The Practice of Travel Medicine: Guidelines by the Infectious Diseases Society of America

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EXECUTIVE SUMMARY

Travel medicine is devoted to the health of travelers who visit foreign countries. It is an interdisciplinary specialty concerned not only with prevention of infectious diseases during travel but also with the personal safety of travelers and the avoidance of environmental risks.

The field has evolved as a distinct discipline over the last 2 decades. It is represented by an international society—the International Society of Travel Medicine (ISTM)—and by an active clinical group within the American Society of Tropical Medicine and Hygiene (ASTMH). Those who practice in the field come from a wide range of specialty training experiences; however, it is members of the infectious disease community who have frequently taken the lead in providing the evidence base for practice. Accompanying the growth of travel medicine has been a parallel effort in defining a body of knowledge and standards for its practice. These guidelines set forth the minimum standards for knowledge, experience, and practice in travel medicine and review the major content areas in the field.

Travel medicine standards are increasingly based on evidence and are moving away from reliance on the opinion of experts. Where possible, recommendations in this document have been graded using the Infectious Diseases Society of America—United States Public Health Service grading system (table 1) [1]. As a young discipline, however, expert opinion and experience still dominate many of the topic areas, highlighting the need for continued investigation in the field.

Setting. Most travel medicine care should be performed in a specialized travel clinic by persons who have training in the field, particularly for travelers who have complex itineraries or special health needs (C-III). Primary care physicians and nonspecialists should be able to advise travelers who are in good health and

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Practice guidelines are systematically developed statements to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances [1]. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation [1]. It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. Infectious Diseases Society of America considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Department of Health and Human Services.

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Table 1. Infectious Diseases Society of America–United States Public Health Service grading system for ranking recommendations in clinical guidelines.

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation for use
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from ⩾1 properly randomized, controlled trial
II	Evidence from ⩾1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

NOTE. Adapted from [1].

visiting low-risk destinations with standard planned activities.

Knowledge base. The knowledge base for the travel medicine provider includes epidemiology, transmission, and prevention of travel-associated infectious diseases; a complete understanding of vaccine indications and procedures; prevention and management of noninfectious travel-associated health risks; and recognition of major syndromes in returned travelers (e.g., fever, diarrhea, and rash) (A-III) (table 2). All providers should access Web-, text-, and journal-based resources. The US Centers for Disease Control and Prevention (CDC) provides authoritative advice on travel health (http://www.cdc.gov/travel).

Competency in travel medicine. Appropriate knowledge and aptitude for practicing travel medicine may be demonstrated by achieving a certificate of knowledge in the field (table 2). Maintaining competency includes ongoing education and performing pretravel consultations on a frequent and regular basis (B-III).

Pretravel risk assessment. The key element of the pretravel visit is a health risk assessment of the trip (A-II) (table 3). This balances the health of the traveler (the traveler's age, underlying health conditions, medications, and immunization history) with the details of the planned trip (the season of travel, itinerary, duration, and planned activities).

Spectrum of travel medicine advice. Topics of health education and advice that should be covered for all travelers include vaccine-preventable illness, avoidance of insects, malaria chemoprophylaxis (for itineraries that include a malaria risk), prevention and self-treatment of traveler's diarrhea, responsible personal behavior, sexually transmitted infections and safety, travel medical insurance, and access to medical care during travel (A-II) (table 3). Other topics should be covered as indicated by the risk assessment. Consistent and clear advice that is provided in both verbal and written form will help to increase traveler compliance with preventive measures (A-II). The interaction between traveler and health care provider should be collaborative and affords the opportunity to enhance preventive health knowledge.

Records and procedures. (1) Permanent records should be maintained for the pretravel visit, including records of traveler demographic data and health history, travel health risk assessment, and immunizations, recommendations, and prescriptions given (A-III) (table 4). (2) Standard procedures for immunization should be followed, including informed consent, vaccine storage, administration, record-keeping, and reporting of adverse events (A-III).

Immunization. (1) The pretravel visit should be used to update vaccinations that are routinely recommended according to US schedules and based on the traveler's age and underlying health status (A-I) (table 5). These vaccinations include tetanus, pertussis, diphtheria, *Haemophilus influenzae* type b, measles, mumps, rubella, varicella, *Streptococcus pneumoniae*, and influenza vaccinations. Vaccination against hepatitis A and B, poliomyelitis, and *Neisseria meningitidis* may be recommended for travel, as well as for routine health care.

