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# CLINICO-DEMOGRAPHIC PROFILE OF SCRUB TYPHUS IN UTTARAKHAND

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**ABSTRACT**

**BACKGROUND:** Scrub typhus(ST) a rickettsial infection caused by Orientia tsutsugamushi and transmitted by trombiculid mites"chiggers" particularly Leptotrombidium deliense. It is one of the differential diagnoses of haemorrhagic fevers, especially if associated with acute respiratory distress syndrome and/or jaundice. A necrotic eschar at the inoculating site of the mite is pathognomic of ST.The western Himalayan regions of India, has been witnessing increased incidence of acute febrile illnesses over the years.

**AIM & OBJECTIVES** : 1) To determine the frequency of ST in a tertiary health care hospital in Uttarakhand. 2) To understand the clinical spectrum and associated complications. 3) To analyze the demographic profile of ST cases.

**MATERIAL & METHODS**: The retrospective study was carried out, over a period of 24 months (August 2015 to July 2017), which included cases of AFI, clinically suspected of ST. Serological testing was carried out by using commercial ELISA for specific IgM antibodies against O.tsutsugamushi.

**RESULTS:** Out of the total 3854 cases of AFI attending the tertiary care hospital, the microbiology laboratory received a total of 760 clinically suspected cases of ST for serological testing, 494 cases (12.81%) were found positive for IgM antibodies against O.tsutsugamushi.The common symptoms noted were fever with headache, myalgias, gastrointestinal intolerance, followed by breathlessness, rash and jaundice. Eschar was seen only in 69 patients. The most common complication noticed was ARDS (8.29%) followed by hepatitis (6.88%), petechial heamorrhagic spots (38.3%) and sepsis (6.07%). Mortality rate was found to be 1.8%. The cases were mainly seen in the months between August to October which correlates the infection with the rainy season.

**CONCLUSION:** ST should be considered as one of the differential diagnosis of AFI. Timely diagnosis and management becomes crucial to decrease/limit the diease burden, thus thwarting the onset of complications and mortality.

**KEYWORDS :** Orientia tsutsugamushi, AFI, ST

## INTRODUCTION

ST one of the alarming rickettsial infections, endemic in regions of eastern Asia and the south western Pacific. It is estimated that about one million cases of ST occur each year[1]. ST, an acute febrile disease caused by *Orientia tsutsugamushi,* which is a Gram negative, obligate intracellular bacterium. It is transmitted to humans by the bite of the larval stage of trombiculid mites (chiggers)[2].The infection is called ST because it generally occurs after exposure to areas with secondary (scrub) vegetation. Uttarakhand a mountainous and least urbanized state of northern India. During the rainy season, areas at lower altitudes have an average temperature of $20^0$C to $35^0$C, which is conductive to the spread of arthropod vectors. An outbreak of ST in these hilly regions have been reported by various authors[3]. Factors essential for establishment of infection are coexistence and intimate relationship among *O. tsutsugamushi*, chiggers, rats and secondary or scrub vegetation are known as zoonotic tetrad [4].

After incubation period of 10-12 days, patient develops constitutional symptoms such as fever, rash, myalgias and headache or with severe complications like multiple organ dysfunctions syndrome involving organs like kidney, liver, lungs, CNS or with circulatory collapse with haemorrhagic features [5,6].Bacteremia is detected 1–3 days before the onset of fever followed by generalized lymphadenopathy 2-3 days later[7]. A necrotic eschar at the inoculating site of the mite is pathognomic of scrub typhus. ST should be included in differential diagnosis (in addition to leptospirosis, malaria or dengue fever) of AFI, in patients with haemorrhagic fever especially if associated with jaundice and/or ARDS[6]. Apart from clinical history, serological testing and molecular methods helps in diagnosing ST. [8]

The disease is usually self limiting with spontaneous recovery. Severe cases if not treated with appropriate antibiotic, may culminate into serious complications. The present study was undertaken to determine the frequency of ST by using serological methods and analyze their clinic-demographic profile in this hilly belt.

## MATERIALS AND METHOD

**Study Design :** Retrospective study

**Study Location :** Microbiology Department, Tertiary care hospital, Dehradun.

**Study Duration :** August 2015 to July 2017.

**Sample size** : 760 clinically suspected cases of ST.

**INCLUSION CRITERIA** :

Patients with AFI, irrespective of age and gender, presenting with fever more than 7 days under the suspicion of ST

**EXCLUSION CRITERIA:**

1. Pregnant women.
2. Patients with genetic disorders.
3. Patients presenting with AFI where aetiology was other than ST.

