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Etiology of Acute, Non-Malaria, Febrile Illnesses in Jayapura, Northeastern Papua, Indonesia

Narain H. Punjabi,* Walter R. J. Taylor, Gerald S. Murphy, Sri Purwaningsih, Helena Picarima, John Sisson, James G. Olson, Samuel Baso, Ferry Wangsasaputra, Murad Lesmana, Buhari A. Oyofo, Cyrus H. Simanjuntak, Decy Subekti, Andrew L. Corwin, and Thomas L. Richie

U.S. Naval Medical Research Unit No. 2, Jakarta, Indonesia; Tulane University School of Public Health, New Orleans, Louisiana; Jayapura Provincial Hospital, Jayapura, Papua, Indonesia; National Institute of Health Research and Development R.I., Jakarta, Indonesia

Abstract. We conducted a prospective, inpatient fever study in malaria-endemic Papua, Indonesia to determine non-malaria fever etiologies. Investigations included malaria blood films, blood culture, paired serologic samples analysis for dengue, Japanese encephalitis, leptospirosis, scrub typhus, murine typhus, and spotted fever group rickettsia. During 1997–2000, 226 patients (127 males and 99 females) 1–80 years of age (median age = 25 years) were enrolled. Positive blood cultures (n = 34, 15%) were obtained for *Salmonella* Typhi (n = 13), *Escherichia coli* (n = 8), *Streptococcus pneumoniae* (n = 6), *Staphylococcus aureus* (n = 5), *Streptococcus pyogenes* (n = 1), and *Klebsiella pneumoniae* (n = 1). Twenty (8.8%) patients were positive for leptospirosis by polymerase chain reaction. Eighty (35.4%) of 226 patients had ≥ 1 positive serology, diagnostic for 15 rickettsial and 9 dengue cases. Acid-fast bacilli–positive sputum was obtained from three patients. Most common confirmed (81 of 226, 35.8%)/suspected diagnoses were typhoid fever (n = 41), pneumonia (n = 29), leptospirosis (n = 28), urinary tract infections (n = 20), rickettsioses (n = 19), dengue (n = 17), and meningitis/encephalitis (n = 15). There were 17 deaths, 7 (46.7%) were caused by meningitis/encephalitis. Multiple positive serologic results and few confirmed diagnoses indicate the need for improved diagnostics.

INTRODUCTION

Throughout Papua, Indonesia, malaria has been an important disease for many years, accounting for 16% of all hospitalizations, 14% of all hospital deaths, and 20% of all outpatient consultations.[1,2] Consequently, most febrile patients are considered to have malaria and are given empirical treatment out of fear of missing life-threatening *Plasmodium falciparum* infection.[3] Serious consideration of other etiologies may not occur unless there is no clinical response to antimalarial treatment. The lack of affordable diagnostic tests and knowledge of the prevalence of other infectious diseases means that febrile patients are not managed optimally. Ordering microbiologic tests late in the patient's illness may be of limited use if patients have also received empirical antibiotic treatment and/or have shown development of complicating nosocomial infections. The inability to pay for investigations is another impediment. These factors may promote the development of antibiotic and antimalarial resistance and unnecessary morbidity and mortality.

There are limited data on the epidemiology of other febrile illnesses in Papua. Scrub typhus (infection with *Orientia tsutsugamushi*) was a significant cause of illness and disability in the United States military in Papua during the Second World War.[4,5] In the Dutch colonial era, there were descriptions of several infections, including scrub typhus, leptospirosis, granuloma inguinale, and cholera.[6–9] In Jayapura, in northeastern Papua, the first outbreak of dengue hemorrhagic fever was reported in 1997 in hospitalized patients,[10] and in 2003, another outbreak was documented in Merauke in southeastern Papua.[11] Around the port of Jayapura, just more than one-third (n = 31) of 87 rats harbored *Xenopsylla cheopis* (Oriental rat flea) and 9 (11%) of 82 were positive for antibodies against *Rickettsia typhi*. Thus, the potential exists for the transmission of murine typhus and plague.[12]

In 1960, serologic surveys in southeastern Papua detected antibodies against poliomyelitis and several flaviviruses: Japanese encephalitis (JE) virus, dengue virus 1 and 2, and Murray Valley encephalitis virus.[13] In 1996, Spicer described a serologically confirmed clinical case of JE in a four-year-old boy in Timika in southern Papua,[14] and a follow-up serologic study in the same area found evidence of JE, Murray Valley encephalitis virus and Kunjin virus.[15] An outbreak of influenza A occurred in the highlands of Jayawijaya Regency, approximately 150 km south of Jayapura.[16] Although these reports give an indication of some of the infectious diseases in Papua, there has not been a prospective study that has assessed the causes of non-malaria fevers in patients. We report a prospective non-malaria fever survey at Jayapura Provincial Hospital (JPH), the main public hospital in Jayapura.

