

Scrub Typhus Death: Losing the Precious Time

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Abstract

Introduction: Scrub typhus is an acute febrile illness caused by the bacteria *Orientia tsutugamushi*. Owing to the increase in the number of cases and a suspected death due to scrub typhus, the director of health services, Kerala state, requested a death audit and an outbreak investigation in the Nedumangad and Palode areas of Thiruvananthapuram district and the Department of Community Medicine, Medical College, Thiruvananthapuram was called in for technical expertise and this outbreak investigation was undertaken.

Methodology: The methodology involved a death audit for a suspected death due to scrub typhus, fever surveillance for detection of scrub typhus cases among admitted patients in two local hospitals, training need assessment using a rapid assessment questionnaire and house visit of three confirmed cases of scrub typhus in the recent past.

Results: The death audited was likely due to Scrub typhus. Scrub typhus could have caused an acute kidney injury aided by rhabdomyolysis, or it could have precipitated an acute exacerbation of an already existing kidney disease resulting from the patients' long-standing untreated diabetes mellitus. The presence of rats and shrubs in the area, the history of active involvement of the patient in the sanitation works of the area, the history and clinical finding of eschar in the patient along with two positive IgM Scrub typhus lab reports done in an interval of fifteen days, are strongly suggestive. Two out of the ten blood samples collected for the fever surveillance tested positive for scrub typhus IgM. Training need assessment revealed good knowledge among health care workers, but minimal experience of dealing with actual cases. The household visits identified potential environmental risk factors like abundance of shrub vegetation, rat infestations, involvement in activities like clearing of shrubs, and contact with pets.

Conclusion: A strong suspicion is necessary for an early diagnosis of scrub typhus and scrub typhus co-infections. Delay in the initiation of treatment could be a potential reason for death due to scrub typhus. The absence of eschar should not be taken as a criterion for ruling out scrub typhus. The community should be empowered for early treatment seeking. Surveillance should be strengthened. Capacity building of health professionals may facilitate early case detection, treatment and prevention of deaths.

Introduction

Scrub Typhus or tsutugamushi disease is an acute febrile illness caused by bacteria of the family Rickettsiaceae and named *Orientia tsutugamushi*. Scrub typhus is endemic in 'the tsutugamushi triangle', which includes Japan, Taiwan, China, and South Korea. Cases have also been reported from Nepal, Northern Pakistan, Papua New Guinea, and Queensland and Northern New South Wales in Australia [1].

Scrub typhus is essentially an occupational disease among rural residents in the Asia-Pacific region. In oil-palm workers in Malaysia, the incidence of antibodies to scrub typhus declines with declining grass density between the rows of maturing oil-palm [2]. This correlates with the decline of chigger populations in this habitat. An increase in the prevalence of scrub typhus has been reported from some Asian countries, which coincides with the widespread use of β -lactam antimicrobial drugs and urbanization in rural areas [3].

During World War II, the disease had occurred among troops in the Indian states of Assam and West Bengal. It had also been reported in 1965 during the Indo-Pak war. Scrub typhus is prevalent in many parts of India but specific data are not available [4]. There have been outbreaks in areas located in the sub-Himalayan belt, from Jammu to Nagaland. There were reports of scrub typhus outbreaks in Himachal Pradesh, Sikkim and Darjeeling (West Bengal) during 2003-2004 and 2007. Outbreaks of scrub typhus are reported in the southern India during the cooler months of the year [1].

Scrub typhus is a re-emerging infectious disease in India. The reported number of cases of

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Scrub typhus from different parts of the country particularly from large tertiary care hospitals do not give a true picture of prevalence of scrub typhus in the country. Yet, there are not many community based studies in our country.

Scrub Typhus is being reported in the Kerala state since 1998 by the State Prevention of Epidemic and Infectious Disease (PEID) cell and by the Directorate of Health Services since 2012. The cases are being reported especially from the capital city of Thiruvananthapuram. According to Kerala District Health Services (DHS) data on communicable diseases for 2013, there were 68 cases of scrub typhus in 2013 in Kerala state. Among these 49 were from Thiruvananthapuram district. In 2014, 433 cases and 6 deaths were reported from the state of Kerala. Of these 360 cases and 3 deaths were from the Thiruvananthapuram district [5]. As per DHS data, there were 4 deaths in 2012 but none in 2013. In 2014, deaths were reported again [5] and in the light of that, DHS planned an outbreak investigation and death audit. The Department of Community Medicine, Medical College, Thiruvananthapuram was called in for technical expertise and this investigation was undertaken.

