Risk Factors for Acquiring Scrub Typhus among Children in Deoria and Gorakhpur Districts, Uttar Pradesh, India, 2017

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ST, caused by the bacterium Orientia tsutsugamushi, is transmitted by the bite of trombiculid mites, which live in moist soil covered with vegetation (6). Several risk factors, including certain household characteristics, work-related practices, and behaviors, have been identified among adult ST patients (7–11). Household characteristics include location of the house near a grassland, vegetable field, or ditch; presence of mud floors; piled weeds inside the house; and scrub vegetation in the vicinity (7). Work-related practices include working in vegetable fields or hilly areas and working in short sleeves or with bare hands (8). Certain behaviors such as lying on grass and squatting to defecate or urinate also are associated with ST (8,10,11). Because these risk factors are region specific, we conducted an exploratory case-control study among children in Gorakhpur and Deoria districts of Uttar Pradesh to identify factors associated with ST infection.

The Study

We conducted AFI surveillance in public health facilities in Deoria (n = 5) and Gorakhpur (n = 3) districts during October 3–November 11, 2017, a period coinciding with AES outbreaks in Gorakhpur district. We enrolled children 2–15 years of age with a >3-day history of fever, from whom we collected 2 mL of blood after obtaining written informed consent from parents and assent from children 7–15 years of age. We screened serum samples for IgM and IgG against O. tsutsugamushi by using ELISA kits (Scrub Typhus Detect; InBios International Inc., Seattle, WA, USA). For our study, an optical density value >0.5 indicated IgM positivity. This cutoff has 93% sensitivity and 91% specificity for ST diagnosis (12). An optical density value <0.5 indicated IgM and IgG negativity.

Febrile children who were positive for O. tsutsugamushi IgM were considered case-patients, whereas patients who were seronegative for IgM and IgG were considered controls. Case-patients and controls and their parents or guardians were interviewed in their houses by using a pretested structured questionnaire to collect information on sociodemographics, household characteristics, behaviors, and environmental exposures during the 2 weeks before fever onset. Interviewers were blinded to the case-patient or control status of children except during the first week of study.

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Studies group members are listed at the end of this article.

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We calculated crude odds ratios (ORs) and 95% CIs associated with different exposures. We included variables with p value ≤0.2 in univariate analysis in a stepwise backward elimination model to identify variables for inclusion in the final unconditional multiple logistic regression model by using Stata 13 (StataCorp LLC, College Station, TX, USA).

We recruited 819 AFI patients, of whom 155 (18.9%) had O. tsutsugamushi IgM (case-patients) and 409 (49.9%) were seronegative (controls) (online Technical Appendix Table 1, https://wwwnc.cdc.gov/EID/article/24/12/18-0695-Techapp1.pdf). We excluded 255 (31.1%) patients who had only O. tsutsugamushi IgG. We interviewed all case-patients and 406 controls. All case-patients and controls were from rural areas. The mean age of case-patients was higher than controls (7.0 vs. 6.3 years; p = 0.018); 39% of case-patients and 51% controls were ≤5 years of age. A higher proportion of case-patients than controls were from households that owned agricultural land (83% vs. 73%; p = 0.017) (Table 1).

Aside from fever, clinical signs and symptoms among patients varied (online Technical Appendix Table 2). Five ST patients, who did not receive doxycycline/azithromycin, had onset of neurologic manifestations and required hospitalization; they recovered after administration of azithromycin.

Univariate analysis showed that ST patients were more likely than controls to live in houses located within or adjoining fields, houses with unpaved surroundings with mud or unkempt grass, and mud-floored houses (Table 2). In addition, a higher proportion of case-patients lived in households that used wood or cow dung for cooking and stored this fuel indoors. Compared with controls, children with ST were more likely to have played in agricultural fields, defecated in agricultural fields, bathed in a river or stream, carried grass bundles on their heads, handled fodder for cattle, or visited or accompanied parents to an agricultural field during the 2 weeks before fever onset (Table 2).

