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Committee to Advise on Tropical Medicine and Travel (CATMAT)

Fever in the Returning International Traveller Initial Assessment Guidelines

Preamble

The Committee to Advise on Tropical Medicine and Travel (CATMAT) provides the Public Health Agency of Canada (PHAC) with ongoing and timely medical, scientific, and public health advice relating to tropical infectious diseases and health risks associated with international travel. PHAC acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and medical practices, and is disseminating this document for information purposes to both travellers and the medical community caring for travellers.

Persons administering or using drugs, vaccines, or other products should also be aware of the contents of the product monograph(s) or other similarly approved standards or instructions for use. Recommendations for use and other information set out herein may differ from that set out in the product monograph(s) or other similarly approved standards or instructions for use by the licensed manufacturer(s). Manufacturers have sought approval and provided evidence as to the safety and efficacy of their products only when used in accordance with the product monographs or other similarly approved standards or instructions for use.

Introduction

Fever in the international traveller is a common syndrome seen in the post-travel setting, and may herald serious and life-threatening illness, the most important of which is malaria. All febrile patients or patients complaining of fever should therefore be asked about recent travel. While fever in the returning traveller may be due to benign self-limited infections, such as common agents of travellers' diarrhea, or typical cosmopolitan causes unrelated to travel, it must be initially construed as a medical emergency, and warrants prompt and thorough evaluation. Accurate diagnosis and appropriate management necessitate a comprehensive travel history, including details about travel itinerary (destination, arrival and departure dates), the style of travel, pre-travel preparations, as well as potential exposures or medical treatment or care received abroad and a complete physical examination, with particular attention paid to systems with localizing symptoms or signs. The judicious use of laboratory testing should follow, with minimal essential tests outlined in the stepwise algorithm below.

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This document is designed to:

- Guide front-line clinicians, including those working in the emergency room, walk-in clinics, and primary care practices, in the initial evaluation and management of fever in the returning traveller;
- Provide front-line clinicians without ready access to inpatient, internal medicine, or infectious diseases support with guidance in the evaluation and management of fever in the returning traveller beyond the initial phase.

Epidemiology of fever in the returning traveller

Fever in the returning traveller may be due to tropical infections or illnesses that have more of a cosmopolitan distribution globally. Numerous large series of illness after international travel have repeatedly identified malaria (20-30%) [1], acute travellers' diarrhea (10-20%), and respiratory tract infections (10-15%) as the top causes of fever in travellers [2-11] (Table 1). Other common causes of fever in the returning traveller include dengue (5%), enteric fever due to *Salmonella enterica* serovar Typhi or Paratyphi (2-7%), skin and soft tissue infections (2-11%), rickettsioses (3%), urinary tract and sexually transmitted infections (2-3%), viral hepatitis (3%), and non-specific viral or mononucleosis-like syndrome (4-25%) [2-11]. In febrile returning pediatric travellers, malaria (35%), viral syndromes (28%), unspecified febrile illnesses (11%), dengue (6%), and enteric fever (6%) are the most well-represented etiologies [12]. Fever after international travel may be due to non-infectious causes as well, and include diverse etiologies such as drug reactions, pulmonary emboli, inflammatory conditions such as inflammatory bowel disease (IBD), malignancy, and hyperthyroidism.

Destination-specific analysis is helpful for establishing the epidemiology of travel-acquired illness [13] (Table 2). A history of travel to the Indian sub-continent in a febrile returned traveller should raise the suspicion of enteric fever: of 416 cases of imported typhoid in the United Kingdom over a three year period, 70% were imported from India and Pakistan [14]. Malaria, on the other hand, illustrates a very different epidemiology among imported cases, with relative risks highest among travellers in sub-Saharan Africa [15]. Unlike malaria, dengue fever is more likely to be acquired from South Asia, Southeast Asia and Latin America, rather than from Africa [13].

Purpose of travel is another useful piece of the travel history. People who travel for the purpose of visiting friends and relatives (VFR), including VFR children, constitute a particular risk group for acquisition of travel-related infections [12], particularly malaria [16] and enteric fever [4], and in the case of VFR children, acute viral hepatitis [17].