Materials and Methods

An investigation was conducted in view of reports of scrub typhus in Thiruvananthapuram, in Palode and Nedumangad areas, on 23rd January 2014. This investigation was conducted by a multidisciplinary team. It consisted of members from the Directorate of Health Services, Kerala, Departments of Community Medicine and Microbiology, Medical College, Thiruvananthapuram, State Prevention of Epidemic and Infectious Disease cell, Kerala and Department of Animal Husbandry. We were assisted and supported by field staff of Taluk Hospital, Nedumangad and Community Health Centre, Palode and Anganwadi workers at Palode.

The main activities carried out were a Death audit, Fever surveillance for detection of scrub typhus cases, training need assessment and visit to the households of recently reported cases. The team of seven members first visited the Nedumangad general hospital. From there we went to Palode for the death audit and field visits. We also visited the fever cases at Community Health Centre-Palode. Field visit at Nedumangad was done on the way back. Blood samples were collected from ten suspected cases with fever from the Nedumangad Taluk hospital and Palode community health centre. IgM Elisa for scrub typhus was done at Microbiology lab in Thiruvananthapuram Medical College. Inbios International's Scrub Typhus Detect IgM ELISA System was used. It is a qualitative ELISA and it detects IgM antibodies to *O. tsusugamushi* in serum. No fixed cut-off control was supplied and it was required to be determined by the end-user due to endemic nature of disease in many countries, which was estimated in this lab to be 0.38.

A rapid training need assessment was done for staff nurses, health workers and their supervisory staff. A brief questionnaire which contained 10 questions on scrub typhus was used their responses were analysed. Two other houses having patients with confirmed scrub typhus in the recent past were also visited.

Ethical considerations and clearance: This investigation was carried out as an outbreak investigation, requested by the Directorate of Health Services, Kerala. Therefore it was exempted from obtaining clearance from the Institution Ethics Committee. However, all

procedures for obtaining informed consent from the participants were carried out. Prior information was given to the local health authorities and hospital administrators. Confidentiality and privacy was maintained at every step of the investigation.

Results

Results of death audit

The deceased was a 43 year old male. He had been working in a tyre shop in the state of Gujarat in the past. Since the last 4 years, he had been working in Kerala, as a Rubber tapper in the day and as security personnel at a bank during night hours. He was actively involved in sanitation works of the area.

He consulted Palode local hospital with complaints of fever off our day's duration and abdominal pain. He was referred that day itself to Medical College Hospital, Thiruvananthapuram but he did not heed to this advice. Two days later, he consulted another local hospital and he was prescribed some medicines. With these medicines he had some symptomatic relief. Five days later, he consulted an alternative medicine hospital. They referred him to Thiruvananthapuram Medical college, but he went back home. The next day, he was taken to Thiruvananthapuram Medical College after developing difficulty in walking.

After being admitted, the patient reported fever, severe myalgia and productive cough of 10 days duration and breathlessness, yellowish discolouration of urine and eyes with decreased urine output of 3 days duration. On examination, he had pallor, icterus, severe muscle tenderness, epigastric tenderness and an eschar on the medial side of his left upper arm.

Initial investigations revealed thrombocytopenia and elevated total serum bilirubin and liver enzymes, blood urea and serum creatinine. Serum amylase (439 U/L) and lipase (2059 U/L) were elevated. Rapid malaria test was negative, Dengue IgM and IgG were negative, Weils antibody was negative. Scrub typhus IgM result came out as Reactive (value 1.641) against the cutoff of 0.54. Hanta virus Puumala IgM was also Reactive (value 0.394). He had developed rhabdomyolysis and showed elevated urine myoglobin(1776 ng/L) and CPK (201 U/L).

As the patient developed a new onset murmur, an echocardiography was done which showed severe mitral regurgitation, moderate aortic regurgitation, tricuspid regurgitation, and pericardial effusion. He developed complete heart block. Tip of the spleen became palpable. His blood culture showed only growth due to contamination.

