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Sero surveillance of Scrub typhus in a tertiary care hospital at Madurai, Tamilnadu, South India.

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Abstract
Introduction: *Scrub typhus is a rickettsial infection which is caused by Orientia tsutsugamushi and transmitted by the bite of the chigger of a mite. Delay in diagnosis can be fatal otherwise the treatment is simple, doxycycline being the drug of choice. Indirect immunoflurescence is considered gold standard but it is not used in India as it is costly and also not available. There is need for rapid, economic and simple test for the diagnosis of scrub typhus. This study was taken up to study the seroprevalence of scrub typhus in Southern districts of Tamilnadu and to compare two commonly used serological methods; rapid test and IgM ELISA.* ***Materials and methods:*** *This is a prospective study in which 842 serum samples from clinically suspected cases collected over a period of 12 months and they were processed for the detection of IgM antibodies for scrub typhus by ELISA and Rapid test. Samples were also tested for leptospirosis and dengue fever which are the other common causes of fever prevalent in this region.* ***Results:*** *Total number of samples processed was 842 out of which 477 were males and 365 were females. Among the 842 samples 76 were sero positives. Positivity was higher in males in the age group of patients between 41 and 60 yrs of age. There was 100% correlation between ELISA and rapid method. There is a peak incidence during the months November and December. Fever was the most common manifestation and eschar was seen in 12 cases and no mortality reported.* ***Conclusion:*** *Scrub typhus is on the rise in southern part of Tamilnadu and it is considered to be one of the endemic diseases coming under pyrexia of unknown origin. The geographical distribution is not confined to any particular area. It is widespread in almost all districts around Madurai. The peak incidence is during post monsoon in the months of November and December. Since IgM ELISA and Rapid immunochromatography tests show 100% correlation, rapid test can be used for quick diagnosis of Scub typhus.*
Keywords: *Elisa-enzyme linked immunosorbent assay, rapid test, scrub typhus*

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I. Introduction

Scrub typhus is an acute febrile illness prevalent all over the world .Nowadays, cases are reported in many states of India including Tamilnadu. But diagnosis is still lacking in many states .Scrub typhus is a rickettsial infection which is caused by *Orientia tsutsugamushi* and transmitted by some species of trombiculid mites ("chiggers", particularly a *Leptotrombidium deliense*).. The bite of this mite leaves a characteristic black eschar that is useful to the doctor for making the diagnosis[1]. The observation of the eschar is often missed and other signs and symptoms of the disease are not characteristic thus posing the problem of delayed diagnosis by the clinician. Failure of timely diagnosis leads to significant morbidity and mortality . With timely diagnosis treatment is easy, affordable and often successful with dramatic response to antimicrobials. As antimicrobials effective for rickettsial diseases are usually not included in empirical therapy of nonspecific febrile illnesses, treatment of rickettsial diseases is not provided unless they are suspected. Several tests are available with their own advantages and limitations[2]. Among all the serological tests available, Weil-Felix test is the cheapest and easily available, but this is unreliable. Indirect immunofluorescence test, the gold standard is beyond affordability specially in poor countries and needs expertise for interpretation as the choice of cut-off values for positive diagnosis is influenced by several factors such as antibody kinetics, geography, negative seroconversion and seasonality[3].

IgM ELISA has been evaluated and found to be quite satisfactory, but samples need to be pooled for ELISA which can lead to delayed diagnosis thus influencing the overall outcome. Rapid tests have come into vogue which are economic, rapid and single tests can be carried out.

This study was carried out to know the seroprevalence of scrub typhus in clinically suspected patients and to compare a rapid test which is simple, and economic test with IgM ELISA for the diagnosis of scrub typhus.

