayyl district; figure 3). Significant alveolar echinococcosis hotspots were detected in the southwest and centre of the country in the Osh region (11 communities in Alay district, including the local community of Sary Mogol, and one in Chong-Alay district) and in the Naryn region (five communities in Jumgal district and three in At-Bashy district; figure 3).

Last, we did not find significant correlation between the SIRs of cystic echinococcosis and of alveolar echinococcosis with the number of health facilities per local community (Spearman's ρ=0·05, p=0·25 for cystic echinococcosis; and Spearman's ρ=0·02, p=0·68 for alveolar echinococcosis), or with the distance to the nearest health facility (Spearman's ρ=0·03, p=0·44 for cystic echinococcosis; and Spearman's ρ=0·07, p=0·14 for alveolar echinococcosis; appendix 2 p 28).

Discussion

Our analyses at the local community level have revealed remarkable within-country variation in the surgical incidence and geographical distribution of cystic echino-coccosis and alveolar echinococcosis. Cystic echino-coccosis cases were widespread, with significant hotspots in 17 local communities in four distinct regions. By contrast, alveolar echinococcosis cases were clustered in southwest and central Kyrgyzstan, with significant hotspots in 20 local communities located in two regions.

The annual surgical incidence of cystic echinococcosis of 13·1 per 100 000 population in Kyrgyzstan is comparable only to the annual incidence of cystic echinococcosis of about 10 per 100 000 population in highly endemic Peru in the 2009–14 period.[3] In 2016 in Europe, notifications of cystic echinococcosis and alveolar echinococcosis combined were 0·2 per 100 000 population, with the highest incidence rate in Bulgaria (3·76 per 100 000 population).[18] The annual countrywide surgical incidence of alveolar echinococcosis of 3·02 per 100 000 population in Kyrgyzstan is the highest ever registered.[3]

Ongoing echinococcosis transmission is suggested by the proportion of new cystic echinococcosis and alveolar echinococcosis cases in children younger than 15 years. Two surgical cystic echinococcosis cases in patients aged 1 year were reported in the study period. Although these early cases might seem to be unusual given the disease latency and slow growth of cysts, cystic echinococcosis can occur at all ages with variable latency,[19] and evidence exists of surgical cystic echinococcosis cases in children aged 1 year elsewhere.[20]
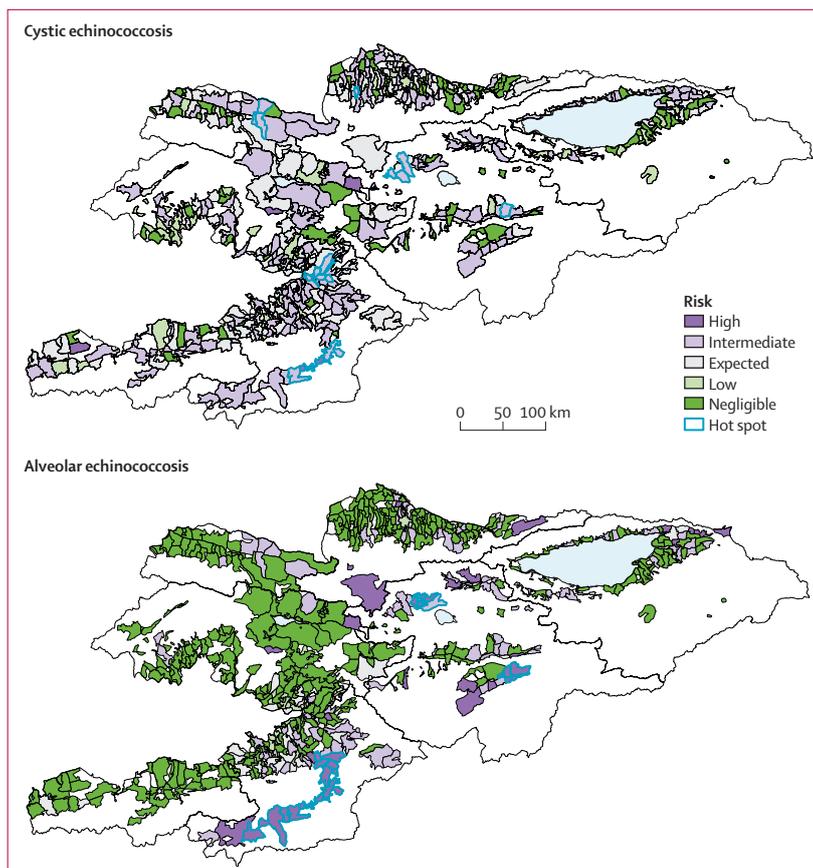

