An epidemiological outbreak of scrub typhus caused by Orientia tsutsugamushi – A comprehensive review

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ABSTRACT

Scrub typhus is a vector-borne infectious disease caused by Orientia tsutsugamushi a gram-negative bacterium belonging to order Rickettsiales, endemic in Asia-Pacific region known as “Tsutsugamushi triangle.” This review aims to describe the seasonal outbreak of scrub typhus endemic in many places of India and in a global map which will be systematically analyze the current situation. The review focused on the diagnosis methods used to detect the disease also on the severity and complications during the clinical presentation. The data of scrub typhus outbreaks in different countries from 2000 to 2020 were retrieved from various sources. Gradually, increased case load and incidence rates have been recorded. The majority of the reported cases were from the North-East region of India during the cooler months. In Odisha, very few case reports were found, mostly from the capital, Bhubaneswar, but other areas have no records as it is still considered as an underreported disease. We concluded that India has experienced a large increase in scrub typhus incidence and documented an expansion in geographic distribution throughout the country. Therefore, people in rural areas need to be more conscious and aware to prevent the spread. Although no vaccine is available, several other preventive measures can be taken.

1. INTRODUCTION

Orientia tsutsugamushi (OT), a causative agent of acute febrile disease scrub typhus, belongs to the Rickettsiaceae family in Rickettsiales. The term “scrub” is used due to the vegetation type that bears vector. The word “typhus” is derived from the Greek word “typhus,” which means “fever with stupor or smoke” [1]. “Tsutsuga” means “small and dangerous,” and “Mushi” means “insect or mite.” It requires a host cell for growth as it is an intracellular bacterium. According to the World Health Organization, it has been categorized as one of the world’s most underdiagnosed/underreported diseases [2]. Electron microscopy has revealed that the structure of the outer envelope, the outer membrane cell wall is thicker than the inner membrane. At the same time, it is totally reversed in other species of Rickettsia [3]. The difference in 16s rRNA sequence and some morphological and biochemical characteristics is the main reason that the bacterium has been recently transferred to genus Orientia, which is newly added in the Rickettsiaceae family [4].

Leptotrombidium mites transmit OT during their larval stage of development, known as “chiggers.” The incubation period is 6–21 days. Clinically, it can be distinguished by high fever, rash, eschar, lymphadenopathy, pneumonitis, and meningitis. If untreated, it can lead to severe multiple organ failure and death [5]. The mortality rate range from 1 to 40%, depending on different endemic areas and encountered strains of OT [3].

2. METHODS

2.1. Data Sources

Epidemic-prone diseases are collected from the Integrated Disease Surveillance Program (IDSP) weekly which comes under the national center of disease control. Most of the data were collected from scientific databases such as PMC-NCBI, Google Scholar, PubMed, Scopus, and Scientific index. A systematic literature review of epidemiological studies of scrub typhus was carried out in this analysis from the epidemiological exposure records.

2.2. Study Eligibility Criteria

The main collection criteria are based on clinical manifestation with the presence of eschar and laboratory diagnoses such as enzyme-linked immunosorbent assay (ELISA), Weil-Felix (WF) test, IFA test, or nested polymerase chain reaction (PCR) test targeting a 56-kDa gene clinical presentation symptoms and specific complications. Figure 1 illustrates the Preferred Reporting items for Systematic Review and Meta-analysis (PRISMA) flow diagram of identification, screening,
eligibility, and inclusion which include in our search criteria. Approximately 324 reports have been collected from different sources and many of them were excluded as those have no clear evidence. In the end, 133 articles met the selection criteria and were approved for the analysis.

2.3. Statistical Analysis
Although this is a review article, no specific statistical analysis is done. The data are based on mean standard deviation, analysis by student t-test, Chi-square test, or Fisher exact test was considered as many researchers presented in their research articles. Mostly, $P > 0.05$ was supposed to be statistically significant.

