J Nepal Health Res Counc 2024 Apr.-Jun.; 22 (63): 376-385

# Risk Factors and Clinico-laboratory Characteristics of Scrub Typhus in Children Admitted to a Tertiary Pediatric Hospital of Nepal

Ram Hari Chapagain,[1,2] Santosh Adhikari,[1] Bihungum Bista,[3] Tribhuwan Bhattarai,[2] Prabhat Thapa[1]

[1]Kanti Children's Hospital, Nepal, [2]National Academy of Medical Sciences (NAMS) Kathmandu, Nepal, [3]Kathmandu University, Nepal.

## ABSTRACT

**Backgrounds:** Scrub Typhus is a re-emerging illness with considerable morbidity and mortality and affected children have nonspecific sign symptoms. This study was conducted to find out the risk factors, clinical characteristics and laboratory profile and treatment outcome of scrub typhus among the children admitted in tertiary level pediatric hospital for febrile illness.

**Methods:** A case control study was conducted among hospitalized children with acute febrile illness in a government pediatric referral hospital of central Nepal for two years (2021 to Sept 2023), who were tested using Scrub Typhus Antibody Rapid Test Kit.

**Results:** We recruited 137 participants, comprising 68 cases of scrub typhus and 69 controls who had fever as a presenting complain, tested negative for scrub typhus and are matched with case in terms of age, gender, place of residence, and most importantly devoid of chronic health issues like leukemia, solid tumor, tuberculosis or kala-azar. Almost all cases i.e. 98.5% (n=67) had fever which is followed by abdominal pain 19.1% (n=13), headache 11.8%(n=8), vomiting 10.3%(n=7) and abdominal distension 8.8%(n=6). Hepatomegaly was commonest finding among scrub typhus positive cases comprising 50% (n=34) followed by lymphadenopathy 29.4% (n=20), splenomegaly 27.9% (n=19), eschar 17.6% (n=12) and rashes 10.3% (n=7). Cases having thrombocytopenia and leukocytosis were 51.5% (n=35) and 32.3% (n=22) respectively. Among scrub typhus cases, 17.6% (n=12) needed pediatric intensive care, 20.6% (n=14) had some sort of complications (i.e., meningitis, acute kidney injury, septic shock, acute respiratory distress syndrome), 46.3% (n=31) became afebrile within 24 hours of therapy, 29.8% (n=20) needed 48 hours to become afebrile. There were about 80% cases with the habit of taking naps on the ground. Those who reside other than cemented houses were with an increased risk factor of about 72%. Those who were not having good beds were at an increased risk factor of almost 100%. There were 62% of cases with bushes near their home and about 100% cases where they store animal fodder in their home. There were 63% who have any sort of animal in their bedroom.

**Conclusions:** Engaging in agricultural work like working on fields, planting and livestock, working with bare hands/ feet, and having naps on the ground and living in houses made of mud dung and wood are the risk factors for the scrub factor. Fever, lymphadenopathy, hepatomegaly, splenomegaly are the common signs and symptoms and thrombocytopenia and increased levels of creatinine are the significant laboratory finding of scrub typhus in children.

**Keywords:** Children; clinico-laboratory; Nepal; risk factor; scrub typhus.

## INTRODUCTION

Scrub Typhus, a mite borne zoonosis endemic in the so called tsutsugamushi triangle, is a re-emerging illness in the tropics with considerable morbidity and mortality.[1,2] The causative organism, Orientia tsutsugamushi, is transmitted to humans by the Chiggers bite of the trombiculid mites, possibly Leptotrombidium deliense[3]. People engaging in outdoor activities and farmers are at a higher risk of being in contact with scrub typhus as mites are widely distributed in different types of vegetation e.g., forests, rice paddies and plantations[4]. Affected children usually present as a nonspecific febrile

**Correspondence: Dr Ram Hari Chapagain, Kanti Children's Hospital, Kathmandu, Nepal.**
**Email: chapagainrh2007@gmail.com**

illness with about 40% of typical eschar.[5] This disease is most common in resource limited settings such as rural areas.[6] There are several studies from Nepal, done for clinic-laboratory characteristic along with therapeutics of Scrub typhus, many of them including pediatric population. However, there is limited knowledge regarding underlying risk factors for Scrub typhus in Nepalese context. This study aims to determine the risk factors, clinical characteristics and laboratory profile and treatment outcome of scrub typhus among the acute febrile illness children attending in a pediatric referral hospital of central Nepal.

