Treatment Guidelines
from The Medical Letter®

Published by The Medical Letter, Inc. • 145 Huguenot Street, New Rochelle, NY 10801 • A Nonprofit Publication

Volume 10 (Issue 118) June 2012
www.medicalletter.org

Tables

Advice for Travelers

Patients planning to travel to other countries often ask for information about appropriate vaccines and prevention of diarrhea and malaria. More detailed advice for travelers is available from the Centers for Disease Control and Prevention (CDC) at www.cdc.gov/travel. Guidelines are also available from the Infectious Diseases Society of America (IDSA).[1]

VACCINES

Common travel vaccines are listed in Table 2 on page 47. In addition to travel-specific vaccines, all travelers (including children) should be up to date on routine immunizations. Guidelines for routine adult immunization are available in a separate issue.[2] Immunocompromised or pregnant patients generally should not receive live virus vaccines, such as those for measles and yellow fever, although in some situations the benefit might outweigh the risk.[3]

HEPATITIS A — Hepatitis A vaccine, which is now part of routine childhood immunization in the US, is recommended for all unvaccinated travelers going to countries with intermediate or high hepatitis A endemicity (see Table 1 for low-risk areas).[4] The two hepatitis A vaccines available in the US, *Havrix* and *Vaqta*, are usually administered in two IM doses. Patients who receive a first dose of one vaccine will respond to a second dose of the other.

Antibodies reach protective levels 2-4 weeks after the first dose. Even when exposure to the disease occurs sooner than 4 weeks after vaccination, the traveler is usually protected because of the relatively long incubation period (average 28 days) of hepatitis A. Second doses given up to 8 years after the first dose have produced protective antibody levels.[5]

For adults >40 years old, immunosuppressed patients and those with chronic liver disease or other chronic medical conditions who will be traveling to an endemic area in <2 weeks, a 0.02 mL/kg IM dose of immune globulin should be given in addition to the initial dose of vaccine. The same dose should be given to children <1 year of age and to travelers who elect not to receive the vaccine if they will be traveling for <3 months; a dose of 0.06 mL/kg IM should be given for travel lasting 3 months or longer. For travel durations of >5 months, the dose should be repeated.[6]

Table 1. Low-Risk Areas For Hepatitis A & B*

Hepatitis A[1]	Hepatitis B[2]
Asia Pacific (includes Japan, South Korea, Singapore)	Argentina
East Asia (includes China)	Australia
Southeast Asia (includes Indonesia, Phillipines, Vietnam)	Canada[3]
Australasia (includes Australia, New Zealand)	Chile
Caribbean	Costa Rica
Europe	Cuba
North America	Hungary
	Mexico
	New Zealand
	Nicaragua
	Panama
	Paraguay
	United States[3]
	Uruguay
	Western Europe[4]

* All other areas are intermediate to high risk; vaccine is indicated.
1. Regions with a low or very low level of hepatitis A endemicity (KH Jacobsen and ST Wiersma. Vaccine 2010; 28:6653.
2. Countries with a low (<2%) prevalence of hepatitis B surface antigen (wwwnc.cdc.gov/travel/page/diseases/htm).
3. Risk is intermediate in Alaska natives and is high in indigenous populations of northern Canada.
4. Risk is intermediate in Greece, Portugal and Spain.

HEPATITIS B — Hepatitis B vaccine, which is now part of routine childhood immunization in the US, is recommended for all travelers going to intermediate- or high-risk areas (see Table 1 for low-risk areas). In addition, travelers who may engage in behaviors that can increase the risk of transmission, such as injection drug use, unprotected sexual contact with new partners, dental treatment, skin perforation practices (tattoos, acupuncture, ear piercing) or medical tourism involving

invasive medical treatment (injections, stitching), should, regardless of destination, be immunized against hepatitis B.

Two hepatitis B vaccines are available in the US: *Engerix-B* and *Recombivax-HB*. A 3-dose series started with one vaccine may be completed with the other. An interrupted series can be completed without being restarted.

HEPATITIS A/B — A combination vaccine *(Twinrix)* containing the same antigenic components as pediatric *Havrix* and *Engerix-B* is available for patients ≥18 years old. The combination vaccine can be used to complete an immunization series started with monovalent hepatitis A and B vaccines. *Twinrix Junior* is available outside the US for children 1-15 years old.

INFLUENZA — Influenza may be a risk in the tropics year-round and in temperate areas of the Southern Hemisphere from April to September. Outbreaks have occurred on cruise ships and on organized group tours in any latitude or season.[7]

Seasonal influenza vaccine directed against strains in the Northern Hemisphere is sometimes available in the US until the end of June; the US Advisory Committee on Immunization Practices (ACIP) recommends that persons for whom seasonal influenza vaccine is indicated[8] consider being vaccinated before travel to the Southern Hemisphere during influenza season or to the tropics at any season, or when traveling in a group with persons from the Southern Hemisphere during their influenza season (April-September).[9] In some years, the vaccine strains are the same in both hemispheres. If the vaccine strains are different, high-risk patients from the Northern Hemisphere who travel to the Southern Hemisphere during that region's influenza season could also consider being immunized on arrival because the vaccine active against strains in the Southern Hemisphere is rarely available in the Northern Hemisphere. Seasonal influenza vaccines are prepared in eggs; hypersensitivity reactions could occur.

There is no commercial vaccine available for pathogenic strains of avian influenza (H5N1, H7N2, H9N2, H7N3, H7N7), but an inactivated vaccine against avian H5N1 is FDA-approved and is included in the US Strategic National Stockpile.

JAPANESE ENCEPHALITIS — Japanese encephalitis is an uncommon but potentially fatal mosquito-borne viral disease that occurs in rural Asia, especially near pig farms and rice paddies. It is usually seasonal (May-October), but may occur year-round in tropical regions. The attack rate in travelers has been very low.[10]

Vaccination is recommended for travelers who expect a long stay (≥1 month) in endemic areas or heavy exposure to mosquitoes (such as adventure travelers) during the transmission season. Vaccination should also be considered for travelers spending <1 month in endemic areas during the transmission season if they will be sleeping without air conditioning, screens or bed nets, or spending considerable time outside in rural or agricultural areas, especially in the evening or at night.[11] Some Medical Letter reviewers suggest that, given the rarity of the disease in US residents, compulsive use of insect repellents and judicious avoidance of exposure to mosquitoes between dusk and dawn might be reasonable alternatives to vaccination for short-term travelers.

Two vaccines are FDA-approved in the United States. *Ixiaro*, a Vero cell culture-derived formulation, is administered in two doses 28 days apart.[12,13] *JE-Vax*, a mouse-brain preparation, is the only one approved for use in children, but it is no longer available. According to the CDC, physicians may chose to use *Ixiaro* off-label in children.[14] One study found that *Ixiaro* administered at half the adult dose was safe and induced a good immune response in children 1-3 years old.[15] The adult dose is under investigation for use in children ≥3 years old. Vaccines are available for pediatric use in Asia.

MEASLES — Travel continues to be a cause of measles cases and outbreaks in the US.[16,17] The measles vaccine is no longer available in a monovalent formulation. It is available as an attenuated live-virus vaccine in combination with mumps and rubella (MMR). Adults born in or after 1957 (1970 in Canada) and healthcare workers of any age who have not received 2 doses of live measles vaccine (not the killed vaccine that was commonly used between 1963 and 1968) after their first birthday and do not have a physician-documented history of infection or laboratory evidence of immunity should receive two doses of MMR vaccine, separated by at least 28 days.

Previously unvaccinated children ≥12 months old should receive 2 doses of MMR vaccine at least 28 days apart before traveling outside the US. Children 6-11 months old should receive 1 dose before traveling, but will still need two more doses for routine immunization, one at ≥12 months and another at least 28 days later.