MATERIALS AND METHODS

Study site. Jayapura is located on the northeastern coast of Papua and is the provincial capital of Papua. The JPH serves a catchment area including Jayapura (population = 210,000), the towns of Abepura (population = 46,000) and Sentani (population = 30,000), and the surrounding countryside, including the palm oil plantations of Arso. Abepura and Sentani also have small public hospitals that treat patients with fevers. Annual visits to the JPH are approximately 130,000 outpatients and 14,000 inpatients. The leading inpatient and outpatient diagnoses are malaria, diarrhea, tuberculosis, anemia, and respiratory tract infections. Malaria transmission is low in Jayapura but intense in Arso.[3,17]

A household survey conducted in 2002 provided some indication of water use and waste disposal in Jayapura. Approximately 57% of the houses are equipped with plumbing for running water, and 51% of houses have in-house toilets. The six rivers traversing Jayapura are used for human waste disposal by 16% of households and as source of water by 2.5% of the households (Indonesian Central Bureau of Statistics, 2002).

This research protocol was approved by the Scientific Working Group of the Indonesian Ministry of Health, the

* Address correspondence to Narain H. Punjabi, SOS Medika Jalan Puri Sakti, 10 Cipete, Jakarta Selatan 12410, Indonesia. E-mail: narainhp@yahoo.com

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Ethics Committee of the Indonesian Ministry of Health and the Committee for the Protection of Human Subjects of the United States Naval Medical Research Unit No. 2 (NAMRU-2) in Jakarta (DoD CPHS #30835, 19 August 1997) in compliance with all applicable Federal regulations governing the protection of human subjects.

Study protocol. The study was conducted during November 1997–February 2000. Entry criteria were: a history of fever or axillary temperature ≥ 38°C on admission, a negative malaria slide examination result, and voluntary consent to participate in the study. Study patients were admitted to a designated study ward under the care of one of the hospital's attending physicians who made all management decisions. A study physician repeated the malaria blood smear initially performed by the hospital, performed the initial clinical assessment (history, physical examination), saw the patients daily, communicated any relevant clinical or laboratory findings to the attending physician, and assured the performance of study-related tests. These tests were blood culture, Giemsa-stained malaria slide, and use of acute-phase and convalescent-phase serum samples obtained 7–10 days apart (predischarge or at home). Other investigations were performed as clinically indicated (e.g., microscopic analysis of sputum, urine, and cerebrospinal fluid samples by Gram stain and Ziehl-Nielsen [ZN] stain, culture, drug sensitivity, and chest radiograph). Blood cultures were processed immediately by the hospital and the Jayapura NAMRU-2 Laboratory. Culturing and antibiotic sensitivity testing of isolated organisms followed standard microbiological procedures.[18,19] The study paid for all inpatient costs and all research tests.

Serum samples were frozen at –20°C and later transferred to the NAMRU-2 Laboratory in Jakarta for blinded analysis. The following analyses were performed: 1) an enzyme-linked immunosorbent assay (ELISA) for IgM and IgG against *R. typhi*, *O. tsutsugamushi*, and spotted fever group rickettsia (PanBio, Windsor, Queensland, Australia);[20] 2) an in-house, endpoint, dilutional ELISA for murine typhus (provided by A. Richards, U.S. Naval Medical Research Center, Silver Spring, MD); 3) an ELISA for IgM against *Leptospira* (Panbio) (positive specimens were subsequently tested by polymerase chain reaction [PCR] and the leptospirosis microscopic agglutination test [MAT] with five antigens, including 24 reference and field live strains provided by the World Health Organization [WHO] Collaborating Center for Leptospirosis, Pasteur Institute, Paris, France[21]); 4) a hemagglutination inhibition (HI) assay for antibodies against dengue virus;[22] and 5) an in-house HI assay for JE virus and an IgM ELISA Kit (PanBio).

Patient classification. Patients were classified as having either a confirmed or a suspected diagnosis. These diagnoses were based on the clinical picture, response to treatment and the results of the microbiologic, serologic, and radiologic tests. With multiple positive test results, more weight was given to the test that most likely explained the clinical picture, e.g., a positive blood culture with a pathogenic bacterium was given more weight than a serologic test result. When a confirmed diagnosis was based on serologic results alone, only one positive serologic test result and no other positive test results defined a confirmed case. A four-fold increase in antibody titers or IgM seroconversion was considered confirmatory for a given disease. Single titer, positive serologic results were evidence of exposure to a given disease and were considered supportive of a clinically suspected diagnosis. One Widal test result with a titer > 1:200 was classed as a suspected case of typhoid fever, if there were no other diagnoses that could better explain the patient's illness; this classification is consistent with guidelines in Indonesia.[23] At the time of the study, one HI IgG titer ≥ 1:1,280 was considered diagnostic for dengue (WHO 1986 guidelines).[24] However, the 2009 WHO Dengue guidelines classify this antibody response as being highly suggestive of acute dengue infection (http://whqlibdoc.who.int/publications/2009/9789241547871eng.pdf). We have used the 2009 guidelines and classified such patients as having suspected dengue. Leptospirosis was confirmed if *Leptospira* were detected by PCR.