Figure 3: **Hotspots of surgical cystic and alveolar echinococcosis at the local community level in Kyrgyzstan, 2014–16**
The local administrative units of Kyrgyzstan do not cover the entire country, but only the settlements and their surroundings. The white spaces are unsettled areas that do not fall within any local administrative unit.

We found that a higher proportion of patients with primary cystic echinococcosis and alveolar echinococcosis were female than male, which is similar to findings in other studies.[2,5] Being female has been identified as a potential risk factor for cystic echinococcosis by means of systematic review and meta-analysis.[21] However, our findings might reflect a confounding factor. For example, women might take care of the dogs and hence have exposure to their faeces more frequently than do men. Previous work done in southern Kyrgyzstan did not identify being female as a potential risk factor for alveolar echinococcosis.[22] Instead, dog ownership was found to increase alveolar echinococcosis risk.[15] Moreover, women at a reproductive age might also have an increased likelihood of being diagnosed with alveolar echinococcosis as a result of more frequent abdominal ultrasound scans to check their reproductive health.

There are remarkable geographical variations in the incidences of cystic echinococcosis and alveolar echino-coccosis at the local community scale, ranging between 0 and 176 per 100 000 population for cystic echinococcosis and 0 and 246 per 100 000 population for alveolar

echinococcosis. Moran's *I* statistic suggests a more clustered distribution of alveolar echinococcosis than that of cystic echinococcosis. The clustered distribution of alveolar echinococcosis in southern and central Kyrgyzstan might suggest the presence of ecological features supporting the presence of a larger population of competent intermediate hosts.[23] The presence of significant alveolar echinococcosis hotspots in local communities in the At-Bashy district in central Kyrgyzstan is in line with high prevalence of *E multilocularis* in foxes (64%), dogs (18%), and rodents (6·6%) estimated between 10 and 15 years previously in the same area.[24–26] This finding is consistent with the long alveolar echinococcosis latency of 10–15 years.[2] By contrast, only 0·3% of rodents were found to be infected with *E multilocularis* in the neighbouring Kochkor district,[26] where we did not detect significant hotspots of alveolar echinococcosis.

Echinococcosis control strategies include interruption of parasite transmission, control of the parasite in animal reservoirs, and education to enhance awareness of the disease. For alveolar echinococcosis, regular anthelminthic baiting of foxes was proven to reduce the environmental contamination with eggs in an experimental setting,[27] but this approach has not been established so far. We strongly encourage One Health approaches to echinococcosis control, such as by sharing data, objectives, and costs across sectors, by designing integrated strategies against zoonotic diseases (eg, rabies, leishmaniasis, and brucellosis), and by actively engaging the local communities most affected.