Multivariable analysis showed that children residing in houses within or adjoining fields (adjusted OR [aOR] 1.56, 95% CI 1.02–2.38) and that stored firewood indoors (aOR 1.61, 95% CI 1.06–2.45) had higher odds of acquiring ST. Open defecation (aOR 2.0, 95% CI 1.18–3.39), playing in (aOR 5.2, 95% CI 1.92–14.2) or visiting (aOR 1.65, 95% CI 1.07–2.52) agricultural fields, and handling cattle fodder (aOR 2.05, 95% CI 1.13–3.70) also were associated with ST (Table 2).

Conclusions

In Gorakhpur and Deoria districts, recent exposure to the outdoor environment, either while defecating or playing in agricultural fields, as well as visiting agricultural fields, storing firewood indoors, and handling fodder for cattle were associated with higher risk for acquiring ST among children. Of these risk factors, defecation in the agricultural field was the most common exposure at the population level. The observed association of ST and defecation in fields is consistent with the findings from an ST outbreak in Manipur, India, where persons who defecated or urinated in the jungle or bushy areas were found to be at higher risk for ST (11). In Gorakhpur and Deoria districts, about one third of the study population had toilets, a finding consistent with the 2015 national level survey, which indicated that 29.5% of the households in rural Uttar Pradesh had sanitary toilets and 27.3% of households that had access to toilets were using them (http://www.mdws.gov.in/sites/default/files/Swachh%20Report%20Eng.PDF). Efforts to prevent ST in the region therefore also need to focus on constructing household and community toilets, as well as behavior change communication about avoiding open defecation in the fields. In addition, storing firewood and fodder indoors attracts rodents that can harbor mites. Mites present on the firewood and fodder collected from fields might expose children to mite bites during storage or handling of the cattle fodder.

Table 1. Sociodemographic details of cases and controls, Deoria and Gorakhpur districts, Uttar Pradesh, 2017

<table>
<thead>
<tr>
<th>Variables</th>
<th>% Case-patients, n = 155</th>
<th>% Controls, n = 406</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–5</td>
<td>39</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>6–10</td>
<td>46</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>11–15</td>
<td>14</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Mean age, y (SD)</td>
<td>7.0 (3.2)</td>
<td>6.3 (3.5)</td>
<td>0.0176</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>61</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>39</td>
<td>39</td>
<td>0.882</td>
</tr>
<tr>
<td>District</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deoria</td>
<td>56</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Gorakhpur</td>
<td>44</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Religion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hindu</td>
<td>92</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>11</td>
<td>0.348</td>
</tr>
<tr>
<td>Median duration of fever, d (IQR)</td>
<td>7 (4.5–10.0)</td>
<td>5 (4–8)</td>
<td></td>
</tr>
<tr>
<td>Household owns agricultural land</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>17</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>83</td>
<td>73</td>
<td>0.017</td>
</tr>
</tbody>
</table>

*Values are percentages unless otherwise indicated. IQR, interquartile range.
Our study had limitations. First, although OT IgM is detectable as early as 4 days after fever onset (13), some ST patients in our study might have been negative for IgM and hence misclassified as controls. However, such nondifferential misclassification is likely to underestimate the actual association. Further, the median duration of fever was 7 days (interquartile range 4.5–10.0 days) among case-patients and 5 days (interquartile range 4–8 days) among controls (Table 1), indicating minimal possibility of such misclassification. Some controls might have been misclassified as case-patients because of persistence of IgM from previous infection (14). However, this possibility is less likely considering that IgM peaks by 4 weeks of infection and declines rapidly thereafter (15). Second, our control-patients were AFI patients from healthcare facilities and not healthy children from the general population. Nevertheless, the behaviors of children visiting healthcare facilities before their febrile illness and children from the general population are less likely to be different.

For prevention of ST among children in Gorakhpur and Deoria districts, communication messages should focus on changing behaviors such as defecating or playing