## METHODS

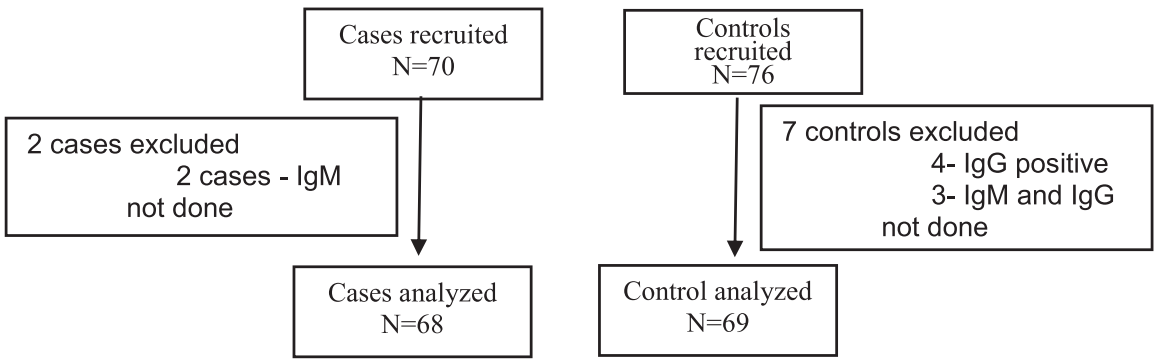
An unmatched case- control (1:1) study was conducted among hospitalized children with febrile illness. Patients with or acute fever with suspicion of scrub typhus in a government pediatric referral hospital of central Nepal for two years starting from Sep 2021 to Sep 2023. We recruited 137 children less than 14 years of age over the period of 2 years presenting with acute fever of more than 4 days after excluding other obvious systemic or local causes of fever (such as respiratory tract infection, urinary tract infection, abscesses, cellulitis, etc.) through clinical examination. Single Blood samples were collected from the hospitalized patients suspected of scrub typhus, presenting with acute febrile illness. The IgM antibody to Orientia tsutsugamushi was detected by using Scrub Typhus Antibody Rapid Test Kit, Qingdao Hightop Biotech Co Ltd. China

To assess the risk factors associated with the disease, a case-control study was conducted among the children admitted in Hospital. Febrile children who were positive for O. tsutsugamushi IgM or IgG were considered cases, whereas children who were seronegative for IgM and IgG were considered controls. Age and geographical area matched controls with 1:1 were selected from the children whose Scrub typhus serology is negative. Chronic health issues like Leukemia, solid tumors, tuberculosis, Kala azar were ruled out prior to enrolling in control group. Information on demographic characteristics, occupation, living environment, leisure activities, and sanitation/hygiene practices was collected from cases and controls using a pre-designed pro forma. Cases and controls were also questioned about exposure to domestic animals.

Written informed consent from the guardian/ caretaker for each patient and assent for children of 7 to 14 years was obtained prior to their enrollment in the study. During the time of admission, a structured questionnaire was administered to assess the demographic variables of the patients who consented to the study. In addition, clinical characteristics, laboratory test results and risk factors were recorded for the patients who were enrolled in the study. This study was approved by the Institutional Review Board of the Kanti Children's Hospital, Kathmandu, Nepal. The collected data were entered in Epi info 3.5 from CDC and exported to STATA 15. The association between the different demographic variables and the scrub typhus was determined using the chi square test, frequency distribution and univariate logistic regression analysis. Significant variables from the univariate logistic regression analysis were selected for the multivariable logistic regression analysis. Odd ratios were subsequently calculated, and the exposures found to be significant (P<0.05) were incorporated into a binary logistic regression model.

## RESULTS

**Figure Showing the flow chart of Cases and controls.**




There were 137 participants in our study. Among them, 68 were cases and 69 were controls. The sociodemographic profile of the participants is shown in table 1.

| Table 1. Demographic profile of participants. | | | |
|---|---|---|---|
| **Variables** | **Case(N=68) Frequency (%)** | **Control(N=69) frequency (%)** | **P value** |
| **Gender** | 68 (49.6) | 69 (50.4) | |
| Female | 22 (43.1) | 29 (56.9) | 0.241 |
| Male | 46 (53.5) | 40 (46.5) | |
| **Age** | | | |
| Less than 5 years | 33(45.83) | 39(54.17) | 0.303 |
| Above than 5 years | 35(54.69) | 29(45.31) | |
| **Residing** | | | |
| From Kathmandu | 65(55.56) | 52(44.44) | 0.001 |
| Outside Kathmandu | 3(15.00) | 17(85.0) | |
| **Type of House** | | | |
| Pakka house | 20 (74.1) | 7 (25.9) | 0.009 |
| Kachha house | 47 (43.1) | 62 (56.9) | |

62.6% of cases were working in the field. There was a maximum of 65% of the cases about 65% who have been in planting and live stocks. The risk factors for the cases were those who go in contact with scrub illness which is about 66%. Similarly, there were cases of 69% who have been in contact with animals. There were 65 % of cases who are associated with cleaning the animal waste and 75% of the cases are working with bare hands. The barefoot people are at higher risk 66.7% as there has been barefoot in the community.

