

Treatment Guidelines

from The Medical Letter®

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Advice for Travelers

Patients planning to travel to other countries often ask physicians for information about immunizations and prevention of diarrhea and malaria. More detailed advice for travelers is available from the Centers for Disease Control and Prevention at 877-FYI-TRIP (877-394-8747) or www.cdc.gov/travel.

IMMUNIZATIONS

Common travel immunizations are listed in the table on page 27. In addition to receiving travel-specific vaccines, all travelers (including children) should be up to date on routine immunizations. Guidelines for routine adult immunization will be published in a future issue of *Treatment Guidelines*. 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 licensed in the US is no longer available. An oral vaccine called *Dukoral* is available in some European countries (Chiron) and in Canada (Sanofi Pasteur). It is not currently recommended for routine use in travelers. Vaccination might be considered for travelers who plan to work in refugee camps or as health care 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 Canada, Australia, New Zealand, South Korea, Japan or western Europe. The majority of hepatitis A cases imported into the US by travelers are related to travel in Mexico and Central America.¹

Vaccination of adults and children usually consists of two IM doses separated by 6-18 months. Additional booster doses are not needed.² Two hepatitis A vaccines are available in the US. 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.^{3,4}

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).⁵ Children under 1 year of age and other travelers who cannot receive the vaccine should be given immune globulin (IG) (0.02 mL/kg IM if traveling for <3 months, 0.06 mL/kg IM if traveling for >3 months).

HEPATITIS B — Vaccination against hepatitis B is recommended for unvaccinated travelers going to intermediately or highly endemic areas if they plan to stay for a long time, return frequently, or live among the local population. It is also recommended for short-stay travelers planning to receive medical or dental care, or to undergo cosmetic needle punctures for tat-

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toos or body piercing. Anyone who might have unprotected sexual contact with new partners should be immunized against hepatitis B.

Primary immunization consists of 3 doses given IM at 0, 1 and 6 months. An accelerated 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. An accelerated schedule of 0, 7 and 21 days with a fourth dose at 12 months can also be used if necessary, but is not FDA-approved. A 2-dose schedule of adult *Recombivax* at 0 and 4-6 months is approved in the US for adolescents 11-15 years old.⁶

An interrupted hepatitis B vaccination series does not need to be restarted. A 3-dose series started with one vaccine may be completed with the other. Post-vaccination serologic testing is recommended for health care workers.

HEPATITIS A/B — A combination vaccine (*Twinrix*) containing the same antigenic components as *Engerix-B* and pediatric *Havrix* is available for patients ≥ 18 years old. It is given in 3 doses at 0, 1 and 6 months; at least 2 doses should be given before travel. An accelerated schedule of 0, 1 and 3 weeks with a fourth dose at 12 months can be used if necessary, but is not FDA-approved.⁷

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 October. Outbreaks have occurred on cruise ships and on organized group tours in any latitude or season.⁸

Influenza vaccine against strains in the Northern Hemisphere is sometimes available in the US until the end of June. High-risk patients (>50 years or 6-23 months old, pregnant women, or anyone ≥ 6 months old with chronic disease) from the Northern Hemisphere who travel to the Southern Hemisphere during that region's influenza season should consider being immunized on arrival because the vaccine active against strains in the Southern Hemisphere is rarely available in the Northern. There is no commercial influenza vaccine available for pathogenic strains of avian influenza (H5N1, H7N2, H9N2, H7N3, H7N7). Since standard commercially available influenza vaccines include N1 and N2, it is biologically plausible that they might offer some protection against avian flu strains with these neuraminidases.

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.⁹ A vaccine is available in the US (*JE-Vax*) and should be considered for travelers >1 year old who expect a long stay (usually considered ≥ 4 weeks) in rural areas or heavy exposure to mosquitoes (such as adventure travelers).

Three doses are given over 2 to (preferably) 4 weeks. Local injection-site reactions, mild systemic adverse effects such as fever, headache and myalgias, and allergic reactions including urticaria and angioedema, can occur in up to 20% of patients. Whenever possible, the last dose should be given at least 10 days before departure due to the unpredictable allergic adverse effects. The duration of immunity is unknown; a booster can be given after 24 months.

