Multidrug-Resistant Typhoid Fever With Neurologic Findings on the Malawi-Mozambique Border

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(See the Major Article by Neil et al, on pages 1091–9 and the Editorial Commentary by Crump, on pages 1107–9.)

Background. Salmonella enterica serovar Typhi causes an estimated 22 million cases of typhoid fever and 216 000 deaths annually worldwide. We investigated an outbreak of unexplained febrile illnesses with neurologic findings, determined to be typhoid fever, along the Malawi–Mozambique border.

Methods. The investigation included active surveillance, interviews, examinations of ill and convalescent persons, medical chart reviews, and laboratory testing. Classification as a suspected case required fever and $1$ other finding (eg, headache or abdominal pain); a probable case required fever and a positive rapid immunoglobulin M antibody test for typhoid (TUBEX TF); a confirmed case required isolation of Salmonella Typhi from blood or stool. Isolates underwent antimicrobial susceptibility testing and subtyping by pulsed-field gel electrophoresis (PFGE).

Results. We identified 303 cases from 18 villages with onset during March–November 2009; 214 were suspected, 43 were probable, and 46 were confirmed cases. Forty patients presented with focal neurologic abnormalities, including a constellation of upper motor neuron signs ($n = 19$), ataxia ($n = 22$), and parkinsonism ($n = 8$). Eleven patients died. All 42 isolates tested were resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole; 4 were also resistant to nalidixic acid. Thirty-five of 42 isolates were indistinguishable by PFGE.

Conclusions. The unusual neurologic manifestations posed a diagnostic challenge that was resolved through rapid typhoid antibody testing in the field and subsequent blood culture confirmation in the Malawi national reference laboratory. Extending laboratory diagnostic capacity, including blood culture, to populations at risk for typhoid fever in Africa will improve outbreak detection, response, and clinical treatment.

Typhoid fever is a systemic illness that often presents with fever, headache, and abdominal pain. The etiologic agent is Salmonella enterica serovar Typhi (Salmonella Typhi), which is transmitted by the fecal-oral route. Multiple severe complications can occur, including intestinal hemorrhage, intestinal perforation, hepatitis, pneumonia, abscess, and neuropsychiatric abnormalities [1]. An estimated 22 million cases and 216 000 deaths occur worldwide each year [2].

Typhoid fever is endemic in Malawi and Mozambique [3–7]. Both are considered medium-incidence countries with estimated rates of 10–100 per 100 000 persons per year [2]. Multidrug-resistant strains of Salmonella Typhi, defined as resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole, have
been identified in reports from Ghana [8], Egypt [9], Kenya [10], Nigeria [11], Democratic Republic of the Congo [12], and South Africa [13]. Previous reports from Malawi and Mozambique have described only fully susceptible strains [4, 6, 14, 15].

We investigated an outbreak of unexplained febrile illnesses with neurologic findings, later determined to be typhoid fever, in villages along the Malawi–Mozambique border. The outbreak was detected in June 2009 when Neno District health personnel in Malawi identified hospitalized patients from the region with a distinctive constellation of findings including fever, headache, confusion, inability to walk, dysarthria, and hyperreflexia. A tendency to hold limbs in a flexed posture, neck stiffness, ataxia, clonus, and convulsions were also described in certain patients. Gastrointestinal complaints reportedly were present in a minority of patients but were not prominent.

Personnel from the Ministry of Health in Malawi and the Ministério da Saúde in Mozambique conducted the investigation with representatives from the Atlanta-based Centers for Disease Control and Prevention (CDC, an agency of the US Department of Health and Human Services) and CDC’s office of the Global AIDS Program, Malawi. The objectives were to characterize the outbreak, determine the etiology, and recommend prevention and control measures.

MATERIALS AND METHODS

Outbreak Area
The affected villages are located in a remote area of Neno District, Malawi, and Tsangano District, Mozambique, at an altitude of approximately 1600 m. The international border runs through the area (Figure 1). Nsambe Health Centre in Malawi, which is located approximately 8.5 km from the affected villages, serves the health needs of the population; Neno District Hospital is 1 hour away by motor vehicle.