There were about 80% cases with the habit of taking naps on the ground. Those who work near bushes were having more chances of having scrub. Those who reside other than cemented houses were at an increased risk of about 72%. Those who were not having good beds were at an increased risk factor of almost 100%. There were 62% of cases with bushes near their home and about 100% cases where they store animal fodder in their home. About 72% of cases were having dung and wood as fuel material to cook food. There were 63% who have any sort of animal in their bedroom. This is shown in table no. 2

| Table 2 A. Risk factors associated with scrub typhus. | | | |
|---|---|---|---|
| **Variables** | **Case (N=68) Frequency (%)** | **Control (N=69) frequency (%)** | **P value** |
| **Work in Farming** | | | |
| Yes | 57 (62.6) | 34 (37.4) | 0.000 |
| No | 11 (24.4) | 35 (75.6) | |
| **Work in Planting/harvesting/ and livestock** | | | |
| Yes planting and livestock | 49 (64.5) | 27 (35.5) | 0.002 |
| Yes Planting only | 6 (40.0) | 9 (60.0) | |
| Yes Livestock | 4 (80.0) | 1 (20.0) | |
| No | 7 (25.0) | 21 (75.0) | |
| **Crop encountered with** | | | |
| Rice, Maize, Wheat | 40 (58.8) | 28 (41.2) | 0.367 |
| Others | 14 (70.0) | 6 (30.0) | |
| **Contact duration with livestock** | | | |
| Frequently | 53 (65.4) | 28 (34.6) | 0.062 |
| Occasionally | 4 (36.4) | 7 (63.6) | |

| Table 2 A. Risk factors associated with scrub typhus. | | | |
|---|---|---|---|
| **Variables** | **Case (N=68) Frequency (%)** | **Control (N=69) frequency (%)** | **P value** |
| **Contact with Livestock** | | | |
| Animals | 49 (69.0) | 22 (31.0) | 0.071 |
| Others | 4 (40.0) | 6 (60.0) | |
| **Clean animal waste** | | | |
| Yes | 53 (65.4) | 28 (34.6) | 0.041 |
| No | 1 (20.0) | 4 (80.0) | |
| **Use of gloves while working** | | | |
| Yes | 3 (75.0) | 1 (25.0) | 0.872 |
| No | 8 (61.5) | 5 (37.8) | |
| | 46 (62.2) | 28 (37.8) | |
| **What you wear when working in field** | | | |
| Bare foot | 12 (66.7) | 6 (33.3) | 0.807 |
| Sandals | 39 (59.1) | 27 (40.9) | |
| Shoes | 6 (66.7) | 2 (33.3) | |
| **How often are rodents seen in the house?** | | | |
| Often | 40 (65.6) | 21 (34.4) | 0.000 |
| Sometime | 21 (48.8) | 22 (51.2) | |
| Rarely | 4 (36. 4) | 7 (63.6) | |
| Never | 3 (13.6) | 19 (86.4) | |

| Table 2 B. livelihood and residence related risk factor for scrub typhus. | | | |
|---|---|---|---|
| **Variables** | **Case Frequency (%)** | **Control frequency (%)** | **P value** |
| **How often do you take a nap on the ground?** | | | |
| Yes | 28 (80.0) | 7 (20.0) | 0.000 |
| No | 40 (39.2) | 62 (60.8) | |
| **Have you worked near bushes?** | | | |
| Often | 28 (40.9) | 27 (49.1) | 0.161 |
| Sometimes | 36 (53.7) | 31 (46.3) | |
| Never | 4 (26.7) | 11 (73.3) | |
| **Roof materials** | | | |
| Cemented | 28 (34.6) | 53 (65.4) | 0.000 |
| Other than cemented | 40 (71.4) | 16 (28.6) | |
| **Construction materials** | | | |
| Mud/dung/wooden | 20 (74.1) | 7 (25.9) | 0.009 |
| Cemented | 47 (43).1 | 62(56.9) | |
| **Sleeping material at night** | | | |
| Good bed | 63 (47.7) | 69 (52.3) | 0.022 |
| Others | 5 (100.0) | 0 (0.0) | |
| **Change of clothes before bed** | | | |