MEASLES — Adults born after 1956 (1970 in Canada) 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 a single dose of measles or measles-mumps-rubella (MMR) vaccine before traveling. Both are attenuated live-virus vaccines.

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.

Low-Risk Regions For Hepatitis A & B*

Hepatitis A	Hepatitis B
United States	United States ¹
Canada	Canada ¹
Western Europe (all countries)	Mexico
South Korea	Costa Rica
Japan	Chile
Australia	Argentina
New Zealand	Paraguay
	Uruguay
	Western Europe ²
	Hungary
	Australia
	New Zealand

* All other areas are intermediate to high risk; vaccine is indicated.

1. Risk is high in Alaska natives and indigenous populations of northern Canada.

2. Risk is intermediate in Greece, Italy, Portugal, Malta and Spain.

Some Immunizations for Travel

Vaccines	Adult Dose (Volume)	Pediatric Age	Pediatric Dose (Volume)	Standard Primary Schedule	Duration of Protection
Hepatitis A					
<i>Havrix</i> (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
<i>Vaqta</i> (Merck)	50 U IM (1 mL)	1-18 yrs	25 U IM (0.5 mL)	0 and 6-18 mos	
Hepatitis B					
<i>Engerix-B</i> (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
<i>Recombivax-HB</i> (Merck)	10 mcg IM (1 mL)	Birth-19 yrs	5 mcg IM (0.5 mL)	0, 1 and 6 mos	
Hepatitis A/B					
<i>Twinrix</i> (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					
<i>JE-Vax</i> (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					
<i>Menomune</i> (Sanofi Pasteur)	50 mcg of each antigen SC (0.5 mL)	≥2 yrs	50 mcg of each antigen SC (0.5 mL)	Single dose	Repeat every 5 yrs if ongoing risk
<i>Menactra</i> (Sanofi Pasteur)	4 mcg of each antigen IM (0.5 mL) (18-55 yrs)	11-17 yrs	4 mcg of each antigen IM (0.5 mL)	Single dose	No data. Likely longer than <i>Menomune</i>
Rabies					
<i>Imovax</i> (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 ²	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 ³
<i>RabAvert</i> (Chiron)	≥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 ²	
Typhoid					
<i>Typhim Vi</i> (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
<i>Vivotif Berna</i> (Berna Products)	1 cap PO (contains 2-6x10 ⁹ viable CFU of <i>S. typhi</i> Ty21a)	≥6 yrs	1 cap PO (contains 2-6x10 ⁹ viable CFU of <i>S. typhi</i> Ty21a)	1 cap every other day x 4 doses	Repeat every 5 yrs if ongoing risk
Yellow Fever					
<i>YF-Vax</i> (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. 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.

3. Antibody levels below complete virus neutralization at a 1:5 serum dilution by the rapid fluorescent focus inhibition test.

MENINGOCOCCAL — Meningococcal vaccine is recommended for adults and children at least 2 years old who are traveling to areas where epidemics are occurring, or to 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 who will have

prolonged contact with the local population, such as those living in a dormitory or refugee camp, or working in a health care setting.^{10,11}

Two quadrivalent vaccines are available against *Neisseria meningitidis* serogroups A, C, Y, and W135. *Menomune* contains meningococcal capsular polysaccharides. *Menactra* contains capsular polysaccharides conjugated to diphtheria toxoid.¹²

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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. Eight cases of Guillian-Barre syndrome have been reported in adolescents who received *Menactra*, but cause and effect have not been established.¹³

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 endemic (Nigeria, India, Pakistan, Afghanistan) or to areas with documented outbreaks. 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 booster dose of IPV.

RABIES — Rabies is highly endemic in Africa, Asia (particularly India) and parts of Latin America, but the risk to travelers is low. Pre-exposure immunization against rabies is recommended for travelers with an occupational risk of exposure, for those planning extended stays in endemic areas where immediate access to medical care might be limited, especially children, and for outdoor-adventure travelers.^{14,15} The 2 vaccines available in the US (*Imovax*, *RabAvert*) are both given in the deltoid (not gluteal) muscle at 0, 7 and 21 or 28 days.

