Scrub typhus in Bhutan: a synthesis of data from 2009 to 2014

Tshokey Tshokey, Tashi Choden, Ragunath Sharma

ABSTRACT

Scrub typhus is an acute, febrile illness caused by the bacterium Orientia tsutsugamushi, that affects millions annually in the endemic Asia-Pacific region. In untreated cases, the case-fatality rates range from 6% to 35%. In Bhutan, there was a probable outbreak in Gedu in 2009, which resulted in heightened awareness of the disease. Nevertheless, information on scrub typhus in Bhutan is limited and scattered and the epidemiology has yet to be established. To report the current picture of scrub typhus in Bhutan, this review gathered data from scholarly databases, surveillance reports, the Annual health bulletin, research publications and laboratory test reports from hospitals. The weight of evidence indicates an increasing burden of scrub typhus since the Gedu incident, coupled with increased awareness and testing. Another outbreak in a rural primary school in 2014 resulted in two deaths. More hospitals now have testing facilities and laboratory-confirmed cases have been increasing since 2009, with seasonal trends. This review highlights the need for in-depth surveillance and reporting, increased awareness among health-care workers, and initiation of prevention and control programmes in the country.

Key words: Bhutan, Gedu, Orientia tsutsugamushi, scrub typhus

BACKGROUND

Scrub typhus is an acute febrile illness caused by the bacterium Orientia tsutsugamushi. The infection results from bites of chigger mites that are primarily associated with rodents of the genus Rattus. With an incubation period of 10–14 days, scrub typhus presents with acute onset of fever, headache, malaise, swollen lymph nodes and maculopapular rashes by the end of the first week of fever. Without treatment, the case-fatality rate remains at 6–35% but can be as high as 60% in some outbreaks. It has been described as a seriously neglected life-threatening tropical disease. It is also a travel-associated disease, and has great importance among military personnel. Scrub typhus is known to be endemic to the Asia-Pacific region, covering a triangular area known as the “tsutsugamushi triangle”, extending from Afghanistan and Pakistan in the west to China and Korea in the east and the islands of the south-western Pacific and northern Australia in the south. In this region, an estimated one million cases occur annually, especially among those engaged in logging, clearing of land and working in rice fields. The disease is focally distributed throughout the region, from the low coastal lands to a height of over 3200 m in the Himalayas. Scrub typhus is being increasingly reported from new areas within the endemic Asia-Pacific region and also beyond the described triangle, with recent descriptions in a patient from Dubai in the Middle East and in children in Kenya, Africa.

In the Indian city of Darjeeling, a study in 2005 showed that the incidence of scrub typhus increased from 2/100 000 population in July to 20/100 000 population in September and decreased to zero in December. One of the first studies on scrub typhus in Bangladesh, a prospective sero-epidemiologic survey across six major teaching hospitals in Bangladesh using an immunoglobulin M (IgM) enzyme-linked immunosorbent assay, found that 24% (287/1209) had evidence of recent exposure to Orientia tsutsugamushi. Seropositivity differed between regions but there was no clustering of cases and no difference between urban and rural residents. Cases of scrub typhus have been increasingly reported in mainland China, from 1248 in 2006 to 8886 in 2012. There have been several studies on outbreak or clusters of scrub typhus cases from different states of India. In a survey of the eastern Himalayas (Indian districts bordering the Bhutan foothills) for endemcity of scrub typhus among small mammals, chiggers were the most prevalent ectoparasites, with clusters of single hosts harbouring up to 600 mite larvae. Of the 573 mammals sampled, 357 (62%) were infested with trombiculid larvae, and rodents and insectivores were both equally good hosts for larval mites, with 68% infestation in both cases. Despite increasing reports of significant burden, the true incidence of human infections in south central Asia still remains unknown.

Bhutan is a small Himalayan country between India and China. It has a population of about 750 000, with a population density...
of 9 to 64 people/km² in different districts. The country has over 70% forest cover and the economy is mostly agricultural, with 70% of the population living in rural areas. Bhutan can be conveniently divided into three regions: the north bordering China, dominated by the Great Himalayas with terrains and high mountains above 3700 m; the lesser Himalayas above 1500 m; and the Duars plain, bordering India in the south. With four distinct seasons, the mean daily temperature can vary from 5 °C in winters to 25 °C in summer and the average annual rainfall varies from less than 500 mm in the northern Himalayas and 500–1000 mm in the inner central valleys to 2000–5000 mm in the southern foothills. Bhutan lies within the zone that is endemic for scrub typhus, and the environment of wide scrub vegetation, high humidity, extensive agricultural activities and abundant rodent population, especially in the middle and southern part of the country, makes it conducive for transmission of the organism, although the disease was not documented until recently. Earlier infections may have been missed, owing to a lack of diagnostic facilities and poor awareness among health-care workers. However, many non-malarial and non-typhoid febrile cases that responded rapidly to doxycycline or chloramphenicol in daily medical practice could have been scrub typhus. The disease was only highlighted with a probable outbreak of some febrile illness in 2009. The infection is now increasingly reported from many parts of the country.