**Procedure methodology**

Cases negative by initial routine investigations for AFI, but with strong clinical suspicion of ST were further evaluated for the detection of antibodies to *O. tsutsugamushi* by using IgM ELISA (In BIOS International kit) . 5ml of blood samples were collected in EDTA vial & plasma was separated by centrifugating at 2000 rpm for 15 minutes. Samples were processed as per manufacturer's instructions.

## RESULTS

Out of total 3854 cases of AFI, 760 (19.71%) clinically suspected cases of ST enrolled in the study were further evaluated for antibodies to *O. tsutsugamushi,* by using IgM ELISA kit, 494 cases were found positive for ST (494/760x100=65%). The rest 266 samples were serologically negative. Thus, the frequency of seropositive ST cases was found to be 12.81% (494/3854 X 100) (Table1). To evaluate the efficacy of IgM ELISA, serum samples from 80 healthy asymptomatic volunteers were subjected to IgM ELISA and all were negative for ST. The sensitivity and positive predictive value of IgM ELISA was found to be 65% and 100% respectively. Mostly the positive cases (34.21% ) were seen in the age group of 30-39 years. Males 337,(68.21%) outnumbered females 157, (31.78%) with the ratio of 2.1:1. (Table 2)

Among the analyzed cases, 61.78% ( 301/494 x 100) belonged to rural area and 38.21 %(187/494 x 100) belonged to urban area. Commonest factor predisposing to ST was presence of scrub vegetation around the houses of the positive cases, followed by the history of infestation by rats. Patients involved in activites such as open field defecation, grass cutting and visit to forest also contributed to infection with *O.tsutsugamushi*, to certain extent. (Table 3).

Most of the cases were positive in rainy months from August to October each year. (Image 2). Although, most of the seropositive cases presented with clusters of clinical symptoms, fever and headache were

associated with all cases. Gastrointestinal symptoms such as nausea, vomiting and abdominal pain were also commomly encountered. Myalgia, rash and conjuctival congestion were relatively less common.(Table 4).

Lymphadenopathy was most commonly noticed sign (35.9%). Eschar was associated with 14.3% of cases, common sites being back, axilla, thigh and groin. Petechial haemorrhagic spots indicating thrombocytopenia was observed in (38.3%) cases. Other signs noticed were hepatomegaly, splenomegaly and jaundice.( Table 5).

Complications developed in 27.12% (134/494x100) of positive cases, the most common complication was ARDS (8.29%) followed by hepatitis (6.88%), sepsis (6.07%), disseminated intravascular coagulopathy (2.22%) and osteomyelitis (1.21%). Other complications encountered were meningitis, pleural effusion, cholangitis, myocarditis and peripheral neuropathy. Nine patients expired due to complications like ARDS, hence the mortality rate was 1.8 % (9/494x100) which was seen in middle to elderly age group.(Table 6).

**Table 1: Clinical diagnosis v/s serological diagnosis of ST cases**

| **CLINICALLY DIAGNOSED CASES (n=3850)** | SEROLOGICALLY DIAGONOSED CASES (n=760) | |
|---|---|---|
| **760 (760/3850x100=19.71%)** | IgM ELISA (+) | IgM ELISA (-) |
| | 494 (494/760x100= 65%) | 266 (266/760x100=53. 84%) |

**Table 2: Age and sex wise distribution of seropositive cases of ST (n=494)**

| Age groups | **Male** | **Female** | **Total** |
|---|---|---|---|
| < 18 | **06** | **07** | **13** |
| 18 -29 | 84 | 41 | 125 |
| 30 -39 | 122 | 47 | 169 |
| 40 -49 | 74 | 39 | 113 |
| 50 -59 | 27 | 11 | 38 |
| >60 | 24 | 12 | 36 |
| **TOTAL** | **337(68.21%)** | **157(31.78%)** | **494** |

**Table 3: Presence of predisposing factors in cases of ST**

| **Predisposing factors** | **Cases** | **Percentage** |
|---|---|---|
| Vegetation around houses | 385 | 78% |
| Infestation by rats | 321 | 65% |
| Open field defecation | 247 | 50% |
| Grass cutting | 241 | 48% |
| Visit to forest | 187 | 38% |

