


Tropical Fever in the Returning Traveler

Fever is a frequent and important symptom of an illness acquired in the tropics. To initiate appropriate therapy and infection-control measures, physicians must establish an etiologic diagnosis as quickly as possible.

By J.D. MacLean, MD

Fever is a frequent and important symptom of an illness acquired in the tropics. Occasionally, fever is the only objective evidence of serious disease.

To initiate appropriate therapy and infection-control measures, a physician must attempt to establish an etiologic diagnosis as quickly as possible.

Tropical fevers can, however, be a daunting challenge for most physicians, who lack familiarity with the great diversity of fever-inducing tropical infections.

For this reason, studies defining the relative frequency of febrile illnesses imported to North America are a useful starting point

for any diagnostic investigation.^{1,2}

Such studies consistently show that malaria, dengue, hepatitis A, bacterial dysentery and enteric fever represent more than 85% of imported tropical fevers (Table 1).³

Diagnostic Approach

Two important considerations that must guide any investigation of tropical fevers are:

- The exceedingly rare possibility of a highly transmissible agent that might threaten health-care professionals and the community; and

Tropical Fevers

Table 1

Final Diagnosis in Cases of Fever in Outpatients on Return From the Tropics

587 Consecutive Fevers at the Montreal General Hospital (1981-1988)

| Diagnoses | Occurrence (%) |
|---|----------------|
| Malaria | 32 |
| URI/pharyngitis | 7 |
| Hepatitis | 6 |
| Pneumonia/acute bronchitis | 5 |
| Shigella/Salmonella*/Campylobacter | 5 |
| Pyelonephritis | 4 |
| Dengue | 2 |
| Enteric fever | 2 |
| Infectious mononucleosis | 2 |
| Drugs/alcohol | 1 |
| Rickettsia | 1 |
| Amoebic liver abscess | 1 |
| Tuberculosis | 1 |
| Meningitis | 1 |
| Acute HIV infection | 0.3 |
| Systemic fungal infection | 0.3 |
| Miscellaneous | 5 |
| <i>Unknown</i> | 25 |

URI: upper-respiratory illness

HIV: human immunodeficiency virus

*nonenteric fever

Bolded diagnoses represent fevers more specifically of tropical origin

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- The need for early, specific curative therapy to prevent serious morbidity and mortality (some tropical diseases progress rapidly).

History of the Illness. The best clues for identifying a causative agent can usually be obtained from a patient's history. A description of the illness, its fever pattern, pre-travel vaccinations and prophylactic medica-

Table 2

Physical Findings in Selected Febrile Illnesses

| Disease | Incubation period (days) | Adenopathy (%) | Rash (%) | Splenomegaly (%) |
|-------------------------------|--------------------------|----------------|----------|------------------|
| Malaria (<i>falciparum</i>) | 5-24* | 3 | 0-5 | 24 |
| Amoebic liver abscess | | 0 | 0 | 0-17 |
| Typhoid | 5-21 | 10 | 5-56 | 39-65 |
| Miliary tuberculosis | | 6-46 | <1 | 0-54 |
| Dengue (classic) | 2-7 | | 71 | |
| Acute retrovirus (HIV-1) | 7-42 | 36-58 | 25-50 | ~0 |
| Tick typhus | 5-7 | 20-51 | 67-99 | 6-19 |
| Ebola | 2-21 | 4 | 50-75 | ~0 |

HIV: human immunodeficiency virus
 * Average or range of data from one or more published studies. These studies have typically involved hospitalized individuals.
 ~0: there are no published data, and the author presumes the level to be zero.¹

tions may provide diagnostically important information.

A detailed travel itinerary (including a list of destinations with dates visited) is essential for the estimation of incubation periods and possible exposures to diverse pathogens.

Although many infectious agents are widespread throughout most tropical areas, other pathogens have well defined focal distribution restricted to specific countries or regions of countries. Most standard medical textbooks have sections on the geographic location of diseases.

It is useful to have a knowledge of the incidence of various fevers in travelers returning to North America from tropical countries when establishing diagnostic probabilities.