After a bite or skin-penetrating 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. The CDC has published a list of cell culture rabies vaccines available outside the US.¹⁶ Without pre-exposure immunization, treatment requires rabies immune globulin (RIG) and 5 doses (over 28 days) of an approved vaccine. Most rabies vaccines available globally are safe and effective. RIG is a blood product and its purity and potency may be less reliable in developing countries.

TETANUS, DIPHTHERIA AND PERTUSSIS (DTaP) — Children should receive 3 or (preferably) 4 doses of DTaP prior to 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.

A single dose of one of two new combination vaccines, *Adacel* and *Boostrix*, that include tetanus toxoid, diphtheria toxoid and acellular pertussis antigens (Tdap), is now recommended as a replacement for a

routine tetanus-diphtheria (Td) booster in adolescents 11-18 years old (*Adacel* or *Boostrix*) and in adults 19-64 years old (*Adacel*), but is not specifically indicated for travelers.¹⁷

TICK-BORNE ENCEPHALITIS (TBE) — TBE occurs in Scandinavia, western and central Europe and countries of the former USSR, mainly in rural forested areas.¹⁸ Risk is greatest from March 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, is usually given in 3 doses over 9-12 months, but can be given over as few as 2 or 3 weeks, and is available in Europe (*Encepur* – Chiron; *FSME-Immun Inject* – Baxter AG). It can be obtained in Canada through the Emergency Drug Release Program by contacting the Special Access Programme, Health Protection Branch (613-941-2108).

TYPHOID — Typhoid vaccine is recommended for travelers to the Indian Subcontinent and other developing countries in Central and South America, the Caribbean, Africa and Asia, especially if they will be visiting friends or relatives or traveling outside routine tourist destinations.^{19,20} 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 live-attenuated oral vaccine (*Vivotif Berna*) 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 from the day before the first capsule until 7 days after the last.

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.²¹ Some countries in Africa require an International Certificate of Vaccination (or physician's waiver letter) against yellow fever 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.²² Boosters are given every 10 years, but

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immunity probably lasts much longer. If other live vaccines (measles, MMR) 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 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 encephalitis has also occurred, primarily in infants; for this reason the vaccine should be avoided if possible in infants <9 months old and it is contraindicated in infants <6 months old. Travelers >60 years of age have a greater risk of systemic adverse effects.

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*. *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, persistent (>3 days) or associated with fever or bloody stools, self-treatment for 1-3 days with ciprofloxacin, levofloxacin, norfloxacin or ofloxacin is usually recommended.²³ Azithromycin is an alternative²⁴ and is the drug of choice for travelers to areas with a high prevalence of fluoroquinolone-resistant *Campylobacter*, such as Thailand and India.²⁵ It can also be used in pregnant women and children (10 mg/kg/d x 3d), and patients who do not respond to a fluoroquinolone in 48 hours.

A non-absorbed oral antibiotic derived from rifampin, rifaximin²⁶ is approved for treatment of travelers' diarrhea caused by noninvasive strains of

Some Drugs for Treatment of Travelers' Diarrhea

Drug	Dosage	Cost ¹
Azithromycin – <i>Zithromax</i> (Pfizer)	1000 mg once or 500 mg once/d x 3d	\$34.64 51.96
Ciprofloxacin – average generic	500 mg bid x 1-3d	30.48
<i>Cipro</i> (Bayer) sustained release <i>Cipro XR</i>	1000 mg once/d x 1-3d	35.28 32.16
Levofloxacin – <i>Levaquin</i> (Ortho-McNeil)	500 mg once/d x 1-3d	34.65
Norfloxacin – <i>Noroxin</i> (Merck)	400 mg bid x 1-3d	22.56
Ofloxacin – <i>Floxin</i> (Ortho-McNeil)	300 mg bid x 1-3d	37.26
Rifaximin – <i>Xifaxan</i> (Salix)	200 mg tid x 3d	33.39

1. Cost for 3 days (except *Zithromax* 1000 mg), based on the most recent data (February 28, 2006) from retail pharmacies nationwide available from Wolters Kluwer Health.

