

# Analysis of the Epidemiological, Clinical Characteristics, Treatment and Prognosis of Human Brucellosis During 2014–2018 in Huludao, China

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**Purpose:** To describe the incidence trend, demographic and clinical characteristics, treatment and prognosis, epidemiological history and risk factors of human brucellosis in Huludao, China.

**Patients and Methods:** A total of 1887 brucellosis patients were reported in Huludao, China from January, 2014 to December, 2018 and the case questionnaires from 1149 patients were collected from Huludao Municipal Center for Disease Control and Prevention. Demographic characteristics of the patients and the information relating to the patients' clinical manifestations, diagnosis, treatment and prognosis were collected and analyzed.

**Results:** The number of annually reported brucellosis patients has dropped from 711 to 187 during the study period, with the incidence decreased from 27.31/100,000 in 2014 to 7.15/100,000 in 2018. A total of 1149 individual data were collected, with a mean age of 49.59±13.14 years and 75.7% were male. Patients aged more than 60 years were more likely to have arthralgia/myalgia than the other age groups, and patients who had an enlarged spleen in male were more than female ( $P<0.05$ ). There were more acute brucellosis cases, less sub-acute and chronic brucellosis cases in the ethnic minority (83.6%, 5.5% and 11.0%, respectively) than that in the Han nationality (64.7%, 22.2% and 13.0%, respectively,  $P<0.05$ ). For antibiotic therapy, "Doxycycline plus rifampicin or streptomycin" was the most commonly used drug combination. Sheep/goat was the main contacted animal and feeding/grazing was the most frequent transmission route; no personal protective measures were the major risk factor.

**Conclusion:** The incidence of human brucellosis is still high in Huludao, China, and this is mostly associated with contacting with domestic animals and barely taking protective measures. The most common clinical manifestations of brucellosis patients in Huludao were fatigue, hyperhidrosis, fever, and arthralgia/myalgia, the most common route of exposure was feeding and grazing, and the major species of livestock was sheep/goat. The most commonly adopted treatment option was antibiotic therapy, and most patients responded well to treatment. The integrality and accuracy of the notifiable epidemiological case questionnaire needs to be improved in order to provide more factual and objective information for both the physicians and policy-makers.

**Keywords:** human brucellosis, epidemiological characteristics, clinical features, treatment and prognosis

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## Plain Language Summary

Brucellosis is a zoonosis that can cause huge damage to both animals and humans. People can get infected with brucellosis mainly through close contact with infected animals and consumption of contaminated meat, milk or dairy products. A better understanding of the

epidemiological and clinical characteristics of human brucellosis is of great significance to prevent and control this disease. In this paper, we retrospectively analyzed the epidemiological and clinical characteristics as well as the treatment and prognosis of the reported cases in Huludao, China. We found that the human brucellosis incidence in Huludao is high, and that is likely to be associated with the close contact with domestic animals and barely taking personal protective measures. There are statistically significant differences of some symptoms in different age groups, gender, ethnicity and district in this study, and these results have to be explored in the future considering that the missing values in the notifiable epidemiological case questionnaires could affect the statistical differences. The integrality and accuracy of the notifiable epidemiological case questionnaire needs to be improved in order to provide more factual and objective information for both the physicians and policy-makers.

## Introduction

Brucellosis is one of the most frequently encountered zoonosis and classified as one of the neglected infectious diseases in the world.<sup>1</sup> The outbreak or epidemic of brucellosis can cause huge damage to humans and animals both physically and economically, especially in developing countries. People can get infected with brucellosis mainly through close contact with infected animals and consumption of contaminated meat, milk or dairy products.<sup>2,3</sup> Human brucellosis still poses great challenges to physicians such as the identification of markers for disease severity, progression, and treatment response, and the development of improved treatment regimens.<sup>4</sup>

In China, human brucellosis has been classified as a notifiable infectious disease since 1955, the national incidence of human brucellosis had increased from 1.40/100,000 in 2005 to 4.22/100,000 in 2014 and then decreased slightly to 3.44/100,000 in 2016.<sup>5</sup> It also has varied across provinces and even cities within the same province.<sup>6</sup> The Northeast, Northwest and Inner Mongolia have always contributed the most number of human brucellosis patients since the first two cases reported in 1905.<sup>6,7</sup> Liaoning is a coastal province located in the northeastern part of China, the human brucellosis incidence of Liaoning province increased from 3.37/100,000 in 2012 to 6.65/100,000 in 2015, which was even higher than the incidence of the whole nation in the same period. And the greatest number of human brucellosis cases was reported from Huludao,<sup>8</sup> a city located in the southwest part (40°N and 120°E) of Liaoning province.<sup>9</sup>

In order to prevent and control the human brucellosis, the active surveillance for brucellosis has been included in

the national priority communicable disease surveillance since 2005 in China. According to the “National Human Brucellosis Surveillance Program (Trial)” in 2005,<sup>10</sup> all confirmed cases need to be investigated with a case questionnaire and reported through the Chinese National Notifiable Infectious Disease Reporting Information System (NIDRIS), an internet-based system which was launched nationwide by Chinese government in 2004 in order to achieve timely online monitoring of individual disease cases. Due to the rising trend of human brucellosis incidence in China, the case questionnaire was modified in 2016 in order to provide more effective information to prevent and control the disease; for instance, the antibody titre of the serum agglutination test (SAT) was divided into specific levels, and the drugs used for treating human brucellosis were added.