(2) Vaccination against yellow fever is usually indicated for travelers to countries in the zone of endemicity for yellow fever (areas in Africa and South America where conditions are conducive to yellow fever transmission) (A-III). In addition, under International Health Regulations (IHRs), some countries that lie within or outside of the zone of endemicity may require yellow fever vaccination as a condition for entry. Recent recognition of serious adverse events associated with yellow fever

vaccination requires that a careful risk-benefit assessment be performed before administration of the vaccine.

(3) Hepatitis A vaccination should be considered for all travelers (A-III). Booster doses following the primary 2-dose series are not currently recommended (A-II).

(4) Vaccination against Japanese encephalitis, rabies, tick-borne encephalitis, and typhoid fever should be administered on the basis of a risk assessment (A-III). Quadrivalent (A/C/Y/W-135) meningococcal vaccine should be administered to travelers at risk. It is required by Saudi Arabia for religious pilgrims to Mecca for the Hajj or Umrah.

Traveler's diarrhea. Traveler's diarrhea is the most common disease among travelers. Management of traveler's diarrhea includes education and advice about prevention, food and liquid hygiene (A-III), and provision for prompt self-treatment in the event of illness (A-I) (table 6). The elements of self-treatment include hydration; treatment with loperamide for control of symptoms, if necessary (when there is no temperature >38.5°C or gross blood in the stool); and a short course (single dose to 3 days of therapy) of a fluoroquinolone antibiotic (A-I). Antibiotic resistance of enteric pathogens, particularly *Campylobacter* species, in the destination country needs to be considered. For those travelling to these destinations, as well as for other travelers, azithromycin may be indicated (B-II). Combination treatment with loperamide and an antibiotic may be considered for travelers with moderately severe diarrhea (B-III). Antibiotic prophylaxis is not recommended for most travelers (A-III).

Malaria. (1) Malaria is one of the most severe infectious diseases among travelers (tables 7 and 8). Nearly all cases in travelers are preventable. Methods for prevention and best management of malaria include awareness of risk, avoidance of mosquito bites, compliance with chemoprophylaxis, and prompt diagnosis in the event of a febrile illness either during or on return from travel (A-I). When seeking medical care after return from travel, travelers should be instructed to inform their health provider of their travel history.

(2) Travelers at risk for malaria should practice the following measures to prevent mosquito bites: wearing of protective clothing to cover exposed skin, application of repellents, and sleeping in areas protected by netting (preferably impregnated with a residual insecticide, such as permethrin) and screens (A-I). Currently, repellents that contain 20%–50% N, N diethylmetatoluamide (DEET) are considered to provide sufficient protection (B-II).

(3) The choice of chemoprophylaxis should be made following a careful assessment of malaria risk during the trip. In addition, whether the traveler has contraindications to a particular antimalarial should be considered.

(4) The malaria risk assessment includes the itinerary, the species of malaria at the destination (and whether the most severe form of malaria, that due to *Plasmodium falciparum,* is present and whether it is resistant to chloroquine or other antimalarials), the season of travel, activities, duration, and access to medical care. Consultation with the latest resource information is necessary.

Personal safety and environmental health. (1) All travelers should be aware of personal safety during travel and exercise responsible behavior (A-III). Road and pedestrian safety, risk of blood-borne infections, avoidance of animal bites, awareness of the risk of assault, sexually transmitted infections, and moderation in alcohol use should be discussed.

(2) Travelers should understand the effects that air, sea, and land travel, sun, altitude, and heat and cold may have on their health. To prevent deep venous thrombosis (DVT), long-haul travelers with journeys of 6–8 h and longer should avoid constrictive clothing around their waist and lower extremities, exercise their calf muscles, and maintain hydration (A-III). Travelers with increased risk factors for DVT may consider wearing below-the-knee support stockings (B-II) or receiving low molecular weight heparin (B-I).

(3) Ascent to altitudes of 2500–3500 m (8200–11500 feet) is often associated with various forms of high altitude illness. Staged ascent is an effective way to decrease the risk of altitude illness. Travelers who need to ascend rapidly may take acetazolamide for prevention (B-I).

Post-travel care. Health professionals who advise travelers should be able to recognize major syndromes in returned travelers (e.g., fever, diarrhea, respiratory illness, and rash) and either provide care for the traveler or promptly refer them for appropriate evaluation and treatment (A-III).