E. coli in travelers ≥12 years of age. In clinical trials it has been similar in efficacy to ciprofloxacin, with fewer adverse effects.²⁷ It should not be used in infections associated with fever or blood in the stool or those caused by *Campylobacter jejuni*.

Packets of oral rehydration salts (*Ceralyte*, *ORS*, and others) mixed in potable water can help maintain electrolyte balance, 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, might benefit from prophylaxis. 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.²⁸ 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.

MALARIA

No drug is 100% effective for prevention of malaria; travelers should be told to take other protective measures against mosquito bites in addition to medication.²⁹ Countries with a risk of malaria are listed in the table.

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Some countries with endemic malaria transmission may not have malaria in the most frequently visited major cities and rural tourist resorts. Insect bite prevention is an important adjunct to malaria prophylaxis. 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.

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: Countries with a risk of malaria, footnotes 4, 5, and 6).

CHLOROQUINE-RESISTANT MALARIA — Three drugs of choice with similar efficacy, listed with their dosages in the table on page 31, 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 drug,³⁰ but it can cause headache, GI disturbances and mouth ulcers. Single case reports of Stevens-Johnson syndrome and hepatitis have been published.^{31,32} Atovaquone/proguanil should not be given to patients with severe renal impairment (CrCl <30 mL/min).

Mefloquine (*Lariam*, and others) has the advantage of once-a-week dosing, but is contraindicated in patients with a history of any psychiatric disorder, and also in those with a history of seizures or cardiac conduction abnormalities. 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.³³ 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-daily alternative. Doxycycline should not be taken concurrently with antacids, oral iron or bismuth salts. A fourth drug, **primaquine phosphate**, is available for patients unable to take other antimalarial drugs. Several studies have shown that daily primaquine can provide effective prophylaxis against chloroquine-

Countries with a Risk of Malaria¹

AFRICA		
Angola	Equatorial Guinea	Namibia
Benin	Eritrea ³	Niger
Botswana	Ethiopia ³	Nigeria
Burkina Faso	Gabon	Rwanda
Burundi	Gambia, The	São Tomé and Príncipe
Cameroon	Ghana	Senegal
Cape Verde ²	Guinea	Sierra Leone
Central African Republic	Guinea-Bissau	Somalia
Chad	Kenya	South Africa ³
Comoros	Liberia	Sudan
Congo	Madagascar	Swaziland
Côte d'Ivoire	Malawi	Tanzania
Democratic Republic of the Congo	Mali	Togo
Djibouti	Mauritania	Uganda
	Mauritius ³	Zambia
	Mayotte	Zimbabwe ³
	Mozambique	
AMERICAS		
Argentina ^{3,4}	El Salvador ^{3,4}	Paraguay ^{3,4}
Belize ^{3,4}	French Guiana	Peru ³
Bolivia ³	Guatemala ^{3,4}	Suriname ³
Brazil	Guyana	Venezuela ³
Colombia ³	Haiti ⁴	
Costa Rica ^{3,4}	Honduras ^{3,4}	
Dominican Republic ^{3,4}	Mexico ^{3,4}	
Ecuador ³	Nicaragua ^{3,4}	
	Panama ^{3,5}	
ASIA		
Afghanistan	Iraq ^{3,4}	Tajikistan
Armenia ^{3,4}	Korea, North ^{3,4}	Thailand ³
Azerbaijan ^{3,4}	Korea, South ^{3,4}	Turkey ^{3,4}
Bangladesh ³	Kyrgyzstan ³	Turkmenistan ^{3,4}
Bhutan ³	Laos ³	Uzbekistan ⁴
Cambodia ³	Malaysia ³	Vietnam ³
China, People's Republic ^{3,6}	Myanmar ³	Yemen ³
East Timor	Nepal ³	
Georgia ^{3,4}	Pakistan	
India	Philippines ³	
Indonesia ³	Saudi Arabia ³	
Iran ³	Sri Lanka	
	Syria ^{3,4}	
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. Island of Saõ Tiago only (limited risk).
3. No malaria in major urban areas.
4. Chloroquine is the drug of choice for prophylaxis.
5. Chloroquine is recommended west of the Canal Zone.
6. Chloroquine is recommended except in Hainan and Yunnan provinces.

resistant *Plasmodium falciparum* and *P. vivax*.³⁴ 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.

