Illness in Travelers

- 50 million people travel from industrialized to developing countries each year
- 22%-64% report some illness
- Up to 10% of travelers consult a physician on or after a trip
- 1 in 100,000 travelers will die

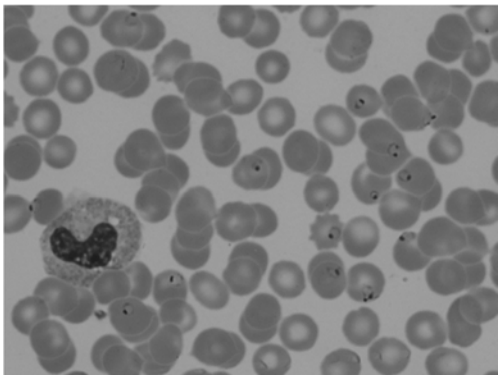
Steffen R , Rickenbach M, Wilhelm U, et al. Health problems after travel to developing countries. J Infect Dis 1987; 156: 84 – 91

Fevers from Around the World: Travel Associated Infections

- Epidemiology of febrile illness in returning travelers
- Malaria
- Typhoid fever
- African tick bite fever
- Emerging and re-emerging viral infections
  - Dengue fever
  - Chikungunya
  - Zika virus

Fever in a Pregnant Traveler

- A woman at 33 weeks gestation presented with fever, chills, and body aches.
- Returned from visiting relatives in India 6 days earlier.
- At her obstetrician's direction she had not taken any medications during her 8 week trip.
- Treated with empiric antibiotics but fever persisted.
- An infectious diseases physician requested that a blood smear be performed.



Plasmodium falciparum

Fever in a Pregnant Traveler

- She developed increasing shortness of breath and a chest x-ray was performed.

Fever in a Pregnant Traveler

- She was intubated and mechanically ventilated.
- She underwent a 6 unit exchange transfusion and treatment with intravenous quinidine and clindamycin
- The baby developed signs of distress and was delivered by emergency C-section in the ICU
- Mother and child both recovered completely and left the hospital

Anopheles Mosquitoes

- Of the approximately 430 *Anopheles* species, only 30-40 transmit malaria
- Transmitted only by adult females
- Primary malaria vectors in Africa
  - *An. gambiae* and *An. funestus*
  - Strongly anthropophilic
- Most active at dusk and dawn
- Intrinsic incubation period 10–21 days

Malaria in the U.S., 2008

- 1298 cases
  - US resident 75%
  - Foreign resident 25%
- Origin
  - Africa 70%
    - West Africa 87%
  - Asia 21%
    - India 67%
- Reason for travel
  - VFR 65%
  - Tourism 6%
  - Missionary 8%
  - Business 7%
  - Student 3%
- Species
  - *P. falciparum* 41%
  - *P. vivax* 15%
  - *P. malariae* 1.5%
  - *P. ovale* 1.4%
  - *P. knowlesi* 0.1%
  - Unknown 41%
- Chemoprophylaxis
  - 28%
- Outcome
  - Severe 9%
  - Mortality 0.15%

Centers for Disease Control and Prevention. Malaria Surveillance — United States, 2008. MMWR 2010;59(No. SS-7).

Malarial Antigen Targets for Rapid Diagnostic Tests

- Histidine-rich protein 2 (PfHRP2)
  - *P. falciparum* only
  - Expressed on RBC membrane surface
  - Remains in blood for ≥28 days after initiation of antimalarial therapy
- *Plasmodium* aldolase
  - Parasite glycolytic enzyme
  - Pan malarial antigen (PMA)
- Parasite lactate dehydrogenase (pLDH)
  - Parasite glycolytic enzyme
  - pan malarial antigen (PMA)

Diagnostic Performance of Rapid Diagnostic Tests versus Blood Smears for Malaria in US Clinical Practice

852 consecutive blood samples 2003–2006

Thick and thin smears

Blinded malaria RDTs

Positive and discordant test results verified by PCR

	Sensitivity, %	Specificity,%	PPV,%	NPV,%
Malaria (n=95)				
Blood smear	85	100	99	93
RDT	97	99	92	98
Plasmodium falciparum (n=74)				
Blood smear	88	100	100	95
RDT	100	99	90	100

Clin Infect Dis 2009; 49:908–13

Guidelines for Treatment of Malaria in the U.S.
Uncomplicated *P. falciparum* Malaria *or* Species Not Identified