INTRODUCTION

The discipline of travel medicine has developed dramatically over the last 25 years. This development led to the founding of the ISTM in 1991 and of a clinical group devoted to travel and tropical medicine within the ASTMH in 1989. Two journals covering travel medicine have been established: the *Journal of Travel Medicine* in 1994 and *Travel Medicine and Infectious Diseases* in 2003. For the infectious diseases community, travel medicine has provided opportunities to focus on an emerging discipline. These guidelines have been developed to help define the field and provide guidance for those wishing to practice travel medicine.

Travel medicine is devoted to the health of travelers who visit foreign countries. It is an interdisciplinary specialty concerned not only with prevention of infectious diseases during travel but also with personal safety and prevention of environmental risk. It differs from tropical medicine, because it focuses primarily on pretravel preventive care of persons and less on the diagnosis and treatment of illness acquired in the tropics. However, travel medicine specialists should be able to recognize

and either treat or triage common syndromes in returned travelers.

Several factors have contributed to the establishment of travel medicine as a specialty field [2, 3]. First, the number of travelers has increased, as have the length, diversity, and complexity of their travel itineraries and activities. Over the last decade, the number of travelers crossing international borders has grown from 457 million in 1990 to 763 million in 2004 [4]. These travelers spent the equivalent of 623 billion dollars in 2004.

This increase in global travel has led to more frequent illness during travel and to instances of disease that is imported back to the country of origin [5]; disease that may spread to susceptible contacts (e.g., measles imported to the United States by returned travelers and migrants [6, 7], Severe Acute Respiratory Syndrome, sexually transmitted infections (STIs), tuberculosis, and multidrug-resistant bacteria). The failure of health care professionals to accurately advise the traveler of health risks and the failure of the traveler to either seek or follow pretravel advice may lead to excess morbidity and mortality from diseases such as malaria [8, 9].

Second, formal epidemiologic studies have defined the risk for acquisition of many illnesses, especially for 2 of the most important diseases among travelers, diarrhea and malaria. Studies of traveler's diarrhea evolved from the descriptive in the 1960s [10], to the establishment of etiology and risk factors in the early 1970s [11, 12], to prophylaxis of illness with antimicrobials in the late 1970s and 1980s [13], to self-treatment of diarrhea in the 1980s and 1990s [14, 15], and finally to new agents for treatment based on developing drug-resistance patterns [16, 17]. For malaria, changing epidemiology and drug resistance in parasites have required a more formal approach to the use of chemoprophylaxis—one that is defined by the risk of contracting malaria and the safety, cost, and tolerability of antimalarial drugs.

Third, there has been tremendous growth in the field of vaccinology, with the release of new vaccines to prevent infections, some which are related to travel. This progress has led to the development of standards for the use of vaccines in clinical practice.

Fourth, an awareness has developed among practitioners that prevention of illness in travelers includes not only the provision of vaccines and chemoprophylactics but also a discussion of topics such as personal behavior and safety during travel, prevention of altitude illness, and access to medical care in the event of illness. In addition, an important aspect of travel medicine is the need to advise the many travelers who are at the extremes of age, those with complex medical conditions, and the large group of ethnic travelers who travel to their country of birth to visit friends and relatives (VFRs). VFRs are travelers who were born in a resource-poor region of the world, who now live in industrialized nations, and who return to their country of birth to visit friends and relatives. They present unique challenges in providing pretravel health care [18, 19].

Lastly, there has been the realization that preventing illness in travelers is only part of the goal of travel medicine. Travelers and the health care practitioners who advise them should consider the impact that a vacation, business venture, or service project has on the cultural, ecological, physical, and sexual health of the local population at the travel destination. The devastating effects of the earthquakes and tsunamis in Asia in December 2004 on both tourists and indigenous peoples have made clear the interdependency of the tourist industry with the local culture.

This document will define a standard for the practice of travel medicine and will also present guidelines for 3 of the essential areas in the discipline: vaccine use in travel, the management of traveler's diarrhea, and the prevention of malaria. Because recommendations for the administration of specific vaccines or antimalarials may change from those provided in this document, additional authoritative sources, as outlined in the Appendix, should be consulted when putting these guidelines into practice. For each vaccine that is licensed in the United States, the Advisory Committee on Immunization Practices (ACIP) (http://www.cdc.gov/nip/acip), often in conjunction with other authoritative bodies, such as the American Academy of Pediatrics, the American College of Physicians, or the Infectious Diseases Society of America, has developed recommendations that are published by the CDC. These statements and the publication *Health Information for International Travel* (known as the Yellow Book) [20] remain the definitive resources for US practitioners. This document will provide guidance on their practical application. Several excellent reviews [21–23] and textbooks in travel medicine should also serve as resources [24–27]. Being able to access and use the many resources available in travel medicine is an important aspect of its practice.