3. RESULTS
3.1. Geographical Distribution and Global Outbreak
Although this disease has been recognized since 313 A.D. and has threatened billions of people in different regions of Asia and Australasia, it is still considered an underdiagnosed and underreported illness [6]. Previously, it was restricted to a specific area ranging from Russia to Japan in the north, Northern Australia in the south to Pakistan, and Afghanistan in the west known as the “tsutsugamushi triangle” ranging a broad area of 13 million km$^2$ [Figure 2] [7]. However, there are confirmed cases of increasing and spreading in other areas such as Dubai, United Arab Emirates [3] Chile, Peru, and Africa. During World War II, confederated forces suffered more destruction due to scrub typhus than the different outcomes of the war in Southeast Asia [8]. The diversity of species and epidemic characteristics in other countries such as China, Japan, South Korea, Taiwan, Hong Kong, and Thailand is represented, as a graph shown in Figure 3 [4-13].

The season of scrub typhus usually starts in May gradually increases every month; maximum cases were reported in June and July called pick months. The studies correlate with the climate and life patterns of organisms. From 2006 to 2016, there is a high rate of increased cases in China [9]. Compared to China, Japan showed the maximum cases during November [10]. Alike to Japan, October and November are the peak months in South Korea [11]. In South Korea, the Scrub typhus has been identified for the 1st time during the Korean War, but the disease was not revealed to the Korean population; however, until 1986, it was new to Korean citizens [12]. It has become widespread and regarded as the most widely recognized Rickettsia disease in South Korea. The age distribution differs in different countries. The age group varies in South Korea, that is, the patients of 60–69 years are supposed to be more affected [12]. The gender difference was not observed. In Japan, the most common age group was 51–75 years which was 62% of total reported cases, while in China, the suffered people of the same age group were <1/2 of the total patients [10]. In Thailand, the first human case was reported in 1952 [4] and the confirmed cases increased rapidly during 1980–2000, where 50–59-year-old patients were more affected [4]. In many of the cases, it has been seen that the main reason for the cause of scrub typhus disease and spread is the outdoor activity, working in farms and forestry, uneducated, and lifestyle. Furthermore, the articles showed that rural people are more supposed to be affected than people staying in urban areas.

Besides the countries narrated above, there are many other countries such as Taiwan, Hong Kong, Thailand, and the Maldives with scrub typhus reports in the tsutsugamushi triangle and southwest Pacific islands including Indonesia and the Philippines, and the landmass of Australia for almost a century [8,14].

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**Figure 1:** The study selection process for the included, data are represented by the PRISMA flow diagram.
3.2. Outbreak in India

Scrub typhus has an outbreak in different regions of India, but it spread out as an epidemic in Assam and West Bengal during the Second World War. The vector mites are primarily present in equatorial rain forests, subarctic terrains, and semi-deserts in the Himalayan regions as these are the diverse ecological niches. Heat and humidity give steady and supreme conditions to the transmission of the infection. These environmental niches are called mite islands or Typhus islands [15,16]. This disease mainly occurs during winter in southern regions, whereas in northern Himalayan states, it is seen
Table 1: Scrub typhus outbreak in India (By laboratory findings).