- Atovaquone-proguanil (Malarone™) daily x 3 days
- Artemether-lumefantrine (Coartem™) 6 doses over 3 days
- Quinine sulfate x 3 (or 7) days plus Doxycycline (or Clindamycin) x 7 days
- Mefloquine x 2 doses

If chloroquine-sensitive (Central America west of Panama Canal; Haiti; the Dominican Republic; and most of the Middle East)

- Chloroquine x 4 doses over 48 hours

www.cdc.gov/malaria/pdf/treatmenttable.pdf

Guidelines for Treatment of Malaria in the U.S.
Uncomplicated Malaria Non-Falciparum Species

- *Plasmodium malariae* or *P. knowlesi*
  - Chloroquine
- *Plasmodium vivax or Plasmodium ovale* acquired outside Papua New Guinea or Indonesia
  - Chloroquine plus Primaquine*
- *P. vivax acquired in* Papua New Guinea or Indonesia
  - Atovaquone-Proguanil
  - Alternatives: Quinine plus Doxycycline, or Mefloquine
  - Plus Primaquine*

* if not G6PD deficient

www.cdc.gov/malaria/pdf/treatmenttable.pdf

Guidelines for Treatment of Malaria in the U.S. Severe Malaria*

- Intravenous Quinidine plus Doxycycline or Clindamycin
- *Investigational new drug (contact CDC for information):* Artesunate followed by atovaquone-proguanil (Malarone™), doxycycline (clindamycin in pregnant women), or mefloquine
- Switch to oral antimalarial medication once parasite density <1% and able to take oral medications

Features of severe malaria: Impaired consciousness/coma, severe normocytic anemia, renal failure, pulmonary edema, acute respiratory distress syndrome, circulatory shock, disseminated intravascular coagulation, spontaneous bleeding, acidosis, hemoglobinuria, jaundice, repeated generalized convulsions, and/or parasitemia of > 5%

CDC Malaria Hotline: (770) 488-7788 Monday-Friday 8 am to 4:30 pm EST (770) 488-7100 after hours, weekends and holidays. www.cdc.gov/malaria/pdf/treatmenttable.pdf

Fever after Safari

- A healthy 51-year-old woman spent a week on safari in South Africa. On the day she returned to the Chicago, she developed fever, chills, sweats, and fatigue. She noticed three lesions; one on her abdominal wall and two on her lower extremities.
- T 102.6
- WBC 3.86, Platelets 145K

African Tick Bite Fever

Amblyomma variegatum
Alan R. Walker, wikimedia

- *Rickettsia africae*
- Vectors: *Amblyomma hebraeum, Amblyomma variegatum*
  - Aggressive, human-biting ticks, high rates of infection with *R. africae*; cases often occur in clusters, frequently described among groups of persons on safari or adventure races
- Fever, solitary or multiple eschars, regional lymphadenopathy, maculopapular rash
- Treatment: doxycycline

Signs and Symptoms of African Tick Bite Fever

Characteristic	Frequency (%)
Fever	59–100
Headache	62–83
Myalgia	63–87
Neck muscle myalgia	81
Inoculation eschar	53–100
Multiple eschars	21–54
Regional lymphadenitis	43–100
Cutaneous rash	15–46

Lancet Infect Dis 2003; **3:** 557–64
J Emerg Med 2015; 48 (5): 562–5
IDCases. 2016; 5: 78–79

Recurrent Fever after Return from Study Abroad

- 20 yo woman with 4 days of fever, chills, headache
- Similar illness 6 weeks ago during a semester abroad in Gujarat, India treated with oral ciprofloxacin with improvement
- Returned to college in U.S. 3 weeks ago and illness recurred. Blood cultures + Salmonella; treated with ciprofloxacin IV x 14 days; fever recurred 4 days later.
- Advised to have another PICC line placed and a repeat course of ciprofloxacin. Parents sought a second opinion.
- T 103.6 100 140/72 non-localizing exam
- WBC 5.6 Platelets 233 AST 42 CRP 3.0

Recurrent Fever after Return from Study Abroad

- OSH blood culture results reviewed:
  - *Salmonella enterica* subspecies *enterica* serotype typhi
  - Antibiotic susceptibility results:
    - Ciprofloxacin S
    - Nalidixic acid R
- Treated with azithromycin 1g then 500 mg daily x 7 days with resolution of her illness