The application of evidence-based standards to travel medicine is a challenge. The specialty is new and has not had the time required to develop a vast evidence base. Therefore, for many areas, expert opinion defines practice. Where possible, however, our recommendations are graded according to accepted standards [1].

THE PRACTICE OF TRAVEL MEDICINE

In an effort to define criteria for the practice of travel medicine, it is helpful to first consider how travel medicine has been practiced. The ISTM surveyed its membership in 1994 [28]. Although this sample was biased in favor of practitioners who were members of an organization devoted to travel medicine, it still provides a window into practice styles. What was clear from the survey was that the global practice of travel medicine in the mid-1990s was extremely diverse. Recent smaller surveys indicate that travel medicine practice continues to be diverse

[29, 30]. Care of travelers was provided by those with formal training in tropical and travel medicine who saw thousands of travelers each year in organized travel clinics, as well as by individuals with generalist training who saw only a few patients in the context of their general practice. Most clinics (94%) were located in North America, Western Europe, and Australia (57% were in the United States), patients were most frequently seen in a private office setting (41%), and physicians nearly always directed the clinics (in 94% of clinics). Most clinics saw a modest number of patients: fewer than 20 patients per week were seen in 61% of clinics (14% saw <2 patients per week), and only 13% saw >100 patients per week. In the United States, even fewer patients were seen; 62% of clinics saw <10 patients per week. This finding raises an important question: what number of patients is sufficient to develop and maintain the necessary skills in travel medicine?

Although physicians usually directed the travel medicine service, nurses frequently rendered advice and care. This was particularly true for clinics in the United States, where nurses were the sole providers of advice 22% of the time and participated in pretravel care 58% of the time. Currently, in general practice settings in the United Kingdom, nearly all travel medicine advice is provided by nurses. Therefore, any guidelines for practice need to be applicable to nonphysician health care practitioners. Seventy-five percent of clinics evaluated ill travelers in follow-up.

The training of physicians who practiced travel medicine demonstrated wide regional variations. Physicians in Canada were more likely to have trained in family practice (54%), physicians in Europe were more likely to have trained in infectious diseases and tropical medicine (77%) and physicians in the United States were more likely to have trained in infectious diseases (59%) and internal medicine or family practice (38%). Occupational health, emergency medicine, and public health were also well represented.

BENEFITS OF A FORMAL PRACTICE OF TRAVEL MEDICINE

Although travel medicine is practiced in multiple contexts, there has been a trend to render pretravel care in the context of specialized services (e.g., at a travel clinic) by providers who have training in the field. We consider this model to be the ideal standard of practice, particularly when travelers are embarking on complex itineraries (e.g., visiting multiple countries or unusual or remote destinations), undertaking activities that put them at unusual risks (e.g., adventure travel and missionary postings), or have special health needs (C-III). However, when it is not possible to deliver care in these specialized settings, all providers of travel health advice should adhere to the standards presented in this document. It is expected that primary care physicians and nonspecialists will be able to advise healthy travelers who are going to relatively low-risk destinations, such as travel to a vacation resort in Mexico. If they are not comfortable doing this, they should refer the traveler to a travel clinic.

In specialized clinics travelers should receive individualized and up-to-date advice on vaccine-preventable illness, malaria, and diarrhea, advice on how to care for chronic medical conditions during travel, and required and/or recommended immunizations. Do travelers consult specialized travel clinics? Recent studies indicate that North American and European travelers seek pretravel health advice 35%–50% of the time [31, 32], but only 10%–20% visit a designated travel clinic [33]. VFRs who travel for the purpose of visiting friends and relatives in developing regions seek pretravel care even less often [18, 19]. However, a survey from Canada was more encouraging about the number of travelers seeking pretravel care, demonstrating that 68% of "high-risk" travelers consulted a travel clinic [34]. If all travelers to areas associated with health risk are to be protected, an improved effort needs to be made to inform travelers, health care providers, and the travel industry of the benefits of pretravel health care [35].

