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THE ETIOLOGY OF FEBRILE ILLNESS IN ADULTS PRESENTING TO PATAN HOSPITAL IN KATHMANDU, NEPAL

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Abstract. In Nepal, many infections remain poorly characterized, partly due to limited diagnostic facilities. We studied consecutive febrile adults presenting to a general hospital in Kathmandu, Nepal. Of the 876 patients enrolled, enteric fever and pneumonia were the most common clinical diagnoses. Putative pathogens were identified in 323 (37%) patients, the most common being *Salmonella enterica* serotype Typhi and *S. enterica* serotype Paratyphi A (117), *Rickettsia typhi* (97), *Streptococcus pneumoniae* (53), *Leptospira* spp. (36), and *Orientia tsutsugamushi* (28). Approximately half of the *Salmonella* isolates were resistant to nalidixic acid. No clinical predictors were identified to reliably distinguish between the different infections. These findings confirm the heavy burden of enteric fever and pneumonia in Kathmandu, and highlight the importance of murine typhus, scrub typhus, and leptospirosis. Given the lack of reliable clinical predictors, the development of cheap and accurate diagnostic tests are likely to be of great clinical utility in this setting.

INTRODUCTION

The infectious causes of febrile illness remain poorly characterized in many parts of the world, largely due to limited diagnostic microbiology facilities. Sentinel hospital-based studies performed over defined periods of time have provided useful clinical and public health information in countries that lack resources for long-term routine diagnostic testing.[1] This approach has been used in sub-Saharan Africa and Southeast Asia to determine the relative importance and antimicrobial susceptibility patterns of common pathogens, and to provide clinical predictors in well-defined patient populations.[2–6] Additionally, application of these methods has resulted in the identification of emerging or previously unrecognized pathogens among the same populations.[7,8]

In Nepal, febrile illness is one of the most common reasons for seeking medical attention, but there is limited information on the frequency of specific infections. While the burden of some infections (e.g., enteric fever) is believed to be substantial, the importance of others (e.g., leptospirosis and rickettsial diseases) is undefined. The provision of accurate epidemiologic data for common pathogens will enable resources to be directed towards key areas and will be of practical importance to clinicians. For populations where microbiologic facilities cannot be permanently established, validated clinical predictors may help guide therapeutic interventions.

We conducted a study to assess the etiology of bloodstream and other infections in a cohort of adults with fever presenting to a large general hospital in Kathmandu. To address seasonal variation, the study was conducted over two study periods (winter and monsoon seasons). A secondary aim of the study was to identify areas for future focused research.

MATERIALS AND METHODS

Setting. Kathmandu (population > 1.5 million), the largest city in Nepal, is situated at an altitude of 1,300 meters. The climate varies from cool, dry winters (December to February), to the hot monsoon season (June to September). Traditionally, the monsoon season is characterized by a heavy burden of enteric infections, while respiratory tract infections are more predominant in winter.

Patan Hospital is one of three large general hospitals within the Kathmandu metropolitan area. It has 251 beds and provides inpatient and outpatient medical, surgical, pediatric, obstetrics, and gynecology services, and serves as a primary care facility. Each year Patan Hospital has approximately 250,000 outpatient visits, 30,000 Emergency Department visits, and 15,000 admissions. Bed occupancy for medical wards runs at almost 100%, and approximately 90% of the patients are resident in the immediate Kathmandu Valley area (Bagmati Zone).

Patients. The winter study took place between January 16 and March 15, 2001 and the monsoon study between July 2 and August 10, 2001. All adults (≥14 years old) with fever (axillary temperature ≥38°C) when assessed in the outpatient clinic or Emergency Department, or within 24 hours of admission to a medical ward, were considered for entry into the study. After providing written informed consent, the patients were interviewed and examined, and the data were recorded on standardized assessment forms. Information collected included demographics, history of acute and chronic symptoms, past medical history, recent antimicrobial therapy, and physical examination findings. Venous blood and urine samples were collected. All outpatients were requested to return for their laboratory results and clinical evaluation 5–7 days after presentation. For those who did return, another blood sample was taken for additional serologic studies. The study protocol was reviewed and approved by the Nepal Health Research Council and the Institutional Review Board of the Centers for Disease Control and Prevention.

