

## Outbreak Reports

## An Outbreak of Febrile Histoplasmosis Among Chinese Manganese-Mine Workers in Cooperative Republic of Guyana in 2019

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### Summary

#### What is already known on this topic?

Cases of histoplasmosis have been reported in every continent except Antarctica but are fairly rare in China. High prevalence of histoplasmosis has been observed in Central America, Caribbean, and South America. Infections of *Histoplasma* are acquired through a respiratory route, particularly inhalation of aerosols from disturbed soils enriched with excreta from birds and bats. These infections are most common in persons involved with removing soil, visiting caves, cleaning old houses, or felling trees, etc.

#### What is added by this report?

This is the first report of cluster infections of *Histoplasma* among overseas Chinese workers. A strong dose-dependent association of illness onset and disease severity with the exposure intensity to the soils and wastes possibly contaminated by the *Histoplasma* has been proposed. Long labor times, repeated entering of contaminated tunnels, working in high-dust environments are likely to result in earlier illness onsets, more severe clinical courses, and even fatal outcomes. More importantly, none of the patients used reliable personal protection equipment (PPE), such as common masks while working, that would prevent the inhalation of more *Histoplasma* spores.

#### What are the implications for public health practice?

The epidemiological findings of this outbreak investigation highlight a probable risk of infection with *Histoplasma* when entering without PPE into the environment with bats living around, such as caves or mines. Effective education and communication might be needed among residents and travelers. This outbreak expands our knowledge of the control and prevention of fungal disease in China.

At the beginning of April 2019, China National Health Commission (NHC) and China Center for Disease Control and Prevention (China CDC) received reports of a cluster of febrile illness involving about ten Chinese workers in a manganese ore in Cooperative Republic of Guyana. The enterprise applied to NHC for permission for evacuating the patients back to China for further treatment. A special Chinese medical team composed of the experts of epidemiology, medical bacteriology, clinical and emergency medicines was deployed to Georgetown, Guyana on April 6, 2019 to provide the support in clinical and public health, to identify the potential etiology and to assess the potential threat, especially the risk of international transmission.

### Outbreak Recognition and Initial Response

On March 28, 2019, six Chinese males with fever visited the local Pakera District Hospital (PDH) in Matthews Ridge. They complained of non-productive coughing, headaches, weakness and joint pain, and two of them had severe symptoms. All of them came from a manganese ore mine nearby. After hospitalization, the District Medical Officer (DMO) notified this event to the Chief Medical Officer (CMO) of the Ministry of Public Health (MOPH) of Guyana immediately and MOPH operationalized its emergency responses operations quickly. One day later, a patient's condition suddenly deteriorated and died with a manifestation of hemorrhagic and multi-organ failure. The rest of the five patients were further transferred to Georgetown Public Hospital (GPH) on March 30, 2019. In the following days, eight more cases including seven Chinese workers and one Guyanese worker were successfully identified and transferred to GPH. Two other mild cases with only mild fever stayed in PDH. Another severe patient displayed multi-organ failure

and died in GPH on April 3, 2019.

Based on the signs and symptoms of the six patients, the MOPH of Guyana issued a working case searching definition: a person who had fever, with or without any one of the below symptoms with unexplained reasons such as cough, headaches, weakness, muscle, and/or joint pains since March 1, 2019 in Matthews Ridge. Healthy miners in the manganese ore mine who had entered the same abandoned tunnels and the close contacts of the patients were placed under medical observation. Up to April 15, 2019, a total of 16 patients were identified. Two Chinese patients died, and two cases (one Chinese patient and one Guyanese patient) were discharged. Because the Guyanese patient showed negative laboratory test results and had no exposure to the abandoned mines, he was excluded from the final case-list. A total of 24 miners including 10 healthy co-exposed miners and 14 close contacts were under medical observations in Matthews Ridge.

## Pathogen Detection

Various tissue specimens from the two fatal cases and blood samples from surviving patients were transferred to the laboratories of China CDC. Next-generation sequencing (NGS) technology based on Illumina MiSeq platform identified different lengths of specific gene sequences of *Histoplasma capsulatum* in seven different samples of two fatal cases and one severe case, including lung and blood samples. Up to April 15, 7 cases were laboratory confirmed as being infected with *Histoplasma capsulatum*. Therefore, 7 of 15 patients were laboratory confirmed cases and the remaining 8 patients were clinically diagnosed cases (Table 1).

