Emerging Pathogens and New Recommendations in Travel Medicine

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Most travelers to third-world countries encounter health-related problems during their stay and may require medical attention on returning home. Although malaria is still the most common diagnosis among travelers to the developing world, several other infectious diseases, such as avian influenza, dengue fever, chikungunya fever, leishmaniasis, and multidrug-resistant tuberculosis, are growing in importance. Clinicians need to stay informed about travel requirements and vaccine recommendations for US citizens. [Infect Med. 2008;25:352-386]

More than half of travelers to the developing world experience a health-related problem during their trip, with 8% requiring medical attention on their return because of persistent symptoms. [1] The GeoSentinel database, a collaborative effort among 31 travel medicine clinics on 6 different continents, suggests that the most common diagnoses in these persons continue to be malaria (24%), dengue fever (6%), acute traveler's diarrhea (4%), and typhoid fever (2%). [2] In recent years, however, the changing epidemiology of several pathogens has posed new risks to travelers. Among these are avian influenza, multidrug-resistant tuberculosis (MDR-TB), chikungunya virus (CHIKV) infection (ie, chikungunya fever), leishmaniasis, and dengue fever (DF). These emerging infections and new travel requirements and vaccine recommendations are summarized in this article.

Avian influenza
Influenza A virus of the H5N1 subtype, now known as avian influenza virus, is carried globally by wild birds and has caused significant morbidity and mortality among domesticated birds such as chickens, ducks, and turkeys. According to the World Bank, in Southeast Asia alone, avian influenza outbreaks since 2003 have resulted in the death or destruction of more than 140 million birds at a cost of more than $10 billion. [3]

Human cases of avian influenza are uncommon but have been reported since 1996. From 2003 to 2008, 369 human cases occurred in Asia, Africa, Eastern Europe, and the Middle East, resulting in 234 deaths (63% of cases). [4,5] Most cases occurred in previously healthy children and young adults aged 10 to 19 years who had direct or close contact with H5N1-infected poultry or contaminated surfaces. In general, the H5N1 strain does not easily infect humans. It is difficult for it to spread from person to person, and prolonged contact is usually required for transmission to occur. For instance, in Thailand in 2004, probable transmission occurred between an ill child and her mother, and in June 2006 in Indonesia, 8 persons were infected in one family.

Although person-to-person transmission remains very limited, [6] scientists are concerned that the H5N1 virus could one day gain the ability to infect humans and easily spread from one person to another. With little to no immune protection in the human population, a worldwide influenza pandemic could result. Currently, the CDC does not recommend that the general public avoid travel to countries affected by the H5N1 virus. However, it does recommend protective measures before, during, and after travel to regions where H5N1 is endemic (Table 1). [7,8]
### Table 1 – Protective measures for travel to where avian influenza virus is endemic

**Before travel**

- Obtain information about disease risks and health recommendations for specific travel destinations. These can be found at the CDC's Traveler's Health Web site at [www.cdc.gov/travel/](http://www.cdc.gov/travel/).
- Assemble a travel health kit that contains basic first aid and medical supplies, including a thermometer and alcohol-based hand gel containing at least 60% alcohol.
- Update vaccinations and obtain prescriptions for necessary medications.
- Identify in-country health care resources.
- Inquire about any health screening requirements at ports of entry.
- Consider purchasing additional health insurance that covers medical evacuation in case of illness. Information on this topic can be found at the US Department of State Web site: [http://travel.state.gov/travel/tips/tips_1232.html](http://travel.state.gov/travel/tips/tips_1232.html).

**During travel**

- Avoid all contact with domestic and wild birds. This includes avoiding places where birds are raised or kept and avoiding surfaces soiled with bird feces or secretions.
- Avoid undercooked poultry products.
- Frequently wash hands with soap and water or an alcohol-based hand gel.
- Seek medical help immediately if symptoms of illness appear.
- If illness develops, stop the spread of germs by covering the mouth and nose with a tissue when coughing or sneezing (or into your upper sleeve if a tissue is not available), discarding the tissue in a wastebasket, and then cleaning hands. (Persons may be asked to wear surgical masks to protect others.)
- Defer further travel until symptoms resolve, unless traveling locally for medical care.
- Do not bring birds or bird products back into the United States. Individual penalties can include a fine of up to $250,000 and 5 years in prison.