A thorough travel history with an understanding of what illnesses are possible based on dates and style of travel, geographic risks, and specific travel itinerary including activities and behaviors is essential to narrowing the differential diagnosis and ruling out life-threatening travel-acquired infections. Incubation period, defined as the time from initial exposure and infection to manifestation of symptoms, is also useful in refining the differential diagnosis. For instance, travel-acquired illnesses with short incubation periods including dengue, chikungunya, and travellers' diarrhea, can be reliably excluded if symptoms do not manifest until >2 weeks after leaving the endemic area. Similarly, travel-acquired illnesses with long incubation periods such as tuberculosis (TB), hepatitis B (HBV), or visceral leishmaniasis can be discounted as travel-related if symptoms occur within days of returning from a one-week trip abroad. It is important to consider the earliest and latest possible dates of exposure in ill returned short and long-term travellers to better inform the use of the incubation period in formulating a differential diagnosis. The following step-wise algorithm is designed to guide the clinician through his or her initial assessment of a returned traveller with fever, and in rare cases, to provide further guidance when inpatient support or specialist consultation is delayed or unavailable.

Table 1: Top specific diagnoses in single[2;3;5-11] and multi-centre [4;12] analyses of fever in the returning traveller

1. Malaria (20-30%)	6. Skin and soft tissue infections (2-11%)
2. Acute travellers' diarrhea / gastroenteritis (10-20%)	7. Rickettsioses, including African tick bite fever, Mediterranean spotted fever (tick typhus) (3%)
3. Respiratory tract infections (RTI) (10-15%)	8. Acute urinary tract infection / sexually transmitted infection (UTI / STI) (2-3%)
4. Dengue fever (5%)	9. Viral hepatitis (3%)
5. Enteric fever (*S. enterica* serovar Typhi or Paratyphi) (2-7%)	10. Mononucleosis- or viral-like syndrome (4-25%)

(CATMAT statements are available at http://www.phac-aspc.gc.ca/tmp-pmv/catmat-ccmtmv/index-eng.php)

Table 2: Top specific diagnoses by region of travel in multi-centre [4;13] analyses of fever in the returning traveller

Sub-Saharan Africa	Malaria, RTI, diarrheal illness, skin and soft tissue infections
Southeast Asia	Dengue fever, RTI, diarrheal illness, malaria
South Central Asia / Indian sub-continent	Enteric fever, dengue fever, malaria, diarrheal illness
South America	Diarrheal illness, RTI, dengue fever, malaria
Caribbean / Central America	Diarrheal illness, RTI, dengue fever, malaria

Evaluation of fever in the returning traveller

Objective: Exclusion of life-threatening, highly communicable, or treatable illness

STEP 1: History of travel	
A. PRE-TRAVEL PREPARATIONS	**Pre-travel consultation**: date, location, contact details
	Immunizations received and dates; oral versus injectable formulation if applicable; completion of full vaccination series for travel and for routine childhood immunizations
	Malaria prophylaxis: drug, dose, schedule, adherence, duration, side effects
	Other prophylaxis: drug, dose, schedule, adherence, duration, side effects
	Other personal protective measures: standby treatment of malaria / travellers' diarrhea; bednets; clothing; insecticide use
	Air transportation preparations: deep vein thrombosis (DVT) prophylaxis, medications for jet lag
	Environmental risk preparations: sun, extreme heat, altitude
B. SPECIFIC TRAVEL ITINERARY	**Dates of travel** (approximation of incubation period)
	Season of travel: rainy, dry
	Specific destinations: regions; urban, rural; proximity to fresh water; jungle, desert
	Reason for travel: tourism, business, visiting friends and relatives (VFR), other
	Style of travel: accommodation; off typical tourist routes; camping, trekking
	Local population: possible TB contacts, outbreaks, illnesses
	Transportation: crowding; use of animals such as camels, elephants

C. EXPOSURE HISTORY*	**Street foods / Local water** (enteric fever, travellers' diarrhea)
	Arthropod bites (malaria, dengue, chikungunya, arboviruses, *Rickettsia*, African trypanosomiasis)
	Uncooked meat / unpasteurized dairy (trichinosis, brucellosis, toxoplasmosis)
	Blood and body fluid exposure: sexual encounters, tattoos, piercings, injections including immunizations, intravenous (IV) drug use, and rabies post-exposure prophylaxis (PEP) (human immunodeficiency virus [HIV], HBV, hepatitis C virus [HCV], herpes simplex virus [HSV], syphilis, gonorrhea (gonococcus) / *Chlamydia trachomatis* [GC/CT])
	Fresh water activities: swimming, kayaking, rafting (schistosomiasis, leptospirosis)
	Animal exposures (Q-fever, brucellosis, tularemia, anthrax, rabies, Crimean-Congo hemorrhagic fever)
	Safari (rickettsioses, African trypanosomiasis)

*For epidemiology of specific diseases, please refer to websites of the WHO (World Health Organization) (http://www.who.int/topics/en/), or the Public Health Agency of Canada (PHAC) (http://www.phac-aspc.gc.ca/tmp-pmv/info/index-eng.php), the U.S. Centers for Disease Control and Prevention (CDC) (http://wwwnc.cdc.gov/travel/content/diseases.aspx).