Epidemiologic Investigation
Beginning in June 2009, activities included structured interviews with recovered or convalescing persons in affected villages; interviews, chart reviews, and examinations of acutely ill patients; and review of medical records of patients admitted to Neno District Hospital with a clinically compatible illness. Two village-based clinics, 1 in Malawi and 1 in Mozambique, were established. Neno District outbreak response personnel conducted active surveillance by periodically visiting affected villages to identify possible cases and by prospectively documenting persons presenting at Nsambe Health Centre and the village clinics with signs and symptoms compatible with the illness under investigation. District personnel in Malawi and Mozambique worked together to maintain a unified database of cases.

Laboratory Investigation
In July and August 2009 clinical samples of serum, cerebrospinal fluid, nasopharyngeal swabs, rectal swabs, stool, and urine from acutely ill and convalescent patients were subjected to testing at CDC laboratories, including polymerase chain reaction (PCR) for neuroinvasive and other pathogens (e.g., enteroviruses, arboviruses, and herpesviruses). Serologic testing was performed for viral pathogens as appropriate. Additional testing included viral culture, random primer PCR, and 16S ribosomal RNA sequencing. Autopsy specimens from 1 decedent, including central nervous system tissue, meninges, lung, spleen, kidney, and liver, were examined histologically.

Because no capacity exists to perform blood or stool cultures locally, a rapid antibody-based diagnostic kit for *Salmonella* Typhi (TUBEX TF, IDL Biotech, Bromma, Sweden) was used in the field starting in August 2009 for preliminary serologic testing, following the product insert instructions. The same test was repeated at CDC for some specimens; if results were discordant the CDC result was used for purposes of case classification. After
capacity to collect and transport specimens to reference laboratories was established, confirmatory blood and stool cultures were performed at the Community Health Study Unit, Malawi’s national reference laboratory. Blood specimens were inoculated to commercially prepared BD BACTEC or BBL Septi-Check blood culture bottles according to manufacturer’s specifications for manual subculture (BD, Franklin Lakes, New Jersey). When available, stool and rectal swab specimens were collected for culture. All specimens were transported to the reference laboratory at times ranging from immediately after collection to 1 week, depending on availability of transportation. Specimens were subcultured according to CDC standard protocols for isolation of *Salmonella* Typhi from blood and stool specimens [16]. Isolates were biochemically confirmed to be *Salmonella* and serotyped as Typhi by using specific antisera for Vi, O9, and H diarrheal illness (abdominal pain, vomiting, diarrhea, or constipation), joint pain, muscle pain, headache, neck pain or stiffness, difficulty walking or talking, arms held in flexion, or mental status changes, with no alternative explanation for the illness. A probable case required fever and a positive rapid typhoid test (TUBEX TF), and a confirmed case required either a blood culture yielding *Salmonella* Typhi, or fever and a stool culture yielding *Salmonella* Typhi. Patients with positive malaria smears were counted as cases only if there was no response to an initial course of antimalarial medication.

A neurologic case was defined as illness in a patient with objective, focal neurologic findings documented in the medical chart or elicited on examination. The presence of altered mental status or dysarthria did not satisfy the definition of a neurologic case because in this setting, these findings could not reliably differentiate true neurologic deficits from symptoms referable to severe systemic illness. Similarly, reports of hearing loss or vertigo did not satisfy the definition of a neurologic case because of the necessarily subjective nature of the complaints in this setting.

**Case Definition**

We defined a suspected case of typhoid fever as illness in a resident of Neno District, Malawi, or Tsangano District, Mozambique, with onset on or after 1 March 2009, who presented with fever (subjective or with a documented temperature \(\geq 38^\circ\text{C}\)), and at least 1 of the following signs and symptoms: gastrointestinal illness (abdominal pain, vomiting, diarrhea, or constipation), joint pain, muscle pain, headache, neck pain or stiffness, difficulty walking or talking, arms held in flexion, or mental status changes, with no alternative explanation for the illness. A probable case required fever and a positive rapid typhoid test (TUBEX TF), and a confirmed case required either a blood culture yielding *Salmonella* Typhi, or fever and a stool culture yielding *Salmonella* Typhi. Patients with positive malaria smears were counted as cases only if there was no response to an initial course of antimalarial medication.

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**Water Source Assessment**

Water samples from unprotected springs in 2 villages and from a semiprotected spring in 1 village, all of which were used as drinking water sources, were tested for total coliform bacteria and *Escherichia coli* by using presence-absence broth with 4-methylumbelliferyl-\(\beta\)-d-glucuronide (Hach Company, Loveland, Colorado).