| Table 2 B. livelihood and residence related risk factor for scrub typhus. | | | |
|---|---|---|---|
| **Variables** | **Case Frequency (%)** | **Control frequency (%)** | **P value** |
| Bed/Cot/Foam | 0 (0.0) | 1 (100.0) | 0.318 |
| Floor/ground | 34 (45.9) | 40 (54.1) | |
| Other | 34 (55.7) | 27 (44.3) | |
| **Any bushes close to the house?** | | | |
| Yes | 56 (62.2) | 34 (37.8) | 0.000 |
| No | 12 (25.5) | 35 (74.5) | |
| **Storage of animal fodder in house?** | | | |
| Yes | 7 (100.0) | 0 (0.0) | 0.006 |
| No | 61 (46.9) | 69 (53.1) | |
| **Source of cooking fuel** | | | |
| Wood/dung | 38 (71.7) | 15 (28.3) | 0.000 |
| Clean fuel | 30 (35.7) | 54 (64.3) | |
| **Any animals in the bedroom?** | | | |
| Yes | 10 (62.5) | 6 (37.5) | 0.287 |
| No | 58 (48.3) | 62 (51.7) | |
| **Heard about scrub** | | | |
| Yes | 7 (38.9) | 11 (61.1) | 0.229 |
| No | 61 (51.3) | 58 (48.7) | |
| **Have you heard of fever carried by mites?** | | | |
| Yes | 7 (36.8) | 12 (63.2) | 0.438 |
| No | 60 (51.7) | 56 (48.3) | |
| **Any substance used in skin to protect?** | | | |
| Yes | 7 (41.2) | 10 (58.8) | 0.450 |
| No | 61 (51.7) | 59 (48.3) | |

Almost all cases i.e. 98.5% (n=67) had fever which is followed by abdominal pain 19.1% (n=13), headache 11.8% (n=8), vomiting 10.3% (n=7) and abdominal distension 8.8% (n=6). Hepatomegaly was commonest finding comprising 50% (n=34) followed by lymphadenopathy 29.4% (n=20) and splenomegaly 27.9% (n=19). Eschar was seen in 17.6% (n=12) whereas rashes were evidenced in 10.3% (n=7). About 26.5% (n=18) children were dyspneic but crepitation was heard in 14.7% (n=10) children with scrub typhus. Cases having thrombocytopenia and leukocytosis were 51.5% (n=35) and 32.3% (n=22) respectively. There were about 80% cases with the habit of taking naps on the ground. Those who reside other than cemented houses were with an increased risk factor of about 72%. Those who were not having good beds were at an increased risk factor of almost 100%. There were 62% of cases with bushes near their home and about 100% cases where they store animal fodder in their home. There were 63% who have any sort of animal in their bedroom. This is shown in table no. 3.

| Table 3. Clinical-laboratory findings of patients admitted in Kanti children's hospital. | | |
|---|---|---|
| **Variables** | **Case Frequency (%)** | **Control Frequency (%)** |
| Dyspnea | | |
| Yes | 18 (26.5) | 8 (11.6) |
| No | 50 (73.5) | 61 (88.4) |
| Rash | | |

| Table 3. Clinical-laboratory findings of patients admitted in Kanti children's hospital. | | |
|---|---|---|
| **Variables** | **Case Frequency (%)** | **Control Frequency (%)** |
| Yes | 7 (10.3) | 6 (8.7) |
| No | 61 (89.7) | 63 (91.3) |
| Lymphadenopathy | | |
| Yes | 20 (29.4) | 3 (4.3) |
| No | 48 (70.6) | 66 (95.7) |
| Hepatomegaly | | |
| Yes | 34 (50.0) | 17 (24.6) |
| No | 34 (50.0) | 52 (75.4) |
| Splenomegaly | | |
| Yes | 19 (27.9) | 9 (13.0) |
| No | 49 (72.1) | 60 (87.0) |
| Eschar | | |
| Yes | 12(17.6) | 0 (0.0) |
| No | 56(82.4) | 69(100.0) |
| Crepitation | | |
| Yes | 10(14.7) | 4 (5.8) |
| No | 58(85.3) | 65 (94.2) |
| **Laboratory findings** | | |
| Platelets | | |
| Lesser than 150000 | 35(51.5) | 24(34.8) |
| More than 150000 | 33(48.5) | 45(65.2) |
| Complete Blood Count | | |
| Less than 11000 | 46(67.7) | 54(78.2) |
| More than | 22(32.3) | 15(21.8) |
| Creatinine | | |
| Normal | 67(98.5) | 66(97.0) |
| High | 1(1.5) | 2(3.0) |