Due to the above-mentioned background, concern has been increasing about the importance of the awareness level of human brucellosis in communities<sup>11</sup> and also the clinical manifestations, diagnosis, and treatment protocols of human brucellosis.<sup>12,13</sup> Considering little is known about the differences of clinical manifestations, diagnosis and the efficiency of different treatment regimens between different age groups, gender, ethnicity and areas in the existing studies, the present study aimed to describe the demographic, clinical and epidemiological characteristics as well as the treatment and prognosis of human brucellosis cases in Huludao, China, compare the differences of clinical manifestation and diagnosis in different age groups, gender, ethnicity and district, in order to help the clinicians identify human brucellosis cases more quickly and offer reliable information about effective treatment options in this study area.

## Materials and Methods

### Data Source

All data about the brucellosis cases from 2014 to 2018 in the present study were collected from the Municipal Center for Disease Control and Prevention (CDC) in Huludao. In China, when a patient is diagnosed with brucellosis, the case needs to be reported to the Chinese National Notifiable Infectious Disease Reporting Information System (NIDRIS), an epidemiological case questionnaire needs to be conducted and reported at the same time according to the “National Human Brucellosis Surveillance Program for (Trial)”.<sup>10</sup>

## Case Definition and Notifiable Epidemiological Case Questionnaire

According to the “Diagnostic criteria for Brucellosis (WS 269–2007)”<sup>14</sup> issued by National Health Commission of the people’s Republic of China in 2007, the diagnosis of brucellosis was based on a combination of epidemiological history, clinical manifestations (fever, hyperhidrosis, arthralgia and myalgia, fatigue, hepatomegaly, enlarged spleen, lymphadenectasis and testicle swelling), and laboratory tests, including the serum agglutination test (SAT), complement fixation test (CFT), Anti-human immunoglobulin test (Coomb’s test), and the isolation and identification of bacteria from blood, marrow and other bodily fluids and excretions. Only SAT was adopted for confirmation of positive case in the study area, and on the basis of having any symptoms above, the clinical diagnoses of human brucellosis were divided into three groups according to the course of the disease: acute (0–3 months), sub-acute (3–6 months) and chronic (more than 6 months).

The epidemiological case questionnaire<sup>11</sup> included demographic and epidemiological characteristics, clinical manifestations, physical examination and laboratory findings, treatment and prognosis. In 2016, some new information such as the clinical diagnosis, the different levels of antibody titre and the drugs used for treating brucellosis were added in the new version of the case questionnaire.

## Treatment and Prognosis

According to the “Guidelines for diagnosis and treatment of brucellosis (Trial)”<sup>15</sup>, the treatment for brucellosis was divided into three types: general therapy, antibiotic therapy and Traditional Chinese Medicine (TCM). General therapy refers to paying attention to rest and nutrition and symptomatic treatment such as taking physical measures to treat fever. “Doxycycline plus rifampicin or streptomycin” is the preferred antibiotic treatment, especially for acute brucellosis; the drug combination of “Doxycycline plus compound sulfamethoxazole/trimethoprim or rifampicin plus fluoroquinolones” are recommended in case the preferred treatment is ineffective. For refractory cases, “fluoroquinolones or third-generation cephalosporins” was recommended and all patients were followed up by telephone to record the prognosis.

## Descriptive Analysis, Mapping and Statistical Analysis

The continuous variables were described as mean  $\pm$  standard deviations and the categorical variables were described

as number and proportion (%). We defined the “N” and “n” as the total number of patients recording a certain variable and the number of cases with a positive result, and the proportion is n/N. The spatial distribution of human brucellosis was plotted using GeoDa 1.14.0 (a free and open-source software tool, <https://geodacenter.github.io/download.html>). The data in this study were analyzed using IBM SPSS Statistics 21.0 (IBM, Asian Analytics Shanghai). The Linear-by-Linear Association was used to analyze the differences of incidence; the One-way ANOVA (Analysis of Variance) was used to analyze the differences in continuous variables; Chi-square or Fisher’s exact test was used for categorical variables. The ordinal logistic regression was adopted to analyze the course distribution of brucellosis in different age groups, gender, ethnic group and administrative divisions. *P*-values less than or equal to 0.05 were considered as statistically significant.

## Ethics

Research Institutional Review Board of the Huludao Municipal Center for Disease Control and Prevention approved the study protocol, determined that the collection of data from human brucellosis cases was part of continuing public health surveillance of a legally mandated notifiable infectious disease and the study was exempt from institutional review board assessment. All the data were supplied and analyzed in the anonymous format, without any access to the personal identifying information.