Laboratory methods. Blood samples were inoculated into Myco/F Lytic™ blood culture bottles (Becton Dickinson Microbiology Systems, Cockeysville, MD), incubated at 35°C,

and manually examined for growth twice a day for seven days using a handheld ultraviolet lamp to detect fluorescence of the indicator at the bottom of the bottle. Preliminary identification of bacteria was made on site by standard microbiologic tests. All blood culture bottles and isolates were transported to the Clinical Microbiology Laboratory at Duke University Medical Center where terminal subcultures for bacteria and mycobacteria were performed after a total of eight weeks incubation, identities of the isolates were confirmed, and antimicrobial susceptibility tests were performed according to the recommendations of the National Committee for Clinical Laboratory Standards.[9,10]

Serum samples were tested for antibodies to human immunodeficiency virus (HIV) types 1 and 2 (Determine™ HIV-1/2; Abbott Laboratories, Tokyo, Japan) and positive samples were confirmed by Western blot. Sera were also tested for IgM antibodies to dengue virus, *Leptospira* species, *Orientia tsutsugamushi*, and *Rickettsia typhi* (INDX® Multi-Test Dip-S-Ticks® SDLST; Integrated Diagnostics, Inc., Baltimore, MD). The latter multi-test assay was read according to the manufacturer's instructions, with grading of the reaction intensity from 0 (non-reactive) to 4+ (strongly positive) for each antigen. Only test results graded as 3+ or 4+ were considered positive for the purposes of this study due to the frequency of low-level background positivity for many of the antigens tested. This decision was made following the testing of sera from 100 healthy adult Kathmandu residents (57 males) collected in July and August 2001. Of this control group, 61 had positive test results for *R. typhi* (87% graded < 3+), 21 for *Leptospira* species (86% graded < 3+), 14 for *O. tsutsugamushi* (100% graded < 3+), and none for dengue virus.

Urine samples were tested on site for antigens of *Legionella pneumophila* serogroup 1 and *Streptococcus pneumoniae* by the NOW® *Legionella* and NOW® *Streptococcus pneumoniae* Urinary Antigen Tests (Binax, Inc., Portland, ME). Antimicrobial activity in urine was detected by a modification of the method developed by Liu and others;[11] the modification involved using *Bacillus subtilis* ATCC 6633 instead of *Bacillus stearothermophilus* ATCC 7953. Thin blood smears were stained using a modified Wright stain and examined microscopically for the presence of malaria parasites.

Data analysis. Data were analyzed using Epi-Info version 6.0 (Centers for Disease Control and Prevention, CDC, Atlanta, GA). Two-sided *P* values were calculated using the chi-square test or Fisher's exact test for dichotomous and ordinal variables. Continuous variables were compared using a two-sided Wilcoxon rank sum test and the Student's *t*-test. Multivariable logistic regression was performed using STATA version 7.0 (Stata Corp., College Station, TX) to evaluate variables associated with diagnoses. The final model for each diagnosis included covariates that were potential confounding variables or were associated with the outcome with $P < 0.1$ on bivariable analysis. Variables were removed in a stepwise manner and final associations were recorded as odds ratios (ORs) with 95% confidence intervals (CIs).

RESULTS

During the two study periods, 876 (370 winter and 506 monsoon) febrile adults were enrolled (Table 1). The predominant occupational groups were housewives (33%), students (26%), farmers (11%), and merchants (7%). Most patients were from metropolitan Kathmandu or the surrounding valley, with approximately 10% of the patients coming from the Terai, the lowland region bordering India. Enteric fever and lower respiratory tract infections were the most common initial clinical diagnosis. Murine typhus, scrub typhus, and leptospirosis were not listed as part of the differential diagnosis for any of the study patients. Only 140 patients (18%) required admission to the hospital and of these, only seven (5%) died before discharge.

TABLE 1
Clinical characteristics of patients presenting with fever to a hospital in urban Nepal

Characteristic	Winter (n = 370)	Summer (n = 506)
Age (years), median (range)	27 (14–85)	25 (14–89)
Female	196 (53%)	213 (42%)
Recruitment rate (no./day)	6	13
Clinical diagnosis at presentation		
Enteric fever	92 (27%)	260 (58%)
Lower respiratory tract infection	106 (31%)	24 (6%)
Upper respiratory tract infection	34 (10%)	25 (6%)
Urinary tract infection	49 (14%)	34 (8%)
Meningitis/encephalitis	4 (1%)	15 (3%)
Place of enrollment		
Emergency room	112 (30%)	286 (61%)
Outpatient clinic	252 (68%)	177 (38%)
Inpatient	6 (2%)	5 (1%)
Admission	60 (16%)	80 (17%)
Ethnicity		
Brahmin	70 (19%)	111 (23%)
Chettri	94 (26%)	112 (23%)
Newar	109 (29%)	115 (24%)
Tibeto-Burmese	25 (7%)	21 (4%)
Other	71 (20%)	122 (25%)