STEP 2: History of fever and clinical features		
A. FEVER PATTERN	**Daily / Continuous**	**Common**: malaria, travellers' diarrhea, RTI, enteric fever
		Uncommon: rickettsioses
		Rare: HIV, Q-fever, brucellosis, TB
	Saddleback (biphasic)	**Common**: malaria, dengue
		Uncommon: leptospirosis
		Rare: yellow fever, arbovirus
	Relapsing	**Common**: malaria, enteric fever
		Uncommon: amoebic liver abscess, leptospirosis
		Rare: HIV, Q-fever, brucellosis, TB, endemic mycoses, borreliosis
B. INCUBATION PERIOD (DEFINITION: TIME FROM EXPOSURE / INFECTION TO DISEASE MANIFESTATION)	**<2 weeks**	**Common**: malaria, travellers' diarrhea, dengue, RTI, influenza
		Uncommon: rickettsioses, meningitis
		Rare: yellow fever, arbovirus, viral hemorrhagic fever
	2-6 weeks	**Common**: malaria, enteric fever
		Uncommon: hepatitis A virus (HAV), katayama fever, amoebic liver abscess, hepatitis E virus
		Rare: HIV, Q-fever, brucellosis, East African trypanosomiasis
	>6 weeks	**Common**: malaria
		Uncommon: HBV, amoebic liver abscess, TB
		Rare: HIV, visceral leishmaniasis, endemic mycoses, West African trypanosomiasis, HCV

C. FEVER DURATION AT VISIT	**<7 days**	**Common**: malaria, travellers' diarrhea, dengue, enteric fever, RTI
		Uncommon: rickettsioses, leptospirosis, meningitis
		Rare: yellow fever, arbovirus
	7-21 days	**Common**: malaria, enteric fever
		Uncommon: rickettsioses, viral hepatitis, leptospirosis
		Rare: HIV, Q-fever, brucellosis
	>21 days	**Common**: malaria, enteric fever
		Uncommon: TB, HBV, bacterial endocarditis
		Rare: HIV, Q-fever, brucellosis

Arbovirus: includes other mosquito-borne viruses such as chikungunya, mayaro, O'nyong-nyong, Ross River, sindbis, equine encephalitis, WNV, La Crosse, Oropouche, Rift Valley fever, and tick-borne viruses such as Kyasanur Forest, Omsk, and Crimean-Congo hemorrhagic fever

STEP 3: Primary laboratory investigations after comprehensive physical examination including thorough skin examination
Returned travellers with fever should undergo <u>at least</u> the following investigations: The febrile traveller to a malaria endemic area [1] should be considered to have malaria until proven otherwise. Travel history should be cited on all laboratory requisitions.
1. Complete blood count with differential; liver enzymes; electrolytes; creatinine
2. Malaria smears ± antigen detection dipstick at least 3 times over 24-48 hours
3. Blood cultures x 2 (*S. enterica* serovar Typhi or Paratyphi; meningococcus; common agents of bacteremia)
4. Urinalysis (± urine culture)
Consider the following supplementary tests based on history and epidemiology:
5. Stool culture for enteropathogens x 1 (*Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *E. coli* O157:H7)
6. Chest x-ray
7. Stool for ova and parasites (*Cyclospora, Cryptosporidium, Entamoeba histolytica, Giardia*)
8. Dengue serology if probable incubation period <2 weeks AND traveller to South Asia, Southeast Asia, or Latin America
9. Acute serology tube to be saved in lab and paired with convalescent sera if no diagnosis in 10-14 days

Consider referral to a person with expertise in tropical medicine or infectious diseases (as available) if primary laboratory investigations yield no definitive diagnosis and patient is not improving, or patient is at risk of complications (e.g., pregnant women, children, underlying co-morbidities, immunocompromised, etc). Additional support, if required, may be sought through the Canadian Malaria Network (http://www.phac-aspc.gc.ca/tmp-pmv/quinine/index-eng.php)

STEP 4: Empiric management for presumed travellers' diarrhea or enteric fever ± rickettsioses in adult travellers i, ii

Consider if patient fulfills the following criteria:

1. Undifferentiated fever; and
2. Negative malaria smears [1]; and
3. Patient has not improved over past 48-72 hours; and
4. All other cultures and tests have been ordered and are pending or non-contributory