Drugs of Choice for Prevention of Malaria

Drug	Adult dosage	Pediatric dosage	Duration
CHLOROQUINE-RESISTANT AREAS†:			
Drug of Choice¹:			
Atovaquone/proguanil ² – <i>Malarone, Malarone Pediatric</i>	1 adult tablet once/d ³	11-20 kg: 1 peds tab/d ³ 21-30 kg: 2 peds tabs/d ³ 31-40 kg: 3 peds tabs/d ³ ≥41 kg: 1 adult tab/d ³	Start: 1-2d before travel Stop: 1 wk after leaving malarious zone
OR Mefloquine ⁴ – <i>Lariam, and others</i>	1 tablet once/wk ⁵	≤9 kg: 4.6 mg/kg base (5 mg/kg salt) once/wk ^{5,6} 10-19 kg: ¼ tablet once/wk ^{5,6} 20-30 kg: ½ tablet once/wk ^{5,6} 31-45 kg: ¾ tablet once/wk ^{5,6} >46 kg: 1 tablet once/wk ^{5,6}	Start: 1-2 wks before travel Stop: 4 wks after leaving malarious zone
OR Doxycycline – <i>Vibramycin, and others</i>	100 mg once/d	2 mg/kg/d ⁷ (up to 100 mg/d)	Start: 1-2d before travel Stop: 4 wks after leaving malarious zone
Alternative⁸:			
Primaquine phosphate ^{9,10}	30 mg base daily ¹¹	0.5 mg/kg base/d ¹¹	Start: 1d before travel Stop: 7d after leaving malarious zone
CHLOROQUINE-SENSITIVE AREAS†:			
Drug of Choice¹:			
Chloroquine phosphate ¹² <i>Aralen, and others</i>	300 mg base ¹³ once/wk	5 mg/kg base (8.3 mg/kg salt) once/wk ¹³ (up to 300 mg base/wk)	Start: 1-2 wks before travel Stop: 4 wks after leaving malarious zone
<p>† Chloroquine-resistant <i>Plasmodium falciparum</i> occurs in all malarious areas except Central America (excluding Panama east 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, Oman, Saudi Arabia and Iran).</p> <p>1. For prevention of relapse after departure (“presumptive anti-relapse therapy”; “terminal prophylaxis”) from areas where <i>P. vivax</i> and <i>P. ovale</i> are endemic, some experts prescribe in addition primaquine phosphate 30 mg base/d or, for children, 0.5 mg base/kg/d for 14 days after departure from the malarious area. Others prefer to rely on surveillance to detect cases when they occur, particularly when exposure was limited or doubtful. See also footnote 10.</p> <p>2. There have been several isolated reports of <i>P. falciparum</i> resistance in Africa (E Schwartz et al, Clin Infect Dis 2003; 37:450; A Farnert et al, BMJ 2003; 326:628).</p> <p>3. Available as a fixed-dose combination: adult tablets (<i>Malarone</i>; 250 mg atovaquone/100 mg proguanil) and pediatric tablets (<i>Malarone Pediatric</i>; 62.5 mg atovaquone/25 mg proguanil). To enhance absorption, it should be taken with food or a milky drink.</p> <p>4. Resistance to mefloquine is a significant problem in the malarious areas of Thailand and in the areas of Myanmar and Cambodia that border on Thailand.</p> <p>5. 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.</p> <p>6. For pediatric doses <1/2 tablet, it may be advisable to have a pharmacist crush the tablet, estimate doses by weighing, and package them in gelatin casules.</p> <p>7. Not recommended for children <8 years old.</p> <p>8. The combination of weekly chloroquine (300 mg base) and daily proguanil (200 mg) is recommended by the World Health Organization (www.WHO.int) for use in selected areas. The combination is no longer recommended by the CDC. Proguanil (<i>Paludrine</i> – Wyeth Ayerst, Canada; AstraZeneca, United Kingdom) is not available alone in the US but is widely available in Canada and Europe. Prophylaxis is recommended during exposure and for 4 weeks afterwards.</p> <p>9. Not approved for this indication by the FDA, but recommended for use by the CDC.</p> <p>10. Patients should be screened for G-6-PD deficiency before treatment.</p> <p>11. In the US, a 26.3 mg tablet of primaquine phosphate contains 15 mg primaquine base. Nausea and abdominal pain can be diminished by taking with food.</p> <p>12. Atovaquone/proguanil, mefloquine, doxycycline or primaquine may be used in patients who are unable to take chloroquine.</p> <p>13. In the US, a 500-mg tablet of chloroquine phosphate contains 300 mg chloroquine base.</p>			