MENINGOCOCCAL — Meningococcal vaccine is recommended for travelers going anywhere in the

Table 2. Some Vaccines for Travel

Vaccines	Adult Dose	Pediatric Age/Dose	Standard Primary Schedule	Duration of Protection
Hepatitis A				
Havrix (GSK)	1 mL IM (1440 EU)	1-18 yrs: 0.5 mL IM (720 EU)	0 and 6-12 mos	Probably lifelong after completion of primary series[1]
Vaqta (Merck)	1 mL IM (50 U)	1-18 yrs: 0.5 mL IM (25 U)	0 and 6-18 mos	
Hepatitis B				
Engerix-B (GSK)	1 mL IM (20 mcg)	Birth-19 yrs: 0.5 mL IM (10 mcg)	0, 1 and 6 mos[2,3]	Probably lifelong after completion of primary series
Recombivax-HB (Merck)	1 mL IM (10 mcg)	Birth-19 yrs: 0.5 mL IM (5 mcg)	0, 1 and 6 mos[3,4]	
Hepatitis A/B				
Twinrix (GSK)	1 mL IM (720 EU/20 mcg)	Not approved for <18 yrs	0, 1 and 6 mos (alternative: 0, 7 and 21-30 days)	Booster recommended at 12 mos with accelerated schedule; otherwise probably lifelong after completion of primary series
Japanese encephalitis				
Ixiaro (Novartis)	0.5 mL IM	Not approved for <17 yrs[5]	0, 28 days	A single booster >1 yr after completion of primary series if ongoing risk[6]
Meningococcal				
Menomune (Sanofi Pasteur)	0.5 mL SC (50 mcg of each antigen)	≥2 yrs: 0.5 mL SC (50 mcg of each antigen)	Single dose	Repeat every 5 yrs[7] with *Menactra* or *Menveo* if ongoing risk
Menveo (Novartis)	0.5 mL IM (10 mcg serogroup A, 5 mcg serogroup C, Y, W135)	≥2 yrs: 0.5 mL IM (10 mcg serogroup A, 5 mcg serogroup C, Y, W135)	≥2-55 yrs: single dose[8]	Repeat every 5 yrs[7] if ongoing risk
Menactra (Sanofi Pasteur)	0.5 mL IM (4 mcg of each antigen)	≥9 mos: 0.5 mL IM 4 mcg of each antigen	9-23 mos: 0, 3 mos ≥2-55 yrs: single dose	Repeat every 5 yrs[7] if ongoing risk
Rabies				
Imovax (Sanofi Pasteur)	1 mL IM (≥2.5 IU of rabies antigen)	Birth: 1 mL IM (≥2.5 IU of rabies antigen)	0, 7 and 21 or 28 days[9]	Routine boosters not necessary; for those engaging in frequent high-risk activities (cavers, veterinarians, laboratory workers), serologic testing is recommended every 2 yrs with booster doses if low levels[10]
RabAvert (Novartis)	1 mL IM (≥2.5 IU of rabies antigen)	Birth: 1 mL IM (≥2.5 IU of rabies antigen)	0, 7 and 21 or 28 days[9]	
Typhoid				
Vivotif (Crucell/Berna)	1 cap PO (contains 2-6x10^9 viable CFU of *S.* Typhi Ty21a)	≥6 yrs: 1 cap PO (contains 2-6x10^9 viable CFU of *S.* Typhi Ty21a)	1 cap every other day x 4 doses	Repeat every 5 yrs if ongoing risk
Typhim Vi (Sanofi Pasteur)	0.5 mL IM (25 mcg)	≥2 yrs: 0.5 mL IM (25 mcg)	Single dose	Repeat every 2 yrs (3 yrs in Canada) if ongoing risk
Yellow Fever				
YF-Vax (Sanofi Pasteur)	0.5 mL SC (4.74 $\log_{10}$ plaque forming units of 17D204 attenuated YF virus)	≥9 mos: 0.5 mL SC (4.74 $\log_{10}$ plaque forming units of 17D204 attenuated YF virus)	Single dose	Booster dose every 10 yrs if ongoing risk

1. Protection likely lasts at least 12 months after a single dose.
2. An alternate schedule is 3 doses given at 0, 1 and 2 months, followed by a fourth dose at 12 months.
3. An accelerated schedule of 0, 7 and 14 days followed by a booster dose at 6 months has been used, but is not FDA-approved.
4. An alternate schedule for adolescents 11-15 years old is 0 and 4-6 months.
5. One study found that *Ixiaro* administered at half the adult dose was safe and induced a good immune response in children 1-3 years old (A Kaltenböck et al. Vaccine 2010; 28:834). The adult dose is under investigation for use in children ≥3 years old.
6. Adults previously vaccinated with *JE Vax* should receive a primary series of *Ixiaro* (MMWR Morb Mortal Wkly Rep 2011; 60:661).
7. Repeat after three years for children vaccinated at <7 years of age.
8. For children 2-5 years old at continued high risk, a second dose may be administered 2 months after the first.
9. Regimen for pre-exposure prophylaxis. If a previously vaccinated traveler is exposed to a potentially rabid animal, post-exposure prophylaxis with 2 additional vaccine doses separated by 3 days should be initiated as soon as possible.
10. Minimal acceptable antibody level is complete virus neutralization at a 1:5 serum dilution by the rapid fluorescent focus inhibition test.

"meningitis belt" (semi-arid areas of sub-Saharan Africa extending from Senegal and Guinea eastward to Ethiopia) from December to June and should also be considered for areas where epidemics of *Neisseria meningitidis* are occurring, particularly for travelers who will have prolonged contact with the local population, such as those living in a dormitory, military institution or refugee camp, or working in a healthcare setting.[18] Saudi Arabia requires a certificate of immunization for pilgrims during Hajj or Umrah.

Three quadrivalent vaccines are available against *N. meningitidis* serogroups A, C, Y and W-135. *Menomune*, which contains meningococcal capsular polysaccharides, is approved for all persons ≥2 years old. *Menactra* and *Menveo*,[19] which contain capsular polysaccharides conjugated to diphtheria toxoid, are approved for children ≥9 months old *(Menactra)*[20] or ≥2 years old *(Menveo)* and for adults ≤55 years old and are preferred for use in this age group, but *Menomune* is an acceptable alternative. None of the vaccines provide protection against serogroup B, which does not have an immunogenic polysaccharide capsule. Group B infections are rare in sub-Saharan Africa.

POLIO — Adults who have not previously been immunized against polio should receive a primary series (2 doses 4-8 weeks apart; third dose 6-12 months after the second) of inactivated polio vaccine (IPV) if traveling to areas where polio is still endemic (Nigeria, Pakistan, Afghanistan) or to areas with documented outbreaks or circulating vaccine-derived strains (see Table 3).[21] Previously unimmunized children should receive a 4-dose primary series of IPV; the minimum interval between doses is 4 weeks. A child who receives 4 doses before age 4 should be given a 5th dose.

If protection is needed within 4 weeks, a single dose of IPV is recommended, but provides only partial protection. Adult travelers to risk areas who have previously completed a primary series and have never had a booster should receive a single booster dose of IPV.

RABIES — Rabies is highly endemic in parts of Africa, Asia (particularly India and Bali, Indonesia), and Central and South America, but the risk to travelers is generally low.[22] Pre-exposure immunization against rabies is recommended for travelers with an occupational risk of exposure, for those (especially children) visiting endemic areas where immediate access to medical treatment, particularly rabies immune globulin, tends to be limited, and for outdoor-adventure travelers.[23] The 2 vaccines available in the US *(Imovax, RabAvert)* are similar.

After a bite or scratch from a potentially rabid animal, patients who received pre-exposure prophylaxis should promptly receive 2 additional doses of vaccine. Without pre-exposure immunization, the ACIP recommends human rabies immune globulin (HRIG) and is now recommending 4 doses of vaccine (over 14 days) instead of 5 doses (over 28 days). Immunosuppressed patients should still receive 5 doses of vaccine.[24] The reduced vaccine dosing schedule may not be included in the manufacturer's prescribing information. According to the CDC, cell culture rabies vaccines available outside the US are acceptable alternatives to FDA-approved vaccines; neural tissue vaccines have high rates of serious adverse effects. HRIG is a blood product, and its purity and potency may be less reliable, if it is available at all, in developing countries. Purified equine rabies immune globulin is available in some countries in Asia and has been used effectively, with a low incidence of adverse reactions.