Among 68 scrub typhus-positive children enrolled in this study, 17.6% (n=12) needed PICU care, whereas only 5.8% (n=4) of the 69 children in the control group needed PICU admission during the course of treatment. Fourteen children with scrub typhus, which accounts for 20.6% among cases, had some sort of complications (i.e., meningitis, meningoencephalitis, septic shock, ARDS), while 7.2% (n=5) among control groups had complications. This is shown in table no. 4

| Table 4. Outcome of the participants. | | |
|---|---|---|
| **Variable** | **Case** | **Control** |
| **Need of PICU admission** | | |
| No | 56(82.4) | 65(94.2) |
| Yes | 12(17.6) | 4(5.8) |
| **Any complication in child** | | |
| No | 53(79.4) | 63(92.8) |
| Yes | 14(20.6) | 5(7.2) |

Looking at the effect of specific therapy (azithromycin/ doxycycline) in children with scrub typhus, 46.3% (n=31) became afebrile within 24 hours of therapy, 29.8% (n=20) needed 48 hours to become afebrile, whereas 23.9% (n=16) had a fever despite receiving treatment for 48 hours. One complicated case, who was a PICU care candidate, was referred within 24 hours.

## DISCUSSION

This study was conducted to identify the risk factor and clinic laboratory profile of scrub typhus in children admitted in tertiary level paediatric hospital. This study identified major occupational, household-related, animal ownership, and demographic risk factors for children suffering from scrub typhus. Clinical diagnosis of scrub typhus is challenging because of its nonspecific clinical manifestations. Furthermore, previous infections, cross-reactivity, and low accuracy of routine diagnostic tests are likely to complicate the diagnosis of scrub typhus Thus, identifying risk factors for this disease is a valuable aid for accurate clinical diagnosis and initiation of early treatment, reducing the risk for potentially fatal complications. Total of 137 cases were included in the study. Sixty-eight children were cases of Scrub typhus with positive test in IgM and IgG serology whereas 69 children with fever and with negative serological test for scrub typhus with age and geographical area matching with cases were taken as controls.

Among the cases, 62.6%(n=57) were working in the field. Involving in agriculture is one of the important risk factors for Scrub typhus. The family working in the field has a higher chance to have scrub Typhus (p=0.00) compared to those not working in field which seen in other studies too.[7-10] There was a maximum of about 65%(n=49) who had been in planting and livestock which is also another risk factor (p=0.002). There were mostly cases involving rice, maize and wheat. The risk factors for the cases were those who go in contact with scrub illness which is about 66% that is true in the studies done in Uttar Pradesh and Bhutan.[9,10] Similarly, 69%(n=49) cases were found to have been in contact with animals and considered as risk factor even though it was found no significant (P=0.071) in our study which is contradictory to the finding of other studies[8,9] Almost 65 %(n=53) of cases are associated with cleaning the animal waste and 75% of the cases are working with bare hands. The barefoot people are also at higher risk as 66.7% of cases had a history of involvement in agricultural work with bare feet.

Rodents are important in the ecology of scrub typhus and it is likely that infected rodent provides the explanation or the occurrence of multiple strains of O. tsutsugamushi within the individual larvae[10]. We also found that those who have been seeing rodents in their surroundings are at higher risk as 66% see rodents often (p=0.000). There were about 80%(n=828) cases with the habit of taking naps on the ground. Those who work near bushes were having more chances of scrub and considered it another risk factor. This was consistent with other studies.[11]

The construction material of the house was also a risk factor. Those children who reside in houses other than cemented houses were at an increased risk ( 72%(n=40) ) children suffering from scrub typhus had a history of residing inside households constructed with materials other than cement like mud, dung and wood. The traditional non cemented housing is more prone to rodents which is also contributing to increased risk. This is similar to the finding by study conducted in Bhutan[9]. There were 62% of cases with bushes near their home and about 100% cases where they store the animal fodder in their home. The similar finding was observed by zympoo J et.al in Bhutan as owning animals was a major risk factor for scrub. About 72% of cases were having dung and wood as fuel material to cook food. There were 63% children among scrub typhus cases who have any sort of animal in their bedroom.

Although the bivariate analysis shows work in farming, planting and livestock, involving in clean animal waste, rodents in bushes, un-cemented traditional housing, storage of animal fodder in house, using wood dung as fuel as a major risk factors for scrub typhus. A study conducted in Bhutan shows harvesting cardamom in traditional housing, outside toilet locations, as well as owning a goat as a domesticated animal and frequently sitting on grass as a risk factor for scrub typhus. We did not found the significant risk factor on multivariate analysis whereas a Malaysian study found that living in a house clustered with other houses, female sex and age >60 years were significantly associated with scrub typhus exposure on multivariate regression modeling.[13]

Scrub typhus is the leading cause of undifferentiated fever in India, Bangladesh(16.8%), Thailand (22.5%) and surroundings areas.[12-13] Fever is the most common characteristic feature present in children with scrub typhus which must be differentiated from other acute febrile illness. We also found all children admitted with scrub typhus IgM positive were presented with complaints of fever. The Common clinical presentations were fever, lymphadenopathy, hepatomegaly, splenomegaly and

crepitation on the chest. These findings were consistent with other studies conducted in Korea, Bangladesh, India and Thailand.[14-22] Apart from fever, there is wide variation in the presenting symptoms and examination findings in children along with scrub typhus.[30,31]

