Treatment Guidelines
from The Medical Letter®

Published by The Medical Letter, Inc. • 1000 Main Street, New Rochelle, NY 10801 • A Nonprofit Publication

IN THIS ISSUE (starts on next page)

Important Copyright Message

Treatment Guidelines
from The Medical Letter®

Published by The Medical Letter, Inc. • 1000 Main Street, New Rochelle, NY 10801 • A Nonprofit Publication

Volume 7 (Issue 87) November 2009
www.medicalletter.org

Tables

Advice for Travelers

Patients planning to travel to other countries often ask physicians 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 1 on page 84. In addition to travel-specific vaccines, all travelers (including children) should be up to date on routine vaccines. Guidelines for routine adult immunization have been published 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.

CHOLERA — The risk of cholera in tourists is very low. The parenteral vaccine previously licensed in the US is no longer available. An oral, whole-cell recombinant vaccine called *Dukoral* is available in some European countries (Crucell/SBL Vaccines) and in Canada (Sanofi Pasteur). It is not currently recommended for routine use in travelers, but might be considered for those who plan to work in refugee camps or as healthcare providers in endemic areas.

HEPATITIS A — Hepatitis A vaccine, which is now part of routine childhood immunization in the US, is recommended for all unvaccinated travelers going anywhere other than Australia, Canada, western Europe, Japan or New Zealand.[3]

Vaccination of adults and children usually consists of two IM doses separated by 6-18 months. Additional booster doses are not needed.[4,5] Two hepatitis A vaccines are available in the US: *Havrix* and *Vaqta*. Patients who received a first dose of one vaccine will respond to a second dose of the other. Second doses given up to 8 years after the first dose have produced protective antibody levels.[6]

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 of hepatitis A (average 28 days). For immunosuppressed patients and those with chronic liver disease who will be traveling to an endemic area in ≤2 weeks, immune globulin (0.02 mL/kg IM) should be given in addition to the initial dose of vaccine. The same dose should be given to children under 1 year of age and other travelers who cannot receive the vaccine if traveling for ≤3 months; a dose of 0.06 mL/kg IM should be given if traveling for >3 months. For travel durations of >5 months, the dose should be repeated.[7]

HEPATITIS B — Vaccination against hepatitis B is recommended for travelers going to intermediate- or high-risk areas (see Table 2 for low-risk areas). Travelers going anywhere who engage in behaviors that may increase the risk of transmission, such as unprotected sexual contact with new partners, dental treatment, skin perforation practices (tattoos, acupuncture, ear piercing) or invasive medical treatment (injections, stitching), should be immunized against hepatitis B.

Two hepatitis B vaccines are available in the US: *Engerix-B* and *Recombivax-HB*. Primary immunization usually consists of 3 doses given IM at 0, 1 and 6 months. An alternate schedule of 3 doses given at 0, 1 and 2 months, followed by a fourth dose at 12 months, is approved for *Engerix-B* in the US. A 2-dose schedule of adult *Recombivax-HB* at 0 and 4-6 months is approved in the US for adolescents 11-15 years old. An

Table 1. Some Vaccines for Travel

Vaccines	Adult Dose (Volume)	Pediatric Age	Pediatric Dose (Volume)	Standard Primary Schedule	Duration of Protection
Hepatitis A					
Havrix (GSK)	1440 EU IM (1 mL)	1-18 yrs	720 EU IM (0.5 mL)	0 and 6-12 mos	Probably lifelong after completion of primary series[1]
Vaqta (Merck)	50 U IM (1 mL)	1-18 yrs	25 U IM (0.5 mL)	0 and 6-18 mos	
Hepatitis B					
Engerix-B (GSK)	20 mcg IM (1 mL)	Birth-19 yrs	10 mcg IM (0.5 mL)	0, 1 and 6 mos	Probably lifelong after completion of primary series
Recombivax-HB (Merck)	10 mcg IM (1 mL)	Birth-19 yrs	5 mcg IM (0.5 mL)	0, 1 and 6 mos	
Hepatitis A/B					
Twinrix (GSK)	720 EU/20 mcg IM (1 mL)	Not approved for <18 yrs	—	0, 1 and 6 mos	Probably lifelong after completion of primary series
Japanese encephalitis					
Ixiaro (Novartis)	0.5 mL IM	Not approved for <17 yrs	—	0, 28 days	No data
JE-Vax (Sanofi Pasteur)	1 mL SC	1-3 yrs >3 yrs	0.5 mL SC 1 mL SC	0, 7 and 14 or (preferably) 30 days	Not established; a single booster is usually given after 24 months if ongoing risk
Meningococcal					
Menomune (Sanofi Pasteur)	50 mcg of each antigen SC (0.5 mL)	≥2 yrs[2]	50 mcg of each antigen SC (0.5 mL)	Single dose	Repeat every 5 yrs[3] with *Menactra* if ongoing risk
Menactra (Sanofi Pasteur)	4 mcg of each antigen IM (0.5 mL) (18-55 yrs)	≥2 yrs	4 mcg of each antigen IM (0.5 mL)	Single dose	Repeat every 5 yrs[3] if ongoing risk
Rabies					
Imovax (Sanofi Pasteur)	≥2.5 IU of rabies antigen IM (1 mL)	Birth	≥2.5 IU of rabies antigen IM (1 mL)	0, 7 and 21 or 28 days[4]	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[5]
RabAvert (Novartis)	≥2.5 IU of rabies antigen IM (1 mL)	Birth	≥2.5 IU of rabies antigen IM (1 mL)	0, 7 and 21 or 28 days[4]	
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)	25 mcg IM (0.5 mL)	≥2 yrs	25 mcg IM (0.5 mL)	Single dose	Repeat every 2 yrs if ongoing risk
Yellow Fever					
YF-Vax (Sanofi Pasteur)	4.74 $\log_{10}$ plaque forming units of 17D204 attenuated YF virus SC (0.5 mL)	≥9 mos	4.74 $\log_{10}$ plaque forming units of 17D204 attenuated YF virus SC (0.5 mL)	Single dose	Booster dose every 10 yrs if ongoing risk