Two weeks after the first test, Scrub typhus IgM was repeated and the result was again reactive (value 2.8). Hantavirus Puumala IgM was also repeated and the result was reactive (value 0.896). Severe kidney and liver damage were detected. Haemodialysis was done 11 times in total. He had worsening of urine output, developed metabolic acidosis with respiratory alkalosis and he progressively deteriorated developing hypotension. He died 30 days after hospitalisation. Cause of death as in death certificate was Scrub typhus with acute kidney injury, infective endocarditis, severe mitral regurgitation, serositis and pancreatitis. Interval between onset of disease symptoms and death was 42 days.

He was provided antibiotic coverage with crystalline penicillin, ceftriaxone, meropenem, metrogl, piperacillin and tazobactam

and azithromycin at different times during hospital stay. He had a history of diabetes mellitus since 13 years of age. He was on oral hypoglycemic agents for 10 years following the diagnosis of diabetes but he had stopped taking any drugs for the past 20 years. History of low urine output occasionally in the past was obtained, for which the deceased used to ask for tender coconut water to rectify the problem.

Results of fever surveillance for detection of scrub typhus cases:

Out of a total of ten samples, two samples were positive for IgM Scrub Typhus collected from the Nedumangad taluk hospital. One was that of a 6 year old school student who had presented with fever for 7 days with generalized lymphadenopathy. He had no rash and no eschar. History of rats at his residence was present. Second case was a 74 year old man with fever for two weeks, cough with expectoration, unilateral swelling of a foot, and axillary lymphadenopathy. He also did not have rashes or eschar. This patient was not suspected to have scrub and IgM Scrub Typhus was done by the treating doctor earlier. IgM Scrub Typhus wasn't checked for this patient earlier.

Results of the rapid training need assessment using a brief questionnaire:

We administered the questionnaire to health personnel at Nedumangad and Palode local hospitals. Response rate was 80%. (n=16). Out of the sixteen participants, thirteen (81.25%) knew about the causative agent of scrub typhus. The mode of transmission was known to nine (56.25%). Eleven (68.75%) were aware about the vector for scrub typhus. Symptoms of scrub typhus were known to fourteen (87.5%), whereas signs of scrub typhus were known to fifteen (93.75%). When asked about one specific sign they will look for in scrub typhus, fourteen (87.5%) answered eschar. Thirteen (81.25%) knew about the Diagnostic test for scrub typhus. Drug of choice for scrub typhus was also known to fifteen (93.75%). When they were asked about whether they think there is a problem of scrub typhus in their area and what control measures could be employed, eight (50%) of them said 'yes' and listed a few control measures like clearing shrubs but eight (50%) didn't think there was a problem in their area. When asked about their experience with scrub typhus cases, only two (12.5%) had previous experience of seeing and handling cases of scrub typhus whereas fourteen (87.5%) were yet to see a case.

Results of visit to the households of reported cases of scrub typhus:

The first case was a 79 yr old female, hypertensive since 10 years who had a short febrile illness with thrombocytopenia one year back and was admitted in the intensive care unit of Thiruvananthapuram medical college with decreased urine output. Renal function tests were abnormal and she had developed altered sensorium. IgM scrub typhus was positive and she had no eschar. She gave a history of close contact with her pet dog. She said there were shrubs in front of the house which was destroyed after that episode of hospitalization as the doctor told them that she fell ill because of those shrubs.

The second we visited was that of a 54 year old man who was hospitalised with fever, headache, vomiting, hepato-renal disease and diastolic dysfunction. His Chest x-ray showed bilateral upper lobe non homogenous patches. He was diagnosed with scrub typhus, treated successfully and discharged after 12 days of hospital stay. He also said that he frequently gets involved in clearing off shrubs. Around his household there were plenty of shrubs. A rat burrow was also seen. Instructions given to the health professionals at Palode community health centre and Nedumangad taluk hospital, based on

observed findings were to be alert to detect scrub typhus early and to initiate treatment without delay. They were also instructed to adopt rodent control measures urgently.

Plan for Follow-up

Planning host animal and vector study

Objective of such a plan was to identify the antibodies from sera of infested rodents, predominant species of rats, degree of infestation of rodents in terms of the chigger index, species specific (rat and mite) chigger index. National Centre for Disease Control, New Delhi was contacted in this regard and they have agreed with the study and has asked to send specimens from at least 10 rats for analysis. The process and specimens to be sent were communicated by them and are as follows.