Thrombocytopenia is the most common hematological parameter with leukocytosis and low level of hemoglobin in scrub typhus patient. We found that thrombocytopenia is strongly correlated to scrub typhus than other types of fever. The increased level of creatinine is also observed in our study. These were common laboratory abnormalities observed in other studies too.[23-25]

Cases who needed PICU care were 17.6% (n=12) whereas 5.8% (n=4) of the control group needed PICU admission during the course of treatment. Fourteen children accounting for 20.6% of cases, had some sort of complications (i.e. Acute kidney injury, Elevated liver enzymes, meningitis, meningoencephalitis, septic shock, ARDS), while 7.2% (n=5) among control groups had complications. None of the cases had mortality during the hospital stay. The proportion of complications among scrub typhus positive cases was higher in other studies done in the adult population. Among the cases enrolled by Bansod et al. 52.1% had renal complications, 48.6% had hepatic complications and 42.1% had respiratory complications. Mortality was also high accounting 17.14%.[26] Mutkule et al. found that 41.4% scrub typhus cases with ARDS while the mortality was only 3.4%.[27] Brummaier et al. had lower prevalence of abnormal liver and renal function tests among the scrub typhus positive case involving children and adults but they had large proportion of missing report of liver and renal function tests.[28] The overall mortality in their study was 1.9%.

After receiving specific therapy (azithromycin/ doxycycline), 46.3% (n=31) cases became afebrile within 24 hours of therapy, 29.8% (n=20) needed 48 hours to become afebrile, whereas 23.9% (n=16) had a fever despite receiving treatment for 48 hours. One complicated case, who was a PICU care candidate, was referred within 24 hours. The median fever clearance time using doxycycline was 28 hours in study done by Brummaier et al. while it was 30 hours in study of Watt et al.[28,29]

In this study, there were about 40% of cases who have heard about scrub and 36% have known about the fever carried by mites and only 42% of cases were using substances to protect the skin. Knowledge of scrub typhus and the mode of infection as well as the preventive methods if can be conveyed to general public possibly can decrease the infection rate of typhus.

There are some limitations of this study. This was a single center study with limited samples. We have tested by point of care test. Data on organ function test were incomplete, especially on liver function test and the results of complications/ organ dysfunction is based on the clinical features and available data of organ function test done on scrub typhus cases.

## CONCLUSIONS

Engaging in agriculture work with working on fields, planting and livestock, working with bare hands and feet, along with having a nap on the ground and living in a house made of mud dung and wood are the risk factors for the scrub typhus. Fever, lymphadenopathy, hepatomegaly, splenomegaly and crepitation of the chest are the common signs and symptoms of Scrub typhus. Thrombocytopenia and increased levels of creatinine are the common laboratory finding of the scrub typhus in children.


## ACKNOWLEDGEMENTS

The authors wish to acknowledge laboratory staff for performing the tests for scrub typhus and for performing the phlebotomies among participants.

## FUNDING

The whole study was funded by National Academy of Medical Sciences (NAMS) faculty grant. Ref: 875/2078/79. The fund provided for the conduct of the study including data analysis, stationary. The funders had no role in the study design, data collection, analysis, decision to publish or preparation of the manuscript.


## REFERENCE


1. Rose W, Kang G, Verghese VP, Candassamy S, Samuel P, Prakash JJ, et al. Risk factors for acquisition of scrub typhus in children admitted to a tertiary centre and its surrounding districts in South India: a case control study. BMC Infectious Diseases. 2019 Dec;19:1-8.doi: https://doi.org/10.1186/s12879-019-4299-2

2. Watt G, Parola P. Scrub typhus and tropical rickettsioses. Curr Opin Infect Dis. 2003 Oct;16(5):429-36. doi: 10.1097/00001432-200310000-00009. PMID: 14501995.

3. Lerdthusnee K, Khlaimanee N, Monkanna T, Sangjun N, Mungviriya S, Linthicum KJ, et al. Efficiency of Leptotrombidium chiggers (Acari: Trombiculidae) at transmitting Orientia tsutsugamushi to laboratory mice. Journal of medical entomology. 2002 May 1;39(3):521-5.doi: https://doi.org/10.1603/0022-2585-39.3.521

4. Tay ST, Ho TM, Rohani MY, Devi S. Antibodies to Orientia tsutsugamushi, Rickettsia typhi and spotted fever group rickettsiae among febrile patients in rural areas of Malaysia. Trans R Soc Trop Med Hyg. 2000 May-Jun;94(3):280-4. doi: 10.1016/s0035-9203(00)90322-5. PMID: 10974999.