1. Protection likely lasts at least 12 months after a single dose.
2. According to the CDC it is safe for children < 2 years old who require vaccination for the Hajj.
3. Repeat after three years for children vaccinated at 2-6 years of age.
4. 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.
5. Minimal acceptable antibody level is complete virus neutralization at a 1:5 serum dilution by the rapid fluorescent focus inhibition test.

accelerated schedule of 0, 7 and 14 days, followed by a booster dose at 6 months, can also be used with either vaccine, but is not FDA-approved.

An interrupted hepatitis B vaccination series can be completed without being restarted. A 3-dose series started with one vaccine may be completed with the other. Post-vaccination serologic testing is recommended for healthcare workers, infants born to HBsAg-positive mothers, hemodialysis patients, HIV-infected and other immunocompromised patients, and sex- and needle-sharing partners of HBsAg-positive patients.

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. It is given in 3 doses at 0, 1 and 6 months. An accelerated schedule of 0, 7 and 21-30 days with a booster dose at 12 months is also approved.[8]

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.

Table 2. Low-Risk Areas For Hepatitis A & B*

Hepatitis A	Hepatitis B
Australia	Argentina
Canada	Australia
Japan	Canada[1]
New Zealand	Chile
United States	Costa Rica
Western Europe (all countries)	Cuba
	Hungary
	Mexico
	New Zealand
	Nicaragua
	Panama
	Paraguay
	United States[1]
	Uruguay
	Western Europe[2]

* All other areas are intermediate to high risk; vaccine is indicated.
1. Risk is intermediate in Alaska natives and is high in indigenous populations of northern Canada.
2. Risk is intermediate in Greece, Portugal and Spain.

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.[9]

Seasonal influenza vaccine directed against strains in the Northern Hemisphere is sometimes available in the US until the end of June and the US Advisory Committee on Immunization Practices (ACIP) recommends that persons for whom seasonal influenza vaccine is indicated[10] 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).[11] 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.

A monovalent vaccine is available to protect against the currently (2009) circulating pandemic influenza A (H1N1) virus.[12] It can be given at the same time as the seasonal vaccine, except not the 2 live attenuated formulations together. Both the seasonal and monovalent influenza vaccines are prepared in eggs. Hypersensitivity reactions could occur.

There is no commercial influenza 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 being 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 equatorial regions. The attack rate in travelers has been very low.[13]

Vaccination is recommended for travelers >1 year old who expect a long stay (≥1 month) in endemic areas or heavy exposure to mosquitoes (such as adventure travelers) during the transmission season. Vaccination also should be considered for travelers spending less than a 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.[14] Some Medical Letter consultants suggest that, given the rarity of the disease in US residents, compulsive use of insect repellents and judicious avoidance of exposure to mosquitoes might be reasonable alternatives to vaccination for short-term travelers.

Two formulations are FDA-approved in the United States: *JE-Vax*, which is a mouse-brain preparation, and the recently approved *Ixiaro*, a non-mouse-brain vaccine, which is preferred for use in adults, but has not been approved for use in children in the US.[15] In clinical trials, 2 doses of *Ixiaro* (one is not enough) appeared to be as effective as *JE-Vax*, and considerably safer.[16]

MEASLES — 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 in the 1960s) 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.[17]

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 subsequent doses for routine immunization, one at 12-15 months and one at 4-6 years.

MENINGOCOCCAL — A single dose of meningococcal vaccine is recommended for adults and children ≥2 years old who are traveling to areas where epidemics are occurring, or to anywhere in the "meningitis belt" (semi-arid areas of sub-Saharan Africa extending from Senegal and Guinea eastward to Ethiopia) from December to June. Saudi Arabia requires a certificate of immunization for pilgrims during the Hajj. Immunization should also be considered for travelers to other areas where *Neisseria meningitidis* is hyperendemic or epidemic, particularly for those who will have prolonged contact with the local population, such as those living in a dormitory or refugee camp, or working in a healthcare setting.[18-20]

Two quadrivalent vaccines are available against *N. meningitidis* serogroups A, C, Y and W135. *Menomune* contains meningococcal capsular polysaccharides. *Menactra,* which contains capsular polysaccharides conjugated to diphtheria toxoid, is preferred, but *Menomune* is an acceptable alternative. Neither vaccine provides protection against serogroup B, which does not have an immunogenic polysaccharide capsule. Group B infections are rare in sub-Saharan Africa.

The most common adverse reactions to *Menactra* have been headache, fatigue and malaise in addition to pain, redness and induration at the site of injection. The rates of these reactions are higher than with *Menomune*, but similar to those with tetanus toxoid. Guillain-Barré syndrome has been reported rarely in adolescents who received *Menactra*, but cause and effect have not been established.[21]

POLIO — Adults who have not previously been immunized against polio should receive a primary series of inactivated polio vaccine (IPV) if traveling to areas where polio is still endemic (Nigeria, India, Pakistan, Afghanistan) or to areas with documented outbreaks or circulating vaccine-derived strains (see Table 3).[22] Previously unimmunized children should also receive a primary series of IPV.

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.