Typhoid Fever

- *Salmonella enterica* subspecies *enterica* serotype typhi
- Fecal-oral transmission
- Fever, headache, dry cough, abdominal pain with constipation or diarrhea
- Blood culture sensitivity 80%
- Emerging multidrug, nalidixic acid-resistant strains
  - Demonstrate reduced susceptibility to flouroquinolones
  - Treatment options: ceftriaxone, azithromycin

Enteric Fever in the U.S. 2008-2012

- 2341 enteric fever cases reported
  - 80% typhoid
  - 20% paratyphoid A
- Foreign travel within 30 days preceding illness onset reported by 86%
  - Travel to southern Asia
    - 82% for typhoid
    - 97% for paratyphoid A
- Increasing nalidixic acid-resistance 2008 to 2012
  - Typhoid: 60 to 68%
  - Paratyphoid A: 91% to 94%

Clin Infect Dis 2016;63(3):322–9

Fever during Return from Thailand

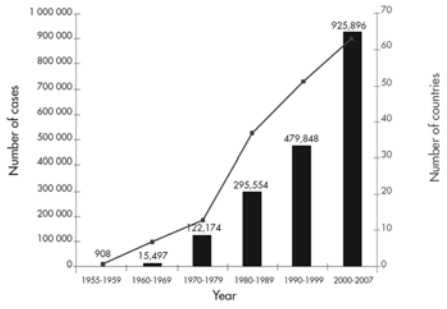
- A 38-year-old male graduate student developed fever, chills, myalgias, arthralgias, headache and photophobia on the flight home from Thailand.
- He claims he received all of his travel immunizations and continues to take mefloquine prophylaxis weekly as directed.
- Ill-appearing, T 39.5°C; no focal findings.
- WBC 2.5 (45% neutrophils/23% bands), AST 95
- Blood cultures, stool culture, stool for ova and parasites, blood smear for malaria, and cerebrospinal fluid examination negative.
- He developed a rash.

- Serum was sent to the CDC for dengue virus serology:

HAI	DEN-1	1:60
	DEN-2	1:320
	DEN-3	1:320
	DEN-4	1:160
IgM ELISA	Strongly positive	

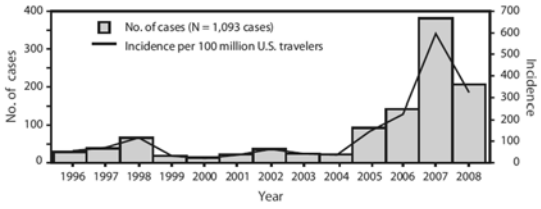
- He gradually recovered, but post-illness fatigue persisted for months.

The Growing Threat of Dengue Fever (DF) and Dengue Haemorrhagic Fever (DHF), 1955–2007



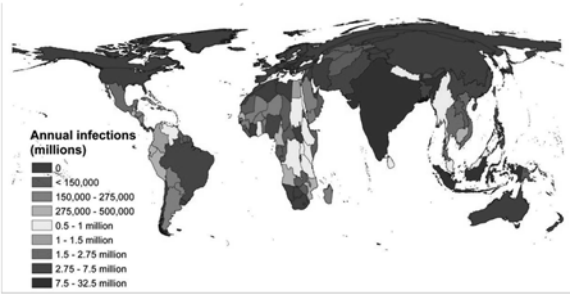
WHO. Dengue: guidelines for diagnosis, treatment, prevention and control -- New edition. 2009

Laboratory-Confirmed Dengue Cases per 100 Million U.S. Travelers — 1996–2008



MMWR / June 18, 2010 / Vol. 59 / No. 23: 715-9

Global Burden of Dengue in 2010



Nature. 2013 Apr 25; 496(7446): 504–5070

Clinical Syndromes of Dengue Virus Infection

- Classic dengue fever
  - Fever, headache, muscle and joint pain, nausea/vomiting, rash (50%), conjunctival injection, hemorrhagic manifestations – e.g., purpura or melena (22% of adults), leukopenia, thrombocytopenia, elevated AST
- Dengue hemorrhagic fever
  - Fever, hemorrhagic manifestations, severe thrombocytopenia (<100K), increased vascular permeability (hemoconcentration, pleural effusion or ascites)

Aedes Mosquitoes

Aedes aegypti

- Live in tropical, subtropical, and some temperate climates
- Transmit Zika, dengue, chikungunya
- Live near and prefer to feed on people - more likely to spread these viruses than other types of mosquitoes