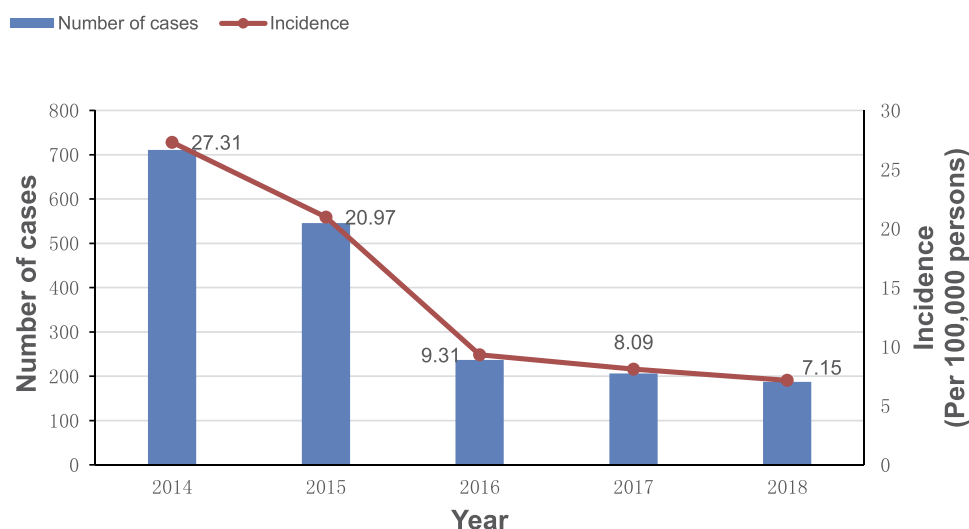
## Results

### Temporal Trend and Seasonality

A total of 1887 human brucellosis cases were reported in Huludao during 2014–2018. The highest incidence was 27.31/100,000 in 2014, then gradually dropped to 7.15/100,000 in 2018, there was a statistically significant difference for the Linear-by-Linear Association ( $\chi^2=48.902$ ,  $P<0.05$ ), and the annual number of human cases reduced from 711 to 187 during these 5 years (Figure 1). An obvious seasonality of human brucellosis was found in Huludao in 2014 and 2015, with the total number of reported cases from March to August accounted for more than 70.0% of all the reported cases in the whole calendar year; however, the seasonality was not noticeable from 2016 to 2018 (Figure 2).

### Demographic Characteristics

Of 1887 reported cases, 1149 (60.9%) epidemiological case questionnaires were collected in this study. Among the 1149



**Figure 1** Annual reported cases and the incidence of human brucellosis in Huludao, China, 2014–2018.

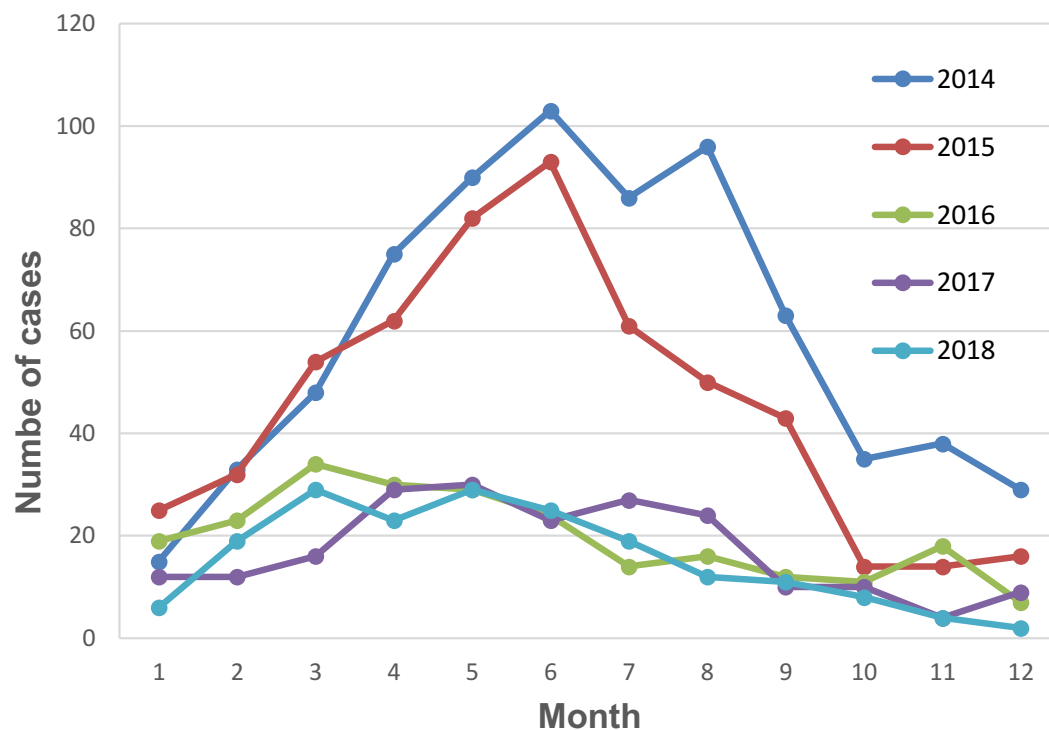
individual cases, the mean age was  $49.59 \pm 13.14$  years, ranged from 3 to 88, and 59.7% (N=1149) of patients were 41–60 years old. As showed in Table 1, 75.7% (N=1149) of the patients were male, 24.3% (N=1149) were female. Among the 772 patients with the ethnicity information, the ratio of the Han nationality (71.4%, N=772) versus the other ethnic minority (28.6%, N=772) was about 2.5:1. Among the 797 patients with the occupation information, farmer/herdsmen constituted the largest proportion (90.6%, N=797), and public service staff accounted for the lowest proportion (0.3%, N=797). Figure 3 shows the regional distribution of human brucellosis in Huludao from 2014 to 2018. Of the 818 brucellosis patients with current address information, the largest proportion (41.9%, N=818) came from Xingcheng county, the least proportion (3.4%, N=818) came from Longgang district.