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

Afghanistan	Djibouti	Niger
Angola	Equatorial Guinea	Nigeria
Bangladesh	Eritrea	Pakistan
Benin	Ethiopia	Rwanda
Bhutan	Gabon	Senegal
Burkina Faso	Gambia	Sierra Leone
Burundi	Ghana	Somalia
Cameroon	Guinea	Sudan
Central African Republic	Guinea-Bissau	Tanzania
	India	Togo
Chad	Kenya	Uganda
Congo	Liberia	Zambia
Côte d'Ivoire	Mali	
Democratic Republic of the Congo	Mauritania	
	Namibia	
	Nepal	

1. Centers for Disease Control and Prevention. Update on the Global Status of Polio. October 1, 2009. Available at: http://wwwnc.cdc.gov/travel/content/in-the news/polio-outbreaks.aspx.

RABIES — Rabies is highly endemic in parts of Africa, Asia (particularly India) and Central and South America, but the risk to travelers is generally low. 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.[23,24] The 2 vaccines available in the US *(Imovax, RabAvert)* are similar; both are given in the deltoid (not gluteal) muscle at 0, 7 and 21 or 28 days.

After a bite or scratch from a potentially rabid animal, patients who received pre-exposure prophylaxis should promptly receive 2 additional doses of vaccine at days 0 and 3. Without pre-exposure immunization, the ACIP recommends rabies immune globulin (RIG) and is now recommending 4 doses (over 14 days) of vaccine instead of 5 doses (over 28 days). Patients with immunosuppression should still receive 5 doses of vaccine.[25] The reduced vaccine dosing schedule may not be included in the prescribing information from the manufacturers of the approved vaccines. 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.[26] RIG is a blood product, and its purity and potency may be less reliable, if it is available at all, in developing countries.

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, and the fourth dose 6 months after the third.

Adults with an uncertain history of primary vaccination should receive 3 doses of a tetanus and diphtheria toxoid vaccine. Two vaccines (*Adacel*; *Boostrix*) containing protein components of acellular pertussis combined with diphtheria and tetanus toxoids (Tdap) are available for adults ≤64 years of age.[27] One of the 3 doses (preferably the first) should be Tdap. The first 2 doses should be administered at least 4 weeks apart and the third 6-12 months after the second. 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. Persons 11-64 years old who have completed a primary childhood series and have not yet received Tdap should receive a single dose of Tdap at the time of their next scheduled routine Td booster. Tdap can be given less than 10 years after the last Td to provide pertussis protection before travel.

TICK-BORNE ENCEPHALITIS (TBE) — TBE occurs in temperate areas of Europe and Asia, from eastern France to northern Japan, and from northern Russia to Albania.[28,29] The risk 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. The vaccine, which is not approved in the US but is available in Canada and Europe (*Encepur* – Novartis; *FSME-Immun* – Baxter AG), is usually given in 3 doses over 9-12 months, but can be given (*Encepur*) over 3 weeks (0, 7 and 21 days). *FSME-Immun* can be obtained in Canada by contacting the Special Access Programme, Health Canada (613-941-2108).

The usual duration of protection after the primary series is 3 years; with the accelerated schedule of *Encepur*, it may be only 12-18 months. Boosters give 5 years of protection for patients <50 years old and 3 years for those ≥50 years old.

TYPHOID — Typhoid vaccine is recommended for travelers to South Asia and other developing countries in 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.[30,31]

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 the first capsule. A purified capsular polysaccharide parenteral vaccine *(Typhim Vi)* for adults and children ≥2 years old is given as a single IM dose at least 2 weeks before departure. Re-vaccination is recommended every 2 years (3 years in Canada).

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 much of tropical South America and sub-Saharan Africa between 15°N and 15°S.[32] Some countries in Africa require an International Certificate of Vaccination against yellow fever, or a physician's waiver letter, from all entering travelers; other countries in Africa, South America and Asia require evidence of vaccination from travelers coming from or traveling through endemic or infected areas. The vaccine is available in the US only from providers certified by state health departments.[33] Boosters are given every 10 years, but immunity probably lasts much longer. If other injectable or intranasal live vaccines are not administered simultaneously with yellow fever vaccine, administration should be separated by one month to avoid a diminished immune response to the vaccines.

Yellow fever vaccine is contraindicated in travelers who have symptomatic HIV infection (and possibly in those with CD4 counts <200 cells/mm^3), are immunocompromised or have egg allergy. 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, especially those with thymus disorders. Vaccine-associated neurologic disease (encephalitis,

Guillain-Barré, Bell's palsy) has also occurred. The vaccine should be avoided if possible in infants <9 months old and it is contraindicated in infants <6 months old.[34] Travelers >60 years of age also have a relatively high risk of systemic adverse effects.[35]

Table 4. Antimicrobial Drugs for Treatment of Travelers' Diarrhea

Drug	Dosage	Cost[1]
Azithromycin	1000 mg once	
generic	or 500 mg once/d	$42.54
Zithromax (Pfizer)	x 3d	64.29
Ciprofloxacin		
generic	500 mg bid x 1-3d	31.44[2]
Cipro (Bayer)		36.30
sustained release		
generic	1000 mg once/d x 1-3d	32.64
Cipro XR		33.78
Levofloxacin	500 mg once/d x 1-3d	
Levaquin (Ortho-McNeil)		44.37
Norfloxacin – *Noroxin* (Merck)	400 mg bid x 1-3d	24.84
Ofloxacin – generic	300 mg bid x 1-3d	32.88
Rifaximin – *Xifaxan* (Salix)	200 mg tid x 3d	49.23

1. Cost of 3 days' treatment based on August 2009 data from retail pharmacies nationwide available from Wolters Kluwer Health.
2. 20 500-mg tablets cost $4 at some discount pharmacies.