Data management and analyses. Data were extracted onto a case record form and checked against the source documents before entry into Microsoft Excel (Microsoft Corporation, Redmond, WA). Data analysis (Stata version 7; Stata Corporation, College Station, TX) was descriptive (categorical and continuous data). Comparison of continuous data between groups was conducted by using the Mann-Whitney U test.

RESULTS

A total of 236 patients were enrolled in the study, but 10 (4.3%, 8 males and 2 females) had malaria identified by repeat blood smear performed by the study physician and were excluded from these analyses. The median age of the 127 males and 99 females was 25 years (range = 1–80 years, interquartile range = 19–33 years). Six children (2.65%) were < 10 years of age. No patients had been referred from other hospitals. For all patients combined, the duration of fever before admission was 5.7 (mean) and 4 (median) days with a range of 1–30 days. After enrollment, these fevers lasted 3 (mean) and 2 (median) days with a range of < 1–47 days. Clinically confirmed or suspected typhoid fever, leptospirosis, and community-acquired pneumonia accounted for just less than 50% of all diagnoses (Table 1).

Deaths. Seventeen of 226 patients died (Tables 1 and 2). The highest case-fatality rate was in patients with a central nervous system (CNS) infection/syndrome (46.7%), followed by patients with a bacteremia of either unknown source or in association with a focal infection.

Positive microbiology and serology. Thirty-four (15.1%) of 226 patients had positive blood cultures: 13 for *Salmonella* Typhi, 8 for *E. coli*, 6 for *Streptococcus pneumoniae*, 5 for *Staphylococcus aureus*, and 1 each for *Klebsiella pneumoniae* and *Streptococcus pyogenes*. All *Salmonella* Typhi and *Streptococcus pneumoniae* isolates were sensitive to commonly prescribed, first-line antibiotics in Indonesia, e.g., chloramphenicol, ampicillin, amoxicillin, and cotrimoxazole.[21] All *S. aureus* isolates were methicillin sensitive. No multidrug-resistant *E. coli* and *K. pneumoniae* were isolated. All patients were treated with antibiotics to which the isolated organisms were sensitive.

Of 226 patients who had acute-phase and convalescent-phase serologic samples available, sufficient serum was only available to test 70 acute-phase samples and 163 convalescent-phase samples. A total of 80 patients had ≥ 1 positive serologic result (Table 1); 55 patients had one positive serologic result (leptospirosis = 22, murine typhus = 16, dengue = 15, spotted fever group typhus = 2); 22 patients had two positive serologic results (leptospirosis = 13, murine typhus = 12, scrub

TABLE 1
Summary of the main clinically confirmed and suspected diagnoses, Jayapura, northeastern Papua Indonesia*

Diagnosis	No.	No. confirmed	Age, years (range)	Sex ratio M:F	Fever duration, days (range)	Fever clearance, days (range)	Bacteriologic result	Serologic result	No. died	CFR (%)
Respiratory infections										
Bacterial pneumonia	29	6	27 (11–65)	20:9	8.3 (1–30)	4.1 (1–47)	*Streptococcus pneumoniae* (4), *Staphylococcus aureus* (1), *S. pyogenes* (1)	MT (1)	2	6.9
Pulmonary tuberculosis	8	3	29 (19–77)	5:3	14.5 (1–30)	1.8 (1–4)	ZN stain positive	0	1	12.5
Bronchitis	8	0	16 (1–60)	5:3	2.5 (1–5)	1.5 (1–10)	Negative	0	0	0
Upper RT infection	6	0	12–40	5:1	1–7	1–4	Negative	0	0	0
Central nervous system										
Meningitis/encephalitis	15	2	23.5 (9–16)	10:5	3 (1–14)	1.5 (1–16)	*S. pneumoniae* (1) *Escherichia coli* (1)	DEN + JE (1)	7	46.7
Urinary tract										
Pyelonephritis/cystitis	20	6	30 (17–56)	7:13	6.5 (1–17)	2.3 (1–7)	BC: *E. coli* (5), *K. pneumoniae* (1)	MT (1) MT + JE (1)	2	9.5
Systemic infections										
Typhoid fever	41	13	22 (8–70)	22:19	4 (1–14)	3 (1–11)	*S.* Typhi (13)	LPT (3) DEN (2) MT (1) LPT + SCR (2) LPT + MT (2) SCR + MT (1) SFG + DEN (1)	1	2.4
Leptospirosis	28	20	25 (13–68)	20:8	4 (1–21)	2.5 (1–20)	Negative	SCR (3) MT (3) DEN (1) SFG (1) SCR+DEN (1)	1	3.6
Rickettsial infections	19	15	29 (8–80)	15:4	5.5 (1–14)	1.5 (0–11)	–	–	0	0
Murine typhus	15	13	–	–	–	–	Negative	LPT (1), DEN (1)	0	0
Spotted fever group	2	2	–	–	–	–	Negative	0		
MT + SFG, MT + SFG + SCR	2	0	–	–	–	–	Negative	0	0	0
Dengue	17†	9	19 (10–32)	7:10	3.5 (1–8)	1.5 (1–4)	Negative	MT (2), SCR (1) SCR + LPT (1)	1	5.9
Sepsis	4	4	34.5 (11–52)	1:3	2.5 (1–7)	1 (1–5)	*S. aureus* (2), *E. coli* (1) *S. pneumoniae* (1)	0	1	25