## Clinical Manifestations, Diagnosis and Laboratory Findings

Table 2 shows the frequency of reported clinical manifestations of human brucellosis patients, the most common symptoms were fatigue (87.5%, N=600), hyperhidrosis (86.6%, N=1057), fever (84.4%, N=1074), arthralgia/myalgia (84.3%, N=1067), while testicle swelling (1.7%, N=962) was the rarest symptom. There were a large number of missing values of “fatigue”, because this symptom was deleted in the case questionnaire in the 2016 version. Thus, we did not analyze the statistical differences of this symptom between different age groups, gender, ethnicity and district.

As shown in Table 3, patients with brucellosis aged more than 60 years old were more likely to have arthralgia/myalgia (90.2%, N=205) than the other age groups (57.1% in 0–20 years group, N=28, 77.3% in 21–40 years group, N=194 and 85.8% in 41–60 years group, N=640), and in male patients, 17.6% (N=760) had enlarged spleen and in female patients, 10.2% (N=235) had enlarged spleen, and these differences were statistically significant ( $P < 0.05$ ). Among the 906 patients with fever, the body temperature was available for 820 (90.5%) patients, the mean body temperature was  $38.75 \pm 0.71^\circ\text{C}$ . Patients from the ethnic minority had higher body temperature ( $38.84 \pm 0.37^\circ\text{C}$ ) than the Han nationality ( $38.60 \pm 0.96^\circ\text{C}$ ) and the proportion of patients who had enlarged spleen (27.8%, N=198) and testicle swelling (3.8%, N=186) in the national minority were larger than that in the Han nationality (10.2%, N=463 and 0.9%, N=451, respectively), according to the statistical analysis between the ethnic minority and the Han nationality. And the brucellosis patients from Xingcheng county had the highest body temperature and constituted the largest proportion of fever, hyperhidrosis, arthralgia/myalgia, hepatomegaly, enlarged spleen and lymphadenectasis.

The data about clinical diagnosis of patients with brucellosis could only be extracted from 289 (25.5% of 1149) cases questionnaires in 2016, 2017 and 2018. As shown in Table 4, there were more acute brucellosis cases, less sub-acute and chronic brucellosis cases in the ethnic minority (83.6%, 5.5% and 11.0%, respectively, N=73) than those in the Han nationality (64.7%, 22.2% and 13.0%, respectively, N=207), Xingcheng county had the largest proportion of acute brucellosis (99.1%, N=113) and the lowest proportion of chronic brucellosis (0%), there was statistically significant difference between males and females



**Figure 2** The number of monthly reported human brucellosis in Huludao, China, 2014–2018.

( $P < 0.05$ ), while there was no statistically significant difference between different age groups ( $P > 0.05$ ).

The laboratory test results were available for 769 (66.9% of 1149) cases, and all these cases (100% of 769) were tested only by serum agglutination test (SAT) and recorded as sero-positive ( $SAT \geq 1:100$ ), with the highest antibody titre of 1:1600 (Table 5).

## Treatment and Prognosis

Treatment information was available only for 823 (71.6% of 1149) brucellosis patients and the most commonly adopted treatment option was antibiotic therapy (97.9%,  $N=823$ ). Due to the fact that the medication information could only be extracted in the 2016 version of the case questionnaire, there were only 89 cases with the drug combination recorded (Figure 4), and “Doxycycline plus rifampicin or streptomycin” was the most commonly used drug combination (67.4%, 60/89). Of the 1149 patients, follow-up information was available only for 768 (66.8%,  $N=1149$ ) patients, and thus the analysis of prognosis distribution was only performed on those 768 patients. Among them, most patients recovered and improved (18.23% and 80.47%,  $N=768$ , respectively), only 1.3% ( $N=768$ ) of patients were not improved (Table 6).