Table 3. Countries with a Risk of Polio[1]

Afghanistan	Equatorial Guinea	Niger
Angola	Eritrea	Nigeria
Benin	Ethiopia	Pakistan
Burkina Faso	Gabon	Rwanda
Burundi	Gambia	Senegal
Cameroon	Ghana	Sierra Leone
Central African Republic	Guinea	Somalia
	Guinea-Bissau	Sudan and South Sudan
Chad	Iran	Tajikistan
China	Kazakhstan	Tanzania
Congo	Kenya	Togo
Côte d'Ivoire	Kyrgyzstan	Turkmenistan
Democratic Republic of the Congo	Liberia	Uganda
	Mali	Uzbekistan
Djibouti	Mauritania	Zambia
	Namibia	

1. Centers for Disease Control and Prevention. Update on the Global Status of Polio. March 22, 2012 Available at: http://wwwnc.cdc.gov/travel/notices/in-the-news/polio-outbreaks.htm. Accessed May 9, 2012.

TETANUS, DIPHTHERIA AND PERTUSSIS — Previously unimmunized children should receive 3 or (preferably) 4 doses of pediatric diphtheria, tetanus and acellular pertussis vaccine (DTaP) before travel. An accelerated schedule can be used beginning at age 6 weeks, with the second and third doses given 4 weeks after the previous dose. The fourth dose is given 6 months after the third; the child must be at least 12 months old.

Adults with an uncertain history of primary vaccination should receive 3 doses of a tetanus and diphtheria toxoid vaccine. The first 2 doses should be administered at least 4 weeks apart and the third 6-12 months after the second. One of the 3 doses (preferably the first) should contain protein components of acellular pertussis combined with diphtheria and tetanus toxoids (Tdap) to also provide protection against pertussis. Two Tdap vaccines (*Adacel*; *Boostrix*) are available for adults.[25] The ACIP recently recommended Tdap for use in adults ≥65 years old.[26] DTaP contains larger amounts of diphtheria

and pertussis antigens than Tdap and is not licensed for use in adults.

Inactivated adsorbed (aluminum-salt-precipitated) tetanus and diphtheria toxoid (Td) has been the standard booster vaccine for adults. A booster dose of Td is recommended every 10 years. All persons ≥11 years old who have completed a primary childhood series and have not yet received Tdap should receive a single dose of Tdap. Tdap can be given regardless of interval since the last Td to provide pertussis protection before travel.

TYPHOID — Typhoid vaccine is recommended for travelers going to areas where there is an increased risk of typhoid fever, including southern Asia, East and Southeast Asia, Central and South America, the Caribbean and Africa, especially if they will be visiting friends or relatives or traveling outside routine tourist destinations.[27,28]

A live attenuated oral vaccine *(Vivotif)* is available for adults and children ≥6 years old. It is taken every other day as a single capsule (at least 1 hour before eating) for a total of 4 capsules, beginning no later than 2 weeks before departure; it protects for about 5 years. The capsules must be refrigerated. Antibiotics should be avoided for at least 72 hours before administration of the first capsule.

A purified capsular polysaccharide parenteral vaccine *(Typhim Vi)* for adults and children ≥2 years old is given at least 2 weeks before departure. A combined hepatitis A/typhoid vaccine (*Vivaxim* – Sanofi Pasteur) is available in Canada.

YELLOW FEVER — Yellow fever vaccine *(YF-Vax)*, a single-dose attenuated live virus vaccine prepared in eggs, should be given at least 10 days before travel to endemic areas, which include tropical South America and sub-Saharan Africa.[29] Some countries require an International Certificate of Vaccination against yellow fever, or a physician's waiver letter, from all entering travelers; other countries require evidence of vaccination from travelers coming from or traveling through endemic or infected areas, including brief airport transits. An updated list of countries requiring proof of yellow fever vaccination is available at www.cdc.gov/travel.

The vaccine is available in the US only from providers certified by state health departments. Boosters are given every 10 years, but immunity probably lasts much longer. Other injectable or intranasal live vaccines may be administered simultaneously with yellow fever vaccine. If that is not possible, administration of other live vaccines should be separated by ≥30 days from that of yellow fever vaccine to avoid a diminished immune response to the vaccines.

Yellow fever vaccine is contraindicated in travelers who have a malignant neoplasm, symptomatic HIV infection,[30] a CD4 count <200 cells/mm^3, a thymus disorder associated with abnormal immune-cell function, or an egg allergy and in those who are immunocompromised. Yellow fever vaccine-associated viscerotropic disease, a severe systemic illness that can cause fatal organ failure, has been reported rarely. It has occurred only in first-time recipients. Vaccine-associated neurologic disease (encephalitis, Guillain-Barré, Bell's palsy) has also occurred.[31] The rates of these diseases are increased in infants and travelers >60 years old.[32] Caution is advised for travelers ≥60 years old who are receiving the vaccine for the first time and for those with asymptomatic HIV infection and moderate immune suppression (CD4 counts 200-499 cells/mm^3). A small case series study found a significant increase in relapse rates among travelers with multiple sclerosis who received yellow fever vaccine.[33] There have been case reports of vaccine-associated neurologic disease in breast-fed infants of recently vaccinated women.[34] The vaccine should be avoided if possible in infants <9 months old; it is contraindicated in infants <6 months old.

OTHER VACCINES

CHOLERA — The risk of cholera in tourists is very low. Vaccination is currently not recommended for routine use in travelers, but should be considered for those who plan to work in refugee camps, in outbreak settings, or as healthcare providers in endemic areas.[35] The parenteral vaccine previously licensed in the US is no longer available. Oral, whole-cell killed vaccines are available outside the US. *Dukoral* (Crucell, The Netherlands), licensed in many European countries and in Canada, is administered in 2 doses 1-6 weeks apart (3 doses in children 2-6 years old). *Shanchol* (Shantha Biotechnics, India) and *ORC-Vax* (Vabiotech, Vietnam) are administered in 2 doses 2 weeks apart to persons >1 year old.[36]

TICK-BORNE ENCEPHALITIS (TBE) — TBE occurs in temperate areas of Europe and Asia; the risk area extends from eastern France to northern Japan, and from northern Russia to Albania.[37,38] The risk of infection is greatest from April to November. Humans acquire the disease through the bite of a tick or, rarely, from eating unpasteurized dairy (mostly goat) products. Immunization is recommended only for travelers who will spend extensive time outdoors in rural areas.

No TBE vaccine is approved in the US, but two safe and effective vaccines are available in Europe (*Encepur* – Novartis; *FSME-Immun* – Baxter AG). The

adult formulation of *FSME-Immun* is also licensed in Canada. Both vaccines are usually given in 3 doses over 6-15 months, but *Encepur* can be given over 3 weeks (0, 7 and 21 days). Two TBE vaccines are available in Russia, but their safety and efficacy are unclear.

A booster dose should be given 3 years after completion of a standard primary series and 12-18 months after use of the accelerated schedule of *Encepur*. Subsequent boosters are given after 5 years for patients <50 years old and after 3 years for those ≥50 years old.

TRAVELERS' DIARRHEA

The most common cause of travelers' diarrhea, usually a self-limited illness lasting several days, is infection with noninvasive enterotoxigenic (ETEC) or enteroaggregative (EAEC) strains of *Escherichia coli*. Infections with *Campylobacter*, *Shigella*, *Salmonella*, *Aeromonas*, *Plesiomonas*, viruses and parasites are less common. In recent years, norovirus has become a more frequent cause of diarrhea in travelers; according to one study, norovirus infection was detected in 15.7% of returning international travelers with diarrhea.[39] Children tend to have more severe illness and are particularly susceptible to dehydration. Travelers to areas where hygiene is poor should avoid raw vegetables, fruit they have not peeled themselves, unpasteurized dairy products, cooked food not served steaming hot, and tap water, including ice.