<table>
<thead>
<tr>
<th>Place</th>
<th>Year</th>
<th>Suspected cases</th>
<th>Diagnosis</th>
<th>Test</th>
<th>Symptoms</th>
<th>Death</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamilnadu</td>
<td>October 2001–February 2002</td>
<td>27</td>
<td>Doxycycline</td>
<td>Chloramphenicol</td>
<td>Weil–Felix Abnormal liver function, abnormal renal function</td>
<td>3</td>
<td>[18]</td>
</tr>
<tr>
<td>Jammu</td>
<td>July–October 2002</td>
<td>12</td>
<td>Tetracycline</td>
<td></td>
<td>Fever (&lt;101°F) Malaise, eschar, conjunctival congestion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Himachal Pradesh</td>
<td>2004</td>
<td>21</td>
<td>Doxycycline Azithromycin</td>
<td>Weil-Felix PCR</td>
<td>Fever, eschar, respiratory distress</td>
<td>3</td>
<td>[17]</td>
</tr>
<tr>
<td>Pondicherry</td>
<td>April 2006–April 2008</td>
<td>50</td>
<td>Doxycycline</td>
<td></td>
<td>Fever (&lt;101°F), Eschar, Multiple organ dysfunction, breathlessness</td>
<td></td>
<td>[22]</td>
</tr>
<tr>
<td>Meghalaya</td>
<td>October 2009–January 2010</td>
<td>24</td>
<td>Doxycycline Azithromycin</td>
<td>Chloramphenicol</td>
<td>Weil-Felix ELISA IgM Fever, splenomegaly, eschar, pain abdomen, altered sensorium, vomiting, lymphadenopathy, hepatomegaly</td>
<td></td>
<td>[28]</td>
</tr>
<tr>
<td>Tamilnadu</td>
<td>September 2010–June 2011</td>
<td>52</td>
<td>Doxycycline</td>
<td></td>
<td>ELISA IgM Eschar Fever, hepatomegaly, Splenomegaly, eschar,</td>
<td>13</td>
<td>[26]</td>
</tr>
<tr>
<td>Himachal Pradesh</td>
<td>July 2010–December 2011</td>
<td>253</td>
<td>Doxycycline Azithromycin</td>
<td></td>
<td>High fever, Chills and rigor, myalgia, abdominal pain, lymphadenopathy,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meghalaya</td>
<td>2010–2012</td>
<td>96</td>
<td>Doxycycline Azithromycin</td>
<td></td>
<td>PCR Eschar, Fever, MODS</td>
<td></td>
<td>[27]</td>
</tr>
<tr>
<td>Tamilnadu</td>
<td>2010–2012</td>
<td>95</td>
<td>Doxycycline Azithromycin</td>
<td></td>
<td>PCR Eschar, Fever, MODS</td>
<td></td>
<td>[27]</td>
</tr>
<tr>
<td>Himachal Pradesh</td>
<td>2010–2012</td>
<td>72</td>
<td>Doxycycline Azithromycin</td>
<td></td>
<td>PCR Eschar, Fever, MODS</td>
<td></td>
<td>[27]</td>
</tr>
<tr>
<td>Pondicherry</td>
<td>2011–2012</td>
<td>68</td>
<td>Doxycycline Azithromycin</td>
<td></td>
<td>Weil-Felix, ELISA Eschar Fever, Eschar, meningitis</td>
<td></td>
<td>[33]</td>
</tr>
<tr>
<td>Andhra Pradesh</td>
<td>August 2011–December 2012</td>
<td>176</td>
<td>Doxycycline</td>
<td></td>
<td>Weil-Felix RICA Fever, breathlessness, Renal failure, respiratory failure</td>
<td>8</td>
<td>[34]</td>
</tr>
<tr>
<td>Kerala</td>
<td>2012</td>
<td>2</td>
<td>Doxycycline</td>
<td></td>
<td>Weil-Felix Fever, Myalgia, Headache, Vomiting</td>
<td></td>
<td>[35]</td>
</tr>
<tr>
<td>Rajasthan</td>
<td>October–December 2012</td>
<td>42</td>
<td>Doxycycline</td>
<td></td>
<td>ELISA IgM MODS, renal impairment, ARDS, meningitis</td>
<td>7</td>
<td>[36]</td>
</tr>
<tr>
<td>Puducherry</td>
<td>September 2012–March 2013</td>
<td>28</td>
<td>Doxycycline Azithromycin</td>
<td></td>
<td>Rapid immunochromatographic, ELISA Fever, myalgia, Headache, vomiting, malaise, lymphadenopathy (seen in children only)</td>
<td></td>
<td>[37]</td>
</tr>
<tr>
<td>North East (Assam, Sikkim)</td>
<td>July 2013–December 2014</td>
<td>228</td>
<td>Doxycycline Azithromycin</td>
<td></td>
<td>ELISA IgM PCR &amp; Sequencing Fever, breathlessness, cough, jaundice, abdominal pain, renal failure, diarrhea, rashes</td>
<td></td>
<td>[38]</td>
</tr>
<tr>
<td>Uttarakhand</td>
<td>July–November 2013</td>
<td>69</td>
<td>Doxycycline</td>
<td></td>
<td>ELISA IgM Fever, myalgia, lymphadenopathy, hepatosplenomegaly, rash, headache</td>
<td>1</td>
<td>[39]</td>
</tr>
<tr>
<td>Andhra Pradesh</td>
<td>September 2013–December 2013</td>
<td>258</td>
<td>Tetracycline</td>
<td></td>
<td>IgM, PCR Fever, lymphadenopathy rashes, eschar</td>
<td></td>
<td>[40]</td>
</tr>
<tr>
<td>Odisha</td>
<td>September 2014–February 2015</td>
<td>25</td>
<td>Doxycycline</td>
<td></td>
<td>ELISA-IgM Fever, eschar, Respiratory distress, splenomegaly, Abdominal pain</td>
<td>1</td>
<td>[19]</td>
</tr>
<tr>
<td>Uttar Pradesh</td>
<td>August–October 2016</td>
<td>46</td>
<td>Doxycycline</td>
<td></td>
<td>ELISA Fever Change in mental health</td>
<td></td>
<td>[41]</td>
</tr>
<tr>
<td>North East (Assam, Nagaland, arunachal Pradesh)</td>
<td>2014 December–2016 December</td>
<td>278</td>
<td>Doxycycline</td>
<td></td>
<td>ELISA- IgM PCR Fever, Acute encephalitis syndrome (AES)</td>
<td></td>
<td>[42]</td>
</tr>
</tbody>
</table>