**Ethics**

This investigation was initiated and conducted in response to an illness outbreak. Human subjects research designees at CDC determined that the activities constituted public health response and program evaluation rather than research. Verbal consent for specimen collection was obtained from patients or guardians.

**RESULTS**

**Epidemiologic Investigation**

A total of 303 persons with illness onset during 1 March–13 November 2009 met the case definition; 214 suspected, 43 probable, and 46 confirmed cases were identified. The outbreak appeared to peak in September 2009 (Figure 2). The median age of patients was 21 years (range, 1–81 years); 125 of 299 (42%) patients with known age were aged 5–19 years. Overall, 166 of 299 (56%) patients in whom sex was known were female; females outnumbered males in all but 2 age groups (Figure 3). Eighty-one persons (27%) were hospitalized, and 11 died (case fatality rate: 4%). Clinical data for the 303 cases are displayed in Table 1.

Forty persons (13%) had objective, focal neurologic findings documented in the medical chart or elicited on examination; 27 (68%) of these patients were hospitalized; 5 (13%) died. An additional 27 persons had altered mental status but no focal neurologic findings. Twenty-six of the 40 persons with focal neurologic signs met criteria for a suspected case, 10 for a probable case, and 4 for a confirmed case. Patients with focal neurologic findings did not differ from those without neurologic findings by age \( (P = .29) \) or sex \( (P = .68) \). The median age of patients with neurologic findings was 18 years (range, 3–57 years), and 53% were female. Neurologic signs and symptoms among all hospitalized patients are displayed in Table 2.

Nineteen of the 40 persons (48%) with objective neurologic manifestations had a constellation of findings indicative of upper motor neuron dysfunction, defined as documentation of at least 2 of the following findings: limb hyperreflexia, spasticity, presence of Babinski sign, or sustained ankle clonus. Other notable neurologic features included ataxia (22, 55%) and features of parkinsonism (gait instability, global slowness of movement, facial masking) (8, 20%). Subjective hearing loss (9, 23%) and vertigo (2, 5%) were noted among the 40 patients with objective, focal neurologic findings and also among patients without objective findings (Table 1). Magnetic resonance imaging of the brain and spinal cord was performed on 3 persons with focal neurologic findings at the time of the
No focal abnormalities were present, although all 3 demonstrated generalized cortical and cerebellar atrophy disproportionate to age.

**Laboratory Investigation**

A total of 412 individual tests for viral, bacterial, parasitic, and rickettsial pathogens were performed on specimens taken at the beginning of the investigation from persons meeting the case definition (Supplementary Table). All pathogen-specific PCR, random-primer PCR, and 16S ribosomal RNA sequencing results were negative for potential pathogens. Serologic testing was negative for acute infection with all viruses tested. All viral cultures were negative. Autopsy specimens from a decedent who had focal neurologic findings revealed only patchy necrosis in the liver; central nervous system samples showed no significant histopathologic changes.

Seventeen patients (8 neurologic) underwent cerebrospinal fluid examination; all parameters tested were normal. Human immunodeficiency virus serologic testing was performed on 14 patients (5 neurologic); serology was positive in 1 non-neurologic patient. Malaria smears were performed in 44 persons (14 neurologic); 8 (18%) were positive (3 neurologic).

**Table 1. Frequency of Selected Clinical Findings Among Patients With Typhoid Fever (N = 303), Neno District, Malawi, and Tsangano District, Mozambique, 2009**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
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<tbody>
<tr>
<td>Muscle or joint pain</td>
<td>229 (76)</td>
</tr>
<tr>
<td>Headache</td>
<td>221 (73)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>119 (39)</td>
</tr>
<tr>
<td>Neck pain or stiffness</td>
<td>117 (39)</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>70 (23)</td>
</tr>
<tr>
<td>Cough</td>
<td>64 (21)</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>43 (14)</td>
</tr>
<tr>
<td>Objective neurologic signs</td>
<td>40 (13)</td>
</tr>
<tr>
<td>Hearing loss (subjective)</td>
<td>28 (9)</td>
</tr>
<tr>
<td>Jaw stiffness</td>
<td>19 (6)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>15 (5)</td>
</tr>
<tr>
<td>Intestinal perforation</td>
<td>4 (1)</td>
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</table>
Table 2. Neurologic Signs and Symptoms Among Hospitalized Typhoid Fever Patients (n = 81), Neno District, Malawi, and Tsangano District, Mozambique, 2009