Diagnostic testing. Putative etiologic agents for fever were identified in 323 (37%) patients, and are presented in Table 2. Blood cultures were received from all enrolled patients. *Salmonella enterica* serotype Typhi (*S.* Typhi) and *S. enterica* serotype Paratyphi (*S.* Paratyphi) were the most common or-

TABLE 2
Diagnostic test results from patients presenting with fever to an urban hospital in Nepal*

Pathogen	Winter	Summer
Bloodstream isolates	37 (10%)	100 (20%)
Salmonella enterica serotype Typhi	21 (6%)	39 (8%)
Salmonella enterica serotype Paratyphi A	7 (2%)	50 (10%)
Escherichia coli	4 (1%)	5 (1%)
Staphylococcus aureus	2 (1%)	5 (1%)
Streptococcus pneumoniae	2 (1%)	0 (0%)
Neisseria meningitidis	1 (0.3%)	0 (0%)
Enterobacter cloacae	0 (0%)	1 (0.2%)
Urinary antigen tests		
Streptococcus pneumoniae	31 (8%)	20 (4%)
Legionella pneumophila serogroup 1	1 (0.3%)	1 (0.2%)
Serologic diagnoses		
Rickettsia typhi	32 (9%)	65 (13%)
Orientia tsutsugamushi	12 (3%)	16 (3%)
Leptospira species	9 (2%)	27 (5%)
Dengue virus	0 (0%)	0 (0%)
HIV	6 (2%)	5 (1%)

* HIV = human immunodeficiency virus.

ganisms isolated from blood during both seasons. No pathogenic fungi or mycobacteria were detected in blood cultures.

Acute serum was available for serologic testing from 864 (99%) patients. Second serum samples were available from 116 (13%) patients, taken a median of five days (interquartile range = 3–8) after acute samples. An additional nine patients demonstrated IgM seroconversion for leptospirosis; seroconversion to other antigens was not demonstrated. Given that the IgM seropositivity rates for *R. typhi* and *Leptospira* species did not differ greatly from the corresponding rates in the control sample, we performed additional testing on some patients. Acute sera from 64 patients with *R. typhi* IgM seropositivity (>2+) were retested by an indirect fluorescent antibody assay (PanBio, Brisbane, Australia). Of these samples, 57 (89%) had IgM antibody titers >1:64, with 33 (58%) having titers ≥1:256. Urine and whole blood samples from 26 patients with *Leptospira* IgM seropositivity (>2+) were tested for *Leptospira* DNA by a polymerase chain reaction (PCR) assay targeting the 16S ribosomal RNA gene.[12] Eleven (42%) of these patients had at least one positive sample.

None of the thin blood smears prepared during the monsoon season were positive for malaria.

Twenty-eight patients had dual etiologic diagnoses, with the most common diagnostic combinations being *R. typhi*/*S. pneumoniae* (6), *R. typhi*/*Leptospira* species (4), *S.* Typhi/*Leptospira* species (3), and *S.* Paratyphi/*R. typhi* (3).

Of the 11 patients with HIV infection (median age = 28 years, age range = 21–51 years, 8 males), five had pneumonia (three with *S. pneumoniae* antigenuria), two had suspected abdominal sepsis (one with *Escherichia coli* bacteremia), one had culture-confirmed enteric fever, one had cellulitis and *Staphylococcus aureus* bacteremia, one had meningitis (cause uncertain), and one had a febrile illness of uncertain etiology.

Antimicrobial susceptibility testing. Among the 60 *S.* Typhi, three were resistant to ampicillin, three were resistant to cotrimoxazole, and 18 were resistant to nalidixic acid. Of the 56 *S.* Paratyphi A isolates available for testing, all were susceptible to cotrimoxazole, only one was resistant to ampicillin, but 43 were resistant to nalidixic acid. Only two *S.* Typhi isolates (both resistant to ampicillin, cotrimoxazole, and nalidixic acid) and one S. Paratyphi isolate (resistant to ampicillin and nalidixic acid) were resistant to more than one class of antibiotic. No *S.* Typhi or *S.* Paratyphi A isolate was resistant to ciprofloxacin by current NCCLS criteria.[9,10]

Antimicrobial activity in urine. A history of prior antibiotic use was recorded in 164 (19%) patients, usually with either a β-lactam (37%) or fluoroquinolone (54%). However, among the 806 patients whose urine was tested, 307 (38%) demonstrated antimicrobial activity. There was no significant difference in the rate of blood culture positivity regardless of whether antimicrobial activity was demonstrated in the urine (14% versus 17%; $P = 0.2$) or whether patients reported prior antimicrobial use (20% versus 14%; $P > 0.05$).