Aedes albopictus

- Live tropical, subtropical, and temperate climates, but can live in a broader temperature range and at cooler temperatures than *Aedes aegypti*
- Feed on animals as well as people - less likely to spread viruses like Zika, dengue, chikungunya

Aedes aegypti and *Aedes albopictus* Mosquitoes: Geographic Distribution in the United States

Aedes aegypti *Aedes albopictus*

Chikungunya: Clinical Manifestations

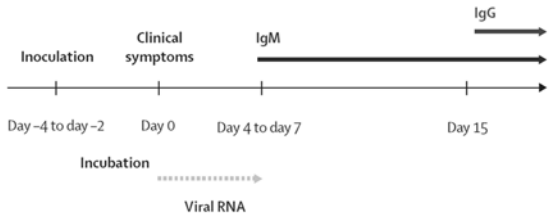
1998 Malaysian and the 2005 Réunion epidemic

	Malaysia 1998 (%) (n=51)	Réunion 2005–2006 (%) (n=504)
Fever	100	100
Arthralgia	78	100
Myalgia	50	60
Headache	50	50
Skin rash	50	39

Lancet Infect Dis 2007; 7: 319–27

Countries and territories where chikungunya cases have been reported (as of April 22, 2016)

Chikungunya Virus Infection Diagnosis



Lancet Infect Dis 2007; 7: 319–27

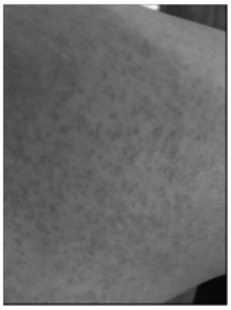
Zika Virus

- 1 in 5 people infected with Zika virus become symptomatic
- Acute onset, fever, maculopapular rash, arthralgia, conjunctivitis, myalgia and headache
- Clinical illness is usually mild lasting for several days to a week
- Severe disease requiring hospitalization is uncommon and case fatality is low
- Complications
  - Guillain-Barre syndrome
  - Zika virus in pregnancy and fetal microcephaly

Zika Virus Infection: Clinical Manifestations

49 travelers December 2015 - February 2016

Rash	95.7%
Fever	81.6%
Arthralgia	63.8%
Conjunctivitis	53.1%
Malaise/fatigue	42.8%
Myalgia	40.8%
Headache	40.8%



Am J Med. 2016 May 31. pii: S0002-9343(16)30536-8.

The Virgin Islands Consortium
Jose Wesley, a Brazilian baby shown on Dec. 23, 2015, was born with microcephaly. His mother was diagnosed with the Zika virus
http://viconsortium.com/featured/first-case-of-zika-virus-causing-abnormal-head-growth-of-children-hits-puerto-rico/

Countries & Territories with Active Zika Virus Transmission

CDC

Zika Virus Diagnosis

- CDC Arbovirus Diagnostic Laboratory
- First week of illness
  - Serum RT-PCR
- Second week of illness (and beyond)
  - Zika virus IgM (potential cross reaction with dengue and yellow fever)
  - Plaque reduction neutralization assay

Zika Virus
Management and Prevention

- No treatment; no vaccine
- Do not treat illness with aspirin or NSAIDs; use acetaminophen
- Avoid mosquito bites
- Women who are pregnant (in any trimester):
  - Consider postponing travel to any area where Zika virus transmission is ongoing.
  - If you must travel to one of these areas, talk to your doctor first and strictly follow steps to prevent mosquito bites during your trip.
- Women who are trying to become pregnant:
  - Before you travel, talk to your doctor about your plans to become pregnant and the risk of Zika virus infection.
  - Strictly follow steps to prevent mosquito bites during your trip

Clinical Features: Zika virus Compared to Dengue and Chikungunya

Features	Zika	Dengue	Chikungunya
• Fever	++	+++	+++
• Rash	+++	+	++
• Conjunctivitis	++	-	-
• Arthralgia	++	+	+++
• Myalgia	+	++	+
• Headache	+	++	++
• Hemorrhage	-	++	-
• Shock	-	+	-