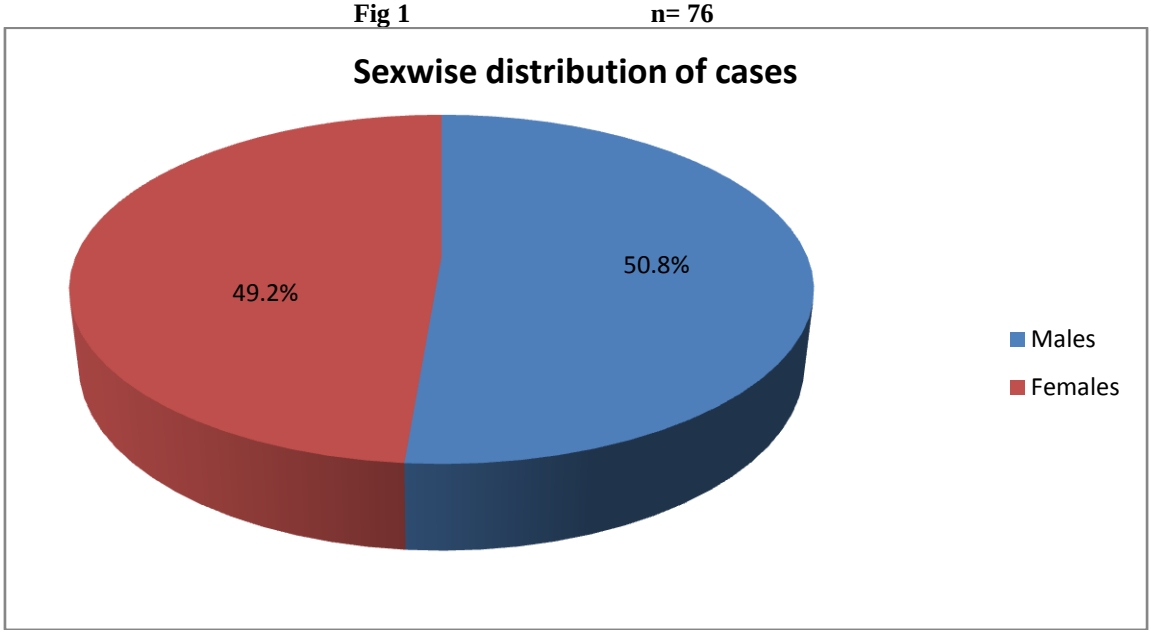
II. Material and Methods

This is a cross-sectional study carried out on serum samples from clinically suspected cases received over a period of 12 months extending from January 2018 to January 2019. The samples were collected from the cases of Pyrexia of unknown origin admitted in Velammal Medical college hospital in Madurai, Tamilnadu.The samples were screened for the presence of IgM antibodies to scrub typhus by the rapid test followed by confirming the presence of IgM antibodies by ELISA test. Samples were also tested for dengue fever, typhoid fever, leptospirosis, tuberculosis and malaria which are the other causes of pyrexia of unknown origin. Detection of IgM antibodies by ELISA- was done using Scrub typhus Detect™ IgM ELISA InBios kit which is a system for the detection of IgM antibodies in human serum to OT derived recombinant antigen. This test is to aid in the detection of human exposure to Orientia tsutsugamushi species. Detection of IgM antibodies by Rapid method was done using SD Biosensor Standard Q Tsutsugamushi, one-step rapid immunochromatographic assay for qualitative detection of IgM/ IgG antibodies to Orientia tsutsugamushi in human serum. Clinical features of the patients were retrieved from hospital medical records. Statistical analysis was done using SPSS 11.5 version. *P*-value was calculated using Chi-square test.