PROVIDER KNOWLEDGE AND TRAINING

Characteristics that should define a practice of travel medicine are listed in tables 2 and 3. These elements are as follows:

- Provider knowledge, training, and experience in the field
- Risk assessment of the traveler
- Provision of advice about prevention and management of travel-related diseases (both infectious and noninfectious)
- Ability to advise travelers of all ages and with diverse health conditions
- Administration of vaccines
- Recognition of key syndromes in returned travelers

Each practitioner providing pretravel consultations, whether they are a physician, nurse, or other licensed health care professional, should receive training in travel medicine that includes both education and experience. Why is it important that pretravel health advice is provided by trained and experienced personnel? There is ample evidence that health care personnel who are not familiar with the important issues in travel medicine make errors in judgment and recommendations, particularly about the prevention of malaria [36–39]. Venues in which to study the fields of travel and tropical medicine range from short-term review courses, to 3-month intensive courses in tropical medicine that may include an overseas clinical experience (often referred to as diploma courses) [40], to 2-year master's-level courses in travel medicine as offered in some European countries. Although it is not necessary that providers of travel medicine have expertise in tropical medicine, they should have sufficient knowledge of syndromes in returned travelers to be able to recognize and triage important post-

Table 2. Elements of a travel medicine practice: provider qualifications.

Category	Element(s)
Knowledge[a]	Geography Travel-associated infectious diseases, including epidemiology, transmission, and prevention Travel-related drugs and vaccines, including storage and handling, indications, contraindications, pharmacology, immunology, drug interactions, and adverse events Noninfectious travel risks, both medical and environmental, including prevention and management Recognition of major syndromes in returned travelers (e.g., fever, diarrhea, rash, and respiratory illness) Access to travel medicine resources, including texts, articles, internet Web sites, and listserv discussions
Experience	Time spent in a travel clinic managing the cases of travelers who have varying medical conditions and are traveling to diverse destinations with a wide variety of planned activities
Continuing education	Short or long courses in travel medicine Membership in specialty society dealing with travel and tropical medicine (e.g., the American Society of Tropical Medicine and Hygiene, the International Society of Travel Medicine, and other national societies) Journal subscription and use

[a] See the body of knowledge defined by the International Society of Travel Medicine [42].

travel syndromes, such as fever, rash, diarrhea, and respiratory complaints (A-III) [41].

The ISTM has defined the body of knowledge in travel medicine (table 3) [42], and both the ISTM and the ASTMH have developed examinations that lead to a certificate of knowledge. The ISTM examination (first administered in 2003) focuses on travel medicine, and the ASTMH examination (first administered in 1996) focuses on tropical and travel medicine [40]. Taking and passing these examinations can contribute to demonstrating competency in the field.

Experience is the other essential component to the optimal practice of travel medicine. One can gain competence only with regular assessment of travelers of all ages who have multiple health conditions, who are traveling to different destinations, and who are planning a wide variety of activities. Although there are only a limited number of sites worldwide that offer formal training, more sites are being developed. Practitioners new to the field are encouraged to join the ISTM and explore the education and training opportunities.

Is there an optimum number of pretravel consultations that, combined with education and training, help to maintain competency? There is no clear evidence to guide the answer. In the travel clinic survey, 14% of persons practicing travel medicine saw <2 patients per week [28]. This would appear to be an insufficient number. Fifteen patients per week was the median number seen in the survey. The committee understands that setting a target number of consultations for maintaining competency would be controversial. Nevertheless, practitioners of travel medicine need to have the regular experience of advising travelers who have a variety of health conditions, destinations, and activities.

THE PRETRAVEL VISIT

Models of Care

Most practices of travel medicine will have physicians, nurses, and/or other health care personnel involved in pretravel care [28]. There are 2 basic models for delivery of care. In the first, the physician obtains the traveler's demographic and travel information, provides the health advice, and facilitates the traveler's decisions regarding immunizations and prophylactic antimalarials. The nurse then reviews vaccine adverse effects, obtains informed consent, and administers the vaccines.

In the second model, the nurse, nurse practitioner, or physician's assistant renders all pretravel care. If nurses (or other nonphysician health care providers) are the sole health care providers, it is necessary to develop detailed protocols that are to be rigorously followed. These should be clinic specific (reflecting the standard of care within the region), remain current, and have standing orders for administration of vaccines and writing of prescriptions. In all settings, the nonphysician health care provider should have a clear line of contact with a physician who has in-depth knowledge of travel medicine.