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>% Cases, n = 155</th>
<th>% Controls, n = 406</th>
<th>OR (95% CI)</th>
<th>p value</th>
<th>aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location of house within or adjoining field</td>
<td>67</td>
<td>52</td>
<td>1.86 (1.26–2.74)</td>
<td>0.002</td>
<td>1.56 (1.02–2.38)</td>
</tr>
<tr>
<td>Mud or grassy approach road to house</td>
<td>41</td>
<td>36</td>
<td>1.21 (0.82–1.76)</td>
<td>0.335</td>
<td></td>
</tr>
<tr>
<td>Mud or grassy pavement in front of house</td>
<td>81</td>
<td>71</td>
<td>1.73 (1.09–2.74)</td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>Mud house floor</td>
<td>72</td>
<td>59</td>
<td>1.88 (1.25–2.82)</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Presence of waterbody within 100 m of house</td>
<td>61</td>
<td>51</td>
<td>1.52 (1.04–2.23)</td>
<td>0.029</td>
<td></td>
</tr>
<tr>
<td>Location of toilet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No toilet</td>
<td>76</td>
<td>57</td>
<td>2.76 (1.59–4.78)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Within house</td>
<td>12</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outside house</td>
<td>12</td>
<td>18</td>
<td>1.36 (0.66–2.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wood or dung fuel</td>
<td>55</td>
<td>34</td>
<td>2.32 (1.59–3.39)</td>
<td>&lt;0.01</td>
<td>1.61 (1.06–2.45)</td>
</tr>
<tr>
<td>Storage of fuel (wood or dung) inside house or veranda</td>
<td>53</td>
<td>34</td>
<td>2.16 (1.48–3.14)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Food waste given to cattle or disposed in common place</td>
<td>30</td>
<td>25</td>
<td>1.27 (0.84–1.92)</td>
<td>0.248</td>
<td></td>
</tr>
<tr>
<td>Spotted rats inside house, daily</td>
<td>80</td>
<td>79</td>
<td>1.09 (0.68–1.73)</td>
<td>0.731</td>
<td></td>
</tr>
<tr>
<td>Spotted rats outside house, daily</td>
<td>43</td>
<td>48</td>
<td>0.81 (0.56–1.17)</td>
<td>0.263</td>
<td></td>
</tr>
<tr>
<td>Presence of scrub vegetation around house</td>
<td>79</td>
<td>73</td>
<td>1.38 (0.88–2.17)</td>
<td>0.154</td>
<td></td>
</tr>
<tr>
<td>Storage of wet food produce inside house or veranda</td>
<td>37</td>
<td>25</td>
<td>1.78 (1.20–2.65)</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Storage of dried food produce inside house or veranda</td>
<td>83</td>
<td>72</td>
<td>1.87 (1.17–2.99)</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Livestock kept inside house or veranda</td>
<td>32</td>
<td>22</td>
<td>1.65 (1.09–2.48)</td>
<td>0.017</td>
<td></td>
</tr>
<tr>
<td>Fodder for livestock stored inside house or veranda</td>
<td>32</td>
<td>22</td>
<td>1.49 (0.99–2.24)</td>
<td>0.055</td>
<td></td>
</tr>
<tr>
<td>Place of drying clothes; bushes, ground, fence, or roof</td>
<td>30</td>
<td>25</td>
<td>1.30 (0.86–1.95)</td>
<td>0.213</td>
<td></td>
</tr>
<tr>
<td>Usual clothing at home for lower body; fully covered</td>
<td>24</td>
<td>21</td>
<td>1.18 (0.76–1.83)</td>
<td>0.451</td>
<td></td>
</tr>
<tr>
<td>Usual clothing at home for upper body; fully covered</td>
<td>8</td>
<td>11</td>
<td>0.71 (0.36–1.38)</td>
<td>0.308</td>
<td></td>
</tr>
<tr>
<td>Usual clothing for school for lower body; fully covered</td>
<td>48</td>
<td>42</td>
<td>1.14 (0.74–1.76)</td>
<td>0.543</td>
<td></td>
</tr>
<tr>
<td>Usual clothing for school for upper body; fully covered</td>