**Table 1** Demographic Characteristics of Human Brucellosis in Huludao, 2014–2018

Variable	Number (Total, N=1149)	Proportion (%)
<b>Age (years)</b>		
0–20	30	2.6
21–40	215	18.7
41–60	686	59.7
>60	218	19.0
<b>Gender</b>		
Male	870	75.7
Female	279	24.3
<b>Ethnicity</b>		
Han Nationality	551	48.0
Ethnic minority	221	19.2
No response	377	32.8
<b>Occupation</b>		
Farmer/Herdsman	722	62.8
Unemployment/Retirees	24	2.1
Worker/Laborer	21	1.9
Student/Teacher	12	1.0
Cadres	3	0.3
Public service staff	2	0.2
Other	13	1.1
No response	352	30.6



**Figure 3** The regional distribution of human brucellosis in Huludao, China, 2014–2018.

## Routes of Exposure and Related Risk Factors

Table 7 shows the species and ways of contacting with live-stock for patients with brucellosis. The most reported species was sheep/goat (97.8%, N=1023); feeding and grazing was the most common way (79.8%, N=1023).

Table 8 shows the risk factors of patients with brucellosis. Only 2.1% (N=851) and 2.2% (N=951) cases used disinfectant and wore protective clothing, respectively, when they were engaged in shearing and contacting with the domestic animals, and 86.6% (N=477) of brucellosis patients drunk from the same well with livestock. By contrast, keeping young lambs

indoors (4.7%, N=471) and consuming undercooked meat, raw milk and dairy products (2.5%, N=394) were not prevalent in Huludao.

## Discussion

Human brucellosis has always been a significant public health issue in China. In this study, the human brucellosis incidence of Huludao reduced from 27.31/100,000 in 2014 to 7.15/100,000 in 2018. When combining the results of Cao S's study (based on the human brucellosis incidence data in Huludao during 2005–2013, while no treatment and prognosis data involved)<sup>16</sup> and the results of the present study, it was found that the incidence of human brucellosis in Huludao increased from 2005 to 2014, then declined to 2018; the whole incidence trend of human brucellosis in Huludao during 2005–2018 was in consistent with the overall incidence trend in China.<sup>5</sup> What is worth mentioning is that the human brucellosis incidence of Huludao in these years was much higher than the national level and most other cities at home and abroad.<sup>6,17</sup> Thus, understanding and mastering the characteristics of the human brucellosis in Huludao is of great significance to prevent and control the incidence of human brucellosis in Liaoning province and even the whole country.

Of 1149 individual data from the epidemiological case questionnaires in this study, patients aged 41–60 years old constituted a large proportion (59.7%), the ratio of male to

**Table 2** Clinical Manifestations of Human Brucellosis in Huludao, 2014–2018

Clinical Manifestations	Total (N)	Number of Positive Patients (n)	Proportion (%)
Fatigue	600	525	87.5
Hyperhidrosis	1057	915	86.6
Fever	1074	906	84.4
Arthralgia/Myalgia	1067	899	84.3
Enlarged spleen	995	158	15.9
Hepatauxe	992	79	8.0
Lymphadenectasis	984	33	3.4
Testicle swelling	962	16	1.7

**Notes:** N: the total number of the patients who recorded whether they had the symptoms; n: the number of patients who had the corresponding symptoms.

**Table 3** Clinical Manifestations of Human Brucellosis in Different Age Groups, Gender, Ethnicity and District in Huludao, China, 2014–2018