Treatment – For mild diarrhea, **loperamide** (*Imodium*, and others), an over-the-counter synthetic opioid (4-mg loading dose, then 2 mg orally after each loose stool to a maximum of 16 mg/d for adults), often relieves symptoms in <24 hours, but some patients complain of constipation after use. Loperamide is approved for use in children >2 years old. It can be used with an appropriate antibiotic to shorten the duration of illness.

If diarrhea persists >3 days, is moderate to severe or is associated with high fever or bloody stools, self-treatment for 1-3 days (Table 4) with a **fluoroquinolone** is usually recommended.[40] **Azithromycin** is an alternative and is the drug of choice for travelers to areas with a high prevalence of fluoroquinolone-resistant *Campylobacter*, such as South and Southeast Asia.[41,42] Azithromycin can be used in pregnant women and children (10 mg/kg/d x 3d), and in patients who do not respond to a fluoroquinolone within 48 hours.

Rifaximin, a non-absorbed oral antibiotic derived from rifampin, is approved for treatment of travelers' diarrhea caused by noninvasive strains of *E. coli* in travelers ≥12 years of age. In clinical trials in patients with diarrhea mostly caused by *E. coli*, it has been similar in efficacy to ciprofloxacin, with fewer adverse effects.[43] It should not be used for invasive infections associated with fever or blood in the stool or those caused by *C. jejuni, Salmonella, Shigella* or other invasive pathogens, or during pregnancy.

Table 4. Antimicrobial Drugs for Treatment of Travelers' Diarrhea

Drug	Dosage
Azithromycin *Zithromax* (Pfizer)*	1000 mg once or 500 mg once/d x 1-3d
Ciprofloxacin *Cipro* (Bayer)*	500 mg bid x 1-3d
sustained-release *Cipro XR**	1000 mg once/d x 1-3d
Levofloxacin *Levaquin* (Ortho-McNeil)*	500 mg once/d x 1-3d
Norfloxacin – *Noroxin* (Merck)	400 mg bid x 1-3d
Ofloxacin – generic	300 mg bid x 1-3d
Rifaximin – *Xifaxan* (Salix)	200 mg tid x 3d

*Also available generically

Packets of oral rehydration salts (*Ceralyte*, *ORS*, and others) mixed in potable water can prevent and treat dehydration, particularly in children and the elderly. They are available from suppliers of travel-related products and some pharmacies in the US, and from pharmacies overseas.

Prophylaxis – Medical Letter reviewers generally do not prescribe antibiotic prophylaxis for travelers' diarrhea, but rather instruct the patient to begin self-treatment when symptoms are distressing or persistent. Some travelers, however, such as immunocompromised patients or those with time-dependent activities who cannot risk the temporary incapacitation associated with diarrhea, might benefit from prophylaxis.[44] In such patients, ciprofloxacin 500 mg, levofloxacin 500 mg, ofloxacin 300 mg or norfloxacin 400 mg can be given once daily during travel and for 2 days after return and are generally well tolerated. According to some Medical Letter reviewers, azithromycin 250 mg once daily can also be used. In short (2-week) studies among travelers to Mexico and US military personnel in Turkey, rifaximin (200-1100 mg/d) was effective in preventing travelers' diarrhea.[45-47] Bismuth subsalicylate (*Pepto-Bismol*, and others) can prevent diarrhea in travelers who take 2 tablets 4 times a day for the duration of travel, but it is less effective than antibiotics and is not recommended for children <3 years old.

MALARIA

No drug is 100% effective for prevention of malaria; travelers should be told to use protective measures against mosquito bites in addition to medication.[48]

Countries with a risk of malaria are listed in Table 5. Some countries with endemic malaria transmission may not have malaria in the most frequently visited major cities and rural tourist resorts. Travelers to malarious areas should be reminded to seek medical attention if they have fever either during their trip or up to a year (especially during the first 2 months) after they return. Travelers to developing countries, where counterfeit and poor quality drugs are common, should preferably buy antimalarials before travel.

CHLOROQUINE-SENSITIVE MALARIA — Chloroquine is the drug of choice for prevention of malaria in the few areas that still have chloroquine-sensitive malaria (see Table 5, footnotes 4 and 5). Patients who cannot tolerate chloroquine should take atovaquone/proguanil, doxycycline, mefloquine or, in some circumstances, primaquine in the same doses used for chloroquine-resistant malaria (see Table 6).

CHLOROQUINE-RESISTANT MALARIA — Three drugs of choice with similar efficacy, listed with their dosages in Table 6, are available in the US for prevention of chloroquine-resistant malaria.

A fixed-dose combination of **atovaquone and proguanil** taken once daily is generally the best tolerated prophylactic,[49] but it can cause headache, insomnia, GI disturbances and mouth ulcers, and it is expensive. Single case reports of Stevens-Johnson syndrome and hepatitis have been published. Atovaquone/proguanil should not be given to patients with severe renal impairment (CrCl <30 mL/min). There have been isolated case reports of treatment-related resistance to atovaquone/proguanil in *Plasmodium falciparum* in Africa, but acquisition of resistant disease in travelers appears to be rare.[50-53] The protective efficacy of atovaquone/proguanil against *P. vivax* is variable, ranging from 84% in Indonesian New Guinea[54] to 100% in Colombia.[55] Some Medical Letter reviewers prefer other drugs for travel to areas where *P. vivax* predominates.

Mefloquine has the advantage of once-a-week dosing, but is contraindicated in patients with a history of any psychiatric disorder (including severe anxiety and depression), and also in those with a history of seizures or cardiac conduction abnormalities.[56] Dizziness, headache, insomnia and disturbing dreams are the most common CNS adverse effects. Adverse effects in children are similar to those in adults, but the drug appears to be better tolerated in children, with a low incidence of CNS effects.[57] If a patient develops psychological or behavioral abnormalities such as depression, restlessness or confusion while taking mefloquine, another drug should be substituted. Halofantrine (not available in the US) should not be taken together with mefloquine, or within 15 weeks of the last dose of mefloquine, due to potentially fatal prolongation of the QT interval; caution is also required when using quinine, quinidine or chloroquine to treat patients who have taken mefloquine prophylaxis.

Doxycycline, which frequently causes GI disturbances and can cause photosensitivity and vaginitis, offers an inexpensive once-daily alternative. Doxycycline should not be taken concurrently with antacids, oral iron or bismuth salts (including *Pepto-Bismol*).

Table 5. Countries with a Risk of Malaria[1]

AFRICA		
Angola	Equatorial Guinea	Niger
Benin	Eritrea[2]	Nigeria
Botswana[2]	Ethiopia[2]	Rwanda
Burkina Faso	Gabon	São Tomé and Príncipe
Burundi	Gambia, The	Senegal
Cameroon	Ghana	Sierra Leone
Cape Verde[3]	Guinea	Somalia
Central African Republic	Guinea-Bissau	South Africa[2]
Chad	Kenya[3]	Sudan and South Sudan
Comoros	Liberia	Swaziland
Congo	Madagascar	Tanzania
Côte d'Ivoire	Malawi	Togo
Democratic Republic of the Congo	Mali	Uganda
Djibouti	Mauritania	Zambia
	Mayotte	Zimbabwe
	Mozambique	
	Namibia	
AMERICAS		
Argentina[2,4]	El Salvador[2,4]	Paraguay[2,4]
Belize[2,4]	French Guiana[2]	Peru[2]
Bolivia[2]	Guatemala[2,4]	Suriname[2]
Brazil	Guyana[2]	Venezuela[2]
Colombia[2]	Haiti[4]	
Costa Rica[2,4]	Honduras[2,4]	
Dominican Republic[2,4]	Mexico[2,4]	
Ecuador[2]	Nicaragua[4]	
	Panama[3]	
ASIA		
Afghanistan	Iran[2]	Saudi Arabia[2]
Azerbaijan[2,4]	Korea, North[4]	Sri Lanka
Bangladesh[2]	Korea, South[2,4]	Tajikistan
Bhutan[2]	Laos[2,6]	Thailand[2,6]
Cambodia[2,6]	Malaysia[2]	Timor-Leste (East Timor)
China[2,5,6]	Myanmar[2,6]	Turkey[2,4]
Georgia[2,4]	Nepal[2]	Vietnam[2,6]
India	Pakistan	Yemen
Indonesia[2]	Philippines[2]	
OCEANIA		
Papua New Guinea	Solomon Islands	Vanuatu

1. Only includes countries for which prophylaxis is recommended. Regional variation in risk may exist within a country. Updated detailed information is available at www.cdc.gov/malaria/map and medical personnel can call the CDC Malaria Hotline at 770-488-7788.
2. No malaria in major urban areas.
3. Limited to island of Saõ Tiago.
4. Chloroquine is the drug of choice for prophylaxis.
5. Chloroquine is recommended in Anhui, Guizhou, Henan and Hubei provinces.
6. Mefloquine resistance has been reported along the borders between Cambodia, China, Laos, Myanmar and Thailand (Laos-Myanmar, Laos-Thailand, China-Myanmar, etc.) and in southern Vietnam. In these areas atovaquone/proguanil or doxycycline is recommended.