(Contd...)
throughout the rainy season. It has been seen that North India is prone to Scrub typhus disease. Outbreaks were seen in the sub-Himalayan belt; from Jammu to Nagaland, mainly found in the whole Himalaya region ranging from Kashmir to Assam, Eastern and the Western Ghats, and the Vindhya and Satpura ranges in the central part of India. Furthermore, in Maharashtra, Kerala, Karnataka, Tamil nadu, Uttar Pradesh, West Bengal, Himachal Pradesh, and Rajasthan, many cases of scrub typhus have been accounted [17] and considered as one of the most re-growing infections of the present time. Although it is widespread in India, still specific prevalence data are not available. In the past few decades, the Rickettsia disease and scrub typhus have shown exponential growth and expanded in India during the cooler months, especially from July to November [Table 1 and Figure 4] [18].

In IDSP, the epidemic-prone diseases are collected weekly under the national center for disease control. The cases reported to IDSP (https://idsp.nic.in/index4.php?lang=1&level=0&linkid=406&lid=3689) of scrub typhus from 2009 to 2020 are during the rainy season and cooler months which start mainly from June, and gradually, the reports are increasing till November and December. The pick month for scrub typhus is from August to September. Every year, the highest cases and deaths are from Rajasthan, Odisha, and Tamilnadu in different years, but the maximum cases and highest deaths are from the northeast region of India [Table 2 and Figure 5].

### 3.3. Outbreak in Odisha
For a long time, scrub typhus was an unseen case in Odisha; for the 1st time in Odisha, 25 cases of scrub typhus were identified and admitted to the hospital in the pediatric department of Kalinga Institute of Medical Sciences, Bhubaneswar, during post-monsoon months of 2014 [19]. Still, this disease remains unnoticed and underreported in many parts of Odisha, and children end up with complications due to negligence. Most cases are collected from the capital city Bhubaneswar; other than that patients die due to lack of diagnosis and proper treatment [20]. The cases were from rural and forest areas as compared to urban areas. However, the pediatric scrub typhus is very common in Odisha and has an undifferentiated fever and varies with gender and activity. The data on scrub typhus in Odisha are still not sufficient for any conclusion. People should be more careful and concerned regarding their different lifestyle practices [21].

### 4. CLINICAL PRESENTATION AND DIAGNOSIS
Rickettsial infections were recorded from different parts of India [22]. People working outdoors suppose to be more affected than the people staying inside their homes or working in a close area [23]. The outbreak findings were done using serological diagnosis tests such as the WF test followed by ELISA (IgM and
IgG), rapid immunochromatographic test, and molecular bases methods such as PCR-nested PCR. The most common serological test method, ELISA for antibody detection, is widely used for diagnosis due to its wide availability and cost-effectiveness. The IgM antibody was seen at the end of the 1\textsuperscript{st} week at a significant level. IgG antibodies are seen by the end of the 2\textsuperscript{nd} week \cite{15}. In reinfection, IgG antibody appears by the end of the 6\textsuperscript{th} day, but IgM levels vary. Diagnosis of scrub typhus was confirmed when a patient with an acute febrile illness had positive serology for scrub typhus and also nested PCR positive, further strengthened by the presence of eschar \cite{24}.