Variables (%, n/N)	Clinical Manifestations							
	Fever (%, N=1074)	Hyperhidrosis (N=1057)	Arthralgia/ Myalgia (N=1067)	Body Temperature (°C) (N=820)	Enlarged Spleen (N=995)	Hepatauxe (N=992)	Lymphaden- Ectasis (N=984)	Testicle Swelling (N=962)
<b>Age (years)</b>								
0–20 (N=30)	92.9 (26/28)	85.7 (24/28)	57.1 (16/28)	38.64±0.65	18.5 (5/27)	0.0 (0/27)	7.4 (2/27)	3.7 (1/27)
21–40 (N=215)	85.9 (171/199)	81.3 (157/193)	77.3 (150/194)	38.82±0.45	11.5 (21/182)	8.2 (15/183)	2.8 (5/181)	1.1 (2/177)
41–60 (N=686)	83.8 (537/642)	87.8 (556/634)	85.8 (548/640)	38.74±0.69	15.3 (92/602)	7.7 (46/599)	3.7 (22/595)	1.9 (11/581)
>60 (N=218)	83.9 (172/205)	88.1 (178/202)	90.2 (185/205)	38.75±0.94	21.7 (40/184)	9.8 (18/183)	2.2 (4/181)	1.1 (2/177)
P-value	0.535	0.130	0.000	0.504	0.055	0.349	0.473	0.684
<b>Gender</b>								
Male (N=870)	84.2 (687/816)	86.8 (701/808)	85.1 (692/813)	38.78±0.75	17.6 (134/760)	8.4 (64/759)	3.7 (28/751)	2.2 (16/731)
Female (N=279)	84.9 (219/258)	85.9 (214/249)	81.5 (207/254)	38.68±0.55	10.2 (24/235)	6.4 (15/233)	2.1 (5/233)	0.0 (0/231)
P-value	0.790	0.742	0.168	0.088	0.007	0.325	0.241	0.093
<b>Ethnicity</b>								
Han nationality (N=551)	85.4 (444/520)	87.5 (449/513)	86.8 (449/517)	38.60±0.96	10.2 (47/463)	10.9 (51/446)	5.4 (25/459)	0.9 (4/451)
Ethnic minority (N=221)	90.0 (197/219)	91.0 (191/210)	86.5 (186/215)	38.84±0.37	27.8 (55/198)	8.8 (17/193)	2.6 (5/192)	3.8 (7/186)
No response (N=377)	79.1 (265/335)	82.3 (275/334)	78.8 (264/335)	38.90±0.35	16.8 (56/334)	3.3 (11/333)	0.9 (3/333)	1.7 (5/325)
P <sub>1</sub> -value	0.002	0.011	0.004	0.000	0.000	0.000	0.002	0.035
P <sub>2</sub> -value	0.094	0.189	0.903	0.000	0.000	0.412	0.115	0.018
P <sub>3</sub> -value	0.001	0.006	0.001	0.000	0.586	0.000	0.002	0.829
<b>Administrative divisions</b>								
Jianchang (N=88)	97.7 (86/88)	89.7 (78/87)	87.7 (71/81)	38.39±0.66	3.1 (2/64)	3.1 (2/64)	0.0 (0/64)	0.0 (0/64)
Lianshan (N=104)	68.5 (63/92)	83.3 (75/90)	78.3 (72/92)	38.60±0.69	18.7 (17/91)	27.5 (25/91)	16.5 (15/91)	3.5 (3/85)
Longgang (N=28)	96.4 (27/28)	67.9 (19/28)	75.0 (21/28)	38.35±0.77	3.6 (1/28)	7.1 (2/28)	10.7 (3/28)	0.0 (0/28)
Nanpiao (N=149)	78.0 (110/141)	84.4 (119/141)	90.1 (121/141)	38.49±1.52	0.0 (0/141)	0.0 (0/141)	1.4 (2/141)	0.7 (1/139)
Suizhong (N=106)	89.3 (67/75)	82.7 (62/75)	74.7 (56/75)	38.53±0.52	8.0 (6/75)	2.7 (2/75)	1.3 (1/75)	0.0 (0/74)
Xingcheng (N=343)	91.7 (297/324)	95.2 (296/311)	91.0 (295/324)	38.86±0.37	27.8 (75/270)	13.1 (35/267)	3.1 (8/259)	2.8 (7/253)
No response (N=331)	78.5 (256/326)	81.8 (266/325)	78.8 (257/326)	38.91±0.33	17.5 (57/326)	4.0 (13/326)	1.2 (4/326)	1.6 (5/319)
P <sub>1</sub> -value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.426
P <sub>2</sub> -value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.321
P <sub>3</sub> -value	0.001	0.003	0.001	0.000	0.333	0.001	0.009	0.870

**Notes:** P<sub>1</sub>-value means the differences among two ethnic groups and the non-respondents or six districts and the non-respondents; P<sub>2</sub>-value means the differences between two ethnic groups or six districts excluding the non-respondents; P<sub>3</sub>-value means the differences between the responded group and the non-respondents.

female was about 3:1, and the riskiest occupation was farmer/herdsmen (62.8%); these results were same as many other provinces or cities in China,<sup>18–20</sup> it might because young and middle-aged men were the main labor force of stockbreeding and the related occupations. Xingcheng county had more cases than other districts, which was in consistent with the previous study.<sup>16</sup>

The high incidence of human brucellosis in Huludao is likely to be associated with the close contact with domestic animals, especially feeding and grazing with sheep or goat, which are supported by some other studies in China,<sup>18,21</sup> but against some studies in other countries which reported that ingestion of raw and unpasteurized dairy products was the

main risk factor.<sup>22–24</sup> In 2016, the options “wearing masks” and “wearing gloves” were added into the case questionnaire, which could provide more detailed distribution information about the adoption of self-protective measures; while for the option “eating undercooked meat or consuming unpasteurized/raw dairy products” that was also added in the new version of the questionnaire, only 2.5% patients confessed this in the study population, which is different from that in some other studies (88.0%, 77.1% and 74.0%, respectively).<sup>22–24</sup> The options “drinking water from same well with livestock” and “keeping young lambs indoors” were removed, however, drinking water from same well with livestock is still a risk factor in Huludao (86.6%,

**Table 4** Clinical Diagnosis of Human Brucellosis in Different Age Groups, Gender, Ethnicity and District in Huludao, China, 2016–2018