When families are traveling together, it is advisable to see them as a unit to provide consistent advice, medications, and immunizations to each person. Adult-based practitioners will need to decide if they are willing to assess, advise, and vaccinate the pediatric traveler. If children are not seen together with adults, the different health care providers should consult with one another to assure consistency of preventive measures.

For small groups (e.g., business, student, and tour groups) traveling together or larger groups (e.g., corporations and missionary, volunteer, and nongovernmental organizations) that send personnel overseas, a presentation may be given to the entire group, followed by short individual appointments for

Table 3. Elements of a travel medicine practice: services provided.

Category	Elements
Assessing the health of the traveler[a]	Assessment of underlying medical conditions, medications, and allergies Assessment of immunization history
Assessing the health risk of travel	Itinerary Season of travel Duration Reason for travel Style of travel Planned activities
Preventive advice[b]	Vaccine-preventable illness Traveler's diarrhea prevention and self-treatment Malaria prevention Insect avoidance measures Other vector-borne and water-borne illness Personal safety, behavior, and sexual health Environmental illness (related to altitude, heat, cold, swimming, and diving) Motion sickness and jet lag Animal bites and rabies avoidance Long-term travelers, expatriates, and business travelers Special needs travelers (e.g., pregnant women, patients with diabetes, immunocompromised patients, and transplant recipients) Travel health resources (e.g., traveler-oriented Web sites) Travel medical kits Travel health and medical evacuation insurance Access to medical care overseas
Vaccination	…
Post-travel assessment	…

[a] Permanent records should be maintained.
[b] Advice should be given both verbally and in writing.

discussion of personal issues or medical conditions and administration of vaccines and prescriptions.

Risk Assessment: The Traveler, the Travel Health Risks, and the Travel Clinic Record

A key goal of the pretravel visit is to define potential travel health risks. Risk assessment includes (1) a determination of the traveler's health (e.g., do they have medical conditions that would affect their ability to complete the planned itinerary or that would alter any prophylactic measures?) and (2) an assessment of the risk of a particular travel itinerary (based on the destination, style of travel, duration, reason for travel, and planned activities). This goes beyond giving routine advice based solely on the destination country. For example, a 5-day business trip to Nairobi, Kenya, carries a different level of health risk than a 2-month residence on the shores of Lake Victoria for a malaria research study.

To maintain consistency between health care providers and to create a permanent medical record of the visit, the practice should generate a standard form. The recommended content of this form and of the pretravel assessment are listed in table 4. This record will document for insurance companies the level of care that has been provided, and information from it can be used to create a database of all travelers.

After recording the traveler's demographic data, itinerary, travel activities, and medical history, an immunization history is obtained and documented. The remainder of the medical record will record the immunizations administered, the prophylactic and self-treatment medications prescribed, and the advice rendered. It is important to document whether a traveler declines to receive any recommended prophylactic measures.

A standard immunization form should be part of the medical record, with the following items recorded:

- Vaccine type
- Dose
- Date of administration
- Manufacturer
- Lot number
- Site of administration
- Name, title of administrator, and signature

The advantages of having a complete immunization record are several. If a traveler reports a vaccine adverse effect, it can be determined which vaccine is causing the reaction, and in

Table 4. The travel clinic record.

Category, element(s)
Traveler demographic data
Name, date of birth, address, telephone number, and email address
Referring physician name, address, and telephone and fax numbers
Referring business name and address (if applicable)
Dates of departure and return
Destination, including countries and areas within countries (e.g., rural vs. urban areas)
Nature of travel (e.g., business, pleasure, visiting friends and relatives, study or teaching, missionary, or service)
Accommodation during travel
Medical history
Including pregnancy (or efforts to become pregnant), cardiac risk factors, pulmonary illness, mental health, immune suppression, and risk factors for HIV infection
Medications taken
Medication or food allergies (particularly to eggs)
Previous tolerance of vaccines or antimalarials
Past history of hepatitis or jaundice
Travel history, including previous travel-related illness
Country of birth and duration of residence, including unusual illness
Immunization history
Advice given
Medications prescribed
Immunization form for vaccines administered
Problems on return and referrals to specialists
Comment section
Signature line

the event of a vaccine recall, lot numbers are available, and patients who need to be contacted can be readily identified.

All administrators of vaccines in the United States are required by the National Childhood Vaccine Injury Act of 1986 [43] to report adverse events via the Vaccine Adverse Reporting System. This can be done either by calling 1-800-822-7967 or by accessing http://www.fda.gov/cber/vaers/vaers.htm. In Canada, the number is 866-234-2345, and the Web site is http://www.hc-sc.gc.ca/dhp-mps/medeff/index_e.html.