Scrub typhus has been included in the national list of notifiable diseases since 2008 and reporting was initiated in 2010 but the notification system is weak and many health-care workers are unaware of the need to notify, resulting in minimal reports. The surveillance manual defines scrub typhus as “characterized by acute onset of fever after several days, headache, profuse sweating, myalgia, eschar, lymphadenopathy and rash” and defines a suspected case as “a case that is compatible with [the] clinical description”. Since 2010, reports on scrub typhus (as rickettsial diseases) have been included in the annual mortality and morbidity reports submitted by the district health offices to the Ministry of Health. These are compiled by the Health Management Information System, in the Annual health bulletin. Almost all of these cases are clinically diagnosed cases, since most hospitals did not have laboratory tests until 2013. At present, the limited data available, in the form of departmental reports and publications, are scattered. This review aimed to compile all the available epidemiological data, to obtain a current picture of the disease in Bhutan.

### METHODOLOGY

All available information on scrub typhus in Bhutan was gathered using web-based searches, surveillance and outbreak reports, the Annual health bulletins of the Ministry of Health, and laboratory test data from the Public Health Laboratory, the Jigme Dorji Wangchuck National Referral Hospital and other district hospitals. The terms “Bhutan” and “scrub typhus” or “Orientia tsutsugamushi” were used to search for any mention of the disease in Bhutan in scholarly databases. The sources of data obtained and used for this synthesis of information are presented in Table 1.

All laboratory-confirmed cases were tested by a single rapid antibody test kit that detects O. tsutsugamushi IgM, IgG and IgA antibodies (SD Bioline Tsutsugamushi assay, Standard Diagnostics Inc, Republic of Korea). The manufacturers of the test kit claim a sensitivity of 99%, a specificity of 96% and a serological agreement of 97.5% with indirect immunofluorescent assay, the accepted gold-standard method.

The current laboratory surveillance system was limited to selected district hospital laboratories in the southern part of Bhutan that collect serum samples from suspected patients and ship them to the Public Health Laboratory in Thimphu. However, any health centre can report any suspected or confirmed cases through the weekly, monthly or annual morbidity and mortality report to the Public Health Laboratory and/or Ministry of Health.

<table>
<thead>
<tr>
<th>Table 1. Data sources obtained and used for the review</th>
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<tbody>
<tr>
<td><strong>Topic of research/report</strong></td>
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<tr>
<td>Vector-borne Disease Control Programme tour report to Chukha Dzongkhag (27–31 July 2009)</td>
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<tr>
<td>Annual health bulletins (2011–2014)¹⁹–²²</td>
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<tr>
<td>Outbreak investigation report on scrub typhus in Singye Namgyel Primary School, Wangduephodrang²³</td>
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<tr>
<td>Clinical characteristics of scrub typhus in Gedu and Mongar (Bhutan)²⁴</td>
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<tr>
<td>Study on clinico-laboratory profile of children with scrub typhus</td>
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JDWRH: Jigme Dorji Wangchuck National Referral Hospital.
Since there was no involvement of patients and only existing data were used, ethical clearance was not required by local guidelines. No personally identifying information was collected. Data analysis was descriptive of the number of cases reported, number of samples tested and annual and seasonal trends of scrub typhus.

**RESULTS**

Two probable outbreak investigation reports, one surveillance report, one hospital-based clinical research study, four Ministry of Health annual reports and one newspaper report of an outbreak were found. Some laboratory reports were also obtained by referring to past records and personal communication with the laboratory staff concerned. No regional or international publications relating to scrub typhus in Bhutan were found.