**Table 4: Clinical profile of seropositive cases of ST**

| **Symptom** | **Cases** | **Percentage** |
|---|---|---|
| Fever | 494 | 100% |
| Headache | 494 | 100% |
| Adominal pain | 182 | 37.3% |
| Myalgia | 108 | 22.1% |
| Rash | 38 | 7.8% |
| Conjuctival congestion | 13 | 2.7% |
| Nausea,vomiting | 218 | 44.2% |

**Table 5: Clinical signs of seropositive cases of ST**

| **Signs** | **Cases** | **Percentage** |
|---|---|---|
| Lymphadenopathy | 172 | 35.9% |
| Eschar | 70 | 14.3% |
| Petechial heamorrhagic spots | 187 | 38.3% |
| Hepatomegaly | 108 | 22.1% |
| Splenomegaly | 70 | 14.3% |
| Jaundice | 47 | 9.6% |

**Table 6: Complications associated with seropositive cases of ST**

| **Complications** | **Cases** | **Percentage** |
|---|---|---|
| ARDS | 41 | 8.29% |
| DIC | 11 | 2.22% |
| Sepsis | 30 | 6.07% |
| Hepatitis | 34 | 6.88% |
| Osteomyelitis | 06 | 1.21% |
| Meningitis | 04 | 0.8% |
| Pleural effusion | 02 | 0.4% |
| Myocarditis | 02 | 0.4% |
| Cholangitis | 02 | 0.4% |
| Peripheral neuropathy | 02 | 0.4% |
| TOTAL | 134 | 27.12% |

## DISCUSSION

Rickettsial infections, mainly ST, has been associated with life threatening illness, in developing countries, including India.[9] Prevalence of ST varies from 0-8% to 60%, globally. [10] In our study, 760 patients with clinical diagnosis of ST were evaluated for IgM antibodies out of which 19.71% were seropositive. Study done in CMC, Ludhaina (2014), reported that out of 772 patients with febrile illness, 12.69% positive for ST[11] which was consistent with our study. Similar study conducted in Nehru Hospital of PGIMER, observed that 24% of patients with fever had ST.[12] Another study in tertiary health care in Goa found that 34% of fever cases were positive for IgM antibodies against *O.tsutsugamushi*.[13] Bhutia and Pradhan, in 2013, screened 204 samples, 63 patients were confirmed positive among which 42 were males and 21females.[14] Ramyasree et al., (2015) reported that out of 39 patients, 23 were males and 16 females.[15] Mahajan (2005) reported that among ST samples, 24% were male and 14.6% females.[5] In Thailand, the positivity for ST was 59.5% with highest prevalence of 77.7% seen in 40-49 years age group with no difference between the sexes.[16] Gurung et al., tested 204 patients with fever, 63 were positive (30%) , out of which 42 were males and 21 females. [14] In our set up, out of 494 seropositive cases of ST, males( 337) outnumbered females (157) with the ratio of 2.1:1, which is well correlated with other studies.[14,15] Our study shows more positivity of ST particularly between 30-39 years of age (34.21%). The male predominance and the infliction of the young and active population been observed in our study, thus indicating the occurrence of ST in populations involved in outdoor activities. Cases involved in occupational activities such as open field defecation, grass cutting and visit to forests were commonly affected. Those residing in the vicinity of scrub vegetation or with the history of infestation of rats were more frequently affected by this stubborn *O.tsutsugamushi*. Vivekanandan M et al., in Pondicherry reported female preponderance.[17]

In our study, 760 clinically diagnosed cases, 494 were found to be positive for antibodies to *O. tstsugamushi* by using IgM ELISA.The remaining 266 sero negative cases were either the true negatives or the cases with the past ST infection, or the missed cases which could have been diagnosed using gold standard tests like immunofluoresence and indirect immunoperoxidase. In our set up positive cases were predominantly from rural area comprising of 61.78% which explains the exposure more to outdoor activites.