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
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<tbody>
<tr>
<td>Dysarthria</td>
<td>44 (54)</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>33 (41)</td>
</tr>
<tr>
<td>Upper motor neuron sign(s)</td>
<td>28 (35)</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td>24 (30)</td>
</tr>
<tr>
<td>Clonus</td>
<td>18 (22)</td>
</tr>
<tr>
<td>Spasticity</td>
<td>12 (15)</td>
</tr>
<tr>
<td>Babinski sign present</td>
<td>5 (6)</td>
</tr>
<tr>
<td>≥2 of these signs</td>
<td>19 (23)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>22 (27)</td>
</tr>
<tr>
<td>Hearing loss (subjective)</td>
<td>19 (23)</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>8 (10)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Tremor</td>
<td>4 (5)</td>
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</table>

One hundred fifty-nine TUBEX TF serologic tests were performed on 129 specimens from 124 persons meeting the case definition (21 confirmed, 43 probable, 60 suspect). At least 1 positive result occurred in 51 (41%) of the cases tested (8 confirmed, 43 probable). Among specimens taken ≥3 days after illness onset, 48 of 88 (55%) persons had at least 1 positive result, and among specimens taken ≥7 days after illness onset, 41 of 66 (62%) persons had at least 1 positive result.

Results were available for 112 blood cultures from 108 persons who met the case definition; Salmonella Typhi was identified in 46 blood cultures (41%) from 44 persons (41%). Three (60%) of 5 stool cultures yielded Salmonella Typhi; 1 of these was from a person who also had documented Salmonella Typhi bacteremia.

Among the 40 patients with focal neurologic findings, TUBEX TF serologic tests were performed on 17 specimens from 14 persons; 11 persons (79%) (including 1 person with a positive blood culture) had at least 1 positive result. Six blood cultures were performed on 5 patients with focal neurologic findings; Salmonella Typhi was identified in specimens from 3 persons (60%). Additionally, Salmonella Typhi was identified in a stool culture from 1 patient.

Antimicrobial susceptibility testing was performed on 42 isolates from patients meeting the case definition; all were resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole, and 4 were also resistant to nalidixic acid (minimum inhibitory concentration [MIC] ≥32). The 4 nalidixic acid–resistant isolates demonstrated decreased susceptibility to ciprofloxacin, with MIC = 0.25, compared with MIC <0.015 for all other isolates. PFGE patterns of 35 of the 42 (83%) isolates tested were indistinguishable with 2 restriction enzymes (XbaI and BlnI) [18]. Four of the remaining isolates were distinguished from the predominant pattern only by the second enzyme (BlnI); 2 differed by the first enzyme (XbaI) but not the second; 1 differed by both enzymes.

Water Source Assessment
Testing of 3 village springs used as drinking water sources detected coliform bacteria and E. coli, markers of fecal contamination.

DISCUSSION
This investigation documented an extended outbreak of multidrug-resistant typhoid fever in rural communities along the Malawi–Mozambique border in which severe neurologic deficits were a prominent feature. The prominence of these neurologic findings during the early stages of the outbreak initially obscured the diagnosis of typhoid fever and led investigators to consider other potential etiologies.

Neuropsychiatric abnormalities are recognized complications of typhoid fever, and abnormal findings on neurologic examination similar to those described in this outbreak have been reported in case series, case reports, and reviews of typhoid fever [19–27]. Spasticity accompanied by abnormal reflexes was documented among 3.1% of persons in a case series of 959 patients in Nigeria [20]. Similar signs were documented among 6.3% of persons in a series of 791 hospitalized patients in India [23], and ataxia was described among 2.3% of persons in a series of 718 patients in India [26].

To our knowledge, this is the first time such prominent signs and symptoms of neurologic impairment have been reported with such a high frequency in an outbreak setting. Reports of outbreaks have presented epidemiologic investigations with minimal clinical information, and other reports that include clinical data have not described these neurologic findings [28–32]. The high frequency of neurologic findings in the setting of a tightly localized outbreak is of particular interest because the affected population is likely to share more genetic and environmental features than a population comprising a multiyear, hospital-based case series. In addition, laboratory evidence confirms that a single clone of Salmonella Typhi predominated in this outbreak, which might not be true in a case series.