Common causes of fever (e.g., viral influenza, pyelonephritis, pneumonia) are sometimes found in returning travelers, but malaria, hepatitis A, enteric fever and

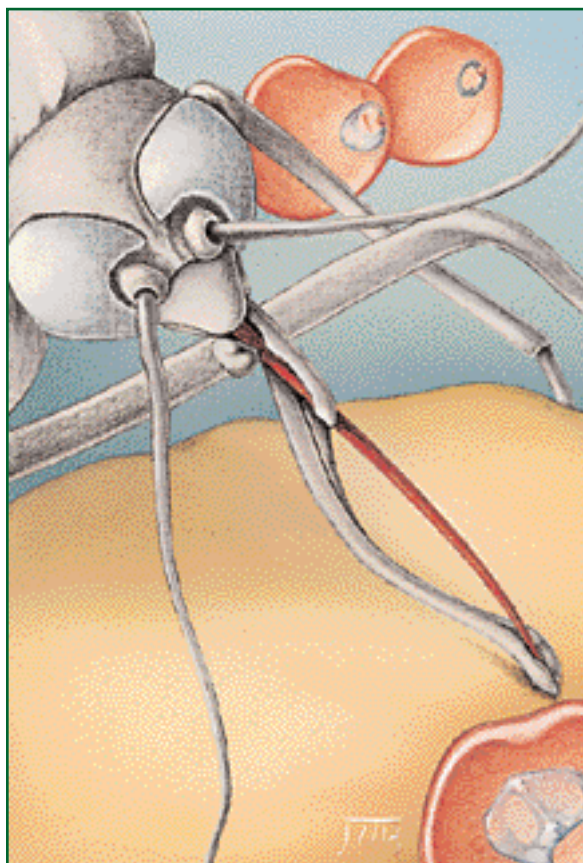
dengue are the most common “tropical” causes of fever in this population. These four illnesses caused fever in 40% of 587 febrile travelers seen in Montreal between 1981 and 1988, and represented 80% of all “tropical” pathogens identified in these patients.

Incubation Period

It is often difficult to determine the incubation period of many febrile illnesses that occur in North America.

Travel dates, however, allow for a reasonably precise estimation of incubation periods for infections acquired in the tropics.

Arboviral illness, haemorrhagic fever and rickettsial disease, for example, all have short incubation periods, and they can be ruled out as a cause of fever that begins four weeks after departure from Africa (Table 2).



Duration of Fever

It is obviously impossible to attribute diagnostic significance to the duration of a fever early in the course of a febrile illness. Some infectious diseases, however, are characterized by self-limited febrile symptoms (e.g., arboviral, rickettsial fevers) that rarely last more than two weeks.

Other pathogens can cause illness where fever is prolonged (e.g., malaria, African trypanosomiasis, tuberculosis).

Fever Patterns

Some fever patterns can be useful tools in diagnosing tropical fevers. For example, the tertian (alternate day) fever pattern of vivax, ovale and (rarely) falciparum malar-

ia is unlikely produced by infections other than malaria parasites. *Plasmodium malariae* characteristically produces a quartan (every third day) fever pattern. While these regularly intermittent fevers are moderately specific, they are not sensitive indicators of malaria. Less than 50% of patients with malaria will have such patterns.

Malaria Chemoprophylaxis

In the past, appropriate use of chloroquine prophylaxis effectively ruled out malaria as a cause of fever (except for the rare post-treatment relapse of *Plasmodium vivax* or *ovale* malaria).

In travelers returning from Central America, Haiti or the Dominican Republic (where malaria remains sensitive to chloroquine), regular use of chloroquine argues strongly against malaria as the cause of fever.

Unfortunately, resistance to antimalarial drugs is widespread throughout the rest of the malarious world. As no drug guarantees complete protection against malaria, the use of antimalarials does not rule out the diagnosis.

As well (because falciparum and, recently, *P. vivax* malaria may only be partially resistant to antimalarial drugs), infections may be temporarily, but not entirely, suppressed.