Bhutan experienced two probable outbreaks of scrub typhus. The first occurred during July 2009 in Gedu, a locality in the south-western part of the country, but similar cases were also noted during the same month in the previous year (personal communication). Cases presented with fever, headache, joint pains and maculopapular rash. Initially, patients were managed as for dengue fever or dengue shock syndrome and some of them tested positive for IgM dengue antibody. During the incident, several people, mostly farmers from the locality, were seen in the outpatient unit, 18 were admitted and three lives were lost. Two of the deceased had signs and symptoms of dengue shock syndrome and also tested positive for dengue IgM. One of the deceased had enteric-fever-like symptoms and gastrointestinal perforation. Overall, the incident had a case-fatality rate of more than 10%. During the investigation, five of the seven febrile patients in the ward had typical eschar. No laboratory test for scrub typhus was carried out. With signs and symptoms of febrile illness, the presence of eschar in many cases, and rapid response to doxycycline in those treated, this was described as a probable outbreak of scrub typhus, the first recognition of the disease in the country. The second outbreak was recent and occurred at a remote boarding primary school in August to October 2014, at Athang, Wangdephodrang district in central Bhutan. In this boarding school, there was abundant scrub vegetation and students lived in crowded rodent-infested hostels. The outbreak affected about 36 children, with seven hospital admissions and two deaths. The cases commonly presented with typical scrub-typhus-like symptoms and most had eschar but the two deceased had signs and symptoms of meningitis/encephalitis. Many cases had severe thrombocytopenia and all of the 12 blood samples collected by the investigating team tested positive for scrub typhus with a rapid-test kit.

Following the report of high numbers of febrile cases in 2008 in Gedu, the Public Health Laboratory collected blood samples for scrub typhus from Gedu hospital in March 2009. A few samples were also, coincidentally, received from Mongar hospital. Of the 33 serum samples sent to the reference laboratory outside Bhutan, 23 (69.7%) had acute scrub typhus infection as tested by indirect immunofluorescent assay. Cases were seen in all age groups, including children as young as 1 year. One patient tested positive for three infections (dengue, scrub typhus and murine typhus). This was the first definite laboratory-confirmed case of scrub typhus in Bhutan using the gold-standard laboratory technique. At the same time, a hospital-based retrospective study looked at the clinico-laboratory profile of children with suspected scrub typhus in the Eastern Regional Referral Hospital, Mongar, between August and October 2009 (personal communication). Participants were severely ill children admitted to the ward with fever and thrombocytopenia. Of the 18 children admitted, 12 had a scrub typhus test result and 10 (83%) of these were positive (personal communication). Three of the children with scrub typhus also tested positive for dengue fever. None were positive for malaria, typhoid or leptospirosis.

The Public Health Laboratory initiated testing for scrub typhus on samples from the district hospitals from 2009. However, without a properly established system, and fuelled by lack of awareness among health-care workers, very few samples were received initially. However, over the years, the number of referred samples and the number of positive results increased, as depicted in Table 2. The test positivity ranged between 22% and 60% among the cases sampled. It was noted that the number of samples increased from two per month in December/January to about 30–75 in June to October, on average, over the 4 years (2009–2012). By November, both the number of samples and the number of positive test results gradually decreased. This showed a seasonal trend of the disease in the hot monsoon and subsequent months, as shown in Fig. 1.

The Jigme Dorji Wangchuck National Referral Hospital took over the testing of scrub typhus from the Public Health Laboratory by end of 2012. The record showed an increase in the number of samples tested for scrub typhus from 269 in 2013 to 336 in 2014. Fig. 2 shows a summary of the total number of cases, depicting an increasing case-load, positivity and seasonal trend similar to the Public Health Laboratory results. Few district hospitals received the test kit by end of 2013 or early 2014. The five hospitals that submitted their test results for this study performed 560 tests in 2014. The Eastern Regional Referral Hospital tested 244 samples but could not provide the number of positive results. Thus, considering the four hospitals, the total number of samples tested was 316, with 38 (12%) positive results.

| Table 2. Scrub typhus tests in the Public Health Laboratory with samples received from the district hospitals (2009–2012) |
|---|---|---|
| Year | Number tested | Number (%) positive |
| 2009 | 5 | 3 (60) |
| 2010 | 70 | 23 (33) |
| 2011 | 153 | 55 (36) |
| 2012 | 92 | 20 (22) |
| Total | 320 | 101 (32) |
A review of the reports in the Annual health bulletin from 2011 to 2014 showed an increase in the number of cases reported, from 91 in 2010 to 351 in 2013 (see Table 3). The reports did not mention any demographic, seasonal or geographic details, or limits to the total number of cases each year. About 59% of the patients required hospitalization and 12% were children aged under 5 years. Despite the increase in reported cases, mortality was rare and sporadic, with only 2 (0.3%) deaths over the time period.

### DISCUSSION

This review is the first of its kind to put the limited and scattered data on scrub typhus together. It has highlighted substantial facts about scrub typhus in Bhutan. Bhutan has environmental, climatic and occupational conditions that are favourable for transmission of *Orientia tsutsugamushi*, especially in the central and southern part of the country. Although awareness of the disease among health-care workers is increasing, the current surveillance activities, notification system and prevention and control programmes are inadequate.