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*, viruses and parasites are less common. 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. It should not be used if fever or bloody diarrhea are present, and some patients complain of constipation after use. Loperamide is approved for use in children >2 years old.

If diarrhea is moderate to severe, persists >3 days or is associated with high fever or bloody stools, self-treatment for 1-3 days with ciprofloxacin, levofloxacin, norfloxacin or ofloxacin is usually recommended.[36] Azithromycin, taken as a single 1000-mg dose or 500 mg daily for 1-3 days, is an alternative[37,38] and is the drug of choice for travelers to areas with a high prevalence of fluoroquinolone-resistant *Campylobacter*, such as Thailand and India.[39,40] 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 in 48 hours.

A non-absorbed oral antibiotic derived from rifampin, rifaximin 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.[41] It should not be used in infections associated with fever or blood in the stool or those caused by *C. jejuni*, *Salmonella*, *Shigella* or other invasive pathogens, or during pregnancy.

One meta-analysis found that combinations of an antibacterial plus loperamide were more effective than an antibacterial alone in decreasing the duration of illness.[42]

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 consultants 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.[43] 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. In one 2-week study among travelers to Mexico, rifaximin (200 mg 1-3x/d) was effective in preventing travelers' diarrhea.[44] 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. It is not recommended for children <3 years old.

MALARIA

No drug is 100% effective for prevention of malaria; travelers should be told to take protective measures against mosquito bites in addition to medication.[45] Countries with a risk of malaria are listed in Table 5.

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

AFRICA		
Angola	Equatorial Guinea	Niger
Benin	Eritrea[3]	Nigeria
Botswana[3]	Ethiopia[3]	Rwanda
Burkina Faso	Gabon	São Tomé and Príncipe
Burundi	Gambia, The	Senegal
Cameroon	Ghana	Sierra Leone
Cape Verde[2]	Guinea	Somalia
Central African Republic	Guinea-Bissau	South Africa[3]
Chad	Kenya[3]	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[3,4]	Dominican Republic[3,4]	Honduras[3,4]
Bahamas, The[3,4,5]	Ecuador[3]	Mexico[3,4]
Belize[3,4]	El Salvador[3,4]	Nicaragua[3,4]
Bolivia[3]	French Guiana[3]	Panama[3,6]
Brazil	Guatemala[3,4]	Paraguay[3,4]
Colombia[3]	Guyana[3]	Peru[3]
Costa Rica[3,4]	Haiti[4]	Suriname[3]
		Venezuela[3]
ASIA		
Afghanistan	Iran[3]	Saudi Arabia[3]
Armenia[3,4]	Iraq[3,4]	Sri Lanka
Azerbaijan[3,4]	Korea, North[4]	Tajikistan
Bangladesh[3]	Korea, South[3,4]	Thailand[3]
Bhutan[3]	Laos[3]	Timor-Leste (East Timor)
Cambodia[3]	Malaysia[3]	Turkey[3,4]
China[7]	Myanmar[3]	Uzbekistan[4]
Georgia[3,4]	Nepal[3]	Vietnam[3]
India	Pakistan	Yemen
Indonesia[3]	Philippines[3]	
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. More detailed information is available at www.cdc.gov/malaria and by phone for medical personnel from the Malaria Branch of the CDC at 770-488-7788.
2. Limited to Island of Saõ Tiago.
3. No malaria in major urban areas.
4. Chloroquine is the drug of choice for prophylaxis.
5. Only Great Exuma Island.
6. Chloroquine is recommended in Bocas del Toro province.
7. Chloroquine is recommended except in Hainan and Yunnan provinces.

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 consider buying 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, 6 and 7). 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** *(Malarone)* taken once daily is generally the best tolerated prophylactic,[46] but it can cause headache, insomnia, GI disturbances and mouth ulcers. 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 Medical Letter consultants do not believe there is a high risk for acquisition of resistant disease.[47-50] In one study of malaria prophylaxis, atovaquone/proguanil was as effective and better tolerated than mefloquine in nonimmune travelers.[51] The protective efficacy of atovaquone/proguanil against *P. vivax* is variable ranging from 84% in Indonesian New Guinea[52] to 100% in Colombia.[53] Some Medical Letter consultants prefer other drugs if traveling 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.[54] Dizziness, headache, insomnia and disturbing dreams are the most common CNS adverse effects. The drug's adverse effects in children are similar to those in adults. If a patient develops psychological or behavioral abnormalities such as depression, restlessness or confusion while taking mefloquine, another drug should be substituted. Mefloquine should not be given together with quinine, quinidine or halofantrine due to potential prolongation of the QT interval; caution is required when using these drugs to treat patients who have taken mefloquine prophylaxis.

Doxycycline (*Vibramycin*, and others), which frequently causes GI disturbances and can cause photosensitivity and vaginitis, offers an inexpensive once-