III. Results

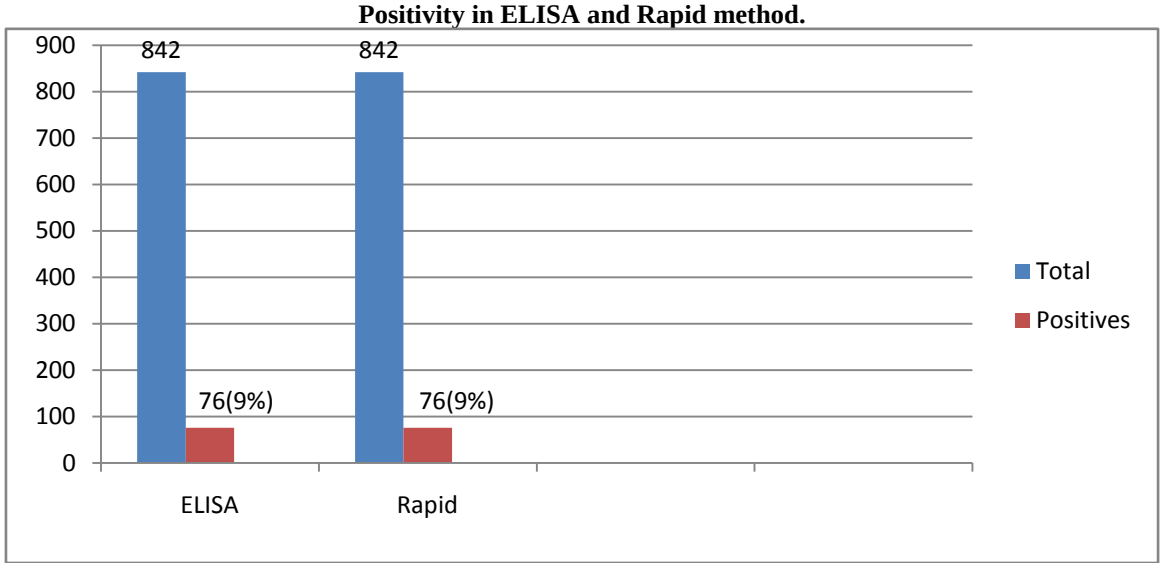
Out of the 842 samples tested, 428 were samples from males(50.8%) and 414 (49.2%) were from females and this is shown in Figure1. It is shown that both sexes were affected almost equally with a slight predominance by the males.

Fig 1 **n= 76**



Among the 842 samples tested, 76 were positive by both ELISA and Rapid test. This is given in Figure 2. It is shown that 9% of the samples were positive for IgM antibodies to Orientia tsutsugamushi by both Rapid test which was used as a screening test and ELISA which was used as a confirmatory test.

Fig 2
Positivity in ELISA and Rapid method.



It was observed in the study that 8 males and females were positive in the age group 1-20 yrs.(10.5%), 8 males(10.5%) and 10 females(13.2%) in the age group 21-40 yrs,18 males(23.6%) and 12 females(15.7%) in the age group 41-60 yrs and 5 males (6.6%)and 7 females(9.2%) were positive for IgM antibodies to Orientia tsutsugamushi. This is given in table no.1

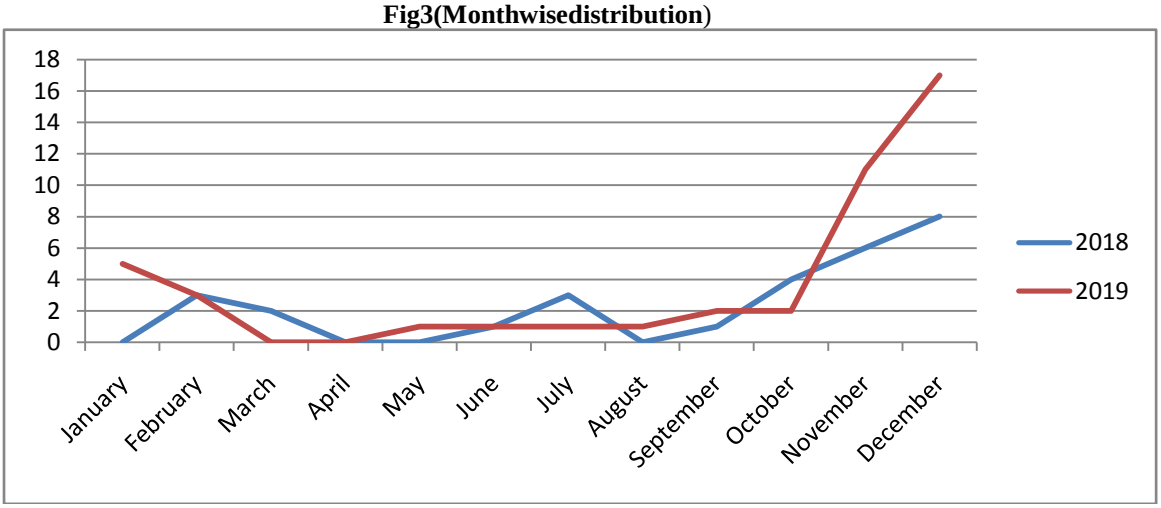
Table 1
Agewise distribution

Age group	**Males (%)**	**Females(%)**
1-20 yrs.	8(10.5%)	8(10.5%)
21-40 yrs	8(10.5%	10(13.2%)
41-60 yrs	**18(23.6%)**	**12(15.7%)**
Above 60 yrs	5(6.6%)	7(9.2%)