MEFLOQUINE-RESISTANT MALARIA — Doxycycline or atovaquone/proguanil are 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.

PREGNANCY — Malaria in pregnancy is particularly serious for both mother and fetus; prophylaxis is indicated if travel cannot be avoided. The safety of atovaquone/proguanil in pregnancy is unknown; outcomes were normal in 24 women treated with the combination in the second and third trimester.³⁵ Proguanil has been used in pregnancy without evidence of toxicity. 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.^{36,37} Chloroquine has been used extensively and safely for prophylaxis during pregnancy. Doxycycline and primaquine are contraindicated in pregnancy.

INSECT BITE PROTECTION

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.

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DEET — The most effective topical insect repellent is N, N-diethyl-m-toluamide (DEET).^{38,39} Applied on exposed skin, DEET repels mosquitoes, as well as ticks, chiggers, fleas, gnats and some flies. DEET is available in formulations of 5-40% and 100%. Medical Letter consultants prefer concentrations of 30-35%; higher concentrations protect longer but do not improve efficacy. 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*) can protect 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 in concentrations of up to 50% is probably safe in children and infants >2 months old; the American Academy of Pediatrics recommends use of concentrations containing no more than 30%. DEET should not be used in infants <2 months old. 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.⁴⁰ DEET has been shown to decrease the effectiveness of sunscreens when it is applied after the sunscreen. Applying a sunscreen before or after a DEET-containing insect repellent did not reduce the effectiveness of the insect repellent.⁴¹

PICARIDIN — Picaridin has been available in Europe and Australia for many years. No data are available concerning the 7% and 15% formulations (*Cutter Advanced*) currently sold in the US.⁴² They might be as effective against mosquitoes as low concentrations of DEET, providing protection for 1-4 hours. Higher concentrations sold in Europe have been shown to protect against mosquitoes for up to 8 hours.⁴³⁻⁴⁵

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. In combination with use of DEET on exposed skin, 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.⁴⁶ Epidemics have occurred in recent years in the Indian Subcontinent, Southeast 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 Hawaii, Puerto Rico, the US Virgin Islands and Mexico.⁴⁷ 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 water or damp soil contaminated by the urine of infected animals.⁴⁸ Travelers at increased risk, such as adventure travelers and those who engage in recreational water activities, should consider chemoprophylaxis 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.

RESPIRATORY INFECTIONS — After febrile and GI illness, respiratory infection is the most common infectious disease affecting travelers.⁴⁹ In the winter of 2003 a new coronavirus caused severe acute respiratory syndrome (SARS) and disrupted travel to much of Southeast Asia and Canada. Although cases of SARS have not been seen since April 2004, the CDC recommends that travelers to China avoid visiting live animal markets.

Currently, outbreaks of avian influenza in poultry merit monitoring. To date avian influenza has been spread to humans primarily from direct contact with sick birds or their feces. The CDC recommends that travelers to countries with documented outbreaks of avian influenza avoid live poultry markets, farms, and contact with sick or dead poultry and surfaces that appear to be contaminated with poultry feces, and only eat poultry products that are well cooked.⁵⁰ Travelers should wash their hands frequently with soap and water or use an alcohol-based hand rub. The CDC does not recommend traveling with a supply of antiviral drugs.