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

Drug	Adult dosage	Pediatric dosage	Duration
All *Plasmodium* species in chloroquine-sensitive areas[2]			
Drug of Choice[3,4]:			
Chloroquine phosphate[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]			
Drug of Choice[3]:			
Atovaquone/proguanil[6] (*Malarone*, *Malarone Pediatric)*	1 adult tablet daily	5-8 kg: ½ peds tab/d 9-10 kg: ¾ peds tab/d 11-20 kg: 1 peds tab/d 21-30 kg: 2 peds tabs/d 31-40 kg: 3 peds tabs/d >40 kg: 1 adult tab/d	Start: 1-2d before travel Stop: 1 wk after leaving malarious zone
OR Doxycycline[7] (*Vibramycin*, and others)	100 mg PO daily	2 mg/kg/d PO, up to 100 mg/d	Start: 1-2d before travel Stop: 4 wks after leaving malarious zone
OR Mefloquine[8]	250 mg PO once/wk[9]	5-10 kg: ⅛ tab once/wk[9,10] 11-20 kg: ¼ tabs once/wk[9,10] 21-30 kg: ½ tab once/wk[9] 31-45 kg: ¾ tab once/wk[9] >45 kg: 1 tab once/wk[9]	Start: 1-2 wks before travel Stop: 4 wks after leaving malarious zone
Alternative:			
Primaquine phosphate[11,12]	30 mg base PO daily	0.6 mg/kg base PO daily	Start: 1d 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 (including Panama north and west of the Canal Zone), Mexico, Haiti, the Dominican Republic, Paraguay, northern Argentina, North and South Korea, Georgia, Armenia, 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 (JD Maguire et al, Lancet 2002; 360:58).
3. Primaquine is given for prevention of relapse after infection with *P. vivax* or *P. ovale*. Some experts also prescribe primaquine phosphate 30 mg base/d (0.6 mg base/kg/d for children) for 14d 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*; 250 mg atovaquone/100 mg proguanil) and pediatric tablets (*Malarone Pediatric*; 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 ß-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 consultants favor starting mefloquine 3 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.

daily alternative. Doxycycline should not be taken concurrently with antacids, oral iron or bismuth salts
.

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 should be reserved for travelers unable to take any other drug; it is somewhat less effective than the alternatives against *P. falciparum*. However, several studies have shown that daily primaquine can provide effective prophylaxis against chloroquine-resistant *P. falciparum* and *P. vivax*.[55] Some experts also prescribe primaquine for 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 treatment with the 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 and in the areas of Myanmar and Cambodia that border on Thailand. It has also been reported on the borders 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 not approved for use during pregnancy. It has, however, been reported to be safe for prophylactic use during the second or third trimester of pregnancy and possibly during early pregnancy as well.[56,57] The safety of atovaquone/proguanil in pregnancy has not been established, and its use is not recommended. However, outcomes were normal in 24 women treated with the combination in the second and third trimester,[58] 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, 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.[59]

DEET — The most effective topical insect repellent is N, N-diethyl-m-toluamide (DEET).[60] 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 consultants prefer concentrations of 30-35%. A long-acting 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. A microencapsulated sustained-release formulation containing 20% DEET *(Sawyer Controlled Release)* is also available and can provide longer protection than similar concentrations of other DEET formulations.

According to the CDC, DEET is probably safe in children and infants >2 months old; the American Academy of Pediatrics recommends use of concentrations 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 has been available in Europe and Australia for many years. Data on the 7% and 15% formulations *(Cutter Advanced)* currently sold in the US are limited. The 20% formulation (*Natrapel 8 Hour*; *GoReady*) has been shown to protect for up to 8 hours; in clinical trials it has been about as effective as 20% DEET.[63-65]

PERMETHRIN — An insecticide available in liquid and spray form, permethrin (*Duranon*, *Permanone*, and others) 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. Using permethrin-impregnated mosquito nets while sleeping is helpful when rooms are not screened or air-conditioned. If bednets or tents are immersed in the liquid, the effect can last for about 6 months. The combination of DEET on exposed skin and permethrin on clothing provides increased protection.

SOME OTHER INFECTIONS

DENGUE — Dengue fever is a viral disease transmitted by mosquito bites that occurs worldwide in tropical and subtropical areas, including cities. Epidemics have occurred in recent years in Southeast Asia (especially Thailand), South Central Asia, sub-Saharan Africa, the South Pacific and Australia, Central and South America and the Caribbean. It has also been reported in travelers from the US vacationing at popular tourist destinations in Puerto Rico, the US Virgin Islands and Mexico.[66] 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 animals.[67] 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, particularly **traffic accidents** and **drowning**, which account for the majority of travel-related deaths, and **sunburn** occur in many travelers.

HIGH ALTITUDE ILLNESS — Rapid exposure to altitudes >8,000 feet (2500 meters) may cause acute mountain sickness (headache, fatigue, nausea, anorexia, insomnia, dizziness); pulmonary and cerebral edema can occur.[68] 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.

Acetazolamide, a carbonic anhydrase inhibitor taken in a dosage of 125-250 mg twice daily (or 500 mg daily with the slow-release formulation *Diamox Sequels*) beginning 1-2 days before ascent and continuing at high altitude for 48 hours or longer, decreases the incidence and severity of acute mountain sickness.[69] The recommended dose for children is 5 mg/kg/d in 2 or 3 divided doses. 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.[70]

Symptoms can be treated after they occur by descent to a lower altitude or by giving supplemental oxygen, especially during sleep. When descent is impossible, dexamethasone (*Decadron*, and others) 4 mg q6h, acetazolamide 250-500 mg q12h, or the two together, may help. Nifedipine (*Procardia*, and others), 20-30 mg twice daily may also be helpful.