5. Rose W, Rajan RJ, Punnen A, Ghosh U. Distribution of Eschar in Pediatric Scrub Typhus. J Trop Pediatr. 2016 Oct;62(5):415-20. doi: 10.1093/tropej/fmw027. Epub 2016 Apr 27. PMID: 27122479.

6. Peter JV, Sudarsan TI, Prakash JA, Varghese GM. Severe scrub typhus infection: Clinical features, diagnostic challenges and management. World J Crit Care Med. 2015 Aug 4;4(3):244-50. doi: 10.5492/wjccm.v4.i3.244. PMID: 26261776; PMCID: PMC4524821.

7. Mørch K, Manoharan A, Chandy S, Chacko N, Alvarez-Uria G, Patil S, et al. Acute undifferentiated fever in India: a multicentre study of aetiology and diagnostic accuracy. BMC Infect Dis. 2017;17:665. doi: https://doi.org/10.1186/s12879-017-2764-3

8. Gautam R, Parajuli K, Sherchand JB. Epidemiology, Risk Factors and Seasonal Variation of Scrub Typhus Fever in Central Nepal. Trop Med Infect Dis. 2019 Feb 2;4(1):27. doi: 10.3390/tropicalmed4010027. PMID: 30717408; PMCID: PMC6473611.

9. Zangpo T, Phuentshok Y, Dorji K, Dorjee C, Dorjee S, Jolly P, et al. Environmental, Occupational, and Demographic Risk Factors for Clinical Scrub Typhus, Bhutan. Emerg Infect Dis. 2023 May;29(5):909-918. doi: 10.3201/eid2905.221430. PMID: 37081000; PMCID: PMC10124658.

10. Thangaraj JWV, Vasanthapuram R, Machado L, Arunkumar G, Sodha SV, Zaman K, et al. Risk Factors for Acquiring Scrub Typhus among Children in Deoria and Gorakhpur Districts, Uttar Pradesh, India, 2017. Emerg Infect Dis. 2018 Dec;24(12):2364-2367. doi: 10.3201/eid2412.180695. PMID: 30457537; PMCID: PMC6256400.

11. Vallée J, Thaojaikong T, Moore CE, Phetsouvanh R, Richards AL, Souris M, et al. Contrasting spatial distribution and risk factors for past infection with scrub typhus andmurine typhus in Vientiane City, Lao PDR. PLoS Negl TropDis. 2010; 4:e909. doi: https://doi.org/10.1371/journal. pntd.0000909

12. Thiga JW, Mutai BK, Eyako WK, Ng'ang'a Z, Jiang J, Richards AL, et al. High seroprevalence of antibodies against spotted fever and scrub typhus bacteria in patients with febrile illness, Kenya. Emerg Infect Dis. 2015;21:688–91.

13. Frances SP, Watcharapichat P, Phulsuksombati D, Tanskul P. Transmission of Orientia tsutsugamushi, the aetiological agent for scrub typhus, to co-feeding mites. Parasitology. 2000 Jun;120 ( Pt 6):601-7. doi: 10.1017/s0031182099005909. PMID: 10874723.

14. Elliott I, Pearson I, Dahal P, Thomas NV, Roberts T, Newton PN. Scrub typhus ecology: a systematic review of Orientia in vectors and hosts. Parasit Vectors. 2019;12:513.doi: https://doi.org/10.1186/s13071-019-3751-x

15. Tay ST, Ho TM, Rohani MY, Devi S. Antibodies to Orientia tsutsugamushi, Rickettsia typhi and spotted fever group rickettsiae among febrile patients in rural areas of Malaysia. Trans R Soc Trop Med Hyg. 2000 May-Jun;94(3):280-4. doi: 10.1016/s0035-9203(00)90322-5. PMID: 10974999.

16. Kingston HW, Hossain M, Leopold S, Anantatat T, Tanganuchitcharnchai A, Sinha I, et al. Rickettsial Illnesses as Important Causes of Febrile Illness in Chittagong, Bangladesh. Emerg Infect Dis. 2018 Apr;24(4):638–45. doi: 10.3201/eid2404.170190. PMID: 29553921; PMCID: PMC5875266.

17. Wangrangsimakul T, Althaus T, Mukaka M, Kantipong P, Wuthiekanun V, Chierakul W, et al. Causes of acute undifferentiated fever and the utility of biomarkers in Chiangrai, northern Thailand. PLoS Negl Trop Dis. 2018 May 31;12(5):e0006477. doi: 10.1371/journal.pntd.0006477. PMID: 29852003; PMCID: PMC5978881.