A rat has to be identified first and two to three millilitres of its blood should be taken, either by a syringe or cutting its throat. Then serum should be separated and kept it in a small vial and it should be sealed and send for detecting antibodies in serum. Then it should be followed by combing for ectoparasite collection (Mite) and the ear pinna should be preserved in 70% alcohol. The material after proper labelling could be sent to National Centre for Disease Control (NCDC) for identifying the vector species.

Planning collection of rodents

The local people had already trapped one rat from the household premises of the deceased and they extended their support in trapping rats. Palode community health centre was contacted for collection of rodents from the areas around the houses of reported scrub typhus cases, employing a community participation approach, in which rat-traps will be kept and rats will be caught by people from the community themselves. Veterinary doctor in the nearby hospital has extended her support in collecting the rat blood samples and taking specimens to be sent to NCDC. Other plans are conducting Household visits at other areas like Balaramapuram where clustering is seen, Serosurveillance in areas with clustering like Palode and Balaramapuram and also further host and vector studies to identify possible hosts such as cats, dogs and other domestic and non-domestic mammals and the roles played by them.

Discussion

The study shows that scrub typhus is an emerging threat in Kerala. This febrile illness affects previously healthy active persons and if undiagnosed or diagnosed late may prove to be life threatening. Recently, several reports of scrub typhus from various parts of India have been published [6,7].

The death audited is likely due to Scrub typhus. Scrub typhus could have caused an acute kidney injury, aided by rhabdomyolysis or it could have precipitated an acute exacerbation of an already existing kidney disease which might have resulted from his long-standing untreated diabetes mellitus. The presence of rats and shrubs in the area, the history of active involvement of the patient in the sanitation works of the area, the history and clinical finding of eschar in the patient along with two positive IgM Scrub typhus lab reports done in an interval of fifteen days, are strongly suggestive of our diagnosis of Scrub typhus.

The deceased in our study reached a tertiary care hospital as late as 8 days since he was first referred to a tertiary centre. The delay in visiting a tertiary centre might have cost his life, as by the time he got there, his hepatic and renal functions were already deranged. The pre-existing co-morbidities of diabetes and a possible compromised kidney function could have also contributed. Diagnosing him would not have been a challenge, as he had the characteristic eschar. If he had been educated well about scrub typhus and empowered enough to seek early diagnosis and treatment, his life could have been saved [8].

Four possible overlapping clinical presentations of scrub typhus have been reported: mild disease, respiratory predominant disease, central nervous system predominant disease (meningoencephalitis), and sepsis syndrome. Early diagnosis and treatment of scrub typhus is possible as it has a characteristic clinical presentation, presence of eschar in 45.5% of cases and availability of an effective and cheap drug, doxycycline [9].

Saifudeen, et al. in 2012 reported the first case of scrub typhus meningoencephalitis in Kerala, a 45-year-old farmer from north Kerala who was initially diagnosed as enteric fever with meningism and a suspicion of leptospirosis, not responding to intravenous ceftriaxone. Only on the seventh day of hospitalization an eschar was found on his groin and a positive Weil-Felix reaction was obtained. Typhoid fever and leptospirosis being much more common in North Kerala and the presentation of this case being similar to those, the limited awareness about scrub typhus and a low index of suspicion, resulted in missing the diagnosis initially [10].

Two cases reported from Vellore in 2003, one a 10-year-old girl who presented with history of fever and myalgia for 10 days and headache and vomiting for 3 days and another, a 12-year-old girl who presented with history of fever and cough for 15 days, loose stools for 5 days and one episode of generalized tonic clonic seizures followed by altered sensorium on the day of admission. The wide clinical spectrum of this infection is reflected by these two cases. The first child with prolonged fever was relatively well whereas the second child had a slightly more prolonged course of the illness, and required intensive care [11].

In a study done in Taiwan in 1998, 33 cases of scrub typhus were admitted at Tri-Service General Hospital, Eschar was seen only in 60% of the cases and 44% had thrombocytopenia (platelet count < 100,000/mm³). Elevation of Aspartate aminotransferase (AST) was seen in 81% and elevation of Alanine aminotransferase (ALT) in 75% [12]. A study conducted in Dehradun had the characteristic eschar in only 14.5% of the cases and also had abdominal pain as a symptom in 26% of the cases [13]. The clinical presentation of the deceased in our study matches with these findings, strengthening our diagnosis of scrub typhus.