## Epidemiological Investigation on the Field

The investigation was conducted by carefully interviewing the patients and their healthy co-workers. The median age of 15 Chinese male patients was 43.5 years old (range: 23-56). The first case displayed clinical manifestation on March 22, 2019 and the peak of disease was on March 30, 2019 (Table 1 and Figure 1). Fever was the most frequent symptom (n=15, 100%), while other symptoms were also noticed including headache (n=10, 67%), muscle pains (n=8, 53%), joint pains (n=8, 53%), weakness (n=7, 47%), cough (n=3, 20%), skin rash (n=3, 20%), and dizziness (n=1, 7%). A clinical evaluation score (range:

0.5 to 100) was assigned to each of the 15 Chinese cases by clinical experts according to illness severity. The more severe the illness was, the higher score was assessed. Among the 15 cases, 2 were fatal cases, 4 were severe cases, and 9 were milder cases (Table 1). The median incubation period of all 15 cases was estimated as 10 days (range 2-11.5 days). The median incubation period of 6 severe and fatal cases [4 days (range 1.5-10 days)] was estimated significantly higher than that of 9 milder cases [12.5 days (range 8.5-13.5 days)].

It was found that all 15 Chinese patients worked in 4 short tunnels (less than 20 meters long) during March 16 and 29, 2019, with varying labor hours. The tunnels were abandoned for more than 50 years. Bats were observed to live inside, and the feces of bats were observed on the ground during the field investigation. The workers entered the tunnels for waste clearance, including shoveling soil and crushing the concrete of the ground without any PPE. Neither the 10 co-workers who had also entered in those tunnels nor the 14 close contacts got sick, resulting an attack rate of 38.5%, and the exposure's odds ratio (OR) of 2.4 (1.495-3.853) ( $p < 0.0001$ ). This strongly highlights that all patients in this event were exposed to the same pathological agent, and the possibility of human-to-human transmission is extremely limited.

## The Relationship Between Exposure Intensity and Disease Severity

As shown in Table 1, the frequency of entry and duration of stay inside of the tunnels among the 15 Chinese patients varied largely. To evaluate the exposure intensity of cases, an equation was used as below:

$$\sum_{F=1}^n (twTLE)$$

Of note,  $n$  was the number of abandoned tunnels (range: 1-4),  $F$  was the times of entry,  $t$  was hours of stay per entry,  $w$  was the type of work including shovel (score=1.5), crush (score=1), and inspection (score=0.5),  $T$  was the date of entry including Period 1 (score=1.5) from March 13 to 22 and Period 2 (score=1) from March 23 to 29,  $L$  was the place of work including the bottom (score=1.5), middle (score=1) and entrance (score=0.5) of the tunnels, and  $E$  indicated whether other work was performed during the stay (Yes scoring 1, No scoring 0.5).

Two distinct profiles of exposure intensity among the patients were clearly noticed. One was above 170 and the other was below 15. A logistic regression

TABLE 1. The epidemiological and clinical characteristics of the 15 Chinese manganese-miner male case-patients in the outbreak of febrile illness in Matthews Ridge, Cooperative Republic of Guyana in 2019.