Table 6. Drugs of Choice for Prevention of Malaria[1]

Drug	Adult Dosage	Pediatric Dosage	Duration
All *Plasmodium* species in chloroquine-sensitive areas[2,3]			
Chloroquine phosphate[4,5] (*Aralen*, and others)	500 mg (300 mg base) PO once/wk	5 mg/kg base (300 mg max) PO once/wk	Start: 1-2 wks before travel Stop: 4 wks after leaving malarious zone
All *Plasmodium* species in chloroquine-resistant areas[2,3]			
Atovaquone/proguanil[6] (*Malarone*, *Malarone Pediatric*, and others)	1 adult tablet PO daily[6]	5-8 kg: ½ peds tab/d[6] 9-10 kg: ¾ peds tab/d[6] 11-20 kg: 1 peds tab/d[6] 21-30 kg: 2 peds tabs/d[6] 31-40 kg: 3 peds tabs/d[6] >40 kg: 1 adult tab/d[6]	Start: 1-2d before travel Stop: 1 wk after leaving malarious zone
Doxycycline[7] (*Vibramycin*, and others)	100 mg PO daily	≥8 yrs: 2 mg/kg/d PO, up to 100 mg/d	Start: 1-2d before travel Stop: 4 wks after leaving malarious zone
Mefloquine[8,9]	250 mg PO once/wk	≤9 kg: 5 mg/kg salt once/wk[10] 10-19 kg: ¼ tabs once/wk[10] 20-30 kg: ½ tab once/wk 31-45 kg: ¾ tab once/wk >45 kg: 1 tab once/wk	Start: ≥2 wks before travel[9] Stop: 4 wks after leaving malarious zone
Alternative: Primaquine phosphate[11,12]	30 mg base PO daily	0.5 mg/kg base PO daily	Start: 1-2d before travel Stop: 1 wk after leaving malarious zone

1. No drug guarantees protection against malaria. Travelers should be advised to seek medical attention if fever develops after they return. Insect repellents, insecticide-impregnated bed nets and proper clothing are important adjuncts for malaria prophylaxis.
2. Chloroquine-resistant *P. falciparum* occurs in all malarious areas except Central America (resistance occurs in Panama east of the Canal Zone), Mexico, Haiti, the Dominican Republic, Paraguay, northern Argentina, North and South Korea, Georgia, most of rural China and some countries in the Middle East (chloroquine resistance has been reported in Yemen, Saudi Arabia and Iran). *P. vivax* with decreased susceptibility to chloroquine is a significant problem in Papua New Guinea and Indonesia. There are also a few reports of resistance from Myanmar, India, the Solomon Islands, Vanuatu, Guyana, Brazil, Colombia and Peru (JK Baird et al, Curr Infect Dis Rep 2007; 9:39). Chloroquine-resistant *P. malariae* has been reported from Sumatra, Indonesia (JD Maguire et al, Lancet 2002; 360:58).
3. Primaquine is given for prevention of relapse after infection with *P. vivax* or *P. ovale*. In addition to primary prophylaxis, some experts also prescribe primaquine phosphate 30 mg base/d (0.5 mg base/kg/d for children) for 14 days after departure from areas where these species are endemic (Presumptive Anti-Relapse Therapy [PART], "terminal prophylaxis"). Since this is not always effective as prophylaxis (E Schwartz et al, N Engl J Med 2003; 349:1510), others prefer to rely on surveillance to detect cases when they occur, particularly when exposure was limited or doubtful. See also footnote 11.
4. Alternatives for patients who are unable to take chloroquine include atovaquone/proguanil, mefloquine, doxycycline or primaquine dosed as for chloroquine-resistant areas.
5. Chloroquine should be taken with food to decrease gastrointestinal adverse effects. If chloroquine phosphate is not available, hydroxychloroquine sulfate is as effective; 400 mg of hydroxychloroquine sulfate is equivalent to 500 mg of chloroquine phosphate.
6. Atovaquone/proguanil is available as a fixed-dose combination tablet: adult tablets (*Malarone*, and others; 250 mg atovaquone/100 mg proguanil) and pediatric tablets (*Malarone Pediatric*, and others; 62.5 mg atovaquone/25 mg proguanil). To enhance absorption and reduce nausea and vomiting, it should be taken with food or a milky drink. The drug should not be given to patients with severe renal impairment (creatinine clearance <30 mL/min).
7. Doxycycline should be taken with adequate water to avoid esophageal irritation. It can be taken with food to minimize gastrointestinal adverse effects. It is contraindicated in children <8 years old.
8. In the US, a 250-mg tablet of mefloquine contains 228 mg mefloquine base. Outside the US, each 275-mg tablet contains 250 mg base. Mefloquine can be given to patients taking β-blockers if they do not have an underlying arrhythmia; it should not be used in patients with conduction abnormalities. Mefloquine should not be taken on an empty stomach; it should be taken with at least 8 oz. of water.
9. Most adverse events occur within 3 doses. Some Medical Letter reviewers favor starting mefloquine 3-4 weeks prior to travel and monitoring the patient for adverse events; this allows time to change to an alternative regimen if mefloquine is not tolerated.
10. For pediatric doses <½ tablet, it is advisable to have a pharmacist crush the tablet, estimate doses by weighing, and package them in gelatin capsules. There is no data for use in children <5 kg, but based on dosages in other weight groups, a dose of 5 mg/kg can be used.
11. Patients should be screened for G-6-PD deficiency before treatment with primaquine. It should be taken with food to minimize nausea and abdominal pain.
12. Not FDA-approved for this indication.

A fourth drug, **primaquine phosphate,** can also be used for prophylaxis, especially in areas where *P. vivax* is the predominant species, but in other areas it should be reserved for travelers unable to take any other drug; it is somewhat less effective than the alternatives against *P. falciparum*. Several studies however, have shown that daily primaquine can provide effective prophylaxis against chloroquine-resistant *P. falciparum* and *P. vivax*.[58] In addition to primary prophylaxis, some experts also prescribe primaquine for "terminal prophylaxis" after departure from areas where *P. vivax* and *P. ovale* are endemic (see Table 6, footnote 3).

Primaquine can cause hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, which is most common in African, Asian, and Mediterranean peoples. Travelers should be screened for G-6-PD deficiency before being treated with this drug. Primaquine should be taken with food to reduce GI effects.

MEFLOQUINE-RESISTANT MALARIA — Doxycycline or atovaquone/proguanil is recommended for prophylaxis against mefloquine-resistant malaria, which occurs in the malarious areas of Thailand, in the areas of Myanmar and Cambodia that border on Thailand, in the border areas between Myanmar and China, and Laos and Myanmar, and in southern Vietnam.

PREGNANCY — Malaria in pregnancy is particularly serious for both mother and fetus; prophylaxis is indicated if travel cannot be avoided. Chloroquine has been used extensively and safely for prophylaxis of chloroquine-sensitive malaria during pregnancy. Mefloquine is now classified as category B (no evidence of risk in humans) for use during pregnancy. It has been reported to be safe for prophylactic use during any trimester of pregnancy.[59] The safety of atovaquone/proguanil in pregnancy has not been established, and its use is not recommended. However, case series that included women who were treated with the combination in all trimesters of pregnancy have not identified major birth defects,[60] and proguanil alone has been used in pregnancy without evidence of toxicity. Doxycycline and primaquine are contraindicated in pregnancy.