It is observed from the table that both males and females in the age group 41-60 yrs. were more commonly involved and above 60 yrs. less commonly involved . Males predominated females in the age group 41-60 yrs and females predominated males in the age group more than 60 yrs . In the age group 1-20 yrs. both the sexes were affected equally.

The cases were more common in the months November and December. There were 109 PUO cases during these months in 2018 and 14 (6+8)were positive for scrub typhus(12.8%) . There were 222 PUO cases during these months in 2019 and 28 (11+17)were positive for scrub typhus(12.8%). There were no cases reported in April in both the years. This is given in fig.3

Fig3(Monthwisedistribution)



It is observed that in both the years 12.8% of the PUO Cases were Scrub typhus.

In this study, 42 of the positive cases were admitted with fever, myalgia and headache as common symptoms, 12 of them with fever and eschar formation, 10 of them with fever and vomiting and 12 of them with fever and rashes. Mortality was nil during the study period. This is given in the following table no.2

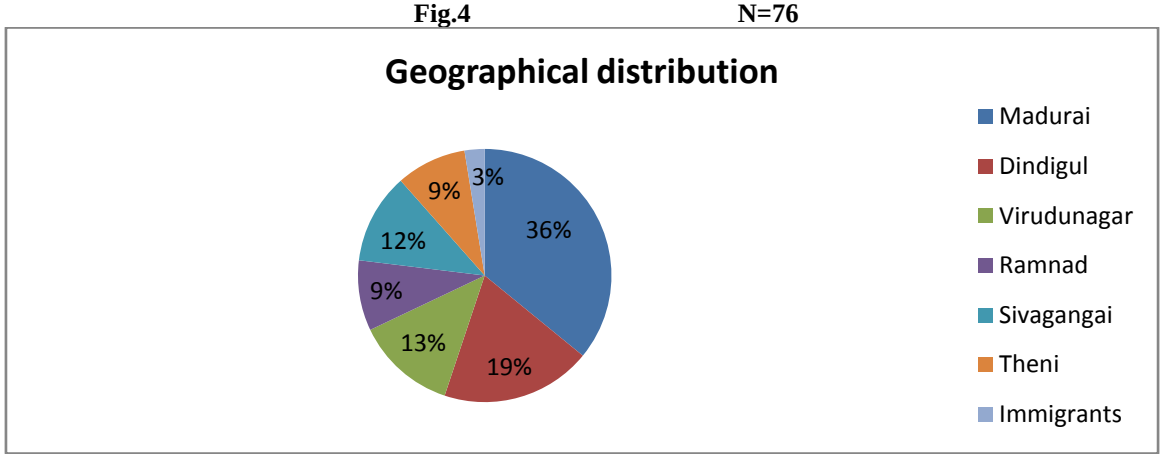
Table 2
Symptomwise distribution n=76

Symptoms	**No.(%)**
Fever, myalgia, headache	42(55.3%)
Fever and Eschar formation	12(15.7%)
Fever and vomitting	10(13.2%)
Fever with rashes	12(15.7%)

It was observed that all patients had invariably fever as the common symptom. Eschar was seen in 12 cases.

Among the 76 positive cases admitted in the hospital,28 cases were from within Madurai district ,48 were from neighbouring districts like Dindigul(15), Virudunagar(10), Sivagangai(8), Ramnad(7), Theni(6) and 2 were immigrants from Andhrapradesh.

Fig.4 N=76



From the figure, it is noted that more cases were in Madurai district(36%) and Dindigul district(19%) which are more like urban areas. The remaining districts are still considered as rural areas. The infection seems to have spread from urban to rural area.