* CFR = case fatality rate; MT = murine typhus; ZN = Ziehl Nielsen staining of sputum; RT, respiratory tract; DEN = dengue; JE = Japanese encephalitis, BC = blood culture; LPT = leptospirosis; SCR = scrub typhus; SFG = spotted fever group.
† Two patients had a highly suggestive diagnosis of dengue on the basis of an IgG titer ≥ 1:1,280.

typhus = 7, dengue = 7, spotted fever group typhus = 3, JE = 2); and 3 patients had three positive serologic results (scrub typhus = 3, dengue = 2, leptospirosis = 2, murine typhus = 1, spotted fever group typhus = 1). Of the 37 patients with a positive IgM ELISA test for leptospirosis, 20 patients were given a confirmed diagnosis of leptospirosis by PCR alone (n = 9) or PCR and MAT (n = 11). Three patients had acid-fast bacilli seen on Ziehl-Nielsen–stained sputum samples.

Respiratory infections. Of the 29 patients with pneumonia, six were blood culture positive. Sputum microbiologic results were non-contributory, and of the 25 chest radiographs, 15 showed abnormal results. Two patients died of respiratory failure, one was positive for *S. aureus* and the other was known to be positive for infection with human immunodeficiency virus (HIV). Eight patients (three were positive for acid-fast bacilli) had suspected pulmonary tuberculosis (PTB); all had abnormal chest radiographic results, consistent with PTB. The HIV status of these patients was unknown. One PTB patient died of respiratory failure. Six and eight patients had upper respiratory tract infections and bronchitis, respectively. None had positive serologic or microbiologic test results and all recovered within 1–4 days.

Typhoid fever. Forty-one patients were diagnosed with typhoid fever. Of these patients, 13 (31.7%) had *S.* Typhi in their blood cultures (confirmed) and these isolates were fully antibiotic sensitive. *Salmonella* Paratyphi was not isolated. Of the 28 culture-negative typhoid fever patients, 16 patients had Widal tests performed and nine of these patients had titers > 1:200. In the remaining 19 patients, who did not have a confirmatory laboratory test performed, the diagnosis was based on clinical presentation and response to therapy.

Median fever duration preadmission was not significantly different ($P = 0.3$) between culture-positive (6 days) and culture-negative (4 days) patients, but fever clearance was significantly longer ($P = 0.0001$) in culture-positive (7 days) than culture-negative (2 days) patients. Most patients were treated with oral chloramphenicol but a small number received ceftriaxone or a fluroquinolone. One 16-year-old patient showed deterioration with shock and died after 13 days. She was culture negative and Widal test positive and was treated with intravenous ceftriaxone. Overall, 12 typhoid patients also had positive serologic results.

Leptospirosis. Leptospirosis was confirmed in 20 patients and suspected in 8 patients; 9 patients had other positive serologic results. Clinically, patients showed fever and few physical signs; one had jaundice and hepatomegaly and another had jaundice and splenomegaly. None had conjunctival injection. Eight (28.6%) patients also had thrombocytopenia. One patient had chest radiographic infiltrates, suggesting leptospiral pulmonary involvement. Patients were treated with a variety of antibiotics except doxycycline. There was one death (14-year-old boy) after five days because of renal failure.

Rickettsial infections. Nineteen patients were given a diagnosis of rickettsial infections. Of these patients, two also had mixed double and triple rickettsial positive serologic results and two others who had murine typhus were also positive for dengue and leptospirosis. Clinical presentations were unremarkable. Only one patient had an erythematous rash, and no eschars were seen. Hepatomegaly and hepatosplenomegaly were detected in three and six patients, respectively. Thrombocytopenia (14, 73.8%), leukopenia (5, 26.3%), and leukocytosis of 29,000 cells/mm^3 (1, 5.3%) were also present.