Advice and Education

After completing a travel health risk assessment, the health care provider can give specific health advice. Because an adequate pretravel consultation will require 15–45 min, it may not be possible to review all possible health and safety scenarios. Therefore, it is necessary to prioritize the health topics on the basis of the likely health risks and the level of risk tolerance of the traveler. The task of the travel medicine provider is to inform and educate. It is then the responsibility of the traveler to act upon the information once the potential risks of travel are understood.

Acceptance of advice and willingness to comply with it are often determined by a cultural understanding of risk. For instance, many VFR travelers incorrectly assume that they are immune to diseases such as malaria and typhoid and, therefore, eschew recommendations to take prophylactic measures. This is often compounded by a limited ability to pay for vaccines and/or preventive medication. These factors are likely to contribute to the disproportionate incidence of malaria and typhoid in this population: 50% of malaria imported into the United States during the period 1999–2003 by US civilians occurred in VFR travelers, compared with 13% imported by vacationers [44–48]; 75% of imported typhoid fever cases also occurred in the VFR population [49].

We recommend that, as a minimum, all travelers are informed about the following (A-I):

- Vaccine-preventable illness (vaccine indications, safety, and tolerability)
- Avoidance of insects (use of protective clothing, repellents, bednets, and insecticides)
- Use of chemoprophylactics against malaria (benefits of a particular regimen vs. potential adverse reactions)
- Prevention and self-treatment of traveler's diarrhea
- Personal behavior and safety
- The importance of obtaining travel and evacuation insurance policies
- Access to medical care during travel

Additional information should be tailored to the particular itinerary. For example, there should be discussion of high-altitude illness for travelers planning to summit Mount Kilimanjaro or trek in Nepal, and river rafters in Africa should be cautioned about fresh water exposure to avoid schistosomiasis.

Education about risk avoidance is a key component of travel medicine, and for low-risk disease, it may be a more cost-effective approach than vaccination [50]. However, the degree to which travelers comply with advice is frequently disappointing. Only 50%–60% of travelers are completely compliant with malaria chemoprophylaxis [51, 52], and >90% will make errors in what they eat and drink within several days of their arrival [53, 54]. Nevertheless, it has been shown that providing travelers with consistent and clear advice about malaria and allowing them to discuss their concerns about the disease and preventive medicines will lead to improved compliance with antimalarial regimens [55–58].

What is the balance between requiring that the health care provider review risks and expecting that the traveler will take initiative and review some risks on their own? It is our position that travelers should assume a degree of responsibility for self-education (and ideally, review information about health risks prior to the travel clinic visit), but the practitioner needs to

provide them with or direct them to the appropriate resources. Written material is important to use, because it will reinforce verbal advice, cover additional topics, and guide the traveler in accessing on-line or other resources. Many travel clinics subscribe to a commercial database that summarizes a wide breadth of country-specific health and safety information that can be printed and given to the traveler (table A1 in the Appendix).

Consent, Vaccine Administration, and Storage

Informed consent, given either verbally or in writing, is a requirement prior to administration of any vaccine. In addition to discussion of the risks and benefits of each vaccine, US federal law requires practitioners to give Vaccine Information Statements to all US travelers prior to receipt of certain vaccines, regardless of the age of the recipient. However, it is prudent to provide a Vaccine Information Statement prior to receipt of all vaccines. Information about and access to Vaccine Information Statements can be found at http://www.cdc.gov/nip/publications/vis.

Vaccines should be stored in refrigerators and freezers that are solely dedicated to this purpose. Vaccines requiring refrigeration should be maintained at 2°C–8°C (35°F–46°F), with an optimal temperature of 5°C (40°F) [59], and those that require frozen storage (e.g., varicella) are to be maintained at −15°C (5°F) or cooler, with an optimal temperature of −20°C (0°F). They should never be stored on the refrigerator door, because the door is exposed to warmer temperatures.

Information Resources

Computer information systems and Web-based resources allow access to continuously updated information. These resources supplement the traditional text-based information and have elevated the practice of travel medicine to a specialty that can respond on a daily basis to changing events. Two of the most important resources are the CDC Traveler's Health page and the World Health Organization (WHO). These sites will verify and interpret global health events for the practicing clinician. A listing of internet resource and commuter databases is provided in Keystone et al. [60], and many of these sites are listed in the Appendix.