Clinical associations. *Enteric fever.* Of the 332 persons with a clinical diagnosis of enteric fever, 84 (25%) had positive blood cultures for either *S. typhi* or S. Paratyphi A. Another 33 patients with other diagnoses had *S. typhi* or S. Paratyphi A isolated from blood. Compared with all other patients in the cohort, patients with culture confirmed enteric fever were more likely to be male (67% versus 52%; $P < 0.01$), students (42% versus 22%; $P < 0.001$), have fewer pulmonary symptoms (43% versus 56%; $P < 0.01$), and have a lower median white blood cell count (6.4 versus 9.7; $P < 0.001$). Additionally, persons with enteric fever were less likely to be admitted (3% versus 19%; $P < 0.001$) and were more likely to present to the outpatient clinic than the Emergency Department (49% versus 33%; $P = 0.02$). As shown in Table 3, only admission to the hospital and leukopenia remained significant associations in the multivariable model.

Murine typhus. Enteric fever was the most frequent clinical diagnosis (50%) among patients who were subsequently diagnosed with murine typhus. No demographic, clinical, or laboratory features distinguished these patients from others in the cohort.

Scrub typhus. Among the 28 patients with scrub typhus, 50% had a clinical diagnosis of enteric fever. Compared with all other patients in the cohort, these patients more frequently came from or recently traveled to the Terai region (relative risk [RR] = 1.4, 95% CI = 1.0–to 2.0) and were often farmers (RR = 2.4, 95% CI = 1.0–5.7). They were more likely to have had symptoms for more than three days before presentation (RR = 1.4, 95% CI = 1.1–1.7), a higher respiratory rate (27 versus 23 breaths per minute; $P = 0.04$), and more often required admission to the hospital (35% versus 16%; $P < 0.001$). These patients were twice as likely to be anemic (hematocrit < 35) than the other patients in the cohort (RR = 1.8, 95% CI = 1.1–2.9). Only anemia at the time of presentation remained significant after controlling for other associated factors (Table 3). Eschar or conjunctival suffusion were not observed in any of the patients with scrub typhus, and lymphadenopathy (axillary) was observed in only one.

Leptospirosis. Half of the 36 patients who were diagnosed with leptospirosis were thought to have enteric fever. Interestingly, five of these patients had positive blood cultures for *S.* Typhi or *S.* Paratyphi A, and sera from three of these patients also demonstrated IgM seroconversion to *Leptospira* species.

Pneumococcal disease. The majority of patients with pneumococcal disease were diagnosed with pneumonia at the time of presentation. However, 25% of these patients were thought to have enteric fever. Compared with all others in the cohort, patients with pneumococcal disease were older (median age = 40 years versus 25 years; $P < 0.001$) and more likely to have a history of chronic lung disease (RR = 2.7, 95% CI = 1.4–5.2). They had a higher respiratory rate (30 versus 23 breaths per minute; $P < 0.001$) and a higher white blood cell count (13.0 versus 9.1; $P < 0.001$). As expected, they were more likely to have pulmonary complaints (RR = 1.7, 95% CI = 1.5–1.9) or abnormal pulmonary examination find-

TABLE 3

Independent clinical predictors of etiology among febrile adults presenting to an urban hospital in Nepal*

Outcome	Variable	Odds ratio (95% CI)	*P*
Enteric fever	Admission to hospital	0.1 (0.04–0.5)	0.001
	Leukopenia	3.5 (1.6–4.7)	<0.001
Pneumococcal disease	Leukocytosis	2.2 (1.1–4.3)	0.019
	Lung field infiltrate on chest radiograph	4.4 (2.1–9.1)	<0.001
	Abnormal pulmonary auscultatory findings	3.1 (1.5–6.3)	0.002
Scrub typhus	Anemia	17.2 (1.2–246.0)	0.04

* CI = confidence interval.

ings (RR = 5.7, 95% CI = 3.2–10.0). When chest radiographs were performed, they were more likely to demonstrate an infiltrate (RR = 7.6, 95% CI = 4.5–12.8). Patients were also more likely to be admitted (RR = 3.0, 95% CI = 1.7–5.2).