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) can cause acute

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mountain sickness (headache, fatigue, nausea, anorexia, insomnia, dizziness); pulmonary and cerebral edema are uncommon.⁵¹ 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 b.i.d. (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.⁵² 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.⁵³

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.

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.⁵⁴

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.⁵⁵ 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.⁵⁶

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, and irritability. It is usually more severe after eastward travel.

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 (2-3 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. Slow-release forms of melatonin were not effective.^{57,58} As a dietary supplement in the US, however, its purity and potency are suspect. In one study, zolpidem (*Ambien*) started the first night after travel and taken for 3 nights was helpful.⁵⁹

MOTION SICKNESS — Therapeutic options for motion sickness remain limited.⁶⁰ The prescription cholinergic blocker scopolamine in a patch or oral formulation can decrease symptoms. *Transderm Scop* is applied to the skin behind the ear 6-8 hours before exposure and changed 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. R Steffen. Changing travel-related global epidemiology of hepatitis A. *Am J Med* 2005; 118 suppl 10A:46S.
2. P Van Damme et al. Hepatitis A booster vaccination: is there a need? *Lancet* 2003; 362:1065.
3. 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.
4. S Iwarson. Are we giving too many doses of hepatitis A and B vaccines? *Vaccine* 2002; 20:2017.
5. BA Connor. Hepatitis A vaccine in the last-minute traveler. *Am J Med* 2005; 118 Suppl 10A:58S.
6. JS Keystone. Travel-related hepatitis B: risk factors and prevention using an accelerated vaccination schedule. *Am J Med* 2005; 118 suppl 10A:63S.
7. JN Zuckerman et al. Hepatitis A and B booster recommendations: implications for travelers. *Clin Infect Dis* 2005; 41:1020.
8. DO Freedman and K Leder. Influenza: changing approaches to prevention and treatment in travelers. *J Travel Med* 2005; 12:36.
9. Centers for Disease Control and Prevention (CDC). Japanese encephalitis in a U.S. traveler returning from Thailand, 2004. *MMWR Morb Mortal Wkly Rep* 2005; 54:123.
10. A Wilder-Smith. Meningococcal disease in international travel: vaccine strategies. *J Travel Med* 2005; 12 Suppl 1:S22.
11. 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.
12. Menactra: a meningococcal conjugate vaccine. *Med Lett Drugs Ther* 2005; 47:29.
13. Center for Disease Control and Prevention (CDC). Update: Guillain-Barre syndrome among recipients of Menactra meningococcal conjugate vaccine—United States, October 2005-February 2006. *MMWR Morb Mortal Wkly Rep* 2006; 55:364.
14. CE Rupprecht and RV Gibbons. Clinical practice. Prophylaxis against rabies. *N Engl J Med* 2004; 351:2626.
15. FX Meslin. Rabies as a traveler's risk, especially in high-endemicity areas. *J Travel Med* 2005; 12 Suppl 1:S30.