PREVENTION OF INSECT BITES

To minimize insect bites, travelers should wear light-colored, long-sleeved shirts, pants, and socks and covered shoes. They should sleep in air conditioned or screened areas and use insecticide-impregnated bed nets. Mosquitoes that transmit malaria are most active between dusk and dawn; those that transmit dengue fever bite during the day, particularly during early morning and late afternoon.[11]

DEET — The most effective topical insect repellent is N, N-diethyl-m-toluamide (DEET). Applied on exposed skin, DEET repels mosquitoes, as well as ticks, chiggers, fleas, gnats and some flies. DEET is available in formulations of 5-100% even though increasing the concentration above 50% does not seem to improve efficacy. Medical Letter reviewers prefer concentrations of 20-35%. A long-acting polymer-based DEET formulation originally developed for the US Armed Forces (US Army Extended Duration Topical Insect and Arthropod Repellent – EDTIAR) containing 25-33% DEET *(Ultrathon)* protects for 6-12 hours. Microencapsulated and liposome-based sustained-release formulations containing 20% DEET *(Sawyer Premium Controlled Release)* and 30% DEET *(Sawyer Ultra 30 Liposome Controlled Release)*, respectively, are also available and are claimed to provide protection for up to 11 hours.

According to the CDC, DEET is probably safe in children and infants >2 months old; the American Academy of Pediatrics recommends use of formulations containing no more than 30%. One study found that applying DEET regularly during the second and third trimesters of pregnancy did not result in any adverse effects on the fetus.[61] DEET has been shown to decrease the effectiveness of sunscreens when it is applied after the sunscreen; nevertheless, sunscreen should be applied first because it may increase the absorption of DEET when DEET is applied first.[62]

PICARIDIN — Picaridin, which appears to be better tolerated on the skin than DEET, is used against flies, mosquitoes, chiggers and ticks. It is available in concentrations of 5-20%. The 20% formulation (*Natrapel 8 Hour*; *GoReady*, and others) has been shown to repel mosquitoes for up to 8 hours.[63-65]

PYRETHROIDS — Permethrin (*Duranon*, *Permanone*, and others), a synthetic pyrethroid insecticide available in liquid and spray form, can be used on clothing, mosquito nets, tents and sleeping bags for protection against mosquitoes and ticks. After application to clothing, it remains active for several weeks through multiple launderings. The combination of DEET on exposed skin and permethrin on clothing provides increased protection. Using pyrethroid-impregnated mosquito nets while sleeping is helpful when rooms are not screened or air-conditioned. Long-lasting insecticide-treated nets that maintain effective levels of insecticide for at least 3 years are available.

SOME OTHER INFECTIONS

DENGUE — Dengue fever is a viral disease transmitted by mosquito bites that occurs worldwide in tropical and subtropical areas, including cities.[66] Outbreaks have occurred in recent years in Southeast Asia, South Asia, sub-Saharan Africa, the South Pacific and Australia, Central and South America, and the Caribbean and there have been sporadic reports in the Middle East.[67] Dengue fever has also been reported in US travelers vacationing at popular tourist destinations in Puerto Rico, the US Virgin Islands and Mexico. Prevention of mosquito bites during the day, particularly in early morning and late afternoon, is the primary way to protect against dengue fever; no vaccine is currently available.

LEPTOSPIROSIS — Leptospirosis, a bacterial disease that occurs in many domestic and wild animals, is endemic worldwide, but the highest incidence is in tropical and subtropical areas. Transmission to humans usually occurs through contact with fresh water or damp soil contaminated by the urine of infected ani-

mals.[68] Travelers at increased risk, such as adventure travelers and those who engage in recreational water activities, should consider prophylaxis with doxycycline 200 mg orally once a week, beginning 1-2 days before and continuing throughout the period of exposure. No human vaccine is available in the US.

NON-INFECTIOUS RISKS OF TRAVEL

Many non-infectious risks are associated with travel. **Injuries**, such as traffic accidents and drowning, account for the majority of preventable travel-related deaths. **Sunburn** also occurs in many travelers.

ACUTE ALTITUDE ILLNESS — Rapid exposure to altitudes >8,000 feet (2500 meters) may cause acute mountain sickness (AMS). Symptoms include headache, fatigue, nausea, anorexia, insomnia, and dizziness; pulmonary and cerebral edema can occur.[69] There is evidence for a genetic predisposition.[70] Sleeping altitude appears to be especially important in determining whether symptoms develop. The most effective preventive measure is pre-acclimatization by a 2- to 4-day stay at intermediate altitude (6000-8000 feet) and gradual ascent to higher elevations.

If rapid ascent to >9100 feet (2800 meters) sleeping altitude cannot be avoided, acetazolamide, a carbonic anhydrase inhibitor taken in a dosage of 125 mg twice daily (or 500 mg daily with the slow-release formulation *Diamox Sequels*) beginning the day before ascent and continuing at high altitude for 2 days or longer, decreases the incidence and severity of AMS.[71] The recommended dose for children is 2.5 mg/kg (max 125 mg) every 12 hours. Although acetazolamide, a sulfone, has little cross-reactivity with sulfa drugs, hypersensitivity reactions to acetazolamide are more likely to occur in those who have had severe (life-threatening) allergic reactions to sulfa drugs.[72] Dexamethasone (*Decadron*, and others) 2 mg every 6 hours or 4 mg every 12 hours has also been shown to prevent AMS in adults. It is not recommended for children.

Severe symptoms can be treated by descent to a lower altitude or by giving supplemental oxygen. When descent is impossible, dexamethasone 4 mg every 6 hours (preferably) or acetazolamide 250 mg every 12 hours, may be used to treat AMS. Dexamethasone, possibly combined with acetazolamide, should be used for cerebral edema. Sustained-release nifedipine (*Procardia XL*, and others), 20 mg every 8 hours or 30 mg every 12 hours may be helpful for prevention and treatment of pulmonary edema.

VENOUS THROMBOEMBOLISM — Prolonged immobilization, particularly during air travel, increases the risk of lower extremity deep vein thrombosis (DVT). Travelers with risk factors for thrombosis (past history of thrombosis, recent surgery, obesity, malignancy, pregnancy, advanced age, limited mobility, thrombophilic disorders, increased platelets) are at even higher risk. Nevertheless, flight-related symptomatic pulmonary embolism is rare.[73]

To minimize the risk, long-distance travelers should be advised to walk around frequently, exercise calf muscles while sitting, and drink extra fluids.[74] Properly fitted compression stockings can decrease the risk of asymptomatic DVT.[75] Giving a single dose of a low-molecular-weight heparin as prophylaxis to travelers at high risk reduced the incidence of asymptomatic DVT in a clinical trial.[76]

JET LAG — Disturbance of body and environmental rhythms resulting from a rapid change in time zones gives rise to jet lag, which is characterized by insomnia, daytime sleepiness, decreased quality of sleep, diminished physical performance, loss of concentration, irritability and GI disturbances. It is usually more severe after eastward travel.[77]

A variety of interventions have been tried, but none are proven to be effective. Shifting daily activities to correspond to the time zone of the destination country before arrival along with taking short naps, remaining well hydrated, avoiding alcohol and pursuing activities in sunlight on arrival may help. The dietary supplement melatonin (0.5-5 mg started on the first night of travel and continued for 1-5 days after arrival) has been reported to facilitate the shift of the sleep-wake cycle and decrease symptoms in some patients. A program of appropriately timed light exposure and avoidance in the new time zone may adjust the "body clock" and reduce jet lag.[78] In one study, zolpidem (*Ambien*, and others) started the first night after travel and taken for 3 nights was helpful.[79] A randomized, double-blind study found that the stimulant armodafinil *(Nuvigil)* 150 mg/d in the morning for 3 days increased wakefulness after eastward travel through 6 time zones.[80]

MOTION SICKNESS — Therapeutic options for motion sickness remain limited.[81] A transdermal patch of the prescription cholinergic blocker scopolamine can decrease symptoms. *Transderm Scop* is applied to the skin behind the ear at least 4 hours before exposure (some experts recommend applying it 6-8 hours before) and changed, alternating ears, every 3 days. Oral promethazine (*Phenergan*, and others) is a highly sedating alternative. Over-the-counter drugs such as dimenhydrinate (*Dramamine*, and others) or meclizine (*Bonine*, and others) are less effective, but may be helpful for milder symptoms.