18. Kim DM, Kim SW, Choi SH, Yun NR. Clinical and laboratory findings associated with severe scrub typhus. BMC Infect Dis. 2010 Apr 30;10:108. doi: 10.1186/1471-2334-10-108. PMID: 20433689; PMCID: PMC2877676.

19. Maude RR, Maude RJ, Ghose A, Amin MR, Islam MB, Ali M, Bari MS, et al. Serosurveillance of Orientia tsutsugamushi and Rickettsia typhi in Bangladesh. Am J Trop Med Hyg. 2014 Sep;91(3):580-583. doi: 10.4269/ajtmh.13-0570. Epub 2014 Aug 4. PMID: 25092819; PMCID: PMC4155564.

20. Varghese GM, Janardhanan J, Trowbridge P, Peter JV, Prakash JA, Sathyendra S, et al. Scrub typhus in South India: clinical and laboratory manifestations, genetic variability, and outcome. Int J Infect Dis. 2013 Nov;17(11):e981-7. doi: 10.1016/j.ijid.2013.05.017. Epub 2013 Jul 26. PMID: 23891643.

21. Sirisanthana V, Puthanakit T, Sirisanthana T. Epidemiologic, clinical and laboratory features of scrub typhus in thirty Thai children. Pediatr Infect Dis J. 2003 Apr;22(4):341-5. doi: 10.1097/01.inf.0000059400.23448.57. PMID: 12690274.

22. Chapagain RH, Agrawal S, Pokharel S, Kayastha M, Bhattrai S, Jha A, et al. Clinico-laboratory profile, complications and therapeutic outcome of scrub typhus in children. doi: https://doi.org/10.33314/jnhrc.v18i2.2730

23. Vivekanandan M, Mani A, Priya YS, Singh AP, Jayakumar S, Purty S. Outbreak of scrub typhus in Pondicherry. J Assoc Physicians India. 2010 Jan;58:24-8. PMID: 20649095.

24. Singh SP, Singh R, Ahmad N. A study of complications of scrub typhus in a tertiary health care institute of Uttarakhand, India. doi:10.5455/2320-6012.IJRMS20140247

25. Sah RK, Chapagain RH, Shrestha SM, Rai GK. Clinico-laboratory Profile and Therapeutic Outcome of Serologically Confirmed Scrub Typhus in Children in Tertiary Care Children's Hospital of Nepal. Pediatric Infect Dis. 2019;4(1):1. doi:10.21767/2573-0282.100065

26. Bansod YV, Aher AA, Bhole P, Rengaraj K, Jadhav P. Clinical Profile and Treatment Outcome in Scrub Typhus Patients in Central India. J Assoc Physicians India. 2021 Sep;69(9):11-12. PMID: 34585890.

27. Mutkule DP, Venkategowda PM, Rao MV, Taggu AN. Scrub typhus: Clinical spectrum and outcome. Indian Journal of Critical Care Medicine [Internet]. 2015 Apr [cited 2024 May 7];19(4):208–13. Available from: https://www.ijccm.org/doi/10.4103/0972-5229.154553

28. Brummaier T, Kittitrakul C, Choovichian V, Lawpoolsri S, Namaik-larp C, Wattanagoon Y. Clinical manifestations and treatment outcomes of scrub typhus in a rural health care facility on the Thailand-Myanmar border. J Infect Dev Ctries [Internet]. 2017 Jun 1 [cited 2024 May 7];11(05):407–13. [Article]

29. Watt G, Chouriyagune C, Ruangweerayud R, Watcharapichat P, Phulsuksombati D, Jongsakul K, et al. Scrub typhus infections poorly responsive to antibiotics in northern Thailand. The Lancet [Internet]. 1996 Jul [cited 2024 May 7];348(9020):86–9. [Article]

30. 30. Pathak S, Chaudhary N, Dhakal P, Shakya D, Dhungel P, Neupane G, et al. Clinical profile, complications and outcome of scrub typhus in children: A hospital based observational study in central Nepal. Munderloh UG, editor. PLoS ONE [Internet]. 2019 Aug 13 [cited 2024 May 13];14(8):e0220905. Available from: doi: 10.1371/journal.pone.0220905

31. Kumar Jana J, Krishna Mandal A, Gayen S, Mahata D, Alam Mallick MS. Scrub Typhus in Children: A Prospective Observational Study in a Tertiary Care Hospital in Eastern India. Cureus [Internet]. 2023 Jul 16 [cited 2024 May 13]; Available from: https://www.cureus.com/articles/168997-scrub-typhus-in-children-a-prospective-observational-study-in-a-tertiary-care-hospital-in-eastern-india doi: 10.7759/cureus.41976