The pathophysiology of focal neurologic abnormalities in typhoid fever is unknown. Possible explanations include host or environmental factors or features specific to the strain of Salmonella Typhi. The reasons for the apparent high prevalence of neurologic disease in this outbreak are also unknown, but possible explanations exist. In part, surveillance bias might have occurred. Persons with neurologic symptoms might have presented for medical care at the health center or been admitted to the hospital at higher rates than persons without neurologic
Resistant manifestations. headache, and mild abdominal pain) but without neurologic illness. This is supported by the fact that when village clinics opened in mid-August to provide easier access to medical care, it became apparent that many persons had an illness compatible with classic typhoid fever with symptoms (eg, fever, headache, and mild abdominal pain) but without neurologic manifestations.

To our knowledge, this is the first time that multidrug-resistant Salmonella Typhi in Malawi or Mozambique has been reported. Of particular note is the finding of nalidixic acid resistance and decreased susceptibility to ciprofloxacin in 4 isolates, which can lead to treatment failure [33–35]. Before the outbreak was determined to be caused by typhoid fever, patients presenting to the village clinics or local health center with fever were empirically treated with antimarial medication or with amoxicillin, chloramphenicol, or trimethoprim-sulfamethoxazole, all of which would have been ineffective against this multidrug-resistant strain of Salmonella Typhi.

Diagnosis of febrile illnesses in resource-poor settings can be difficult. Absence of local blood culture capability prompted us to use a rapid assay for immunoglobulin M antibodies to Salmonella Typhi to help identify the etiology of the outbreak. Following several positive results among the initial tests, arrangements were made to establish blood culture collection in the affected area and to transport culture bottles to the national reference laboratory, where the etiology was confirmed and multidrug resistance was identified. Results of this testing led to an immediate change in treatment recommendations, illustrating the importance of blood culture and antimicrobial susceptibility testing on which to base guidelines for clinical management in an outbreak setting.

This investigation had limitations. Our case definitions for illness were altered after laboratory substantiation of typhoid as the likely etiologic agent of illness, possibly resulting in differential case assessment in the early and later phases of the investigation. Our “suspected” case definition was necessarily broad and atypical for typhoid fever because we wanted to preserve as much as possible the original clinical definition that was applied to the patients early in the outbreak before the etiology was known; this would have resulted in a certain amount of misclassification. In addition, differential access to medical care and laboratory testing at different stages of the investigation might have affected the number of identified cases and the proportion classified as suspected, probable, or confirmed. Malaria and HIV testing were not performed in all patients. Neurologic examinations were not performed on all patients and included primarily those who were hospitalized, which might have resulted in an underestimation of the number of persons with neurologic findings. We did not perform a case-control study or other systematic assessment to determine risk factors for disease, nor did we attempt to isolate Salmonella Typhi from water or other environmental samples. However, widespread, prolonged outbreaks of typhoid fever are often waterborne [6, 28, 29, 36, 37], and the finding of E. coli in the springs used for drinking water is compatible with a waterborne source.

This outbreak demonstrates that typhoid fever should be included in the differential diagnosis when a person who resides in or has traveled to an endemic area presents with fever and neurologic signs or symptoms. The physiologic mechanisms that result in neurologic illness in typhoid fever are unknown and should be explored. Although newer rapid serologic tests can be useful in supporting the diagnosis of typhoid fever in an outbreak setting, confirmatory cultures should be performed to detect drug resistance and guide treatment recommendations.

After the cause of the outbreak was determined to be Salmonella Typhi, recommendations for improvements in water safety led to drilling of borehole wells in the affected area and promotion of point-of-use water chlorination. Targeted educational campaigns to limit other transmission routes (eg, spread through unwashed hands, unsafely prepared food, and inadequate sanitation) were also instituted. Despite these interventions, cases of typhoid fever continued to occur in the area for months, and in accordance with recently published guidelines from the World Health Organization, vaccination has been considered to prevent further transmission of typhoid fever in this area [38].

### Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

### Notes

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**Disclaimer.** The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the CDC.

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Potential conflicts of interest. A. P. received support for travel to meetings for the study or for other purposes from the government of Malawi; R. L. received salary support; D. Talkington reported royalties for an invention not related to this study and travel and expenses paid by CDC.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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