The main limitation of this study is the use of surgical cystic echinococcosis and alveolar echinococcosis cases, which document only a proportion of cases as both diseases can be asymptomatic for prolonged periods—even lifelong for cystic echinococcosis. Moreover, the surveillance system does not collect data on cases that are managed with less invasive approaches other than surgery (appendix 2 p 4). In low economic resource societies, it is also likely that many clinical cases do not present for treatment, or might be misdiagnosed as cancer and left untreated. Additionally, under-reporting might also be present. Thus, surgical incidences are conservative estimates of the actual disease burden. Local administrative units in Kyrgyzstan only cover the settlements and their surroundings. The remaining area is characterised by very high mountains and is likely to be uninhabited. We cannot absolutely exclude the presence of a few rural remote communities with difficult access to health services in these areas. Therefore, we cannot address this issue because of an absence of data. Another potential limitation is considering the place of residence as a surrogate for the place of infection. However, this issue is expected to play a minor part in our study because Kyrgyzstan is a vast and rural country where internal mobility and migratory patterns are drastically reduced. Local communities where the disease has been detected are likely to be the ones where the infection occurred. Evidence supporting our detection of an alveolar echinococcosis hotspot and the non-detection of a cystic echinococcosis hotspot in Sary Mogol is provided by a previous US surveillance study done in 2012 in the same location, revealing an emerging alveolar echinococcosis situation (prevalence of 4·2%), and a low cystic echinococcosis prevalence of 0·25%.[15] It is possible that our study was also biased by local availability of health-care services. However, we found no evidence that hotspots were associated with distance to or local presence of health facilities (appendix 2 p 28). Increased awareness of local medical teams and enhanced diagnostic capacity might have also biased our hotspot detection. However, the first ultrasound survey in Alay valley in 2012 was undertaken because a high incidence of surgical cases was detected through the analysis of surveillance data.[15]

There is an ongoing epidemic of cystic echinococcosis in Kyrgyzstan that appeared in the late 20th century (appendix 2 p 10).[8,9] Although the increase in the number of cases could be due to better access to health care or improved diagnostic capacities, previous work linked it to socioeconomic changes following the dissolution of the Soviet Union in 1991.[28] These changes include weakened public health and veterinary services, and changes in livestock management from state farms to small and private farms, and increased home slaughtering of livestock without veterinary inspection. The evidence of a more recently emerging epidemic of alveolar echinococcosis[10,15] might be linked to a possibly increased dog population that has been colonised by *E multilocularis*, with onward transmission to humans resulting from the close human–dog relationship. However, transmission risk to humans might also be linked to climatic and environmental drivers and be affected by environmental and climate change. These drivers can be identified through spatial models using geographically referenced disease data complemented by satellite remote-sensing data (eg, land surface temperature, rainfall, soil moisture, and landscape composition).[29]

Our efforts to map individual disease cases and to improve the data quality and completeness of administrative boundaries enabled highly precise assessment of cystic echinococcosis and alveolar echinococcosis incidence, patterns of disease geography, and intervention areas. Our high granularity incidence data enabled the detection of cystic echinococcosis and alveolar echinococcosis hotspots in three regions that analyses using district-level aggregated data did not identify (appendix 2 pp 24–25). This finding demonstrates that local variations are concealed when analysing disease incidence at a lower spatial resolution. Furthermore, the spatial analysis methods used in this study can be applied for monitoring and analysis of increasing numbers of cystic echinococcosis and alveolar echinococcosis cases in other countries to sharpen control strategies. Finally, our fine-scale human incidence data in a highly endemic setting provide a unique opportunity for much-needed countrywide ecological studies. Such studies

might help to elucidate potential environmental drivers and spatial risk factors associated with cystic echinococcosis and alveolar echinococcosis, and predict specific geographical locations with increased disease risk where prevention and control can be targeted for more effective and efficient results.

Cystic echinococcosis and alveolar echinococcosis cause a substantial health burden—especially in economically disadvantaged societies. Although WHO prioritises their control,[12] cystic echinococcosis and alveolar echinococcosis continue to be neglected. A well maintained surveillance system for cystic echinococcosis and alveolar echinococcosis seems to be crucial in endemic areas and should be introduced where data collection on echinococcosis in humans and animals relies on voluntary plans. Better quality incidence data can feed high-resolution maps and point specific locations where interventions and resources should be targeted.

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