<td>51</td>
<td>43</td>
<td>1.27 (0.82–1.97)</td>
<td>0.283</td>
<td></td>
</tr>
<tr>
<td>Usual clothing during playing for lower body; fully covered</td>
<td>21</td>
<td>17</td>
<td>1.26 (0.79–1.99)</td>
<td>0.334</td>
<td></td>
</tr>
<tr>
<td>Usual clothing during playing for upper body; fully covered</td>
<td>8</td>
<td>8</td>
<td>1.0 (0.51–1.97)</td>
<td>0.980</td>
<td></td>
</tr>
<tr>
<td>Using clothing while sleeping for lower body; fully covered</td>
<td>19</td>
<td>17</td>
<td>1.1 (0.68–1.78)</td>
<td>0.692</td>
<td></td>
</tr>
<tr>
<td>Using clothing while sleeping for upper body; fully covered</td>
<td>7</td>
<td>7</td>
<td>0.89 (0.42–1.88)</td>
<td>0.763</td>
<td></td>
</tr>
<tr>
<td>Change of clothes before sleep; never or sometimes</td>
<td>86</td>
<td>84</td>
<td>1.24 (0.73–2.11)</td>
<td>0.423</td>
<td></td>
</tr>
<tr>
<td>Do not wear footwear during playing</td>
<td>73</td>
<td>65</td>
<td>1.25 (0.62–1.89)</td>
<td>0.298</td>
<td></td>
</tr>
<tr>
<td>Do not wear footwear while going to school</td>
<td>6</td>
<td>4</td>
<td>1.37 (0.59–3.19)</td>
<td>0.465</td>
<td></td>
</tr>
<tr>
<td>Place of play in 2 wks before illness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indoor</td>
<td>5</td>
<td>17</td>
<td>1</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Agricultural fields</td>
<td>77</td>
<td>76</td>
<td>3.77 (1.68–8.45)</td>
<td>2.68</td>
<td>(1.15–6.27)</td>
</tr>
<tr>
<td>Floor as usual place of sleeping</td>
<td>18</td>
<td>7</td>
<td>9.38 (3.68–23.90)</td>
<td>5.20</td>
<td>(1.92–14.15)</td>
</tr>
<tr>
<td>Practice of washing after playing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usually takes bath</td>
<td>13</td>
<td>14</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usually washes hands or feet</td>
<td>59</td>
<td>60</td>
<td>1.05 (0.60–1.84)</td>
<td>0.769</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>28</td>
<td>25</td>
<td>1.21 (0.65–2.25)</td>
<td>0.225</td>
<td></td>
</tr>
<tr>
<td>Floor as usual place of sleeping</td>
<td>14</td>
<td>11</td>
<td>1.41 (0.81–2.44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Place of defecation in 2 wks before illness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Around house</td>
<td>7</td>
<td>14</td>
<td>1.12 (0.52–2.42)</td>
<td>0.001</td>
<td>0.93 (0.41–2.12)</td>
</tr>
<tr>
<td>Field</td>
<td>76</td>
<td>48</td>
<td>3.62 (2.25–5.82)</td>
<td>2.00</td>
<td>(1.18–3.39)</td>
</tr>
<tr>
<td>Toilet</td>
<td>17</td>
<td>38</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Early morning defecation</td>
<td>30</td>
<td>25</td>
<td>1.28 (0.85–1.93)</td>
<td>0.237</td>
<td></td>
</tr>
<tr>
<td>Swam or bathed in river or stream in 2 wks before illness</td>
<td>11</td>
<td>5</td>
<td>2.37 (1.21–4.67)</td>
<td>0.012</td>
<td>1.74 (0.80–3.77)</td>
</tr>
<tr>
<td>Visited field in 2 wks before illness</td>
<td>61</td>
<td>39</td>
<td>2.49 (1.70–3.63)</td>
<td>&lt;0.01</td>
<td>1.65 (1.07–2.52)</td>
</tr>
<tr>
<td>Carried bundle of grass over head in 2 wks before illness</td>
<td>14</td>
<td>6</td>
<td>2.29 (1.25–4.21)</td>
<td>&lt;0.01</td>
<td>0.75 (0.35–1.61)</td>
</tr>
<tr>
<td>Handled cattle fodder in 2 wks before illness</td>
<td>25</td>
<td>9</td>
<td>3.46 (2.1–5.69)</td>
<td>&lt;0.01</td>
<td>2.05 (1.13–3.70)</td>
</tr>
</tbody>
</table>