Variable (%, n/N)	Diagnosis			OR	P-value
	Acute (n=202)	Sub-Acute (n=51)	Chronic (n=36)		
<b>Age (years)</b>					
0–20 (N=5)	4 (80.0)	0	1 (20.0)	0.80	0.021
21–40 (N=58)	36 (62.1)	14 (24.1)	8 (13.8)		
41–60 (N=167)	117 (70.1)	31 (18.6)	19 (11.4)		
>60 (N=59)	45 (76.3)	6 (10.2)	8 (13.6)		
<b>Gender</b>					
Female (N=80)	48 (60.0)	20 (25.0)	12 (15.0)	1.00	0.037
Male (N=209)	154 (73.7)	31 (14.8)	24 (11.5)	0.57	
<b>Ethnicity</b>					
Han Nationality (N=207)	134 (64.7)	46 (22.2)	27 (13.0)	1.00	0.006
Ethnic minority (N=73)	61 (83.6)	4 (5.5)	8 (11.0)	0.40	
No response (N=9)	7 (77.8)	1 (11.1)	1 (11.1)		
<b>Administrative divisions</b>					
Jianchang (N=60)	13 (21.7)	42 (70.0)	5 (8.3)	1.00	0.344
Lianshan (N=34)	19 (55.9)	3 (8.8)	12 (35.3)	0.68	
Longgang (N=16)	3 (18.8)	1 (6.2)	12 (75.0)	8.03	
Nanpiao (N=3)	0	1 (33.3)	2 (66.7)	7.24	
Suizhong (N=60)	53 (88.3)	3 (5.0)	4 (6.6)	0.07	
Xingcheng (N=113)	112 (99.1)	1 (0.9)	0	0.01	
No response (N=3)	2 (66.7)	0	1 (33.3)		

n=477), and this risk factor was rarely analyzed in previous studies. All these results suggest that concentrating on the animal brucellosis is of great significance in order to prevent and control the human brucellosis.<sup>25</sup>

Of all the cases recorded the clinical manifestations, it was found that the most frequent symptoms were fatigue, hyperhidrosis, fever, arthralgia/myalgia, which is similar to most previous studies.<sup>26–29</sup> It was found that patients aged more than 60 years were more likely to had arthralgia/myalgia than other age groups, and patients who had enlarged spleen in male were more than female; and in another study about clinical characteristics of brucellosis

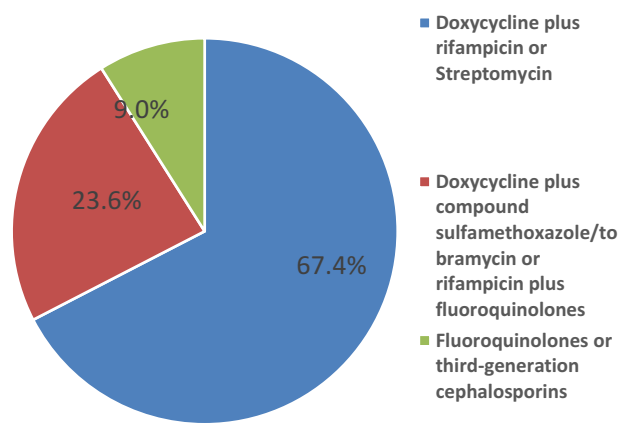
in different age groups,<sup>30</sup> it was reported that patients aged under 3 years old constituted the largest proportion (19.1%) of hepatosplenomegaly. In this study, most patients were diagnosed with acute brucellosis, and there was no statistically significant difference in clinical diagnosis between different age groups and genders, which was different from another study that reporting most (87%) patients under 15 years-old presented as acute cases.<sup>28</sup> Although there are statistically significant differences of some clinical manifestations and diagnoses between different ethnicity and districts in the present study, the results still need to be confirmed in the future considering the large number of

**Table 5** Laboratory Findings of Human Brucellosis in Different Years in Huludao, China (2014–2018)

Positive Serum Agglutination Test (SAT)	2014 (n)	2015 (n)	2016 (n, %)	2017 (n, %)	2018 (n, %)
SAT ≥1:100	195 <sup>†</sup>	330 <sup>†</sup>	2 (2.7)	5 (6.0)	5 (5.9)
SAT ≥1:400			8 (10.7)	20 (23.8)	21 (24.7)
SAT ≥1:800			18 (24.0)	28 (33.3)	35 (41.2)
SAT ≥1:1600			47 (62.7)	31 (36.9)	24 (28.2)
Total (N=769)	195 (25.4)	330 (42.9)	75 (9.8)	84 (10.9)	85 (11.1)

**Note:** <sup>†</sup>there was no specific indication of the antibody titre in the corresponding case questionnaire.

**Abbreviation:** SAT, serum agglutination test.



**Figure 4** The drug combination used for 89 human brucellosis patients in Huludao, China, 2014–2018.

missing values about the ethnicity and district and only few existing studies analyzed these differences. This also reminds us to pay more attention to the integrity and accuracy of the notifiable case questionnaire in the future.