Under such circumstances, malaria parasites may emerge one to four weeks after the cessation of the antimalarial drug, and may produce clinical malaria.

Table 3

Rashes in Febrile Illnesses

| | <u>Patients Affected (%)</u> |
|--|------------------------------|
| Typhoid | |
| 2-mm to 3-mm low-profile pink papules (called rose spots) between nipples and umbilicus by day seven to 10 of fever | 13-56 |
| Miliary tuberculosis | |
| Minute maculopapular lesions (At times, purpuric) | <1 |
| Dengue (classic) | |
| Generalized maculopapular to scarlatiniform rash, most marked over trunk, blanching on pressure Pharyngeal and conjunctival erythema | 71 |
| Ebola | |
| Maculopapular truncal | 10-75 |
| Tick typhus | |
| A small, 3-mm to 5-mm, nontender ulcer with a black center, surrounded by a red halo Often indistinct maculopapular or petechial rash, especially truncal | 67-99 |
| Acute retroviral (human immunodeficiency virus-1) | |
| Maculopapular, roseola-like or urticarial | 25-50 |

Exposure

For the most part, the risk of infection is determined by the nature of the traveler's exposure while in the tropics. Immigrants, health-care workers, back-packers and volunteers will have more intense exposure than short-term tourists residing in first-class hotels. Exposure to tropical rural environments often implies exposure to unsanitary water supplies and inadequate sewage facilities, as well as encounters with differ-

ent insects. Travelers abroad may also have sexual contacts that expose them to a multitude of sexually transmitted diseases.

Physical Examination. A careful physical examination, with particular attention to the ears, sinuses, teeth, urinary tract, prostate and lungs, must be performed to detect a possible focus of infection. Early identification of a focus of infection can prevent many invasive, expensive and sometimes dangerous investigations.

Tropical Fevers

Although the physical examination may not provide a definite diagnosis, it can reveal a spectrum of physical findings that is useful in limiting the etiologic possibilities. The physical signs of many tropical infections, however, overlap to a confusing degree with each other and with infectious diseases that are prevalent in North America.⁴ (Table 2.) The following is a brief discussion of several clinical signs.

Rash

Rashes found in a febrile patient may represent a diagnostic clue about the etiology of the fever.

Rashes may also be “red herrings,” representing a second, unrelated condition (e.g., drug eruptions, insect bites). No rash is 100% diagnostic, but some kinds of rash can help point to a diagnosis (Table 3).

Dengue often has a characteristic morbilliform to scarlatiniform rash, with some conjunctival erythema. The presence of one or more painless eschars is an excellent clue that may signal tick or scrub typhus.

Hemorrhagic rashes are clear indicators of life-threatening illnesses such as meningococemia, Rocky Mountain Spotted Fever, toxic shock syndrome and the viral hemorrhagic fevers (e.g., dengue, Marburg, and Lassa viruses).



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Splenomegaly

Splenomegaly is frequently associated with a variety of common tropical fevers, so it is a less useful sign than rashes, which can have a variety of presentations (Table 2). Absence of splenomegaly is not a useful sign, either.

Many fevers that result in splenomegaly produce the enlargement so slowly that this enlargement may not be noted until the second week of fever or later. Examples of late splenomegaly are malaria and typhoid.

Table 4

Most Common Laboratory Findings in Selected Fevers

| | Liver enzymes | WBC | Platelets | Atypical lymphocytes |
|-----------------------|-----------------|------------|------------|----------------------|
| Malaria | Slightly raised | Low | Low | Nil |
| Typhoid | Slightly raised | Low/normal | Low/normal | Nil |
| Dengue (classic) | Slightly raised | Low | Low | Raised |
| Amoebic liver abscess | Normal | Raised | Normal | Nil |

WBC: white blood cell

Diarrhea

Diarrhea can occur in many systemic infections where the gastrointestinal (GI) tract is not the primary focus of infection. In these circumstances, GI manifestations are frequently minor, compared to dysfunction in other organ systems.