Fever and headache (100%) were the commonest presentation in our study , similar observations seen by Dass et al., from Meghalaya. [18] Fever, cough and vomiting have been reported as complaints in other studies.[18,19] Eschar, the most characteristic feature of ST, may not been seen in all patients, due to variation in serotypes among regions and also eschar is painless and does not itch, so remains undetected. May be because of these reasons ,eschar was seen in 14.3% patients in our study**.** The common sites were neck, groin, forearm and inguinal region. Varghese et al., (2013), reported eschar in 55% patients [20].The presence of eschar and rash varies in different populations in different studies [21]. Vivekanandan,*(2013)*, reported eschar in 46% cases, common sites were axilla, breast and groin [17].

In our study clinical findings were lymphadenopathy, hepatomegaly, splenomegaly, jaundice and petechial haemorrhagic spots. Platelet count was decreased in 187(38.3%) patients. 27.12% of seropositive cases culminated into serious complications. Commonest complication seen was ARDS (8.29%) followed by hepatitis (6.88%), sepsis (6.07%). Other rare complications such as DIC, meningitis, osteomyelitis, pleural effusion, cholangitis and peripheral neuropathy were also seen, which were consistent with other studies.[13,22] Kedareshwar et al.,(2012) found complications like hepatitis (80%) followed by ARDS (60%) and ARF (60%) . [13] Tsay and Chang, observed serious complications like pneumonitis (36%) ARDS (15%), ARF (9%), myocarditis (3%) and septic shock (3%) [22]. Similar study from Pondicherry observed, (MODS) , renal impairment, ARDS and meningitis as important complications[17]. Manipal also reported ARDS (11.5%), meningoenchephilitis (8.5%), pneumonia (5.5%) as complications of ST. [23]

Saifudheen et al.,(2012) reported two cases of meningitis, as complication of ST from Kerala [24], which was consistent with our

study, where we found four cases of meningitis. Singh et al., (2014) found hepatitis (78.7%), ARDS (19.2%), thrombocytopenia (46.8%) and ARF (31.9%) as complications and mortality occurred in 6.4% patients [25]. In our set up, mortality rate was 1.8%. The most common cause of death in our study was ARDS followed by hepatitis. Varghese et al.,(2013) reported mortality in 2.8% cases, attributed to hepatorenal failure, MODS, meningitis and myocardits.[20] Study done by Ponugoti Munilakshmi, found 9.7% mortaility in concurrence with various studies [26,27,28,29]. Mahajan SK, had documented that the mortality rate associated with ST varies between 7-30%.[5] The mortality rate was low in our study, this achievement could be credited to the utilization of IgM ELISA, which might have helped in the early diagnosis, and thereby early institution of the appropriate treatment.

In our study, many cases were encountered during the rainy months of August to October, which could be explained by the occurence of *Leptotrombidium deliense* in rainfall months, with more chiggers attached to the rodents in these months [30]. Various studies also reported the similar seasonal phenomenon.[31,32,17,33].This is because, during these months, farmers are involved in the harvesting activity in the fields, where they are exposed to the bites of larval mites. Further, in the immediate postmonsoon period (September to early months of the year), there is growth of secondary scrub vegetation, which is the habitat for trombiculid mites[34], though transmission of disease occurs throughout the year in tropical areas, whereas in temperate zones transmission is seasonal. Similar observations have been recorded by other authors, whereas Taiwan found the highest number of cases between May and August [35].

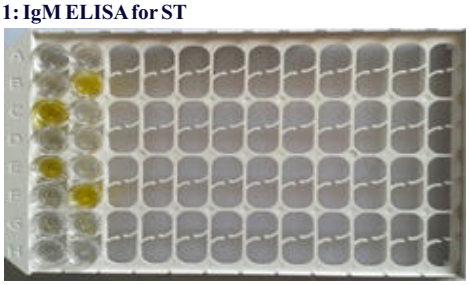
## CONCLUSION

ST has emerged as an important cause of febrile illness. Clinically diagnosed cases of ST should be further evaluated serologically. ST has been seen to be associated with mortality and morbidity therefore prompt diagnosis and treatment becomes mandatory. Apart from the therapeutic concern such as doxycycline and macrolides, environmental preventive measures such as use of mosquito nets/repellants, use of larvicidal agents and eradication of mosquitoes breeding points should be taken into consideration.

## LIMITATION

1. It was not feasible to carry out indirect immunoperoxidase & indirect immunofluorescence antibody assay which are considered gold standard tests for ST.
2. As the study was conducted in a tertiary care hospital, therefore the actual burden of the disease in the community could not be analysed which may be higher.
3. IgG ELISA could not be performed due to limited resources, which would have helped in the diagnosis of past infection thus estimating the prevalence in the hilly area of Uttarakhand.