Travelled to the Indian Sub-Continent or Southeast Asia	Travelled outside the Indian Sub-Continent or Southeast Asia
1. Azithromycin 1000 mg po once daily x 5 days (alternative: 1000 mg po once on day 1, then 500 mg once daily x 6 days) **±** 2. Doxycycline** 100 mg po BID x 7 days	1. Ciprofloxacin 500 mg po BID x 3-7* days **±** 2. Doxycycline** 100 mg po BID x 7 days

i). Step 4 is not a substitute for Step 3 (Primary laboratory investigations after comprehensive physical examination), nor should empiric therapy preclude ongoing and close follow-up of the patient. Undifferentiated fever refers to fever without prominent localizing symptoms or signs, and is often the presenting complaint in many travel-acquired illnesses including malaria and enteric fever. It is essential that all febrile returned travellers to potentially malarious areas undergo malaria screening with 2-3 smears over 48 hours ± rapid antigen testing. Adult patients who have not improved substantially, either subjectively or objectively, over the previous 48-72 hours are candidates for empiric therapy as above while investigations are pending. **These patients require frequent clinical reassessment (every 1-2 days) until either a diagnosis is made and definitive therapy instituted, or until subjective and objective clinical improvement is achieved.** Prior to initiation of empiric therapy as above, all samples for microbiological testing should have been obtained as outlined in Step 3.

ii) Caution must be exercised in the evaluation and empiric therapy of fever in children, given the higher rate of complicated disease in this age group. Clinicians should have a low threshold for admission and initiation of IV therapy for presumed enteric fever, in which case a parenteral third generation cephalosporin (ceftriaxone or cefotaxime) could be considered. Similarly, use of doxycycline and ciprofloxacin is not routine in children and generally reserved for specific cases in which the benefits of these antibiotics are felt to exceed the potential risks (permanent dental staining, arthropathy). Consultation with a specialist experienced in the treatment of pediatric tropical diseases should be considered.

*3-day regimen for suspected travellers' diarrhea; 7-10-day regimen for suspected enteric fever
**this will also cover leptospirosis

Appendix I. Specific tests to rule out common travel-acquired infections that can cause fever

Travel-acquired infection	Diagnostic test(s)
Malaria	1. Thick and thin blood smears ± antigen-based dipstick assay; minimum 2-3 times over 24-48 hours 2. Blood for malaria polymerase chain reaction (PCR) if smears and/or dipstick negative but index of suspicion high
Acute travellers' diarrhea / gastroenteritis (60-80% bacterial)	1. Stool culture for enteropathogens x 1 (will detect *Salmonella, Shigella, Campylobacter*, *E. coli* O157:H7, and often *Yersinia*) 2. Stool for *Clostridium difficile* toxin 3. Stool for ova and parasites (O&P) x 3 (be aware that not all laboratories screen for all protozoa, including coccidia, routinely; check with local laboratory for special staining request requirements) 4. Amoebic serology ± stool *Entamoeba histolytica* ELISA if bloody stool
RTI	1. Chest x-ray 2. Nasopharyngeal swab (NP) swab for viral antigen testing or PCR (influenza A/B, respiratory syncytial virus [RSV], adenovirus, parainfluenza virus 1-3, human metapneumovirus, coronavirus) 3. Sputum for culture and susceptibility (C&S) and acid-fast bacilli (AFB) (as directed by index of suspicion) 4. *Legionella* urine antigen 5. Epstein-Barr virus (EBV) – EBV monospot unreliable in children ≤ 4 years of age; EBV viral capsule antigen (VCA) IgM/IgG, EBV nuclear antigen (EBNA) IgM/IgG 6. (Serology for Q-fever, *Histoplasma, Blastomyces, Coccidioides* as directed by index of suspicion and travel exposures; urinary antigen for *Histoplasma*)
Dengue	1. Acute and convalescent sera (2 weeks after) for dengue IgM and IgG
Enteric fever due to *Salmonella enterica* serovar Typhi or Paratyphi	1. Blood culture x 2 (caution if the patient has received antibiotics as they may have negative blood cultures) 2. Stool culture 3. (Bone marrow aspirate and culture)
Skin and soft tissue infection	1. Clinical diagnosis 2. Skin swab for methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* (MSSA and MRSA) if exudative 3. If ulcerative, smears for Giemsa-stain, biopsy or aspirate for *Leishmania* culture or PCR; consider skin swab to rule out ecthyma ulcer due to *Staphylococcus* or *Pseudomonas*
Rickettsioses	1. Clinical diagnosis – presence of an eschar is diagnostic (but may not be present) 2. Acute and convalescent sera for rickettsial serology