Case No.	Age (years)	Date of Onset	Type of diagnosis	Clinical Outcome	Clinical evaluation score <sup>†</sup>	Details of exposure in the four old mines						Exposure intensity <sup>‡</sup>		
						Date of first entry	Date of last entry	Times of entry	No. of mines	Type of work	Place of work		Hours of stay per time	Other miner's working <sup>§</sup>
1	47	Mar 22	Laboratory confirmed	Dead	100	Mar 16	Mar 22	7	4	Shovel	Bottom	2	Yes	189
2	44	Mar 26	Laboratory confirmed	Dead	100	Mar 16	Mar 25	7	4	Shovel	Bottom	2	Yes	270
3	42	Mar 27	Laboratory confirmed	Coma, ICU	90	Mar 16	Mar 27	5	4	Shovel, crush	Bottom, middle	2	Yes	175
4	51	Mar 25	Laboratory confirmed	ICU	90	Mar 17	Mar 23	5	4	Shovel	Bottom	2	Yes	171
5	49	Mar 29	Laboratory confirmed	Hospitalization	70	Mar 16	Mar 27	7	4	Shovel, crush	Bottom, middle	2	Yes	249
6	33	Mar 29	Clinical diagnosis	Hospitalization	1	Mar 18	Mar 18	1	1	Check around	Bottom	0.1	Yes	0.113
7	44	Mar 28	Laboratory confirmed	Hospitalization	1	Mar 24	Mar 27	4	4	Crush, check around	Bottom	1.5	No	9.6
8	56	Mar 30	Clinical diagnosis	Hospitalization	20	Mar 16	Mar 24	2	4	Check around	Bottom	0.1	No	0.525
9	34	Mar 30	Clinical diagnosis	Hospitalization	30	Mar 18	Mar 28	1	2	Crush	Bottom	1.5	Yes	5.625
10	48	Mar 30	Clinical diagnosis	Hospitalization	1	Mar 16	Mar 16	2	1	Check around	Bottom	0.1	Yes	0.225
11	43	Mar 30	Clinical diagnosis	Hospitalization	5	Mar 17	Mar 27	1	2	Check around	Bottom	0.1	Yes	0.3
12	38	Mar 31	Clinical diagnosis	Discharge	0.5	Mar 16	Mar 16	1	1	Check around	Entrance	0.5	No	0.094
13	50	Mar 26	Laboratory confirmed	ICU	80	Mar 16	Mar 24	7	4	Shovel	Bottom, middle	2	Yes	198
14	41	Apr 11	Clinical diagnosis	Hospitalization	30	Mar 28	Mar 28	1	1	Crush	Middle	1.5	Yes	2.25
15	23	Apr 11	Clinical diagnosis	Hospitalization	30	Mar 28	Mar 29	2	2	Crush	Entrance	6	Yes	12

**Abbreviation:** ICU = intensive care unit. All 15 cases were male. Next-generation sequencing (NGS) technology based on Illumina MiSeq platform identified different lengths of specific gene sequences of *Histoplasma capsulatum* in 7 different samples of 2 fatal cases and one severe case, including lung and blood samples. Up to April 15, 2019, 7 cases were laboratory confirmed being infected with *Histoplasma capsulatum*. All data were updated as of April 15, 2019 when the special Chinese medical team departed from Guyana back to China. † A clinical evaluation score (range: 0.5 to 100) was assigned to each of the 15 Chinese cases by clinical experts according to their illness severity. The more severe the illness was, the higher score was. ‡ Were other miners working close by? †† The exposure intensity was a score representing the exposure degree and risk of infection according to the detailed exposure information of the case-patients. It was calculated by using the equation of  $\sum_{i=1}^n (t_{w_i}/L_i)$ ;  $n$  was the number of the abandoned tunnels (range: 1-4),  $F$  was the times of entry,  $t$  was hours of stay per entry,  $w$  was the type of work including shovel (score=1.5), crush (score=1) and inspection (score=0.5),  $T$  was the date of entry including Period 1 (score=1.5) from March 13 to 22, 2019 and Period 2 (score=1) from March 23 to 29, 2019,  $L$  was the place of work including the bottom (score=1.5), middle (score=1) and entrance (score=0.5) of the tunnels, and  $E$  indicated whether other work was performed during the stay (Yes scoring 1, No scoring 0.5).