The pathogenesis of such diarrheas is not clear, although both falciparum malaria and rickettsial infections damage the vascular supply in the intestinal mucosa.

Finding red blood cells, mucus and increased numbers of white cells in the stool is a valuable sign that indicates the presence of colitis. The usual causes of colitis include *Shigella*, *Campylobacter*, *Salmonella*, *Vibrio parahemolyticus*, *Entamoeba histolytica*, *Balantidium coli* or inflammatory bowel disease.

The greatest number of white blood cells (WBCs) is found in the settings of *Shigella*, *Campylobacter* colitis or inflammatory bowel disease (> 20 white blood cells [WBCs] per high-power field). Finding stool WBCs in large numbers almost always localizes the source of fever to the large intestine.

Some fevers caused by intestinal infec-

tions lack tell-tale intestinal signs or symptoms such as diarrhea or abdominal pain. In typhoid (the classic example), approximately one-third of victims lack intestinal symptoms, while another third are constipated.

Campylobacter and *Shigella* infections sometimes present as fever alone for the first one to three days before diarrhea develops.

Spontaneous Bleeding

Hemorrhage associated with a tropical febrile illness is rare. The tissue disruption or systemic hemorrhagic diathesis represented by this hemorrhage almost always signals a serious illness. Furthermore, some of these infections are highly contagious (e.g., viral hemorrhagic fevers, meningococemia).

Systemic hemorrhagic defects may initially present as petechiae and/or cutaneous purpura; these may herald far more serious blood loss from other sites. Among the viral hemorrhagic fevers, viruses that cause Lassa fever, Bolivian hemorrhagic fever, Marburg disease, Ebola disease and Crimean-Congo hemorrhagic fever can

COMMON QUESTIONS PATIENTS ASK

What Does Fever Mean to Travelers?

Fever, unlike a runny nose, cough, diarrhea or rash, is an extremely serious symptom after return from tropical travel. Fever can be a symptom of malaria, typhoid, hepatitis, dengue and other serious infections. Many of these infections cause death, and some can be spread by person-to-person contact, putting your family members and coworkers at risk.

For these reasons, if you have a fever and have just returned from travel in a tropical region, you should take it seriously. The sooner you see a doctor, the lower your chances are of getting seriously ill. You should not let your fever last any longer than one to two days without seeing a doctor. For malaria (which makes up one-third of tropical fevers), each day you wait increases the chance of severe sickness and death.

What Causes Fevers in Travelers?

One-third of fevers in tropical travelers are caused by malaria. Hepatitis, typhoid, dengue and large-intestine infections are also common. Malaria is the most common cause of death from fever-related illness, and must be taken very seriously. Of course, the usual causes of fever are commonly found in individuals returning from the tropics. The flu, bronchitis, pneumonia, bladder and kidney infections and sinusitis can all occur, and can be serious. Malaria must always be considered, however, and should be ruled out as the cause of your fever.

What Should I Do If I Have a Fever?

If you have returned within the past three months from an area in the tropics where you could have been exposed to malaria, you should assume that you have malaria, even if you have taken or are still taking your antimalarial pills. Antimalarial drugs reduce the risk of malaria, but do not provide 100% protection. You should seek medical help immediately from your doctor. If you cannot see your doctor immediately, go to the emergency department of the largest hospital in your area. Tell your doctor that you have been traveling in a malarious area and that you are concerned about malaria. Make sure that a malaria smear (a blood test for malaria) will be performed, and that the malaria smear will be read and reported before you leave the hospital or clinic. If this cannot be done within two to three hours, you should be very concerned, and you should seek other care. You may want to ask where you can go to see a tropical-disease or infectious-disease specialist.

If the initial tests do not tell you what you have, and your fever is still high, a repeat malaria smear should be done for the next two days, with a referral to a tropical-disease or infectious-disease specialist. You should understand that Canadian laboratories have little experience with malaria, and cannot always make the correct diagnosis.

spread by person-to-person contact, and are a threat to the community.⁵⁻⁷ Noncontagious viral hemorrhagic fevers include those caused by yellow fever and dengue viruses.