**After travel**

- Closely monitor health for 10 days for symptoms of infection.
- If illness suggestive of avian influenza develops, alert a health care provider. (The patient should explain the symptoms and provide information about where travel took place and whether direct contact with poultry or close contact with a severely ill person occurred.)
- Defer travel while ill unless seeking local medical care.
- Limit contact with others as much as possible to help prevent the spread of infection.

Adapted from Centers for Disease Control and Prevention. [www.cdc.gov/travel/content/AvianFluAsia.aspx](http://www.cdc.gov/travel/content/AvianFluAsia.aspx); Department of Health and Human Services. [www.pandemicflu.gov/issues/keepbirdsout.html](http://www.pandemicflu.gov/issues/keepbirdsout.html).
Clinicians should alert travelers to the signs and symptoms of avian influenza. They include not only typical symptoms of influenza but also conjunctivitis; GI symptoms, including nausea, vomiting, and diarrhea; and occasionally neurological changes consistent with encephalitis.\textsuperscript{6,9,10} Travelers should be instructed to seek medical care immediately if these signs and symptoms develop while they are traveling in a region where avian influenza is endemic or when they return home.
No vaccine is available to the general public to prevent avian influenza, although the FDA approved an H5N1 vaccine in April 2007 to be placed in national stockpiles in the event of an avian influenza pandemic. Likewise, no antiviral agent has guaranteed efficacy. Human strains of avian influenza virus have largely been resistant to amantadine and rimantadine. Oseltamivir and zanamivir demonstrate some efficacy, but data are limited and oseltamivir resistance has been reported. Currently, experts advise clinicians against routinely providing oseltamivir to persons who are traveling to regions where avian influenza is endemic. Travelers should be alerted to the potential health risks posed by counterfeit supplies of antiviral drugs that are available on the Internet or in countries with lax drug production and distribution regulations.

Although 59 cases of suspected avian influenza were reported to the CDC between 2003 and 2006, on laboratory analysis, none were confirmed. In addition, no cases of avian influenza have been reported among international adoptees; however, the possibility exists, and like travelers, families preparing to adopt a child from abroad should be alerted to the signs and symptoms of avian influenza.

**Multidrug-resistant tuberculosis**

*Mycobacterium tuberculosis* infects one third of the world's population, and 8 million new cases of TB and 2 million associated deaths occur each year. TB is second only to HIV infection as a cause of death worldwide from a single infectious agent. TB risk among international travelers is well documented, especially among those who are visiting Africa, Asia, Latin America, and the former Soviet Union. Media attention has recently focused on the acquisition of TB during air travel after a person with MDR-TB boarded an international flight against medical advice. First reports of TB transmission occurring in flight surfaced in the early 1990s, prompting the World Health Organization (WHO) to publish guidelines in 1998 for TB prevention and management during air travel. These guidelines were revised in 2006 in response to the increase in MDR-TB and the emergence of extensively drug-resistant TB (XDR-TB). MDRTB is defined as *M tuberculosis* infection that is resistant to isoniazid and rifampin, whereas XDR-TB is defined as resistance to isoniazid, rifampin, any fluoroquinolone, and at least 1 of 3 injectable second-line drugs (ie, amikacin, kanamycin or capreomycin). WHO guidelines state that short flights pose minimal risk of disease transmission, but flights of more than 8 hours may put passengers at increased risk, similar to the risk of TB transmission in other confined spaces. The highest risk is to those in proximity to the index case and is primarily limited to persons seated in the same row, to those 2 rows ahead or behind, and to crew-members working in the same cabin area as the index case. Physicians who counsel patients regarding international travel should familiarize themselves with these guidelines, especially as they pertain to physician responsibilities (Table 2).
Table 2 – Prevention and control of tuberculosis in relation to air travel

Responsibility of physicians

- Inform all patients with infectious TB that they must not travel by air on a flight exceeding 8 hours until they have completed at least 2 weeks of adequate therapy.
- Inform all patients with MDR-TB and XDR-TB that they must not travel by air until they are culture-negative.
- Advise patients with TB who undertake unavoidable air travel of less than 8 hours’ duration to wear a surgical mask or to otherwise keep the nose and mouth covered when speaking or coughing during the flight. This recommendation should be applied on a case-by-case basis and only with the agreement of the airline(s) involved and the public health authorities at departure and arrival.
- Inform relevant health authorities of the intention of a patient with infectious TB to travel against medical advice.
- Inform relevant health authorities when a patient with infectious TB has a recent history of air travel (travel within 3 months).