#### Table 3. Rickettsial diseases reported in the Annual health bulletin, Ministry of Health, Bhutan (2011–2014)\(^{15-22}\)

<table>
<thead>
<tr>
<th>Year</th>
<th>Total number of cases reported</th>
<th>Inpatient</th>
<th>Outpatient</th>
<th>Deaths</th>
<th>Cases in children aged under 5 years</th>
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</thead>
<tbody>
<tr>
<td>2010</td>
<td>91</td>
<td>70</td>
<td>21</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>2011</td>
<td>118</td>
<td>75</td>
<td>43</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>2012</td>
<td>218</td>
<td>146</td>
<td>72</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>2013</td>
<td>351</td>
<td>169</td>
<td>182</td>
<td>1</td>
<td>45</td>
</tr>
<tr>
<td>Total</td>
<td>778</td>
<td>460 (59.1%)</td>
<td>318 (40.9%)</td>
<td>2 (0.3%)</td>
<td>97 (12.5%)</td>
</tr>
</tbody>
</table>
Despite inclusion in the national manual of notifiable diseases in 2008 and initiation of reporting since 2010, the surveillance and reporting of scrub typhus has been weak, leading to minimal reports. It often happened that a manual or guideline was developed but this was not conveyed to field staff for proper implementation. In addition, without adequate laboratory support, febrile illnesses like malaria, enteric fever, leptospirosis, dengue and viral fevers, which remain prevalent, often challenge the diagnosis of rickettsial diseases. In the Bhutanese setting, it is still a clinical dogma to test every unexplained febrile case for malaria and enteric fever. During the past decade, the number of cases of malaria has dropped dramatically but the emergence of dengue fever since 2004 has complicated the matter.

The probable outbreak of scrub typhus in Gedu included some cases of dengue shock syndrome, supported by positive dengue IgM antibody. Apart from the presence of eschar in some cases, supported by a rapid response to doxycycline, there were no laboratory tests confirming scrub typhus in this cluster of febrile cases. Thus, this cluster could have been either dengue or scrub typhus or both. Similar cases in the future need to be taken more seriously and properly investigated, even at the cost of sending biological samples out of the country to establish the causal agent.

Documented cases of scrub typhus have presented with classical symptoms of fever, headache, skin rash and joint pain, with or without eschar in most cases. However, the two deceased during the outbreak in 2014 had meningitis-like signs and symptoms. Scrub typhus has been known to occur with symptoms of meningitis/encephalitis, pneumonia and acute respiratory distress syndrome, and multi-organ dysfunction syndrome. All these support the fact that, in endemic areas, scrub typhus should be considered in the differential diagnosis of patients presenting with meningeal or respiratory symptoms or multi-organ dysfunction syndrome. One of the deceased in the Gedu incident had intestinal perforation and it is worth noting that scrub typhus can precipitate intestinal perforation.

All laboratory tests reported here were solely based on one rapid-test kit and this has been the only test available, even to the present. Although they are rapid and easy to use, the rapid-test kits are not the ideal tool. With increasing reports of cases with sporadic outbreak potential, it would be valuable to have different diagnostic methods at different levels of health facilities, with, for example, rapid-test kits in the lowest-level health centres and more specific tests at the referral hospitals and the Public Health Laboratory. At present, only hospitals in the southern part of the country are supplied with the test kits, on the assumption that scrub typhus is prevalent only in a warm humid climate. This assumption needs to be proven, and until then test kits should be supplied to all hospitals in the country, to help understand the focus of the infection in different areas throughout the country.

There is an urgent need to invest in research on scrub typhus and other rickettsial diseases, to establish their true epidemiology and understand the social, environmental, occupational and behavioural determinants, in order to help develop prevention and control strategies. Health-care workers need to be educated and made aware of the disease and its differential diagnosis with other febrile illnesses. Laboratory test kits should be made available, to enable early diagnosis and prompt treatment of this serious but treatable disease. The general public needs to be educated on recognition of the disease, so they seek medical care early and take measures for prevention and control.

The study has some limitations. Firstly, the overall information available was very limited. No detailed demographic and clinical data could be extracted from the laboratory registers, thereby making inference difficult. Test kits were not widely available, a situation that prevails even now, and the number of tests would have been an underestimate, owing to erratic supply of test kits. Many district laboratories could not give the actual number of tests performed, owing to poor record keeping. Unfortunately, all the laboratory data reported here relied on only one commercial rapid-test kit and it should be understood that such test kits are not the gold standard.

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**REFERENCES**


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