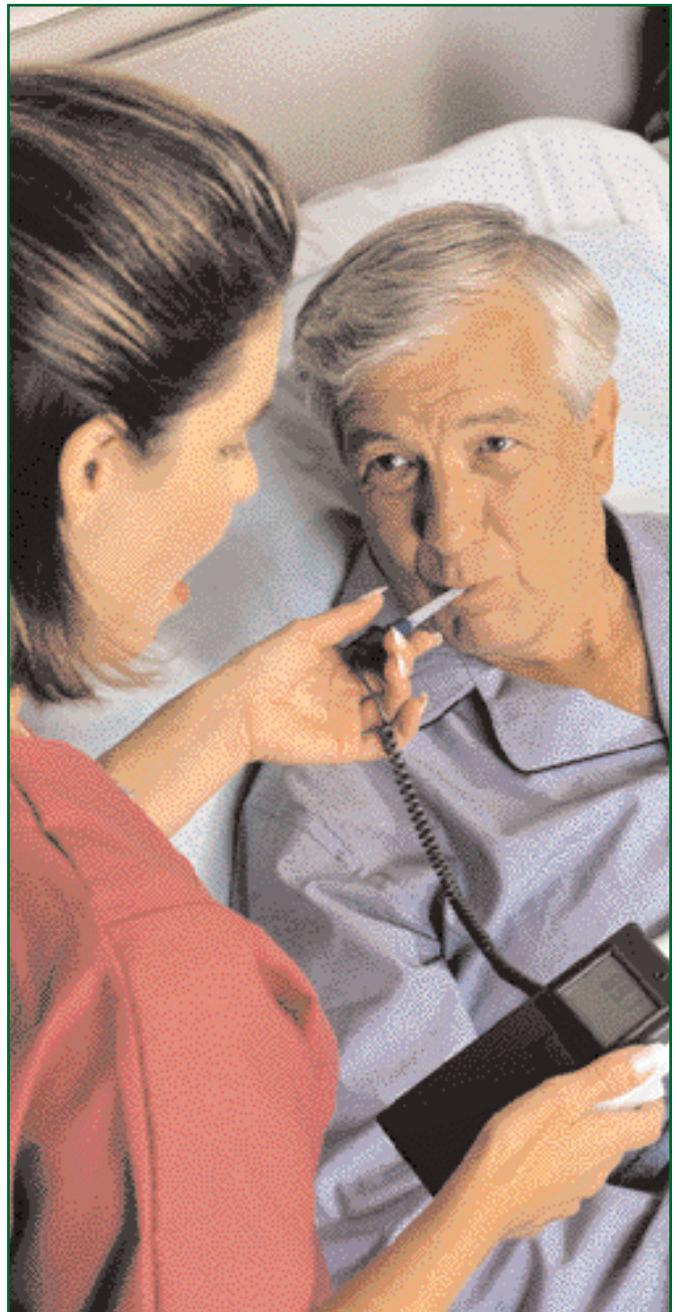
Dengue virus produces two types of illness—the classic dengue fever and dengue hemorrhagic fever (DHF).

In classic dengue fever, petechiae develop in only a small proportion of patients; most patients with DHF have petechiae and major hemorrhages. It is believed that hemorrhagic dengue occurs primarily in individuals who have had prior exposure and antibodies to dengue, a pathogenesis designated “antibody enhancement”.⁸ Tissue disruption as the source of bleeding is a particular problem with some of the intestinal infections acquired in the tropics.

Typhoid fever produces ileocecal ulceration at the sites of lymphoid follicle necrosis, usually in the second or third week of illness. Similarly, bleeding in the respiratory tract may occur with lesions caused by tuberculosis, melioidosis and South American blastomycosis.