**Image 1: IgM ELISA for ST**



IgM ELISA microtiter plate, wells 1C, 1E, 2B & 2F are positive with positive and negative controls.

**Image 2: Monthwise distribbution for ST**

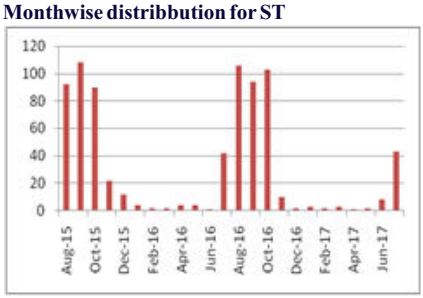



**IMAGE 3:Clinical picture showing eschar in ST**

## REFERENCES


1. Vas LS and Gupta NK 2006; Outbreak of scrub typhus in Jammu – a report. MJAFI., 62:342-3
2. Watt G and Parola P. Scrub typhus and tropical rickettsioses. Curr Opin Infect Dis 2003;16:429-36.
3. Sharma A, Mahajan S, Gupta ML, Kanga A, Sharma V. Investigation of an outbreak of scrub typhus in Himalayan region of India Jpn J Infect Dis 2005; 58 : 208-10.
4. Hase T, Roberts LW, Hildebrandt PK, et al 1978; Stylostome formation by Leptotrombidium mites (Acari: Trombiculidae). J Parasitol., 64 (4):712
5. Mahajan SK. Scrub typhus. J Assoc Physicians India 2005, 53 : 954-8.
6. Kothari VM, Karnad DR, Bichile LS. Tropical infections in the ICU. J Assoc Physicians India 2006; 54 : 291-8.
7. Scheie HG 1947;Ocular changes in scrub typhus. A study of 451 patients.Trans Am Ophthalmol Soc.,45:637 Vas LS and Gupta NK 2006; Outbreak of scrub typhus in Jammu – a report. MJAFI.,62:342-3
8. Yeon JJ, Suk K,Yeh DW, Jun WL, Kun-11 K, Sun HL, 2007;Scrub typhus: Clinical, Pathologic and Imaging Findings.RadioGraphics 27:161-172
9. Tamura A, Ohashi N, Urakami H, Miyamura S. Classification of Rickettsia tsutsugamushi in a new genus, Orientia gen. nov.,as Orientia tsutsugamushi comb. nov. Int J Syst Bacteriol 1995;45:589-91
10. Taylar AC, Hill J, Kelly DJ, Davis DR, Lewis GE Jr. A serological survey of scrub, tick,and endemic typhus in Sabah, East Malaysia.Southeast Asian J Trop Med Public Health1986:17:613-9
11. Oberoi, A.And Varghese, S.R. 014. Scrub typhus-an emerging entity: A study from a tertiary hospital in North India. Ind. J. Pub.Health. 58:281-283.
12. Kumar, V., Kumar, V., Yadav, A.K and Iyengar, S.2014. Scrub typhus is an under-recognized cause of acute febrile illness with kidney injury in India. PLOS Neglected Trop. Dis. 8:261-264.
13. Kedareshwar, P.S., Rodrigues, N.S., Nevrear, R.P. and Dias, L. 2012. Scrub typhus in patients reporting with acute febrile illness at a tertiary health institution in Goa. Ind. J. Med. Res. 136: 1020-1024
14. Bhutia, P.Y. and Pradhan, G.S.2013. Outbreak of Scrub typhus in North eastern Himalayan region-Sikkim-An emerging threat. Ind. J. Med. Microbiol. 31: 72-74.
15. Ramyasree A., kalawat, U., Rani, N.B. and Chaudhury, A. 2015. Seroprevalence of Scrub typhus at a tertiary hospital in Andhra Pradesh. Ind. J. Med. Microbiol. 33(1):68-72.
16. Chanyasanha C, Kittigul L, Puenchitton S, Sangasuwan P. Antibodies titers to rickettsial diseases in blood donor in Bangkok By Indirect immunoloperoxidase technique. Proc Natl Epidemiol Semin Bangkok 1992;167-9.
17. Vivekanandan M, Mani A, Priya YS, Singh AP, Jayakumar S, Purty S.Outbreak of scrub typhus in Pondicherry. J Assoc Physicians India 2010;58:24-8.
18. Dass R, Deka NM, Guwarah GS, Barman H, Hoque R, Mili D, et al.Characteristics of pediatric scrub typhus during an outbreak in the North Eastern region of India:Peculiarities in clinical presentation, laboratory findings and complications. Indian J Pediatr 2011; 78:1365-70.