In this study, SAT was the only used laboratory test, and all patients were found to be positive of SAT. In 2018, the old version of “National Human Brucellosis Surveillance Program (Trial)” was converted by the new version of “National Work Plan for Brucellosis Surveillance”,<sup>31</sup> and a new version of “Diagnosis for Brucellosis” (WS 269–2019)<sup>32</sup> was issued in

2019. The laboratory tests were classified as primary screening test and confirmatory test (SAT or Coomb’s test), which made the confirmed diagnosis of human brucellosis more accurate. Furthermore, Liaoning province was listed as the Class I area, and the number of required monitoring points was increased to four counties or districts from two. The brucellosis case questionnaire was modified as well.<sup>31</sup>

In the present study, most patients with brucellosis were treated with antibiotic therapy and “Doxycycline plus rifampicin or streptomycin” was the most common treatment. As for the prognosis, a total of 99.3% of the 592 patients who were treated with antibiotic therapy responded “improved” and “recovery”. It was reported that the cure rate of antibiotic therapy could reach 93.81% in China,<sup>33</sup> and the combination of antibiotic therapy and TCM was more effective (95.35%) than the antibiotics alone (80.95%).<sup>34</sup>

There were several limitations in the present study that was likely to distort/bias the findings. Of 1887 reported cases from 2014 to 2018 in Huludao, only 1149 (60.9%) case questionnaires were reported. And there were a considerable number of missing values of the individual information except for the age and gender. Additionally, compared with the “brucellosis case report form” in the United States,<sup>35</sup> the China’s human brucellosis case questionnaire is short of some options such as the specific

**Table 6** Treatment and Prognosis of Human Brucellosis in Huludao, China, 2014–2018

		Prognosis		
		Recovery (%)	Improved (%)	Not improved (%)
With treatment information (n=594)	Antibiotic therapy (n=592)	89 (15.0)	499 (84.3)	4 (0.7)
	Traditional Chinese Medicinal therapy (n=2)	0	2 (100.0)	0
Without treatment information (n=174)		51 (29.3)	117 (67.2)	6 (3.5)
Total (N=768)		140 (18.2)	618 (80.5)	10 (1.3)

**Table 7** Exposure Distribution of Livestock Species and Routes of Contacting with Livestock for Human Brucellosis in Huludao, China, 2014–2018

Routes of Contacting with Livestock (N=1023)	Species of Livestock					P-value (Fisher’s Exact Test)
	Sheep/Goat Only (%)	Cattle/Cow Only (%)	Sheep & Cattle (%)	Pig (%)	Dog (%)	
Feeding and grazing (n=816)	801 (98.2)	8 (1.0)	5 (0.6)	1 (0.1)	1 (0.1)	0.007
Slaughter/animal product processing (n=18)	15 (83.3)	1 (5.6)	0	2 (11.1)	0	
Animal trafficking/animal trading (n=8)	8 (100.0)	0	0	0	0	
Veterinary/breeder (n=5)	4 (80.0)	1 (20.0)	0	0	0	
Living around livestock farmer (n=86)	83 (96.5)	2 (2.3)	1 (1.2)	0	0	
Other (n=90)	90 (100)	0	0	0	0	
Total (n, %)	1001 (97.8)	12 (1.2)	6 (0.6)	3 (0.3)	1 (0.1)	

**Table 8** Distribution of Personal Protection Options and High-Risk Behavior of Human Brucellosis Cases in Huludao, China, 2014–2018

Investigated Items	Number of Respondents	Number of People Who Answered “Yes” (%)	Year				
			2014	2015	2016	2017	2018
Adoption of protective measures							
Wearing masks	393	66 (16.8)	-	-	13	7	46
Wearing gloves	369	44 (11.9)	-	-	15	6	23
Wearing protective clothing	951	21 (2.2)	1	15	1	0	4
Using disinfectant	851	18 (2.1)	2	5	0	4	7
High-risk behaviors							
Drinking water from the same well with livestock	477	413 (86.6)	126	287	-	-	-
Keeping young lambs indoors	471	22 (4.7)	11	11	-	-	-
Eating undercooked meat or consuming unpasteurized/raw dairy products	394	10 (2.5)	-	-	4	2	4

**Note:** “-” indicates the item was not included in the case questionnaire in the corresponding year.

usage and dosage of medicine, which can provide more accurate evidence to the physicians and policy-makers. All the above-mentioned things suggest that both physicians and policy-makers need to pay more attention to the surveillance and reporting of brucellosis.

## Conclusion

The incidence of human brucellosis is still high in Huludao, China, this is mostly associated with close contact with domestic animals and lacking of self-protective action. The most common clinical manifestations of brucellosis patients in Huludao were fatigue, hyperhidrosis, fever, and arthralgia/myalgia, the most common route of exposure was feeding and grazing, and the major species of livestock was sheep/goat. The most commonly adopted treatment option was antibiotic therapy, and most patients responded well to treatment. The large number of missing values in the case questionnaires could affect the results of statistical analysis; the integrity and accuracy of the notifiable epidemiological case questionnaire needs to be improved in order to provide more authentic and objective information for both the physicians and policy-makers.

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## Disclosure

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