1. DR Hill et al. The practice of travel medicine: guidelines by the Infectious Diseases Society of America. Clin Infect Dis 2006; 43:1499.
2. Adult immunization. Treat Guidel Med Lett 2011; 9:75.
3. General recommendations on immunizations – recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2011; 60(2):1.
4. RM Klevens et al. The evolving epidemiology of hepatitis A in the United States: incidence and molecular epidemiology from population-based surveillance, 2005-2007. Arch Intern Med 2010; 170:1811.
5. S Iwarson et al. Excellent booster response 4 to 8 years after a single primary dose of an inactivated hepatitis A vaccine. J Travel Med 2004; 11:120.
6. Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). Update: prevention of hepatitis A after exposure to hepatitis A virus and in international travelers. Updated recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2007; 56:1080.
7. R Steffen. Influenza in travelers: epidemiology, risk, prevention, and control issues. Curr Infect Dis Rep 2010; 12:181.
8. Influenza vaccine for 2011-2012. Med Lett Drugs Ther 2011; 53:81.
9. Centers for Disease Control and Prevention (CDC). Use of northern hemisphere influenza vaccines by travelers to the southern hemisphere. MMWR Morb Mortal Weekly Rep 2009; 58:312.
10. SL Hills et al. Japanese encephalitis in travelers from non-endemic countries, 1973-2008. Am J Trop Med Hyg 2010; 82:930.
11. E Mirzaian et al. Mosquito-borne illness in travelers: a review of risk and prevention. Pharmacotherapy 2010; 30:1031.
12. A new Japanese encephalitis vaccine (*Ixiaro*). Med Lett Drugs Ther 2009; 51:66.
13. SB Halstead and SJ Thomas. Japanese encephalitis: new options for active immunization. Clin Infect Dis 2010; 50:1155.
14. CDC. Update on Japanese encephalitis vaccine for children: United States, May 2011. MMWR Morb Mortal Wkly Rep 2011; 60:644.
15. A Kaltenböck et al. Immunogenicity and safety of IXIARO (IC51) in a Phase II study in healthy Indian children between 1 and 3 years of age. Vaccine 2010; 28:834.
16. PJ Edelson and JA Anderson. Reported cases of measles in international air travelers to the United States, August 2005-March 2008. J Travel Med 2011; 18:178.
17. CDC. Measles imported by returning US travelers aged 6-23 months, 2001-2011. MMWR Morb Mortal Wkly Rep 2011; 60:397.
18. R Steffen. The risk of meningococcal disease in travels and current recommendations for prevention. J Travel Med 2010; 17 Suppl: 9.
19. A new conjugate meningococcal vaccine (Menveo). Med Lett Drugs Ther 2010; 52:59.
20. CDC. Recommendation of the Advisory Committee on Immunization Practices (ACIP) for use of quadrivalent meningococcal conjugate vaccine (MenACWY-D) among children aged 9 through 23 months at increased risk for invasive meningococcal disease. MMWR Morb Mortal Wkly Rep 2011; 60:1391.
21. Centers for Disease Control and Prevention (CDC). Update on vaccine-derived polioviruses—worldwide, July 2009-March 2011. MMWR Morb Mortal Wkly Rep 2011; 60:846.
22. C Malerczyk et al. Imported human rabies cases in Europe, the United States, and Japan, 1990-2010. J Travel Med 2011; 18:402.
23. CE Rupprecht and RV Gibbons. Clinical practice. Prophylaxis against rabies. N Engl J Med 2004; 351:2626.
24. CE Rupprecht et al. Use of a reduced (4-dose) vaccine schedule for postexposure prophylaxis to prevent human rabies: recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2010; 59(RR-2):1.
25. Adacel and Boostrix: Tdap vaccines for adolescents and adults. Med Lett Drugs Ther 2006; 48:5.
26. ACIP Provisional Tdap Recommendations. March 21, 2012. Available at www.cdc.gov/vaccines/recs/provisional/Tdap-feb2012.htm. Accessed May 16, 2012.
27. MF Lynch et al. Typhoid fever in the United States, 1999-2006. JAMA 2009; 302:859.
28. JA Whitaker et al. Rethinking typhoid fever vaccines: implications for travelers and people living in highly endemic areas. J Travel Med 2009; 16:46.
29. JE Staples et al. Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2010; 59(RR-7):1.
30. N Bhadelia et al. The HIV-positive traveler. Am J Med 2007; 120:574.
31. AW McMahon et al. Neurologic disease associated with 17D-204 yellow fever vaccination: a report of 15 cases. Vaccine 2007; 25:1727.
32. RE Thomas et al. The safety of yellow fever vaccine 17D or 17DD in children, pregnant women, HIV+ individuals, and older persons: systematic review. Am J Trop Med Hyg 2012; 86:359.
33. MF Farez and J Correale. Yellow fever vaccination and increased relapse rate in travelers with multiple sclerosis. Arch Neurol 2011; 68:1267.
34. S Kuhn et al. Case report: probable transmission of vaccine strain of yellow fever virus to an infant via breast milk. CMAJ 2011; 183:E243.
35. RC Charles and ET Ryan. Cholera in the 21st century. Curr Opin Infect Dis 2011; 24:472.
36. Cholera vaccines: WHO position paper. Wkly Epidemiol Rec 2010; 85:117.
37. A Banzhoff et al. Protection against tick-borne encephalitis (TBE) for people living in and traveling to TBE-endemic areas. Travel Med Infect Dis 2008; 6:331.
38. U Kunze. Is there a need for a travel vaccination against tick-borne encephalitis? Travel Med Infect Dis 2008; 6:380.
39. N Apelt et al. The prevalence of Norovirus in returning international travelers with diarrhea. BMC Infect Dis 2010; 10:131.
40. HL DuPont et al. Expert review of the evidence base for self-therapy of travelers' diarrhea. J Travel Med 2009; 16:161.
41. D Jain et al. *Campylobacter* species and drug resistance in a north Indian rural community. Trans R Soc Trop Med Hyg 2005; 99:207.
42. DR Tribble et al. Traveler's diarrhea in Thailand: randomized, double-blind trial comparing single-dose and 3-day azithromycin-based regimens with a 3-day levofloxacin regimen. Clin Infect Dis 2007; 44:338.
43. KS Hong and JS Kim. Rifaximin for the treatment of acute infectious diarrhea. Therap Adv Gastroenterol 2011; 4:227.
44. HL DuPont et al. Expert review of the evidence base for prevention of travelers' diarrhea. J Travel Med 2009; 16:149.
45. HL DuPont et al. A randomized, double-blind, placebo-controlled trial of rifaximin to prevent travelers' diarrhea. Ann Intern Med 2005; 142:805.
46. AW Armstrong et al. A randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of rifaximin for the prevention of travelers' diarrhea in US military personnel deployed to Incirlik Air Base, Incirlik, Turkey. J Travel Med 2010; 17:392.
47. F Martinez-Sandoval et al. Prevention of travelers' diarrhea with rifaximin in US travelers to Mexico. J Travel Med 2010; 17:111.
48. DO Freedman. Clinical practice. Malaria prevention in short-term travelers. N Engl J Med 2008; 359:603.
49. PJ van Genderen et al. The safety and tolerance of atovaquone/proguanil for the long-term prophylaxis of plasmodium falciparum malaria in non-immune travelers and expatriates [corrected]. J Travel Med 2007; 14:92.
50. E Schwartz et al. Genetic confirmation of atovaquone-proguanil-resistant Plasmodium falciparum malaria acquired by a nonimmune traveler to East Africa. Clin Infect Dis 2003; 37:450.
51. A Färnert et al. Evidence of *Plasmodium falciparum* malaria resistant to atovaquone and proguanil hydrochloride: case reports. BMJ 2003; 326:628.
52. S Kuhn et al. Emergence of atovaquone-proguanil resistance during treatment of *Plasmodium falciparum* malaria acquired by a non-immune North American traveller to west Africa. Am J Trop Med Hyg 2005; 72:407.
53. CT Happi et al. Confirmation of emergence of mutations associated with atovaquone-proguanil resistance in unexposed *Plasmodium falciparum* isolates from Africa. Malaria J 2006; 5:82.