Serious complications which were reported in the 1998 Taiwan study were pneumonitis in 36%, Acute Respiratory Distress Syndrome (ARDS) in 15%, acute renal failure in 9%, myocarditis in 3% and septic shock in 3%. One patient died of ARDS due to delay in diagnosis. Metabolic acidosis, ARDS, altered sensorium and shock were identified as independent predictors of mortality [12]. The deceased in our study had developed metabolic acidosis and shock.

Though eschar is pathognomonic of scrub typhus, and the deceased in our study had an eschar, our fever surveillance and

household visits revealed that absence of eschar cannot rule out the disease. This emphasizes the fact that scrub typhus should be considered in patients with fever, with lymphadenopathy or varying degrees of respiratory distress, particularly if there is an eschar or a history of environmental exposure in endemic areas.

In a tropical country like India, the most common tropical infections causing acute febrile illness are malaria, leptospirosis, scrub typhus, dengue, typhoid and many others. Malaria and dengue, both mosquito-borne infections, are very much prevalent in India. Although co-infections with scrub typhus, dengue and malaria have been reported, these are still not very common. Co-infections and mixed infections pose a difficulty to the physician as the presentation is with unexpected clinical findings and response to treatment is apparently poor [14]. Role of co-infections in the severity of the disease is not clearly identified. Dengue and malaria co-infection is seen to increase the risk of thrombocytopenia. Response to treatment is of diagnostic significance. Hence, a patient with acute febrile illness not responding to appropriate therapy within 48 hours must be investigated for concurrent infection with other tropical infective diseases [14], including scrub typhus.

In a study conducted in China, they documented occurrence periods for the autumn-winter type scrub typhus cases. The seasonal variation of scrub typhus cases in northern China was similar to that reported in Korea, where human cases of scrub typhus were reported to increase in October and peak in November. This pattern was, however, different from those reported in Japan and in southern China. In Japan, a bi-modal pattern of occurrence of cases – one in spring and another in autumn-winter was reported [15,16]. A study done on the prevalence of scrub typhus in rural Southern India, highlights the finding that about 50% of the undiagnosed prolonged fevers that occur during the cooler months of the year in the rural areas of Tamil Nadu, South India, could be due to scrub typhus. Many studies done in the 1960s and 1970s have demonstrated the endemic nature of this disease in many parts of India [17,18]. In Kerala, the winter commences by middle of November and extends till middle of February. Mathai, et al. has reported that more cases in southern India occur during the cooler months. This correlated with the period when the number of field rats infected with *O. tsutsugamushi* is high and also the period when more mites are attached to rodents [7]. This calls for an even higher index of suspicion during winter months. The death in our study has occurred during winter time and our fever surveillance also revealed two out of ten (20%) fever cases tested to be scrub typhus IgM positive. A study from Dehradun showed the number of cases rising with the onset of rains and declining as winter ensued [13]. So, further studies are needed to establish the seasonality of scrub typhus.

Hantaviruses had a co-evolution with their respective rodent carriers and hence their geographical distribution is in accordance with it. So Puumala hantavirus (PUUV) should be absent in India as it's rodent, the bank vole is not there in India or it should be spread by another unidentified rodent [19]. In a 2015 Sri Lankan retrospective study of 23 serologically confirmed past leptospirosis patients, six patients (26%) gave positive test results for two different IgG ELISA Hantavirus formats. Consistently higher results were obtained for European Puumala Hantavirus (PUUV), than Asian Hantaan Virus (HTNV), though not significantly different statistically. This suggests a cross-reaction, as the PUUV is considered to be absent in the

Asian continent [20]. So chances are that the positive result of Hanta IgM Puumala, which was obtained in our investigation was a cross reaction, thus weakening the possibility of the diagnosis being Hanta fever or even a co-infection, which further strengthens our diagnosis of scrub typhus.