Responsibility of public health authorities

- Inform the airline(s) when a person with infectious TB is planning to travel with a commercial air carrier on a flight that exceeds 8 hours.
- Contact the airline(s) when a person with infectious TB is known to have traveled on a commercial air flight of at least 8 hours within the preceding 3 months.
- Promptly contact exposed passengers and crew and advise them to seek medical evaluation.
- Establish country-specific policies and provide guidance to airlines on the risk prevention of infectious diseases.

Responsibility of airline companies

- Deny boarding to any person known to have infectious TB who is intending to travel on a flight that is likely to be at least 8 hours.
- Minimize ground delays to less than 30 minutes if the ventilation system is not in operation.
- Ensure that HEPA filters on all aircraft are changed regularly according to manufacturers’ instructions.
- Ensure that cabin crews receive training on potential exposure to infectious diseases, first aid, and universal precautions when there may be exposure to body fluids.
- Ensure that there are adequate emergency medical supplies (eg, gloves, surgical masks, and biohazard disposal bags) aboard all aircraft.
- Cooperate with health authorities in providing necessary contact information and facilitate contact tracing of passengers and crew.

TB, tuberculosis; MDR, multidrug-resistant; XDR, extensively drug-resistant; HEPA, high-efficiency particulate air.
Greater than the risk of TB acquisition during international air travel is the risk of TB acquisition while visiting a country where the disease is endemic. Although the risk to short term travelers is low, the risk to long term travelers to countries with a high incidence of TB may approach that of the local population and is especially high among health care workers. In a Dutch study of *M. tuberculosis* infection among travelers to areas where the prevalence of TB is high, the risk of infection was 2.8 per 1000 person-months of travel for non-health care workers and 9.8 per 1000 person-months of travel for those with direct patient contact. Travel recommendations related to screening, prevention, and management of tuberculosis are outlined in Tables 2 and 3.

### Chikungunya fever

CHIKV, an arbovirus transmitted by the *Aedes aegypti* mosquito, was first identified in Tanzania in 1953. Chikungunya is derived from the local word "kungunyala" meaning "contorted," and refers to the severe joint pain experienced by infected patients. Acute infection is characterized by fever; headache; myalgias; and a subacute, bilateral polyarthralgia that typically affects the distal joints of the fingers, toes, ankles, and wrists. Rash is frequently observed; among 47 French patients returning from the Indian Ocean islands with CHIKV infection, 24 noted an evanescent pruritic rash over the face, trunk, or extremities accompanied by edema (Figure 1). Among 46 persons in this group of travelers, less common clinical manifestations were bilateral conjunctivitis in 2 patients (4%) and large joint effusions in 7 patients (15%). Common laboratory findings include elevation of liver and muscle enzyme levels, mild thrombocytopenia, and leukopenia.

**Figure 1 - Clinical manifestations of chikungunya fever include a blanching, evanescent rash (A, B) and peripheral edema (C). (From Simon F et al. Medicine [Baltimore]. 200724; used with permission.)**