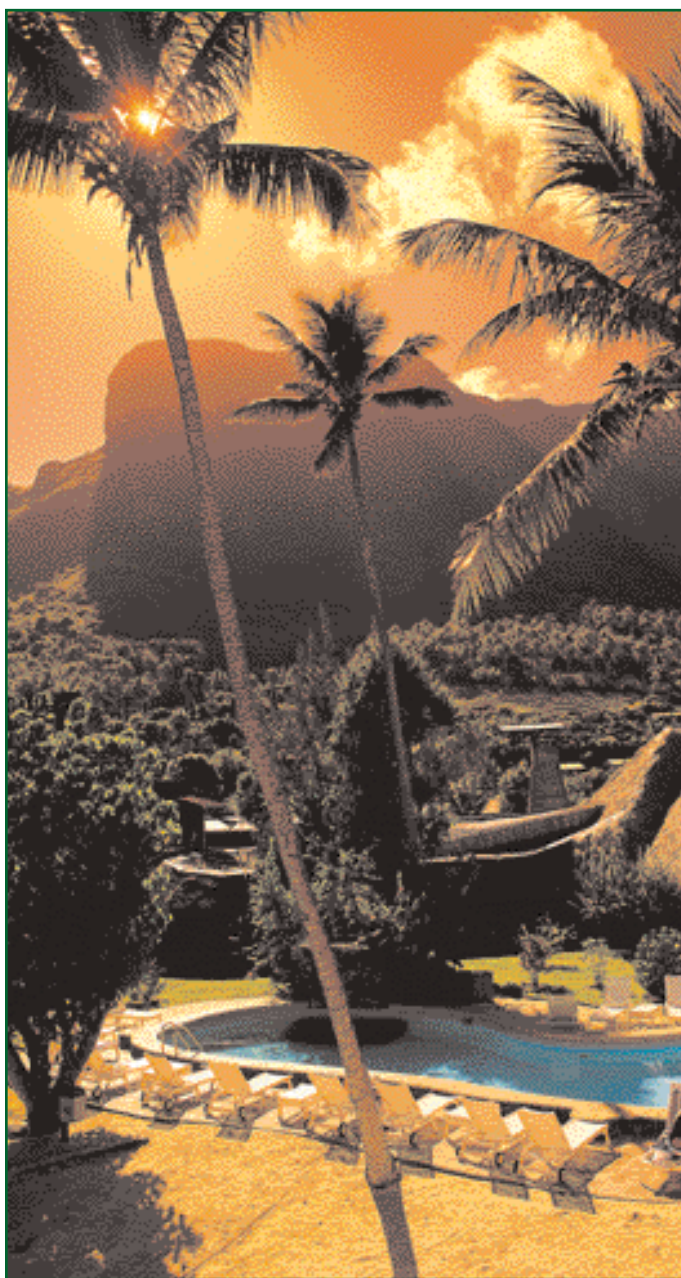
If a fever starts within three weeks of traveling in a region where exposure to viral hemorrhagic fever can occur, expert assistance should be sought immediately. To date, cases of viral hemorrhagic fever have almost always involved patients who traveled or worked in rural Africa.

Very similar illnesses, however, can occur in large regions of South America and central Asia. Information regarding recent and ongoing outbreaks of these viral diseases is available on Web sites such as PROMED, or from the Centers for Disease Control and Prevention (CDC) in Atlanta.



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Tropical Fevers



There are no North American studies that deal with FUO in travelers from the tropics, but studies from the tropics suggest that the list of travel-related etiologies may be large.

If a diagnosis of viral hemorrhagic fever is possible, local public-health officers must be notified immediately so that appropriate action can be initiated to control person-to-person and laboratory spread.

Fever of Unknown Origin

In North American medicine, fever of unknown origin (FUO) refers to a group of disorders characterized by prolonged fever (greater than four weeks) with no obvious etiology after one week of intensive investigation.

There are no North American studies that deal with FUO in travelers from the tropics, but studies from the tropics suggest (and anecdotal reports in North American literature confirm) that the list of travel-related etiologies may be large. Common sources of prolonged fever in travelers include tuberculosis, amoebic liver abscesses, enteric fever and acute retroviral syndrome. Rare causes include visceral leishmaniasis, brucellosis, toxoplasmosis, leptospirosis and systemic fungal infections (e.g., histoplasmosis, coccidioidomycosis).