Urinary tract infections. Urinary tract infections were diagnosed in 13 females and 7 males. Six patients were blood culture positive: *E. coli* (n = 5, one patient was also urine culture positive) and *Klebsiella pneumoniae* (n = 1). Two patients with suspected urinary tract infections also had positive serologic results. Two patients died of renal failure. Both patients were blood culture negative; neither had urine tested by for culture, but both had leukocytes detected by dipstick testing.

Central nervous system infections. A total of 15 patients had fever and CNS symptoms and signs (e.g., altered mental status and convulsions) consistent with an encephalopathy or meningitis. Only two patients underwent a lumbar puncture. Both had low lymphocytic (< 50 cells/μL) predominant CSF, which was culture and stain (Gram, ZN) negative and was probably consistent with an acute encephalitis. Three patients were blood culture positive, supporting a diagnosis of bacterial meningitis, but in one the organism could not be identified. The patient who was *E. coli* positive also had positive JE and dengue serologic results. No patients were positive for *S.* Typhi. A total of seven patients died of their CNS infections. All had reduced consciousness at presentation and did not respond to treatment.

Dengue infection. Of the 17 patients with a diagnosis of suspected dengue, two were given a diagnosis clinically; 15 had positive dengue serologic results, of which two were highly suggestive and four others had concurrent positive serologic results for leptospirosis or rickettsioses. There was one death caused by intractable bleeding in a serologically negative, 34-year-old man with clinically diagnosed dengue hemorrhagic fever.

Other infections. There were a variety of different infections (Table 2). Of note was the death of a patient with diabetes and perioribital cellulitis who had an *S. aureus* bacteremia. Six patients had a diagnosis of gastroenteritis of unknown etiology; all recovered. Two patients had clinical hepatitis (serologic tests were not performed). Thirteen patients with negative blood cultures and serologic results had self-limiting illnesses, possibly viral in origin.

TABLE 2

Miscellaneous causes of fever, Jayapura, northeastern Papua Indonesia*

Diagnosis	No.	Microbiologic result	Serologic result	No. died
Benign self-limiting fevers	13	Negative	Negative	0
Gastroenteritis	6	Negative	Negative	0
Hepatitis	2	Negative	Negative	0
Pelvic inflammatory disease	2	Negative	Negative	0
Orbital cellulitis	1	*Staphylococcus aureus*	Negative	1
Septic arthritis	1	*S. aureus*	Negative	0
Unexplained fever and ARF	1	Negative	Dengue	0
Intraabdominal sepsis	1	*Escherichia coli*	Negative	0
Acute orchitis	1	Negative	Dengue	0
Peritonsillar abscess	1	Negative	Negative	0
Mumps	1	Negative	Negative	0
Non-infectious disease	1	Negative	Negative	0

*ARF = acute renal failure.

DISCUSSION

In this prospective study, which was conducted in a resource-limited tropical hospital, we have shed light on some of the causes of acute fevers other than malaria in hospitalized patients. Some of these diseases have been described briefly before in our region but this is the first, prospectively conducted fever survey in Jayapura.[5,7,10,12]

A number of challenges were faced in this study, perhaps not dissimilar to other small, under resourced, tropical hospitals, which compromised our ability to give patients a correct diagnosis. Our initial diagnostic tools were medical history, physical examination, malaria slide, routine hematologic and biochemical tests, blood culture, Widal test, and basic radiologic tests. Because serologic tests for rickettsioses, JE, dengue, leptospirosis and PCR for leptospirosis were provided by the research team but not used until after the end of the study, they did not contribute to patient management. We did not test systematically for HIV in this study, and culture for tuberculosis was not available.

Although the case-report form used was designed to obtain a detailed medical history, patients and guardians were not always good historians. The initial physical examinations were usually fairly complete but diligence to the follow-up clinical assessments was not as good. This finding may have impaired a proper clinical focus toward the diagnosis of the patient and was compounded by the limited microbiologic diagnostic capacity. Furthermore, patients are often reluctant to undergo a lumbar puncture and, outside of a research setting, have to pay for investigations. Therefore, important investigations are often not conducted as part of routine care, which leads to much empirical treatment. Interestingly, none of the patients with leptospirosis or a rickettsial illness were treated with doxycycline, likely because of a low index of suspicion for these illnesses.

Overall, approximately one third of patients had a confirmed clinical diagnosis on the basis of positive blood cultures for a pathogenic bacterium, positive ZN stains of sputum samples, pure serologic results, positive PCR results (leptospirosis), and consistent clinical pictures. This low figure is consistent with those of other studies.[25,26] However, many patients had several positive serologic results, negative bacteriologic results, and unremarkable, non-specific clinical presentations consistent with several possible diagnoses. We did not diagnose mixed infections but these infections remain a possibility in some patients.