DISCUSSION

This is the first study to systematically examine the infectious causes of febrile illness in Nepal. Using a combination of diagnostic methods, we have documented the heavy burden and seasonal variation of many infections, including enteric fever, pneumococcal disease, murine typhus, scrub typhus, and leptospirosis. The latter three infections, although previously recognized in Nepal, had not been regarded as important causes of febrile illness in Kathmandu. This was reflected by the fact that none of these three diagnoses was featured as part of the initial differential diagnosis for any of the study patients.

Enteric fever was the most common clinical diagnosis in our patient population and *S.* Typhi and *S.* Paratyphi A were the most common bloodstream isolates during both monsoon and winter seasons. Interestingly, *S.* Paratyphi A was responsible for the substantial increase in isolates during the monsoon. The clinical importance of *S.* Paratyphi A infections among travelers to Nepal has been previously documented,[13] and increasing numbers of *S.* Paratyphi A bloodstream isolates have been recorded in India.[14,15] Recent *S.* Paratyphi A isolates from India have limited genetic diversity and probably belong to closely related clones.[16–18]

Enteric fever is well-recognized as an important cause of febrile illness in Nepal,[19–21] and there have been recent concerns about the emergence of antibiotic-resistant *S.* Typhi and *S.* Paratyphi, and especially about clinical failure of ciprofloxacin.[22] The relatively high rate of nalidixic acid resistance, which may be the most reliable indicator of fluoroquinolone resistance,[23] supports this concern. The emergence of fluoroquinolone-resistant *S.* Typhi and *S.* Paratyphi in Nepal is not surprising given that ciprofloxacin is the most widely used antibiotic for the treatment of enteric fever in the country, where it is available from pharmacies without prescription. Furthermore, fluoroquinolone resistance is well-documented in India and other countries in southern and Southeast Asia.[24]

This study, although not the first to document rickettsial infections in Nepal,[25,26] is the first to specifically test for murine typhus as a cause of febrile illness. Our case definition for murine typhus was based on detection of IgM antibodies to *R. typhi* in acute serum samples, and most of our positive sera had high IgM antibody titers to *R. typhi* when retested with an indirect fluorescent antibody test assay. The IgM antibodies to *R. typhi* can be detectable for several months to years following infection,[27] and this presumably accounts for the relatively high seropositivity rate among controls. Therefore, without adequate convalescent specimens, we cannot be certain about the timing of *R. typhi* infections in our patient population. At a minimum, we can say with confidence that infections with *R. typhi* appear to be common in Kathmandu, given the relatively high seroprevalence in both our patient and control populations.

The southern Terai region of Nepal is a suitable environment for scrub typhus.[25] Although we diagnosed scrub typhus among farmers or those living or visiting the Terai, other patients lived in metropolitan Kathmandu and had no reported exposure. These patients were usually diagnosed with enteric fever and, like those with murine typhus, were usually treated with ciprofloxacin.

Previously, leptospirosis has only rarely been documented in Nepal,[28] although the region is a suitable environment for this infection. Underreporting almost certainly occurs because of the lack of readily available tests and the non-specific clinical presentation. We detected cases of leptospirosis during both seasons, and samples from many of these patients also tested positive for *Leptospira* DNA by a PCR, supporting the diagnosis of acute infection. There are good reasons to believe that we have underestimated the true number of patients with this infection. We used a relatively conservative case definition and documented IgM seroconversion in nine patients among the small proportion of patients from whom we obtained second serum samples. We may have documented many more seroconversions had we been able to obtain appropriately timed convalescent samples from a greater number of patients. However, persistence of IgM antibody for a year or longer may occur and cause problems with specificity of the diagnosis.[29]

The most frequent clinical diagnosis other than enteric fever was pneumonia, and this was more common during winter. Given that sputum culture was not performed and adequate convalescent sera were not routinely collected, we have limited insight into the complete spectrum of pneumonia pathogens. Pneumococcal infection was diagnosed by blood culture and the NOW® *S. pneumoniae* urinary antigen test, a diagnostic combination with high sensitivity for detecting community-acquired pneumococcal pneumonia in adults.[30] Not surprisingly, patients with pneumococcal disease were more likely to present with clinical, laboratory, and radiographic changes consistent with pneumonia. However, radiographic infiltrates were occasionally present among patients presenting with scrub typhus (25%), murine typhus (5%), and leptospirosis (6%), and were notably absent from patients with culture-confirmed enteric fever. The two positive *L. pneumophila* urinary antigen test results may be falsely positive given that neither patient had a clinical presentation consistent with pneumonia.