Hematological abnormalities in the acute phase may be associated with bleeding. Affected patients may suffer from a protracted illness characterized by persistent polyarthralgias and a limited ability to perform activities of daily living. Tenosynovitis also may exacerbate these late stage symptoms. Initially limited to Africa and Southeast Asia, CHIKV has recently spread to territories in the western and eastern Indian Ocean and India. In 2006, outbreaks of chikungunya fever in the Indian Ocean islands were attributed to an emerging vector, *Aedes albopictus*. Affected islands included the Comoros, Mauritius, the Seychelles, Madagascar, Mayotte, and Reunion. In Reunion, 265,000 clinical cases occurred among 770,000 inhabitants (34%), resulting in 237 deaths. That year, India reported an estimated 1.3 million cases and the global number of cases was close to 2 million. From 1991 to 2005, only 7 imported cases of CHIKV infection were identified in the United States, compared with 37 cases from 2005 through late September 2006. CHIKV infection should be a consideration in travelers with fever and arthralgias who have recently returned from areas where CHIKV is transmitted. Acute- and convalescent- phase serum specimens can be submitted to the CDC for testing through state health departments. Unfortunately, no vaccine or specific antiviral treatment exists. Therapy consists of supportive care, including rest, fluids, and antipyretics. Late-stage symptoms have demonstrated a dramatic response to short term corticosteroid therapy. The CDC suggests that infected persons should be protected from further mosquito exposure by staying indoors or under a mosquito net during the first few days of illness, thus limiting propagation of the transmission cycle. Recommendations for prevention are detailed.
Cutaneous leishmaniasis

*Leishmania* species are intracellular protozoal parasites transmitted by the sandfly, most often in a rural setting. A wide spectrum of clinical manifestations, such as ulcerative skin lesions, mucocutaneous involvement, and visceral disease (kala azar) exist and are characterized as either Old World (southern Europe, Middle East, Asia, and Africa) or New World (Latin America). Cutaneous leishmaniasis (CL) is endemic to more than 70 countries, with 90% of cases occurring in Afghanistan, Algeria, Brazil, Pakistan, Peru, Saudi Arabia, and Syria.31 Global incidence is increasing, with an estimated 1 to 2 million new cases each year, resulting in more than 70,000 deaths.32 Travel to regions of Central and South America where *Leishmania* is endemic has resulted in an increasing number of imported cases of New World CL in Europe. Between 1995 and 2003, the number of cases increased 3-fold in the United Kingdom. Similarly, between 1990 and 2000, the number of imported cases doubled in the Netherlands.31 Old World CL, most often associated with *Leishmania major* or *Leishmania tropica*, has been identified among US military personnel deployed to Afghanistan, Iraq, and Kuwait.33 From June 2003 to April 2004, more than 600 cases of Old World CL were diagnosed among American soldiers participating in Operation Iraqi Freedom. When cultures could be obtained (n = 308) from biopsies of skin lesions, *L major* was the pathogen in 99% of cases.34

CL is a chronic disease with lesions appearing within 1 to 7 months of exposure.5 Typically, an initial lesion develops at the site of the sandfly bite as a small, erythematous papule. Progressive ulceration follows within 2 weeks to 6 months of infection. Ulcerated lesions are typical of infection caused by New World species and *L major* (Figure 2). More severe cutaneous disease may spread locally or hematogenously to involve deeper tissues. In Latin America, most such cases are caused by *Leishmania braziliensis* and *Leishmania amazonensis*.35
New World cutaneous leishmaniasis caused by *Leishmania major* is characterized by painless, well-demarcated ulcers at the site of sandfly bites.

A detailed review of therapeutic options for CL has been provided elsewhere. Intralesional and parenteral pentavalent antimonials- sodium stibogluconate and meglu-mine antimoniate-have been used successfully, but serious adverse effects, such as myalgias, renal failure, hepatotoxicity, and cardiotoxicity, may occur. In the United States, sodium stibogluconate is available for parenteral use under an investigational drug protocol by contacting the CDC (404-639-3670). Alternative treatment regimens have met with varying success, including amphotericin B and its lipid formulations, pentamidine, and miltefosine. Oral azoles (eg, ketoconazole, fluconazole), topical agents (eg, paromomycin cream), and thermotherapy have also been used. Personal protection against sandflies is necessary for travelers.

The CDC recommendations for prevention are detailed in Table 4.

**Dengue fever**

DF and dengue hemorrhagic fever (DHF) are caused by 4 related but antigenically distinct dengue virus serotypes of the virus family Flaviviridae. DF is a self-limited disease characterized by the sudden onset of fever, severe headache, myalgias, and arthralgias, which are often accompanied by a maculopapular rash. DHF is a more severe disease with a mortality rate between 1% and 50% in developed and developing countries, respectively. It occurs 4 to 7 days after dengue virus infection and is heralded by capillary leakage and hemorrhagic complications. Neutropenia, elevated liver enzyme levels, and disseminated intravascular coagulation are also common. One of the most important risk factors for DHF is previous dengue virus infection. Therefore, the risk to first-time international travelers from areas where the disease is not endemic is low, but the risk increases with subsequent travel.