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16. Human rabies prevention—United States, 1999 Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 1999; 48 (RR-1):1.
17. Adacel and Boostrix: Tdap vaccines for adolescents and adults. *Med Lett Drugs Ther* 2006; 48:5.
18. P Rendi-Wagner. Risk and prevention of tick-borne encephalitis in travelers. *J Travel Med* 2004; 11:307.
19. B Basnyat et al. Enteric (typhoid) fever in travelers. *Clin Infect Dis* 2005; 41:1467.
20. C Luxemburger and AK Dutta. Overlapping epidemiologies of hepatitis A and typhoid fever: the needs of the traveler. *J Travel Med* 2005; 12 Suppl 1:S12.
21. TP Monath and MS Cetron. Prevention of yellow fever in persons traveling to the tropics. *Clin Infect Dis* 2002; 34:1369.
22. Directory available at: www2.ncid.cdc.gov/travel/yellowfever
23. HL Dupont. Travellers' diarrhoea: contemporary approaches to therapy and prevention. *Drugs* 2006; 66:303.
24. 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.
25. D Jain et al. *Campylobacter* species and drug resistance in a north Indian rural community. *Trans R Soc Trop Med Hyg* 2005; 99:207.
26. Rifaximin (Xifaxan) for travelers' diarrhea. *Med Lett Drugs Ther* 2004; 46:74.
27. AL Pakyz. Rifaximin: a new treatment for travelers' diarrhea. *Ann Pharmacother* 2005; 39:284.
28. HL Dupont et al. A randomized, double-blind, placebo-controlled trial of rifaximin to prevent travelers' diarrhea. *Ann Intern Med* 2005; 142:805.
29. LH Chen and JS Keystone. New strategies for the prevention of malaria in travelers. *Infect Dis Clin North Am* 2005; 19:185.
30. P Schlagenhauf et al. Tolerability of malaria chemoprophylaxis in non-immune travellers to sub-Saharan Africa: multicentre, randomised, double blind, four arm study. *BMJ* 2003; 327:1078.
31. M Emberger et al. Stevens-Johnson syndrome associated with Malarone antimalarial prophylaxis. *Clin Infect Dis* 2003; 37:e5.
32. M Grieshaber et al. Acute hepatitis and atovaquone/proguanil. *J Travel Med* 2005; 12:289.
33. TA Albright et al. Side effects of and compliance with malaria prophylaxis in children. *J Travel Med* 2002; 9:289.
34. JK Baird et al. Primaquine for prevention of malaria in travelers. *Clin Infect Dis* 2003; 37:1659.
35. R McGready et al. The pharmacokinetics of atovaquone and proguanil in pregnant women with acute falciparum malaria. *Eur J Clin Pharmacol* 2003; 59:545.
36. CDC. Health Information for International Travel 2005-2006, p 205.
37. 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.
38. Insect repellents. *Med Lett Drugs Ther* 2003; 45:41.
39. MS Fradin and JF Day. Comparative efficacy of insect repellents against mosquito bites. *N Engl J Med* 2002; 347:13.
40. 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.
41. ME Murphy et al. The effect of sunscreen on the efficacy of insect repellent: a clinical trial. *J Am Acad Dermatol* 2000; 43:219.
42. Picardin—a new insect repellent. *Med Lett Drugs Ther* 2005; 47:46.
43. 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.
44. SP Frances et al. Laboratory and field evaluation of commercial repellent formulations against mosquitoes (diptera: culicidae) in Queensland, Australia. *Aust J Entomol* 2005; 44:431.
45. 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.
46. A Wilder-Smith and E Schwartz. Dengue in travelers. *N Engl J Med* 2005; 353:924.
47. Center for Disease Control and Prevention (CDC). Travel-associated dengue infections—United States, 2001-2004. *MMWR Morb Mortal Wkly Rep* 2005; 54: 556.
48. AJ McBride et al. Leptospirosis. *Curr Opin Infect Dis* 2005; 18:376.
49. DO Freedman et al. Spectrum of disease and relation to place of exposure among ill returned travelers. *N Engl J Med* 2006; 354:119.
50. http://www.cdc.gov/travel/other/avian_influenza_se_asia_2005.htm.
51. SA Gallagher and PM Hackett. High-altitude illness. *Emerg Med Clin North Am* 2004; 22:329.
52. 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.
53. BL Strom et al. Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. *N Engl J Med* 2003; 349:1628.
54. MT Ansari et al. Traveler's thrombosis: a systematic review. *J Travel Med* 2005; 12:142.
55. E Ferrari and G Morgan. Travel as a risk factor for venous thromboembolic disease. *Eur J Med Res* 2004; 9:146.
56. MR Cesarone et al. Venous thrombosis from air travel: the LON-FLIT3 study—prevention with aspirin vs low-molecular-weight heparin (LMWH) in high-risk subjects: a randomized trial. *Angiology* 2002; 53:1.
57. A Herxheimer and KJ Petrie. Melatonin for the prevention and treatment of jet lag. *Cochrane Database Syst Rev* 2002; 2:CD001520.
58. N Buscemi et al. Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. *BMJ* 2006; 332:385.
59. AD Jamieson et al. Zolpidem reduces the sleep disturbance of jet lag. *Sleep Med* 2001; 2:423.
60. JF Golding and MA Gresty. Motion sickness. *Curr Opin Neurol* 2005; 18:29.

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