Many positive serologic test results were likely caused by previous infections and/or cross-reactivity and contributed little to diagnosing the acute illness. Furthermore, commercial rapid diagnostic tests are semi-quantitative ELISAs that detect antibodies. Because positive results are based on cutoff values determined by test manufacturers, a positive result is consistent with current, recent, or distant exposure. The weaknesses of serologic results have been described in other fever surveys, and practicing clinicians should first regard positive serologic results as evidence of disease exposure and then

consider carefully their clinical relevance, especially if paired serum samples have not been obtained and if several serologic results are positive.[27–30] Clearly, for a tropical environment, serologic tests need to have much higher specificities and be affordable. Since this study was conducted, there are newer generations of commercially produced, easy to use, antigen-based or antibody-based rapid tests that have undergone evaluation and showed generally good results for dengue but less reliable results for leptospirosis.[31,32]

Despite the lack of sensitivity and/or specificity of our diagnostics, useful information has been gleaned from this study. Confirmed or suspected typhoid fever was the leading diagnosis in our patients. The isolated *S*. Typhi were sensitive to commonly used antibiotics, including inexpensive chloramphenicol. The preadmission illness duration was similar between culture-negative and culture-positive patients but the culture-negative patients had a more rapid fever clearance time (two days versus seven days). Both groups were prescribed the same antibiotics, and the longer fever clearance time in culture-positive patients may have been caused by higher bacterial loads. Apart from the one death, all other typhoid patients had an uneventful clinical course. None experienced complications such as mental status alteration, which is commonly seen in typhoid fever patients in Jakarta and Papua New Guinea.[33,34]

Community-acquired pneumonia was also seen commonly in our patients. Six patients had positive blood cultures, sputum was sent rarely to the laboratory, and there were no facilities to diagnose respiratory viruses or atypical bacteria. The *S. pneumoniae* and *S. aureus* isolated were penicillin and methicillin sensitive, respectively, contrasting with other regions of documented resistance.[35,36]

The highest case-fatality rate was in 15 patients with a CNS syndrome. Only two had lumbar punctures, which is an inadequate number for analysis. One CNS patient (age = 73 years) who did not have a lumbar puncture died. He was blood culture–positive for *E. coli* and had positive serologic results for JE and dengue. This patient illustrates our lack of knowledge of the causes of CNS infections in Jayapura, in addition to cerebral malaria, and the fundamental need to investigate suspected CNS infections by obtaining and analyzing cerebrospinal fluid, a basic but critical clinical investigation.

This study has underlined the importance of typhoid fever, leptospirosis, dengue, and rickettsial infections in the Jayapura area in patients with few helpful physical signs.[10–12] Many patients, including those with blood culture–confirmed pathogens, had positive serologic results for more than one disease. Although this finding hampered classifying patients, clinicians should now include typhoid fever, leptospirosis, dengue, and rickettsioses as differential diagnoses in malaria-negative patients and manage them accordingly.

This study has also illustrated the challenges of conducting fever surveys in tropical countries but has also highlighted the importance of diseases other than malaria. Greater investment in diagnostic microbiology in parallel with the development of algorithms should lead to a higher proportion of patients being given correct diagnoses.

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Authors' addresses: Narain H. Punjabi, Gerald S. Murphy, Helena Picarima, John Sisson, James G. Olson, Ferry Wangsasaputra, Murad Lesmana, Buhari A. Oyofo, Decy Subekti, Andrew L. Corwin, and Thomas L. Richie, U.S. Naval Medical Research Unit No. 2, Jakarta, Indonesia. E-mail: narainhp@yahoo.com. Walter R. J. Taylor, U.S. Naval Medical Research Unit No. 2, Jakarta, Indonesia and Tulane University School of Public Health, New Orleans, LA, E-mail: Bob@tropmedres.ac. Sri Purwaningsih and Samuel Baso, Jayapura Provincial Hospital, Jayapura, Papua, Indonesia. Cyrus H. Simanjuntak, National Institute of Health Researh and Development R.I., Jakarta, Indonesia.