The blood culture positivity rate was lower and the range of bloodstream pathogens was different than reported in other similar studies from Africa and Asia.[2–6] This largely reflects different rates of HIV infection. Among populations with high rates of HIV infection, bloodstream infection were two to three times higher, and included a relatively heavy burden of opportunistic pathogens. In our study, the HIV infection rate was low despite the relatively high-risk study population (i.e., adults with febrile illness). This is important information given the general concern in Nepal about rising HIV infection rates[31] following the increasing prevalence in neighboring India.[32] The estimated HIV prevalence in Nepal in 2001 was 0.5% in adults,[33] although the prevalence is much higher for some groups. For example, approximately half of Nepal's intravenous drug users are HIV infected.[34]

Other infections are notable by their absence or low prevalence in this study. We detected no cases of malaria, supporting the current belief that malaria transmission does not occur in the Kathmandu Valley. Additionally, despite the spread of

dengue virus throughout much of the neighboring region,[35] no patients had serologic evidence of this infection.

We did not intend to perform an exhaustive search for all potential causes of fever among our cohort of febrile adults. Our main purpose was to describe the burden of some of the most likely pathogens, and to use this data as a foundation for further more focused research. Our results may underestimate the true burden for several reasons. First, hospital-based studies tend to underestimate disease incidence.[36] While this approach facilitates use of laboratory services, hospital-based surveillance captures only the most severe illnesses in people who have access to hospital care. Second, antibiotics can be purchased without prescription in Nepal and it is not surprising that more than one-third of the patients had antimicrobial activity detected in urine at the time they presented to hospital. Undoubtedly, antibiotic use reduced the ability to isolate pathogens from blood cultures, although the crude blood culture positivity rate did not differ significantly between those with and without urinary antimicrobial activity. Third, for logistic reasons, we did not aggressively pursue collection of convalescent serum samples, and most of the second serum samples we did collect were taken too early to reliably detect seroconversion. Lastly, several other infections that have been described to cause fever in the area were not systematically pursued. Important among this group is Japanese encephalitis, which is becoming increasingly common in Kathmandu during the monsoon,[37,38] including towards the end of our study period. Other important infections that were not specifically tested for include tuberculosis, hepatitis E, and influenza.

No combination of signs, symptoms, laboratory results, or demographic data could be constructed to reliably distinguish between the different causes of febrile illness. Many cases of murine typhus, scrub typhus, and leptospirosis are undoubtedly diagnosed as enteric fever and treated with ciprofloxacin. Fluoroquinolones have good *in vitro* activity against rickettsiae,[39] and limited data support the clinical efficacy of ciprofloxacin for the treatment of murine typhus.[26,40] However, recent case reports of murine typhus that responded poorly to ciprofloxacin highlight the importance of doxycycline as the drug of choice for treating rickettsial infections.[41,42] Although *in vitro* and animal studies show that fluoroquinolones have activity against *Leptospira interrogans*,[43,44] there is no data on clinical efficacy in humans. In addition to the benefits of optimizing antibiotic therapy for individual patients, the ability to reliably distinguish murine typhus, scrub typhus, and leptospirosis from enteric fever may play an important role in minimizing the use of ciprofloxacin and, thereby, slowing the emergence of fluoroquinolone resistance. In the absence of reliable clinical predictors, this is likely to only be achieved with the increased availability of accurate low-cost diagnostic tests. For the moment, patients who fail to respond to the current first line therapy for "enteric fever" or for those with more severe disease or who require admission, the addition of doxycycline is recommended.

This study demonstrates the usefulness of expanding microbiologic capacity in the developing world and the value of laboratory-based studies in sentinel institutions. Such studies provide a snapshot of important infections and can be periodically repeated for surveillance purposes. Further work should focus on better characterization of rickettsial diseases and leptospirosis in Nepal and improved diagnostic tests for these infections, further characterization of *S.* Typhi and *S.* Paratyphi strains, and characterization of key infectious diseases in children.

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