*aOR, adjusted odds ratio; OR, odds ratio.*
in agricultural fields and unnecessary visits to agricultural fields. Onset of central nervous system manifestations among untreated ST patients underscores the importance of early administration of doxycycline/azithromycin to ST patients in Gorakhpur and Deoria districts to prevent progression to AES.

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The Institutional Ethics Committee of the Indian Council of Medical Research National Institute of Epidemiology approved the study protocol. The CDC Center for Global Health Associate Director for Science reviewed the protocol and determined that CDC was not engaged.

About the Author
Dr. Thangaraj currently works as a scientist with the Indian Council of Medical Research–National Institute of Epidemiology in Chennai, India. His primary research interests include the epidemiology of acute encephalitis syndrome.

References

Address for correspondence: Kayla Laserson, US Centers for Disease Control and Prevention, American Embassy, Chanakypuri, New Delhi 110021, India; email: klaserson@cdc.gov
Risk Factors for Acquisition of Scrub Typhus among Children in Deoria and Gorakhpur Districts, Uttar Pradesh, India, 2017

Technical Appendix

Technical Appendix Table 1. Details of AFI patients enrolled, tested for IgM and IgG antibodies against *O. tsutsugamushi* (OT), and interviewed.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Gorakhpur</th>
<th>Deoria</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFI patients enumerated</td>
<td>372</td>
<td>447</td>
<td>819</td>
</tr>
<tr>
<td>Positive for IgM antibodies against OT (cases), no. (%)</td>
<td>68 (18.3)</td>
<td>87 (19.5)</td>
<td>155</td>
</tr>
<tr>
<td>Negative for IgM and IgG against OT (controls), no. (%)</td>
<td>187 (50.3)</td>
<td>222 (49.7)</td>
<td>409</td>
</tr>
<tr>
<td>Positive for IgG antibodies against OT alone</td>
<td>117</td>
<td>138</td>
<td>255</td>
</tr>
<tr>
<td>Total cases and controls</td>
<td>255</td>
<td>309</td>
<td>564</td>
</tr>
<tr>
<td>Cases interviewed</td>
<td>68</td>
<td>87</td>
<td>155</td>
</tr>
<tr>
<td>Controls interviewed</td>
<td>184</td>
<td>222</td>
<td>406</td>
</tr>
<tr>
<td>Cases and controls interviewed</td>
<td>252</td>
<td>309</td>
<td>561</td>
</tr>
</tbody>
</table>

Technical Appendix Table 2. Clinical features of cases and controls, Gorakhpur and Deoria districts, 2017

<table>
<thead>
<tr>
<th>Symptom or sign</th>
<th>% Cases, n = 155</th>
<th>% Controls, n = 406</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>54</td>
<td>59</td>
<td>0.16</td>
</tr>
<tr>
<td>vomiting</td>
<td>34</td>
<td>26</td>
<td>0.05</td>
</tr>
<tr>
<td>Loose motion</td>
<td>15</td>
<td>12</td>
<td>0.19</td>
</tr>
<tr>
<td>Nasal discharge</td>
<td>20</td>
<td>36</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Skin rash</td>
<td>8</td>
<td>10</td>
<td>0.22</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>27</td>
<td>22</td>
<td>0.11</td>
</tr>
<tr>
<td>cough</td>
<td>45</td>
<td>58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pain in limbs</td>
<td>20</td>
<td>24</td>
<td>0.14</td>
</tr>
<tr>
<td>Dehydration</td>
<td>14</td>
<td>9</td>
<td>0.04</td>
</tr>
<tr>
<td>Periorbital edema</td>
<td>8</td>
<td>7</td>
<td>0.44</td>
</tr>
<tr>
<td>Conjunctival congestion</td>
<td>10</td>
<td>10</td>
<td>0.44</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>6</td>
<td>3</td>
<td>0.04</td>
</tr>
<tr>
<td>Icterus</td>
<td>15</td>
<td>17</td>
<td>0.23</td>
</tr>
<tr>
<td>Odema</td>
<td>1</td>
<td>3</td>
<td>0.16</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>15</td>
<td>10</td>
<td>0.03</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>4</td>
<td>2</td>
<td>0.18</td>
</tr>
<tr>
<td>Skin rash</td>
<td>3</td>
<td>4</td>
<td>0.35</td>
</tr>
<tr>
<td>Eschar</td>
<td>2</td>
<td>1</td>
<td>0.11</td>
</tr>
</tbody>
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