REFERENCES

1. Lavalin International Inc, PT Hasfarm Dian Konsultan. Government of Indonesia and United Nations Development Programme INS/83/013. *Regional Development Planning for Irian Jaya, Health Sector Draft Report*, November 1987, 5–13.
2. Metselaar D, 1961. Seven years malaria research and residual house spraying in Netherlands New Guinea. *Am J Trop Med Hyg 10:* 327.
3. Gunawan S, 1985. A review of the malaria situation in Irian Jaya. *Bull Health Stud 13:* 1–13.
4. Gunther CE, 1940. A survey of endemic typhus in New Guinea. *Med J Aust 2:* 564–573.
5. Griffiths JT Jr, 1945. A scrub typhus (tsutsugamushi) outbreak in Dutch New Guinea. *J Parasitol 31:* 341–350.
6. Hoogerheide C, Ensink GJ, 1956. Cases of scrub typhus in Netherlands New Guinea. *Ned Milit Geneeskd Tijdschr 9:* 99–108.
7. van Thiel P, 1963. Studies on the incidence of leptospirosis in the central mountain region of West New Guinea by means of blood specimens dried on filter cardboard [in Dutch]. *Acta Leiden 32:* 280–285.
8. Vogel LC, Richens J, 1989. Donovanosis in Dutch South New Guinea: history, evolution of the epidemic and control. *P N G Med J 32:* 203–218.
9. De Moor CE, 1963. Cholera or paracholera in west New Guinea. *Ned Tijdschr Geneeskd 107:* 1727.
10. Richards AL, Bagus R, Baso SM, Follows GA, Tan R, Graham RR, Sandjaja B, Corwin AL, Punjabi N, 1997. The first reported outbreak of dengue hemorrhagic fever in Irian Jaya, Indonesia. *Am J Trop Med Hyg 57:* 49–55.
11. Sukri NC, Laras K, Wandra T, Didi S, Larasati RP, Rachdyatmaka JR, Osok S, Saragih JM, Hartati S, Listyaningsih E, Porter KR, Beckett CG, Prawira IS, Punjabi N, Soeparmanto SA, Beecham HJ, Bangs MJ, Corwin AL, 2003. Transmission of epidemic dengue hemorrhagic fever in easternmost Indonesia. *Am J Trop Med Hyg 68:* 529–535.
12. Richards AL, Rahardjo E, Rusidi F, Kelly DL, Dasch GA, Church CJ, Bangs MJ, 2002. Evidence of *Rickettsia typhi* and the potential for murine typhus in Jayapura, Irian Jaya, Indonesia. *Am J Trop Med Hyg 66:* 431–434.
13. Van Tongeren HA, Wilterdink JB, Timmers WC, 1960. Neutralizing antibodies to the virus of poliomyelitis, dengue types 1