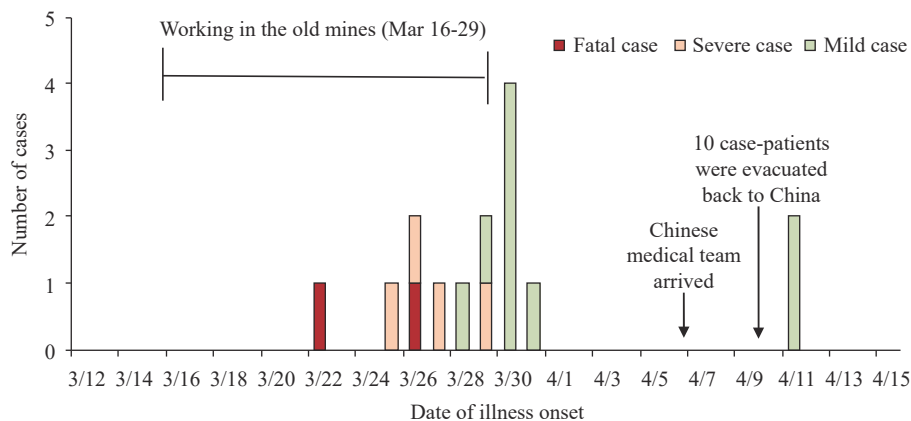


FIGURE 1. The date of illness onset of the Chinese-manganese-miner male case-patients in the outbreak of febrile illness in Matthews Ridge, Cooperative Republic of Guyana in 2019.

model  $[y=11.882\ln(x)+18.405]$  was established by combining the exposure intensity scores of the cases with the individual clinical scores. The distribution of the 15 patients were distinctly divided in two separate areas (Figure 2). Patients with severe clinical manifestations and poor prognosis harbored significantly higher exposure intensity scores, in which 2 fatal cases showed exposure intensity scores of 189 and 270. Patients with low exposure intensity scores underwent mild clinical processes (Table 1). These data indicate a close relationship between the exposure intensity and disease severity.

## Comments

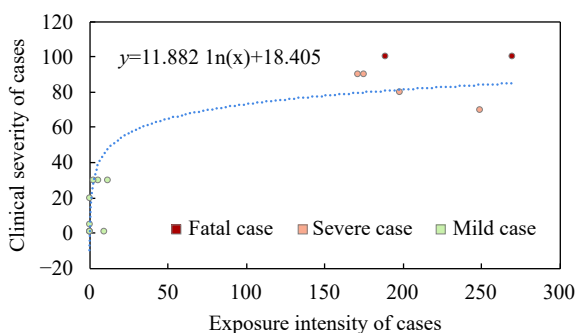


FIGURE 2. The dose-response exposures associated with severity of illness among 15 Chinese-manganese-miner male case-patients in the outbreak of febrile illness in Matthews Ridge, Cooperative Republic of Guyana in 2019.

In this overseas investigation among Chinese workers, a closely dose-dependent association of illness onset and disease severity with the exposure intensity to soil and waste possibly contaminated by the *Histoplasma* has been proposed. Long labor times, repeated entering of contaminated tunnels, working in

dustier environments are likely to result in earlier illness onsets, more severe clinical courses and even fatal outcomes. More importantly, none of the patients used reliable PPE, such as common masks while working, that would prevent the inhalation of more *Histoplasma* spores. Finally, ten patients were successfully evacuated from Guyana to China with a Chinese medical aid aircraft without causing any further transmission. This outbreak practiced and exercised the Chinese medical emergency response overseas, but this investigation was limited because the environmental risk of the mines could not be evaluated. Environmental specimens collected in the mines were not been shipped to China on time due to restricted cooperation on specimen transportation between the countries.

The infection of *Histoplasma* has been reported in some countries in Southern America(1–2), including Guyana(3). During an interview with the staff in the local hospital, we learned that there was a local farmer who underwent similar but mild pathogenesis after entering the same tunnels and collecting feces of bats as fertilizer, highlighting the possibility of a long-term circulation of *Histoplasma* in this region. Although the clinical features of this cluster disease are similar to that of acute infections of *Histoplasma* described elsewhere(4–7), such a cluster outbreak is fairly rare in China. To our knowledge, no definitively confirmed cluster infection of *Histoplasma* in China has been reported. Despite that, there have been a few similar events that occurred in travelers in the caves in the southwestern region of China, inhabited various species of bats, though no reliable pathogen evidence has been obtained. The clinical findings of the cases provide valuable experience to Chinese clinicians to

understand the clinical features of acute infection of *Histoplasma* and will help achieve early detection and efficient treatment for patients. Although information on the miners' reference level of health is not available for further comparative analysis, the epidemiological findings of this outbreak investigation highlight a probable risk of infection with *Histoplasma* when entering without PPE into environments inhabited by bats such as caves or mines. Education and communication initiatives might benefit residents and travelers in this region. This outbreak expands our knowledge of the control and prevention of fungal disease in China. Due to worldwide industrial collaborations and traveling, we need to watch closely for emerging pathogens(8).

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