Cats can be infested by trombiculid mites involving their external ear and can even cause an inflammatory disease of their ear canal. As many ova are produced by one adult female mite, the larvae form a cluster where they emerge and any mammals entering this area can get infested at one single instance, with many mites. The mite infesting a cat typically will not move to a human and if both are infested with chiggers, a simultaneous exposure to chiggers is more likely to have occurred. Infested cats and dogs rarely act as a mechanical vector [21]. In our study there is a history of close contact with dogs for a few scrub typhus positive cases. Further research is required to rule out any role played by cats, dogs and other domestic and non-domestic mammals.

In a study from Dehradun, various environmental predisposing factors to scrub typhus were identified such as living close to forests in 38% of patients, exposure to domestic animals such as rats, cattle and dogs was found in 65% of cases. Living close to shrubs was found in 78% of the patients. Open defecation and cutting of grass were observed in 50% of the cases [13]. This matches very well with the environmental conditions of our deceased patient and also the confirmed cases in the households we visited.

A review of rickettsial outbreaks in 2014 of the last decade indicates its continued presence in several parts of the India. They recommended use of uniform case definition, capacity building for laboratory confirmation and entomology surveys. The Doctors working in such disease-prone areas should be trained to have a high degree of suspicion while dealing with fever cases [8]. This may be attributed to the role of physicians in early detection and prompt diagnosis, thus contributing to effective treatment planning. Our study also puts forward the need for training the health personnel on scrub typhus.

In the last few years, there have been outbreaks of scrub typhus in many areas of south India especially Karnataka and Tamil Nadu. So, Kerala being heavily dependent on neighbouring states for food grains, fruits, and vegetables, there is an increased chance of transport of mites attached to rodents; moreover, there is a recent increase in tourism as well [9].

WHO, after investigating scrub typhus cases have come-up with the following precautions? "In endemic areas, wear protective clothing. Insect repellents containing butyl phthalate, benzyl benzoate, diethyl toluamide, and other substances can be applied to the skin and clothing to prevent chigger bites. Do not sit or lie on bare ground or grass; use a suitable ground sheet or other ground cover. Clearing of vegetation and chemical treatment of the soil may help to break up the cycle of transmission from chiggers to humans to other chiggers [1]. Case identification; public education; and rodent control and habitat modification are the three pillars of programme aimed at controlling the impact of scrub typhus on the human populations [2].

The Strengths observed in this investigation were the availability of confirmed lab reports of IgM Scrub Typhus, the Inter-sectorial co-ordination which was achieved to carry out this investigation

and the Community participation received in the course of the investigation and promised in the further follow up. The limitation of the investigation was relying on serology for diagnosis and not doing PCR.

Conclusion and Recommendations

A strong suspicion is necessary for an early diagnosis of scrub typhus and scrub typhus co-infections. Delay in initiation of treatment could be a potential reason for death due to scrub typhus. Cases of scrub typhus with co-morbidities need to be closely monitored for complications. The absence of eschar should not be taken as a criterion for ruling out scrub typhus, although it has to be specifically looked for. The community should be empowered for early treatment seeking, detection of eschar and lymphadenopathy and reporting of the same to the doctor. Expanding the fever surveillance and sentinel surveillance to include scrub typhus may give a better estimate of its magnitude, trends and other characteristics. Well planned epidemiological studies are also required in this direction.

Potential areas of research include sero-surveillance in affected areas, host and vector studies and discovering the existence of other possible hosts like dogs, cats and other domestic and non-domestic mammals and the roles played by them. Host and vector studies need to be done with collaboration from animal husbandry department in focal points where clustering is seen, to start with. This will improve the capacity of human resource for planning epidemiological investigations when required. Future studies are also recommended for establishing the seasonality of scrub typhus in this part of the world.

Theoretical knowledge of scrub typhus is reasonably good among the health care personnel but their experience with management and control of the disease is minimal. Therefore training on scrub typhus is the need of the hour. Capacity building of health professionals may facilitate early case detection, treatment and prevention of deaths. To begin with, the health personnel of the districts reporting scrub typhus need to be trained. A sensitisation of these professionals can be done at the earliest. Close monitoring and timely referral of suspected/probable cases of scrub typhus with co-morbidities and complications should be done. Integrated Disease Surveillance Programme case definitions for suspect and probable case definitions need to be adhered to for epidemiological surveillance in the absence of laboratory confirmation. Strengthening of laboratory facilities for diagnosing scrub typhus is also needed. Rodent control and vector control should be done effectively and regularly with community participation.

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