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, obesity, malignancy, increased platelets) are at even higher risk. Nevertheless, flight-related symptomatic pulmonary embolism is rare.[71]

To minimize the risk, travelers should be advised to walk around or, if necessary, exercise while sitting by flexing/extending ankles and knees, to drink extra fluids, and to avoid alcohol and caffeine. Compression stockings can decrease the risk of asymptomatic DVT.[72] Giving a single dose of a low-molecular-weight heparin as prophylaxis to travelers at high risk reduced the incidence of DVT in a clinical trial.[73]

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, decreased quality of sleep, loss of concentration, irritability and GI disturbances. It is usually more severe after eastward travel.[74]

A variety of interventions have been tried, but none is 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.[75] In one study, zolpidem (*Ambien*, and others) started the first night after travel and taken for 3 nights was helpful.[76]

MOTION SICKNESS — Therapeutic options for motion sickness remain limited.[77] A transdermal patch or oral formulation 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 and changed, alternating ears, every 3 days. The oral 8-hour tablet *(Scopace)* is taken 1 hour before exposure. 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 2009; 7:27.
3. D Daniels et al. Surveillance for acute viral hepatitis-United States, 2007. MMWR Surveill Summ 2009; 58(SS03):1.
4. P Van Damme et al. Hepatitis A booster vaccination: is there a need? Lancet 2003; 362:1065.
5. JN Zuckerman et al. Hepatitis A and B booster recommendations: implications for travelers. Clin Infect Dis 2005; 41:1020.
6. 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.

7. 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.
8. BA Connor and DJ Patron. Use of an accelerated immunization schedule for combined hepatitis A and B protection in the corporate traveler. J Occup Environ Med 2008; 50:945 .
9. DO Freedman and K Leder. Influenza: changing approaches to prevention and treatment in travelers. J Travel Med 2005; 12:36.
10. Seasonal trivalent influenza vaccine for 2009-2010. Med Lett Drugs Ther 2009; 51:73.
11. 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.
12. H1N1 Vaccine for prevention of pandemic influenza. Med Lett Drugs Ther 2009; 51:77.
13. MR Buhl and L Lindquist. Japanese encephalitis in travelers: review of cases and seasonal risk. J Travel Med 2009; 16:217.
14. ACIP provisional recommendations for the use of Japanese encephalitis virus vaccines, June 24, 2009. Available at www.cdc.gov/vaccines/recs/provisional/downloads/je-july2009-508.pdf. Accessed October 5, 2009.
15. A new Japanese encephalitis vaccine (*Ixiaro*). Med Lett Drugs Ther 2009; 51:66.
16. ST Duggan and GL Plosker. Japanese enecphalitis vaccine (inactivated, adsorbed) [IXIARO]. Drugs 2009; 69:115.
17. ACIP Provisional Recommendations for measles-mumps-rubella (MMR) 'evidence of immunity' requirements for healthcare personnel. Available at: www.cdc.gov/vaccines/recs/provisional/default.htm. Accessed October 5, 2009.
18. A Wilder-Smith. Meningococcal disease: risk for international travellers and vaccine strategies. Travel Med Infect Dis 2008; 6:182.
19. OO Bilukha and N Rosenstein; National Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC). Prevention and control of meningococcal disease. recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2005; 54 (RR-7):1.
20. Committee to Advise on Tropical Medicine and Travel (CATMAT). Statement on meningococcal vaccination for travellers. An Advisory Committee Statement (ACS). Can Commun Dis Rep 2009; 35(ACS-4):1.
21. CDC Vaccine safety updates. GBS and Menactra meningococcal vaccine. Available at: www.cdc.gov/vaccinesafety/updates/gbsfactsheet.htm. Accessed October 5, 2009.
22. Centers for Disease Control and Prevention (CDC). Update on vaccine-derived polioviruses—worldwide, January 2008-June 2009. MMWR Morb Mortal Wkly Rep 2009; 58:1002.
23. CE Rupprecht and RV Gibbons. Clinical practice. Prophylaxis against rabies. N Engl J Med 2004; 351:2626.
24. FX Meslin. Rabies as a traveler's risk, especially in high-endemicity areas. J Travel Med 2005; 12 Suppl 1:S30.
25. ACIP provisional recommendations for the prevention of human rabies. July 10, 2009. Available at www.cdc.gov/vaccines/recs/provisional/downloads/rabies-July 2009-508.pdf. Accessed October 5, 2009.
26. SE Manning et al. Human rabies prevention—United States, 2008: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2008; 57 (RR-3):1.
27. Adacel and Boostrix: Tdap vaccines for adolescents and adults. Med Lett Drugs Ther 2006; 48:5.
28. 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.
29. U Kunze. Is there a need for a travel vaccination against tick-borne encephalitis? Travel Med Infect Dis 2008; 6:380.
30. MF Lynch et al. Typhoid fever in The United States, 1999-2006. JAMA 2009; 302:859.
31. JA Whitaker et al. Rethinking typhoid fever vaccines: implications for travelers and people living in highly endemic areas. J Travel Med 2009; 16:46.
32. ED Barnett. Yellow fever: epidemiology and prevention. Clin Infect Dis 2007; 44:850.
33. Search for yellow fever vaccination clinics. Updated Jan 28, 2008. Available at: wwwn.cdc.gov/travel/yellow-fever-vaccination-clinics-search.aspx. Accessed Oct 5, 2009.
34. AW McMahon et al. Neurologic disease associated with 17D-204 yellow fever vaccination: a report of 15 cases. Vaccine 2007; 25:1727.
35. ED Barnett et al. Yellow fever vaccines and international travelers. Expert Rev Vaccines 2008; 7:579.
36. HL DuPont et al. Expert review of the evidence base for self-therapy of travelers' diarrhea. J Travel Med 2009; 16:161.
37. JA Adachi et al. Azithromycin found to be comparable to levofloxacin for the treatment of US travelers with acute diarrhea acquired in Mexico. Clin Infect Dis 2003; 37:1165.
38. CD Ericsson et al. Loperamide plus azithromycin more effectively treats travelers' diarrhea in Mexico than azithromycin alone. J Travel Med 2007; 14:312.
39. D Jain et al. *Campylobacter* species and drug resistance in a north Indian rural community. Trans R Soc Trop Med Hyg 2005; 99:207.
40. 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.
41. AL Pakyz. Rifaximin: a new treatment for travelers' diarrhea. Ann Pharmacother 2005; 39:284.
42. MS Riddle et al. Effect of adjunctive loperamide in combination with antibiotics on treatment outcomes in traveler's diarrhea: a systematic review and meta-analysis. Clin Infect Dis 2008; 47:1007.
43. HL DuPont et al. Expert review of the evidence base for prevention of travelers' diarrhea. J Travel Med 2009; 16:149.
44. HL DuPont et al. A randomized, double-blind, placebo-controlled trial of rifaximin to prevent travelers' diarrhea. Ann Intern Med 2005; 142:805.
45. DO Freedman. Clinical practice. Malaria prevention in short-term travelers. N Engl J Med 2008; 359:603.
46. 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.
47. 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.
48. A Färnert et al. Evidence of *Plasmodium falciparum* malaria resistant to atovaquone and proguanil hydrochloride: case reports. BMJ 2003; 326:628.
49. 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.
50. 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.
51. D Overbosch et al. Atovaquone-proguanil versus mefloquine for malaria prophylaxis in nonimmune travelers: results from a randomized, double-blind study. Clin Infect Dis 2001; 33:1015.
52. 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.
53. 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.
54. LH Chen et al. Controversies and misconceptions in malaria chemoprophylaxis for travelers. JAMA 2007; 297:2251.
55. DR Hill et al. Primaquine: report from CDC expert meeting on malar-