Acute UTI / STI	1. Urinalysis and urine microscopy 2. Urine culture 3. Urine and/or endocervical swabs for GC/CT 4. Swab for viral PCR of genital vesicles 5. Blood for HIV, HBV, HCV and syphilis serology
Viral hepatitis	1. HAV – HAV IgM, HAV IgG (unless history of previous vaccination) 2. HBV – HBsAg (surface antigen), HBsAb (surface antibody), HBcAb (core antibody), HBeAg (e antigen), HBeAb (e antibody); HBV DNA 3. HCV – HCV total antibody 4. Hepatitis D virus (HDV) – Anti-HDV antigen; serum HDV RNA reverse transcription PCR (RT-PCR) 5. Hepatitis E virus (HEV) – Anti-HEV IgM antibody; blood or stool for HEV PCR 6. EBV – EBV monospot unreliable in children ≤ 4 years of age; EBV VCA IgM/IgG, EBNA IgM/IgG 7. Cytomegalovirus (CMV) – IgM/IgG; CMV antigenemia; serum for CMV PCR
Other potentially travel-acquired infections diagnosed by serology	1. Viral – Chikungunya, arboviruses 2. Bacterial – Q-fever, *Brucella* (can also be cultured from blood or bone marrow), *Leptospira* 3. Fungal – *Histoplasma, Blastomyces, Coccidioides, Cryptococcus* (can detect by serum or CSF or urinary antigen also) 4. Parasitic – *Strongyloides, Schistosoma*, Amoebiasis (can also detect in stool O&P and by stool ELISA)

Appendix II. Additional resources for guidance on fever in the returning traveller

Committee to Advise on Tropical Medicine and Travel (CATMAT) Statements

Canadian Recommendations for the Prevention and Treatment of Malaria among International Travellers (2009)
http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/35s1/index-eng.php

Statement On Persistent Diarrhea In The Returned Traveller (2006)
http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/06vol32/acs-01/index-eng.php

Statement on Travellers and Sexually Transmitted Infections (2006)
http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/06vol32/acs-05/index-eng.php

Public Health Agency of Canada

Travel Health Notices website
http://www.phac-aspc.gc.ca/tmp-pmv/pub-eng.php

National Microbiology Laboratory
http://www.nml-lnm.gc.ca/index-eng.htm

Canadian Malarial Network Coordinators (available on the Public Health Agency of Canada's website)
http://www.phac-aspc.gc.ca/tmp-pmv/quinine/index-eng.php

United States - Centers for Disease Control and Prevention

http://www.cdc.gov/

Viral Special Pathogens Branch, NCID
http://www.cdc.gov/ncidod/dvrd/spb/mnpages/disinfo.htm

VSPB specimen submission info
http://www.cdc.gov/ncidod/dvrd/spb/mnpages/specimen.htm (phone number 404-639-2888)

International

World Health Organization outbreak site
www.who.int/csr/don/en

Promed
www.promedmail.org

Articles for further reading

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Glossary

AFB	Acid fast bacilli
BID	*Bis in die* (twice per day)
CATMAT	Committee to Advise on Tropical Medicine and Travel
CDC	Centers for Disease Control and Prevention
CMV	Cytomegalovirus
CSF	Cerebrospinal fluid
C&S	Culture and susceptibility
DNA	Deoxyribonucleic acid
DVT	Deep vein thrombosis
EBV	Epstein-Barr virus
EBNA	Epstein-Barr virus nuclear antigen
EBV VCA	Epstein-Barr virus viral capsule antigen
ELISA	Enzyme-linked immunosorbent assay
GC/CT	Gonorrhea (gonococcus) / Chlamydia trachomatis
HAV	Hepatitis A virus
HBcAb	Hepatitis B core antibody
HBeAg	Hepatitis B e antigen
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
HSV	Herpes simplex virus
IBD	Inflammatory bowel disease
IgM	Immunoglobulin M
IgG	Immunoglobulin G
IV	Intravenous
MRSA	Methicillin-resistant Staphylococcus aureus
MSSA	Methicillin-sensitive Staphylococcus aureus
NP	Nasopharyngeal swab
O&P	Ova and parasites
PCR	Polymerase chain reaction
PEP	Post-exposure prophylaxis
PHAC	Public Health Agency of Canada
po	*Per os* (by mouth)
RNA	Ribonucleic acid
RSV	Respiratory syncytial virus
RT-PCR	Reverse transcription polymerase chain reaction
RTI	Respiratory tract infection
STI	Sexually transmitted infection
TB	Tuberculosis
UTI	Urinary tract infection
VFR	Visiting friends and relatives
WHO	World Health Organization
WNV	West Nile virus

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