IV. Discussion:

Scrub typhus is prevalent in southern parts of India for sometime. There is an increase in the trend in the last 2 years. This study was focused to know the prevalance of infection in a tertiary care hospital situated in the southern part of Tamilnadu. In this study, 9% of the samples collected for the diagnosis of PUO showed antibodies to O.tsutsugamushi. In this study, it was observed that there is not much variation in the sexwise distribution of the infection, males showed only a slight increase in the incidence(50.8% males and 49.2% females). This is in accordance with the study by Abhay kumar, Amit Jog et al**(1**) who showed more or less the same incidence with a slight increase in the incidence of females whereas Jamil et al**(2)** showed an increase in the male incidence .Sex variation is mainly due to their occupation. Since the people in this study were mostly agriculturalists and both sexes go to fields equally,the incidence may be equal in both sexes.

The prevalence of scrub typhus varies from 0-8% to 60% in different countries **(3,4,5)**In a study from Thailand, the positivity for scrub typhus was 59.5% with highest prevalence in 40-49 (77.7%) year age group with no difference between the two sexes. In our study , the prevalence was 9% with highest prevalence in the age group 41-60 years with no sex differences which is almost similar to the Thailand study **(6).** Sarma *et al***.(7),** tested 150 samples from patients with fever of unknown origin of which 52 were found to be positive for OX K antibodies by Weil-Felix test..Gurung *et al.,* **(8)** tested 204 patients with fever of unknown origin of which 63 were confirmed positive of which 42 were males and 21 were females. In our study, among the 850 patients tested 76 were positive. Of these 76 positive patients, 39 were males and 37 were females. Highest seropositivity was observed in 41-60-years age group. Thus there appears to be high variation in the prevalence in various studies. This variation in the prevalence may be due to the variation in the sample size , and the type of tests done. In our study, the sample size was 850 and the tests done were the rapid test and ELISA Test.

Fever with myalgia was the most common presentation in our study which is similar to a hospital-based study in Taiwan and a study by Dass *et al.,* from the state of Meghalaya, India **(9)** Other presentations included vomiting (50%), headache (30%) and eschar formation (15.7%). No mortality was reported **.** Kammili et al **(10)** in their study proved that arthralgia, haemorrhagic manifestations and rash were common clinical symptoms. Boorugu etal **(11)** from Andhrapradesh proved that fever with myalgia , loose stools and dry cough were common in their studies. But none of these studies showed the presence of Eschar formation but our study had 15.7% cases with eschar formation. This may be due to the variability in the infecting serotype , high skin colour in Indian population and high rates of underdetection due to the painless and non itchy charecterestics of the eschar.Chauhan et al **(12**) proved that eschar formation was related to poor prognosis but in our study all cases with eschar recovered with no sequele.

Cases were more commonly seen during monsoons and post monsoons in our study. Similar study by Monika pathania et al **(13)** also showed that their study at sub himalayan region revealed that the cases were more during monsoons and post monsoons. This may be attributed to the increased occupational exposure due to harvesting leading to more people in the fields and for longer periods of the day in the rainy season.

Indirect Immunofluorescence assay (IFA) is a gold standard for diagnosis of scrub typhus but limited by the requirement of standard slides, paired sera etc. Weil-Felix test is widely used but lacks sensitivity and specificity . IgM ELISA and Rapid ICT have been reported to have good sensitivity and specificity. Evaluation of the SD Bioline ICT in Thailand patients in 2012 has shown that it is more sensitive than IFA with specificity as high as 98.4% in diagnosing acute phase samples. In our study a correlation of 100% between IgM ELISA and SD Bioline Tsutsugamushi rapid diagnostic test was reported similar to a study by Ramyasree et al (14) from Andhra who have shown 97% correlation.

V. Conclusion:

Since Scrub typhus is on the rise in Madurai district, it is necessary to investigate all Pyrexias of unknown origin by simple sensitive snd specific test having equivalence with IgM ELISA, ie.Immunochromatographic test. As ICT detects acute samples, early treatment will be possible.As cases were common in monsoon and post monsoon seasons, the people of both sexes working in the fields should be advised to protect them from the bite of mites during this period.

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