ia chemoprophylaxis I. Am J Trop Med Hyg 2006; 75:402.
56. Centers for Disease Control and Prevention. CDC Health Information for International Travel 2010. Atlanta: U.S. Department of Health and Human Services, Public Health Service, 2009, p 469.
57. BL Smoak et al. The effects of inadvertent exposure of mefloquine chemoprophylaxis on pregnancy outcomes and infants of US Army servicewomen. J Infect Dis 1997; 176:831.
58. R McGready et al. The pharmacokinetics of atovaquone and proguanil in pregnant women with acute falciparum malaria. Eur J Clin Pharmacol 2003; 59:545.
59. Committee to Advise on Tropical Medicine and Travel (CATMAT). Statement on personal protective measures to prevent arthropod bites. Can Commun Dis Rep 2005; 31 (ACS-4):1.
60. TM Katz et al. Insect repellents: historical perspectives and new developments. J Am Acad Dermatol 2008; 58:865.
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. A Wilder-Smith and DJ Gubler. Geographic expansion of dengue: the impact of international travel. Med Clin North Am 2008; 92:1377.
67. A Pavli and HC Maltezou. Travel-acquired leptospirosis. J Travel Med 2008; 15:447.
68. SA Gallagher and PH Hackett. High-altitude illness. Emerg Med Clin North Am 2004; 22:329.
69. B Basnyat et al. Acetazolamide 125 mg BD is not significantly different from 375 mg BD in the prevention of acute mountain sickness: the prophylactic acetazolamide dosage comparison for efficacy (PACE) trial. High Alt Med Biol 2006; 7:17.
70. BL Strom et al. Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. N Engl J Med 2003; 349:1628.
71. D Chandra et al. Meta-analysis: travel and risk for venous thromboembolism. Ann Intern Med 2009; 151:180.
72. M Clarke et al. Compression stockings for preventing deep vein thrombosis in airline passengers. Cochrane Database Syst Rev 2006; (2):CD004002.
73. 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.
74. RL Sack. The pathophysiology of jet lag. Travel Med Infect Dis 2009; 7:102.
75. J Waterhouse et al. Jet lag: trends and coping strategies. Lancet 2007; 369:1117.
76. AO Jamieson et al. Zolpidem reduces the sleep disturbance of jet lag. Sleep Med 2001; 2:423.
77. JF Golding and MA Gresty. Motion sickness. Curr Opin Neurol 2005; 18:29.

Coming Soon in *Treatment Guidelines*:
Antifungal Drugs – December 2009
Drugs for Eye Disorders – January 2010

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., **Blaine M. Houst**, Pharm.D., **Corinne E. Zanone**, Pharm.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
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
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

ADVISORY BOARD:
Jules Hirsch, M.D., Rockefeller University
Gerald L. Mandell, M.D., University of Virginia School of Medicine
Dan M. Roden, M.D., Vanderbilt University School of Medicine

SENIOR ASSOCIATE EDITORS: Donna Goodstein, Amy Faucard
ASSOCIATE EDITOR: Cynthia Macapagal Covey
EDITORIAL FELLOW: Vince Teo B.Sc. Phm, Sunnybrook Health Sciences Centre

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.
1000 Main Street
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 - $167; 3 years - $235. $49/yr. for students, interns, residents and fellows in the US and Canada.
CME: $44 for 26 credits.

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.

Introducing

Treatment Guidelines: Online Continuing Medical Education

Up to 24 credits included with your subscription

www.medicalletter.org/tgcme

For over 25 years, The Medical Letter has offered health care professionals continuing medical education (CME) with *The Medical Letter on Drugs and Therapeutics*. We are now offering CME for *Treatment Guidelines from The Medical Letter* in an online format only, called the Online Series. Each Online Series is comprised of 6 monthly exams and eligible for up to 12 credits. For those who just need a few credits, we also offer the Quick Online Credit Exam (earn up to 2 credits/12 questions). For more information, please visit us at www.medicalletter.org/tgcme.