5. COMPLICATIONS

The patients show symptoms ranging from undifferentiated acute febrile illness of changing seriousness with manifestation such as fever, headache, cough, eschar, myalgia, lymphadenopathy to more dangerous multiple organ failure, and ARDS. High and continuous fever is the most common symptom in patients with temperatures of about 101°F or above for more than 1 week \cite{21}. The incubation period varies from 6 to 21 days, mainly 10 to 12 days \cite{25}. If the patients are left untreated, they develop serious manifestation in 2\textsuperscript{nd} week such as pneumonitis, ARDS, myocarditis, renal impairment, and neurological involvement.

It has been seen that patients were well responded to the antibiotic therapy and not many cases of clinical drug resistance were found. Doxycycline and azithromycin were frequently used as compared to chloramphenicol and tetracycline \cite{26}. The mortality rate of patients with scrub typhus depends on the circulatory load of OT and the type of strains \cite{27}. Deaths are due to delayed identification, improper diagnosis, and drug resistance; such cases have been reported in different states presented in Table 1 \cite{17-45}.

![Figure 4](image1.png) **Figure 4:** The map of India showing the reported cases of scrub typhus by states during 2000–2020.

![Figure 5](image2.png) **Figure 5:** Graphical representation of state-wise outbreak of scrub typhus.
Table 2: Outbreak in India according to IDSP

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
<th>Death</th>
<th>Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>2020</td>
<td>143</td>
<td>8</td>
<td>August and November</td>
</tr>
<tr>
<td>2019</td>
<td>389</td>
<td>14</td>
<td>August and November–December</td>
</tr>
<tr>
<td>2018</td>
<td>628</td>
<td>8</td>
<td>January and August–September</td>
</tr>
<tr>
<td>2017</td>
<td>158</td>
<td>3</td>
<td>June–August</td>
</tr>
<tr>
<td>2016</td>
<td>427</td>
<td>6</td>
<td>April–September</td>
</tr>
<tr>
<td>2015</td>
<td>174</td>
<td>6</td>
<td>August–November</td>
</tr>
<tr>
<td>2014</td>
<td>202</td>
<td>1</td>
<td>July–August and November</td>
</tr>
<tr>
<td>2013</td>
<td>381</td>
<td>8</td>
<td>July–September</td>
</tr>
<tr>
<td>2012</td>
<td>276</td>
<td>8</td>
<td>August–November</td>
</tr>
<tr>
<td>2011</td>
<td>41</td>
<td>3</td>
<td>September</td>
</tr>
<tr>
<td>2010</td>
<td>4</td>
<td>1</td>
<td>October</td>
</tr>
</tbody>
</table>

6. CONCLUSION

Our study showed that OT infection was endemic to a specific area, but it is spreading worldwide and can cause outbreaks and deaths in the next few years if it remains the same. Higher variability among the strains makes the diagnosis difficult. Although doxycycline and azithromycin are effective antibiotics for the treatment of this disease, the diagnosis of scrub typhus is excruciating in India due to its varied clinical presentation, absence of eschar in many patients, and shortage of gold standard tests. Still, data from only these states are not sufficient to draw any valid conclusion about the seriousness of these agents.

7. FUTURE PROSPECTIVE

Till last decade, the disease was epidemic to specific areas. However, in this study, it has been seen that the disease is spreading throughout the globe, but still it is neglected and underreported. Our study will give insight to the researchers to monitor and implement strategies to improve the surveillance system. It will help to understand the severity and complications of scrub typhus and the need for a proper therapeutic drug for children. As well as, it will show the necessity of vaccine development. From a global survey, the genetic diversity can be studied further to identify the most virulent strain from different places which will be the key factor in vaccine development.

8. ACKNOWLEDGMENTS

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9. AUTHORS CONTRIBUTION

All authors made a substantial contribution to the conception, design, and acquisition of data took part in drafting the article or revising it critically for important intellectual content. The authors agreed to submit the manuscript to the esteemed journal, gave the final version of the published, and decided to be accountable for all aspects of the work.

10. CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

11. ETHICAL APPROVALS

As it is a review article, ethical approval is not required.

12. FUNDING SOURCES

There is no funding to report.

13. DATA AVAILABILITY

All data generated and analyzed are included within this research article.

14. PUBLISHER’S NOTE

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