and 2, Murray Valley and Japanese B encephalitis in Papuan populations of Netherlands New Guinea. *Trop Geogr Med 12:* 208–215.
14. Spicer PE, 1997. Japanese encephalitis in western Irian Jaya. *J Travel Med 4:* 46–47.
15. Spicer PE, Phillips D, Pike A, Johansen C, Melrose W, Hall RA, 1999. Antibodies to Japanese encephalitis virus in human sera collected from Irian Jaya. Follow up of a previously reported case of Japanese encephalitis in that region. *Trans R Soc Trop Med Hyg 93:* 511–514.
16. Corwin AL, Simanjuntak CH, Ingkokusumo G, Sukri N, Larasati RP, Subianto B, Muslim HZ, Burni E, Laras K, Putri MP, Hayes C, Cox N, 1998. Impact of epidemic influenza A-like acute respiratory illness in a remote jungle highland in Irian Jaya, Indonesia. *CID 26:* 880–888.
17. Jones TR, Baird K, Bangs MJ, Annis BA, Purnomo, Basri H, Gunawan S, Harjosuwarno S, McElroy RD, Hoffman SL, 1994. Malaria vaccine study site in Irian Jaya, Indonesia: *Plasmodium falciparum* incidence measurements and epidemiological considerations in sample size estimation. *Am J Trop Med Hyg 50:* 210–218.
18. Murray PR, Baron EJ, Pfaller MA, Tenover FC, Yolken RH, eds., 1999. *Manual of Clinical Microbiology*. 7th edition. Washington, DC: American Society for Microbiology Press, 442–458.
19. Bauer AW, Kirby WM, Sherris JC, Hurck M, 1966. Antibiotic susceptibility testing by a standardized single disk method. *Am J Clin Pathol 45:* 493–496.
20. Halle S, Dasch GA, 1980. Use of a sensitive microplate enzyme-linked immunosorbent assay in a retrospective serological analysis of a laboratory population at risk to infection with typhus group rickettsiae. *J Clin Microbiol 12:* 343–350.
21. Faine S, 1982. *Guidelines for the Control of Leptospirosis*. Geneva: World Health Organization, Mimeographed Document no. 67.
22. Innis BL, Nisalak A, Nimmannitya S, Kusalerdchariya S, Chongswasdi V, Suntayakorn S, Puttisri P, Hoke CH, 1989. An enzyme-linked immunosorbent assay to characterize dengue infections where dengue and Japanese encephalitis co-circulate. *Am J Trop Med Hyg 40:* 418–427.
23. Loehoeri S, Prawoto, 1992. The role of Widal test as a diagnostic tool for typhoid fever. *Acta Med Indones 2:* 39–42.
24. World Health Organization, 1986. *Dengue Hemorrhagic Fever: Diagnosis, Treatment, and Control*. Geneva: World Health Organization.
25. Phetsouvanh R, Phongmany S, Soukaloun D, Rasachak B, Soukhaseum V, Soukhaseum S, Frichithavong K, Khounnorath S, Pengdee B, Phiasakha K, Chu V, Luangxay K, Rattanavong S, Sisouk K, Keolouangkot V, Mayxay M, Ramsay A, Blacksell SD, Campbell J, Martinez-Aussel B, Heuanvongsy M, Bounxouei B, Thammavong C, Syhavong B, Strobel M, Peacock SJ, White NJ, Newton PN, 2006. Causes of community-acquired bacteremia and patterns of antimicrobial resistance in Vientiane, Laos. *Am J Trop Med Hyg 75:* 978–985.
26. Blacksell SD, Sharma NP, Phumratanaprapin W, Jenjaroen K, Peacock SJ, White NJ, Pukrittayakamee S, Day NP, 2007. Serological and blood culture investigations of Nepalese fever patients. *Trans R Soc Trop Med Hyg 101:* 686–690.
27. Blacksell SD, Bryant NJ, Paris DH, Doust JA, Sakoda Y, Day NP, 2007. Scrub typhus serologic testing with the indirect immunofluorescence method as a diagnostic gold standard: a lack of consensus leads to a lot of confusion. *Clin Infect Dis 44:* 391–401.
28. Wagenaar JF, Falke TH, Nam NV, Binh TQ, Smits HL, Cobelens FG, de Vries PJ, 2004. Rapid serological assays for leptospirosis are of limited value in southern Vietnam. *Ann Trop Med Parasitol 98:* 843–850.
29. McGready R, Ashley EA, Wuthiekanun V, Tan SO, Pimanpanarak M, Viladpai-Nguen SJ, Jesadapanpong W, Blacksell SD, Peacock SJ, Paris DH, Day NP, Singhasivanon P, White NJ, Nosten F, 2010. Arthropod borne disease: the leading cause of fever in pregnancy on the Thai-Burmese border. *PLoS Negl Trop Dis 4:* e888.
30. Tay ST, Ho TM, Rohani MY, Devi S, 2000. Antibodies to *Orientia tsutsugamushi, Rickettsia typhi* and spotted fever group rickettsiae among febrile patients in rural areas of Malaysia. *Trans R Soc Trop Med Hyg 94:* 280–284.
31. Blacksell SD, Mammen MP Jr, Thongpaseuth S, Gibbons RV, Jarman RG, Jenjaroen K, Nisalak A, Phetsouvanh R, Newton PN, Day NP, 2008. Evaluation of the Panbio dengue virus nonstructural 1 antigen detection and immunoglobulin M antibody enzyme-linked immunosorbent assays for the diagnosis of acute dengue infections in Laos. *Diagn Microbiol Infect Dis 60:* 43–49.
32. Blacksell SD, Smythe L, Phetsouvanh R, Dohnt M, Hartskeerl R, Symonds M, Slack A, Vongsouvath M, Davong V, Lattana O, Phongmany S, Keolouangkot V, White NJ, Day NP, Newton PN, 2006. Limited diagnostic capacities of two commercial assays for the detection of *Leptospira* immunoglobulin M antibodies in Laos. *Clin Vaccine Immunol 13:* 1166–1169.
33. Hoffman SL, Punjabi NH, Kumala S, Moechtar MA, Pulungsih SP, Rivai AR, Rockhill RC, Woodward TE, Loedin AA, 1984. Reduction of mortality in chloramphenicol-treated severe typhoid fever by high-dose dexamethasone. *N Engl J Med 310:* 82–88.
34. Richens J, 1995. Typhoid in the highlands of Papua New Guinea 1984–1990: a hospital-based perspective. *P N G Med J 38:* 305–314.
35. Vourli S, Vagiakou H, Ganteris G, Orfanidou M, Polemis M, Vatopoulos A, Malamou-Ladas H, 2009. High rates of community-acquired, Panton-Valentine leukocidin (PVL)-positive methicillin-resistant *S. aureus* (MRSA) infections in adult outpatients in Greece. *Euro Surveill 14:* pii: 19089.
36. Cardozo DM, Nascimento-Carvalho CM, Souza FR, Silva NM, 2006. Nasopharyngeal colonization and penicillin resistance among pneumococcal strains: a worldwide 2004 update. *Braz J Infect Dis 10:* 293–304.