Choose CME from *Treatment Guidelines from The Medical Letter* and earn up to 24 Category 1 Credits per year in the format that's right for you:

Online Series - Answer 12 questions per issue online. Earn up to 2 credits/exam. Take up to 6 short exams per six-month series and earn up to a total of 12 credits. The Online Series is included with a paid subscription to *Treatment Guidelines*.
Quick Online Credit Exam - Access content for any available issue, answer 12 questions online, and earn up to 2 credits for $12.00 (available to both subscribers and non-subscribers).

ACCREDITATION INFORMATION:
ACCME: The Medical Letter is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The Medical Letter designates this educational activity for a maximum of 2 *AMA PRA Category 1 Credit(s)*™. Physicians should only claim credit commensurate with the extent of their participation in this activity. This CME activity was planned and produced in accordance with the ACCME Essentials.

AAFP: *Treatment Guidelines from The Medical Letter* has been reviewed and is acceptable for up to 15 Prescribed credits by the American Academy of Family Physicians. AAFP accreditation begins 01/01/09. Term of approval is for one year from this date. This exam is approved for 1.25 Prescribed credits. Credits may be claimed for one year from the date of this exam.

ACPE: The Medical Letter is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This issue is acceptable for 2.0 hours of Continuing Education Credit (0.2 CEU).

AANP and AAPA: The **American Academy of Nurse Practitioners (AANP)** and the **American Academy of Physician Assistants (AAPA)** accept *AMA Category 1 Credit* for the Physician's Recognition Award from organizations accredited by the ACCME.

AOA: This activity, being ACCME (AMA) approved, is acceptable for Category 2-B credit by the **American Osteopathic Association**.

MISSION:
The mission of The Medical Letter's Continuing Medical Education Program is to support the professional development of health care professionals including physicians, nurse practitioners, pharmacists and physician assistants by providing independent, unbiased drug information and prescribing recommendations that are free of industry influence. The program content includes current information and unbiased reviews of FDA-approved and off-label uses of drugs, their mechanisms of action, clinical trials, dosage and administration, adverse effects and drug interactions. The Medical Letter delivers educational content in the form of self-study material.

The expected outcome of the CME Program is that knowledge and consideration of the information contained in *The Medical Letter* and *Treatment Guidelines* can affect health care practice and ultimately result in improved patient care and outcomes.

The Medical Letter will strive to continually improve the CME program through periodic assessment of the program and activities. The Medical Letter aims to be a leader in supporting the professional development of health care professionals by providing continuing medical education that is unbiased and free of industry influence.

LEARNING OBJECTIVES:
The objective is to meet the need of health care professionals for unbiased, reliable and timely information on treatment of major diseases.

Activity participants will read and assimilate unbiased reviews of FDA-approved and off-label uses of drugs and drug classes. Participants will be able to select and prescribe, or confirm the appropriateness of the prescribed usage of the drugs and other therapeutic modalities discussed in Treatment Guidelines with specific attention to clinical evidence of effectiveness, adverse effects and patient management. Through this program, The Medical Letter expects to provide the prescribing health care community with educational content that they will use to make independent and informed therapeutic choices in their practice.

Questions start on next page

DO NOT FAX OR MAIL THIS EXAM
To take this exam, go to:
www.medicalletter.org/tgcme

Issue 87 Questions

1. Hepatitis A vaccine is recommended for travelers going to:
   a. Russia
   b. Italy
   c. Spain
   d. Japan

   Pg 83

2. For hepatitis B vaccination, an accelerated schedule of 0, 7 and 14 days can be used with:
   a. *Engerix-B*
   b. *Recombivax-HB*
   c. either vaccine
   d. neither vaccine

   Pg 83

3. Off-season use of seasonal influenza vaccine should be considered for:
   a. travelers to the tropics
   b. travelers to the Southern Hemisphere
   c. traveling in a group with persons from the Southern Hemisphere
   d. all of the above

   Pg 85

4. The preferred vaccine for adults against Japanese encephalitis is:
   a. *JE-Vax*
   b. *Ixiaro*
   c. JE immune globulin
   d. None of the above

   Pg 85

5. The "meningitis belt" where meningococcal meningitis is endemic is in:
   a. the Balkans
   b. the Middle East
   c. Southeast Asia
   d. sub-Saharan Africa

   Pg 85

6. Unimmunized travelers bitten by a potentially rabid animal should receive:
   a. rabies vaccine
   b. rabies immune globulin
   c. both
   d. neither

   Pg: 86

7. A vaccine for tick-borne encephalitis is:
   a. not available in the US
   b. available in Canada
   c. available in Europe
   d. all of the above

   Pg 87

8. Travelers' diarrhea can be treated with:
   a. loperamide
   b. azithromycin
   c. oral rehydration salts in water
   d. all of the above

   Pg 87, 88

9. Among the most effective drugs used for prevention of chloroquine-resistant malaria, the one generally best tolerated is:
   a. atovaquone/proguanil
   b. mefloquine
   c. doxycycline
   d. primaquine phosphate

   Pg 88

10. Mosquitoes that transmit malaria are most active:
    a. in the morning
    b. at midday
    c. in the late afternoon
    d. between dusk and dawn

    Pg 90

11. Which of the following is true?
    a. DEET applied after sunscreen can decrease the effectiveness of sunscreen.
    b. Sunscreen applied after DEET can increase absorption of DEET.
    c. Sunscreen should be applied before DEET.
    d. All of the above

    Pg 91

12. The most effective measure to prevent high-altitude illness is:
    a. acetazolamide 500 mg q12h
    b. dexamethasone 4 mg q6h
    c. nifedipine 30 mg q12h
    d. gradual ascent

    Pg 91, 92

ACPE UPN: 379-000-09-087-H01-P; Release: November 2009, Expire: November 2010