19. Palanivel S, Nedunchelian K, Poovazhagi V, Raghunadan R, Ramachandran P.Clinical profile of scrub typhus in children. Indian J Pediatr 2012;79:1459-62
20. Varghese, G.M., Janardhanan, J., Trowbridge, P. And Peter, J.V. 2013. Scrub typhus in South India: Clinical and laboratory manifestations, genetic variability, and outcome. Int. J. Infect. Dis. 17: 981-987.
21. Ogawa, M., Hagiwara, T., Kishimoto, T. and Shiga, S. 2002. Scrub typhus in Japan: Epidemiology and clinical features of cases reported in 1998. Am. J. Trop. Med. Hyg. 67: 162-165.
22. Tsay, R.W. and Chang, F.Y. 1998. Serious complications in Scrub typhus. J. Microbiol. Immunol. Infect. 31(4): 240-244.
23. Inamdar, S., Thunga, G., Acharya, R., Vijayanarayana, K., Shridharan, N. and Bhrugu, P. 2013. Study of characteristics and treatment pattern of Scrub Typhus in Tertiary Hospital. J. Pharm. Sci. Res. 5(5):107-110.
24. Saifudheen, K., Sajeeth Kumar, K.G., Jose, J., Veena,V. and Gafoor, V.A. 2012. First case of Scrub typhus with meningoencephalitis from Kerala: An emerging infectious threat. Ann. Ind. Acad. Neurol. 15(2): 141-144.
25. Singh, S.P., Singh, R. and Ahmad, N. 2014. A study of complications of Scrub typhus in a tertiary health institute of Uttarakhand, India. Int. J. Res. Med. Sci. 2(1): 246-249.
26. Wang CC, Liu SF, Liu JW, Chung YH, Su MC, Lin MC. Acute respiratory distress syndrome in scrub typhus.Am J Trop Med Hyg 2007;76:1148-52.
27. Yen TH, Chang CT, Lin JL, Jiang JR, Lee KF. Scrub typhus: A frequently overlooked cause of acute renal failure. Ren Fail 2003;25:397-410.
28. Thap LC, Supanaranond W, Treeprasertsuk S, Kitvatanachai S,Chinprasatsak S, Phonrat B. Septic shock secondary to scrub typhus: Characteristics and complications. Southeast Asian J Trop Med Public Health 2002;33:780-6.
29. Cracco C, Delafosse C, Baril L, Lefort Y, Morelot C, Derenne JP, et al. Multiple organ failure complicating probable scrub typhus. Clin Infect Dis 2000;31:191-2.
30. Frances SP, Watcharapichat P, Phulsoksombati D, Tanskul P, Linthicum KJ, 1999;Seasonal occurrence of Leptotrombidium delience (Acari: Trombiculidae) attached to rodents in an orchard near Bangkok, Thailand. J Med Entemol.,36:869-74
31. Mathai E, Lloyd G, Cherian T, Abraham OC, Cherian AM. Serological evidence for the continued presence of human rickettsioses in southernIndia. Ann Trop Med Parasitol 2001; 95 : 395-8.
32. Varghese GM, Abraham OC, Mathai D, Thomas K, Aaron R, Kavitha ML, et al. Scrub typhus among hospitalised patients with febrile illness in South India: magnitude and clinical predictors. J Infect 2006; 52 : 56-60.
33. Sharma PK, Ramakrishnan R, Hutin YJ, Barui AK, Manickam P, Kakkar M, et al 2009;Scrub typhus in Darjeeling India:Opportunities for simple, practical prevention measures. Trans R Soc Trop Med Hyg.,103:1153-8
34. Tilak R. Ticks and mites. In: Bhalwar RV, editor. Textbook on public health and community medicine, 1st ed. Pune: Department of Community Medicine, AFMC, Pune; 2009. p.955-9.
35. Chang WH 1995; Current status of Tsutsugamushi disease in Korea. J Korean Med Sci.,10:227-38