Laboratory Investigations. Potential communicability and mortality, the major concerns in a febrile patient from the tropics, must guide the use of laboratory studies.

Although the diagnosis of communicable diseases (e.g., hemorrhagic fevers, meningococemia) will initially be clinical, investigation of the hemorrhagic fevers requires immediate involvement of public-health officials and the CDC to

limit potential spread. Guidelines for isolation of patients, and the collection and transport of specimens, are available from the CDC.⁹

The most common tropical fevers (e.g., malaria, dengue, amoebic liver abscess, rickettsia) cannot be transmitted through person-to-person contact, and typhoid is not highly communicable in the North American setting. The principle risk associated with these fevers is related to a delay in the diagnosis of malaria.

For example, a delay of hours to days in the diagnosis of malaria may lead to death.¹⁰

Malaria

Malaria is the most common cause of fever in travelers returning from the tropics, and produces few signs or symptoms that are diagnostically useful.⁴

Death from malaria can occur rapidly. The median interval from the onset of fever until death is seven to eight days.

Published reports on travelers who died from malaria showed that there was an average delay of six days before seeking medical help.¹⁰

The clinician and the laboratory dealing with a potential case of malaria cannot afford any delay or error in making the diagnosis.¹¹

Specifically, the malaria smear should never be delayed. The sensitivity of the malaria smear is unrelated to the height of fever. A laboratory should be selected that can give results within an hour, and that can make and read both thick and thin smears.

Alternatively, the laboratory should be able to offer thin smears and a *Plasmodium*

falciparum antigen-capture technique. Occasionally, a blood smear will fail to detect malaria parasites.

Such false-negative results can occur during or after the use of antimalarial prophylactic therapy or other incidental antibiotics, as a result of laboratory error, due to the synchronous development of the schizont stage in *falciparum* malaria or the pathologic process (e.g., blackwater fever).

If the initial blood smears are negative and the diagnosis of malaria is still a consideration, blood examinations should be repeated one or more times daily until a definite diagnosis is established (Table 4).

Typhoid

In 50% to 70% of cases, a diagnosis of *Salmonella typhi* infection is established by positive blood cultures. The diagnostic yield can be increased by 10% to 20% with the culture of a bone-marrow aspirate or a sample of duodenal contents acquired by string test (Enterotest capsule).¹²

Blood cultures should be performed when fever is present (unlike malaria smears, which can be done in the absence of fever). Bone-marrow cultures may also be valuable in patients with a history of antibiotic use.

Dengue

Unlike malaria and typhoid, the presentation of dengue leads more easily to a strong clinical suspicion. A low white-blood-cell count, low platelets and atypical lympho-

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cytes are indirect but helpful laboratory findings.

Dengue and other arboviral infections can usually be diagnosed by the demonstration of a rising serum antibody titer to arboviral antigens in two specimens, drawn two or more weeks apart. Recently, the availability of Ig (immunoglobulin) M tests has reduced dependency on the analysis of paired sera.

These serologic tests are available from the CDC in Atlanta, and at the Canadian Arbovirus Reference Laboratory (CARL) in Winnipeg. Dengue is a relatively hardy

virus, and can often be cultured by these centers, even after shipping a blood specimen by mail.

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Rickettsia

Sensitive and specific rickettsial serologic tests are available

from the CDC and CARL via provincial public-health laboratories, or by special arrangement.

If rickettsial disease is clinically suspected on the basis of an eschar or a rash, treatment with antibiotics is appropriate; serology results almost always arrive too late to be clinically helpful.^{13,14}

Amoebic Liver Abscess

A raised white-cell count with increased neutrophils, normal platelets and normal liver function are all frequent findings in amoebic liver abscesses.

Clinical suspicion leading to a liver ultrasound is currently the standard diagnostic approach, with confirmation by positive amoebic serology, *Entamoeba histolytica* trophozoites in liver-abscess aspiration or a rapid response to metronidazole therapy.¹⁵

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