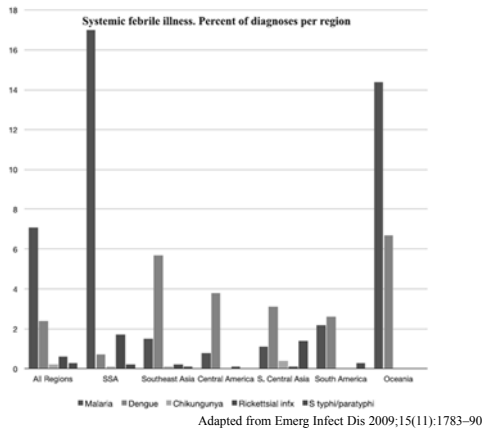
Spectrum of Viral Pathogens in Blood of Malaria-Free Ill Travelers Returning to Canada

- Screened 1,592 specimens for malaria
  - 165 positive for *P. falciparum*, 93 for *P. vivax*, 20 for *P. ovale*, 5 for *P. malariae* and 5 mixed *Plasmodium* infections
- Remaining 1,308 malaria-negative specimens – RT-PCR
  - Dengue virus 33
  - Chikungunya virus 5
  - Untypeable flavivirus 2
  - HAV 12
  - HSV-1 7
  - HSV-2 14
  - CMV 4
  - EBV 194

Emerg Infect Dis 2016; 22(5): 854-61

Common Tropical Diseases by Geographic Area

Geographic area	**Most common tropical illnesses**
Caribbean	Dengue fever, malaria
Central America	Dengue fever, malaria (mostly *P. vivax*)
South America	Dengue fever, malaria (mostly *P. vivax*)
South Central Asia	Dengue fever, enteric fever, malaria (mostly non–*falciparum*)
Southeast Asia	Dengue fever, malaria (mostly non–*falciparum*)
Sub-Saharan Africa	Malaria (mostly *P. falciparum*), tick-borne rickettsiae, acute schistosomiasis, filariasis



Adapted from Emerg Infect Dis 2009;15(11):1783–90

Incubation Period for Tropical Diseases That May Present with Fever <14 days

Disease	Usual incubation period (range)
Chikungunya	2 to 4 days (1 to 14 days)
Dengue fever	4 to 8 days (3 to 14 days)
Zika virus	3 to 12 days
Leptospirosis	7 to 12 days (2 to 26 days)
Malaria (P. falciparum)	6 to 30 days (weeks to months)
Malaria (P. vivax)	8 to 30 days (months to years)
Spotted fever group rickettsia	3 to 21 days
Typhoid fever	7 to 18 days (3 to 60 days)

Incubation Period for Tropical Diseases That May Present with Fever >14 days

Disease	Usual incubation period (range)
Amebic liver abscess	Weeks to months
Hepatitis A	28 to 30 days (15 to 50 days)
Hepatitis E	26 to 42 days (14 to 63 days)
Schistosomiasis	28 to 56 days
Tuberculosis	Weeks to months to years
Visceral leishmaniasis	2 to 10 months (10 days to years)

Evaluation of Fever in Returning Travelers

- CBC and differential, liver function tests, tuberculin skin test, chest x-ray, urinalysis
- Blood smears for malaria
- Blood cultures
- Stool culture and exam for ova and parasites
- Heterophile antibody, EBV and CMV IgM

Evaluation of Fever in Returning Travelers

In selected cases consider:

- Serology (IgM) for dengue, chikungunya, Zika virus, hepatitis A, hepatitis E
- HIV-RNA

In very selected cases consider:

- Serology for *Entamoeba histolytica*, leptospirosis, brucellosis, Q fever
- Blood smears for trypanosomiasis, borreliosis, filariasis
- Bone marrow aspirate for leishmaniasis

Fevers from Around the World: Travel Associated Infections

- Malaria
  - Fever, leukopenia, increased bands, thrombocytopenia, elevated CRP
  - Travel to Sub Saharan Africa, Oceania and Pacific Islands
  - Medical emergency
  - RDT or blood smear
- Typhoid fever
  - Fever, leukopenia, elevated CRP
  - Travel to South Central Asia (India, Pakistan)
  - Blood cultures (prior to antibiotic therapy)
  - Increasing flouroquinolone resistance (nalidixic acid resistance)
- African tick bite fever
  - Fever, headache, inoculation eschars
  - Travel to southern Africa

Fevers from Around the World: Travel Associated Infections

- Dengue fever
  - Fever, rash, myalgia, retro-orbital eye pain, leukopenia and normal CRP
  - Travel to South East Asia, Central/South America
- Zika virus
  - Rash, fever, arthralgias, conjunctivitis, normal CBC
- Chikungunya virus
  - Fever, arthralgias, rash