54. J Ling et al. Randomized, placebo-controlled trial of atovaquone/proguanil for the prevention of *Plasmodium falciparum* or *Plasmodium vivax* malaria among migrants to Papua, Indonesia. Clin Infect Dis 2002; 35:825.
55. J Soto et al. Randomized, double-blind, placebo-controlled study of Malarone for malaria prophylaxis in non-immune Colombian soldiers. Am J Trop Med Hyg 2006; 75:430.
56. LH Chen et al. Controversies and misconceptions in malaria chemoprophylaxis for travelers. JAMA 2007; 297:2251.
57. P Schlagenhauf et al. Use of mefloquine in children – a review of dosage, pharmacokinetics and tolerability data. Malar J 2011; 10:292.
58. DR Hill et al. Primaquine: report from CDC expert meeting on malaria chemoprophylaxis I. Am J Trop Med Hyg 2006; 75:402.
59. P Schlagenhauf et al. Pregnancy and fetal outcomes after exposure to Mefloquine in the pre- and periconception period and during pregnancy. Clin Infect Dis 2012; 54:e124. Epub 2012 Apr 10.
60. MH Irvine et al. Prophylactic use of antimalarials during pregnancy. Can Fam Physician 2011; 57:1279.
61. R McGready et al. Safety of the insect repellent N,N-diethyl-M-toluamide (DEET) in pregnancy. Am J Trop Med Hyg 2001; 65:285.
62. Sunscreens: an update. Med Lett Drugs Ther 2008; 50:70.
63. A Badolo et al. Evaluation of the sensitivity of *Aedes aegypti* and *Anopheles gambiae* complex mosquitoes to two insect repellents: DEET and KBR 3023. Trop Med Int Health 2004; 9:330.
64. SP Frances et al. Laboratory and field evaluation of commercial repellent formulations against mosquitoes (diptera: culcidae) in Queensland, Australia. Aust J Entomol 2005; 44:431.
65. C Constantini et al. Field evaluation of the efficacy and persistence of insect repellents DEET, IR3535, and KBR 3023 against *Anopheles gambiae* complex and other Afrotropical vector mosquitoes. Trans R Soc Trop Med Hyg 2004; 98:644.
66. CP Simmons et al. Dengue. N Engl J Med 2012; 366:1423.
67. MG Guzman et al. Dengue: a continuing global threat. Nat Rev Microbiol 2010; 8(12 Suppl):S7.
68. A Pavli and HC Maltezou. Travel-acquired leptospirosis. J Travel Med 2008; 15:447.
69. SA Gallagher and PH Hackett. High-altitude illness. Emerg Med Clin North Am 2004; 22:329.
70. MJ McInnis et al. Evidence for a genetic basis for altitude illness: 2010 update. High Alt Med Biol 2010; 11:349.
71. AM Luks et al. Wilderness Medical Society consensus guidelines for the prevention and treatment of acute altitude illness. Wilderness Environ Med 2010; 21:146.
72. BL Strom et al. Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. N Engl J Med 2003; 349:1628.
73. D Chandra et al. Meta-analysis: travel and risk for venous thromboembolism. Ann Intern Med 2009; 151:180.
74. SR Kahn et al. Prevention of VTE in nonsurgical patients: Antithrombotic therapy and prevention of thrombosis, 9th ed.: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141:e195S.
75. M Clarke et al. Compression stockings for preventing deep vein thrombosis in airline passengers. Cochrane Database Syst Rev 2006; (2):CD004002.
76. MR Cesarone et al. Venous thrombosis from air travel: the LONFLIT3 study–prevention with aspirin vs low-molecular-weight heparin (LMWH) in high-risk subjects: a randomized trial. Angiology 2002; 53:1.
77. RL Sack. Clinical practice. Jet lag. N Engl J Med 2010; 362:440.
78. J Waterhouse et al. Jet lag: trends and coping strategies. Lancet 2007; 369:1117.
79. AO Jamieson et al. Zolpidem reduces the sleep disturbance of jet lag. Sleep Med 2001; 2:423.
80. RP Rosenberg et al. A phase 3, double-blind, randomized, placebo-controlled study of armodafinil for excessive sleepiness associated with jet lag disorder. Mayo Clin Proc 2010; 85:630.
81. JF Golding and MA Gresty. Motion sickness. Curr Opin Neurol 2005; 18:29.

Treatment Guidelines
from The Medical Letter®

EDITOR IN CHIEF: Mark Abramowicz, M.D.
EXECUTIVE EDITOR: Gianna Zuccotti, M.D., M.P.H., F.A.C.P., Harvard Medical School
EDITOR: Jean-Marie Pflomm, Pharm.D.
ASSISTANT EDITORS, DRUG INFORMATION: Susan M. Daron, Pharm.D., **Corinne E. Zanone**, Pharm.D.

CONSULTING EDITORS: Brinda M. Shah, Pharm.D., **F. Peter Swanson**, M.D.

CONTRIBUTING EDITORS:
Carl W. Bazil, M.D., Ph.D., Columbia University College of Physicians and Surgeons
Vanessa K. Dalton, M.D., M.P.H., University of Michigan Medical School
Eric J. Epstein, M.D., Albert Einstein College of Medicine
Jules Hirsch, M.D., Rockefeller University
David N. Juurlink, BPhm, M.D., PhD, Sunnybrook Health Sciences Centre
Richard B. Kim, M.D., University of Western Ontario
Hans Meinertz, M.D., University Hospital, Copenhagen
Sandip K. Mukherjee, M.D., F.A.C.C., Yale School of Medicine
Dan M. Roden, M.D., Vanderbilt University School of Medicine
F. Estelle R. Simons, M.D., University of Manitoba
Jordan W. Smoller, M.D., Sc.D., Harvard Medical School
Neal H. Steigbigel, M.D., New York University School of Medicine
Arthur M.F. Yee, M.D., Ph.D., F.A.C.R, Weill Medical College of Cornell University

SENIOR ASSOCIATE EDITORS: Donna Goodstein, Amy Faucard
ASSOCIATE EDITOR: Cynthia Macapagal Covey

EDITORIAL FELLOW: Esperance A. K. Schaefer, M.D., M.P.H., Harvard Medical School

MANAGING EDITOR: Susie Wong
ASSISTANT MANAGING EDITOR: Liz Donohue
PRODUCTION COORDINATOR: Cheryl Brown

EXECUTIVE DIRECTOR OF SALES: Gene Carbona
FULFILLMENT AND SYSTEMS MANAGER: Cristine Romatowski
DIRECTOR OF MARKETING COMMUNICATIONS: Joanne F. Valentino
VICE PRESIDENT AND PUBLISHER: Yosef Wissner-Levy

Founded in 1959 by
Arthur Kallet and Harold Aaron, M.D.

Subscription Services

Mailing Address:
The Medical Letter, Inc.
145 Huguenot Street, Ste 312
New Rochelle, NY 10801-7537

Customer Service:
Call: 800-211-2769 or 914-235-0500
Fax: 914-632-1733
Web Site: www.medicalletter.org
E-mail: custserv@medicalletter.org

Permissions:
To reproduce any portion of this issue, please e-mail your request to: permissions@medicalletter.org

Subscriptions (US):
1 year - $98; 2 years - $189; 3 years - $279. $49/yr. for students, interns, residents and fellows in the US and Canada.

E-mail site license inquiries to:
info@medicalletter.org or call 800-211-2769 x315.
Special fees for bulk subscriptions. Special classroom rates are available. Back issues are $12 each. Major credit cards accepted.