The primary vector of dengue virus is *A aegypti*, although infection associated with *A albopictus* also has been reported. Most cases of DF and DHF have been reported in Asia, but in the late 1980s and early 1990s, epidemics occurred in Southeast Asia, the Pacific Islands, the Caribbean, and Latin America. Over the past few years, DF has become endemic to most tropical countries of the South Pacific, Asia, the Caribbean, the Americas, and Africa.

Dengue virus is the most common cause of arboviral disease in the world, accounting for 50 million to 100 million cases and more than 22,000 deaths annually. The marked increase in DF over the past 2 decades in areas where the disease is endemic also has resulted in increased infection rates among travelers. DF and DHF have been diagnosed in up to 16% of febrile travelers returning from the tropics, a 3-fold increase since 1990. From 1977 to 2004, 864 cases of DF were reported in the United States among returning travelers. Rarely, these infected travelers can serve as a source for DF transmission when returning to an *A aegypti*-infested or *A albopictus*-infested area. This phenomenon was demonstrated in Hawaii in 2001, when the arrival of a single viremic traveler from
the South Pacific resulted in a limited local outbreak. A aegypti, a daytime feeder, is found most frequently in or near human habitations. Mosquito breeding sites include artificial water containers, such as discarded tires, uncovered water storage barrels, buckets, and cisterns. Extensive public health measures have been taken to limit these potential breeding sites. For travelers, the most effective preventive measure is the use of insect repellents containing N,N-diethylmeta-toluamide (DEET) and permethrin-impregnated protective clothing. Because the transmission risk is highest during the day, the utility of bed nets at night is limited. Travelers to areas where DF is endemic and epidemic should take precautions to avoid mosquito bites as detailed in Table 4.

Travel requirements and vaccine recommendations

In 2008, yellow fever vaccination requirements expanded to travelers to Costa Rica, Argentina, Paraguay, Bolivia, and Brazil. Specifics may be obtained by reviewing The Yellow Book, CDC Health Information for International Travel 2008 (available on the Web at http://wwwnc.cdc.gov/travel/contentYellowBookUpdates.aspx). A new International Certificate of Vaccination or Prophylaxis (ICVP) was issued in December 2007 and should be used to record yellow fever vaccine administration. Health care practitioners should replace older versions with the current ICVP whenever possible.

In October 2007, the tetravalent meningococcal polysaccharide-protein conjugate vaccine (MCV4), conferring protection against Neisseria meningitidis serogroups A, C, Y, and W-135, was approved for use in children aged 2 to 10 years. The Advisory Committee on Immunization Practices (ACIP) recommends the use of meningococcal vaccine for persons who travel to or reside in countries in which N meningitidis is hyperendemic or epidemic, particularly if contact with the local population will be prolonged. MCV4 is preferred and may now be used among persons aged 2 to 55 years. MPSV4, a tetravalent meningococcal polysaccharide vaccine, remains the recommended vaccine among persons older than 55 years who travel to regions in which N meningitidis is prevalent.

In 2006, an outbreak of mumps in the United States prompted revised recommendations for vaccination. Presently, according to the ACIP, adequate mumps vaccination for international travelers now consists of 2 doses of live virus vaccine instead of 1 dose.

Routine vaccination guidelines for adults have been updated to include herpes zoster vaccination of persons 60 years and older who do not have evidence of past varicella immunity. Evidence of past varicella immunity is described in the 2008 ACIP Adult Immunization Schedule. All adults without evidence of immunity to varicella should receive 2 doses of single-antigen herpes zoster vaccine unless a medical contraindication exists.

CONCLUSION

Because 40 million Americans travel or work abroad annually, physicians should be prepared to provide pre-travel counseling for their patients. To provide comprehensive care, clinicians must maintain a working knowledge of emerging pathogens and travel vaccination recommendations. Travel medicine experts and dedicated Web sites maintained by the CDC and the WHO can provide additional valuable information.

References:


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