Many travel medicine specialists will join a listserv that provides information and discussion about outbreaks of disease or tropical medicine and travel-related clinical cases (Appendix). The ISTM and ASTMH listservs require membership in their respective organizations. ProMED-mail, a program of the International Society for Infectious Diseases, is a moderated global electronic reporting system for outbreaks throughout the world of emerging infectious diseases that is open to all sources. Although the reports are sometimes unverified, every effort is made to provide information that is as accurate as possible.

Text-based resources include, as a minimum, the CDC's *Health Information for International Travel* [20], one or more textbooks of travel medicine [24–26], journals of subspecialty societies with an interest in travel and tropical medicine (Appendix), and a textbook of tropical medicine [61–63].

Additional Travel Clinic Services

The practice of travel medicine may be expanded to include a general vaccine clinic, provision of telephone and email advice to the traveling public and/or health professionals, and pretravel physical examinations. Combining a vaccine clinic with a travel clinic is a natural association; each of the vaccines is available, protocols are in place, and the staff is properly trained. A vaccine clinic may be utilized by immigrants in need of immunizations to obtain visas, students who need immunizations to attend school, veterinarians and animal handlers who require rabies vaccination, health care personnel who need hepatitis B vaccine, and individuals who may not have a primary care physician.

Providing advice via telephone or email is controversial, time-consuming, and may open one to medical-legal issues. Although most clinics are willing to provide advice to health care providers, few clinics are willing to provide it to the general public. It is our recommendation that any verbal or written advice given to the public should be general, rather than specific (B-III). This may be safest from a medical-legal point of view to avoid liability for a deleterious outcome stemming from a recommendation. In providing verbal or email advice to persons who are not patients of the practice, it is neither possible nor practical to obtain all of the necessary medical and itinerary information to properly assess health risks.

For travel medicine services that have established formal agreements with corporations or missionary groups to provide remote advice (via email, telephone, or other mechanism) for their personnel on overseas assignments, the boundaries and expectations should be made clear. These entities may also request services, such as lectures to personnel, evaluation of overseas medical facilities, or post-travel health screening.

Practitioners will need to decide whether to perform pretravel physical examinations. Clinics that are part of a university student health service or an occupational medicine program might perform physical examinations as part of visa or program participation requirements.

VACCINE-PREVENTABLE ILLNESS

General Principles

The risk of vaccine-preventable illness in travelers depends upon their itinerary, the duration of travel, the style of travel, and the activities engaged in during travel, and it is influenced by the traveler's past medical and vaccination history. Risk often varies by season of year and other environmental factors. Although it is difficult to assign an absolute risk of acquiring a

disease for an individual traveler, risk can often be estimated by determining the incidence of illness in endemic populations and the incidence of illness in large numbers of returning travelers. For most vaccine-preventable illness in travelers, the risk is extremely low (usually <1 case per 1000 visits).

In contrast to the challenges in assignment of risk, the efficacy and adverse consequences of vaccines are well documented in studies that lead to US Food and Drug Administration (FDA) approval of a vaccine and in post-marketing reports of adverse events. Therefore, the quality of the evidence for vaccine efficacy is grade I. The strength of most of the recommendations for vaccination of travelers falls in the grade A range, but the quality of evidence to support the recommendation is usually grade III. Although it is difficult to demonstrate cost-effectiveness for travel vaccines on an individual-use basis, when considering the health of thousands of travelers, the burden of expert opinion frequently tilts in favor of vaccination, particularly when the consequences of infection are catastrophic (e.g., as with rabies).

Vaccines for travelers can be divided into 3 categories: those used for routine preventive health, those that may be required for travel (usually according to IHRs), and those that are recommended according to risk for disease acquisition. The pretravel visit provides an excellent opportunity to ensure that the traveler is up-to-date on their routine childhood, adolescent, and adult immunizations (A-I). Accepted standards should be applied to immunization practices [64, 65] according to published schedules [66, 67]. Many infectious diseases potentially encountered during travel, such as measles and tetanus, are prevented as part of routine childhood immunization and, therefore, will not pose a risk if the traveler is up-to-date with routine vaccination. In some circumstances, such as with travelers who are younger than the standard age for immunization or whose departure date does not allow completion of the usual immunization schedule, a modification of standard recommendations will be needed.

For travelers who are uncertain of their prior vaccination history, an effort should be made to obtain documentation of any vaccines received. This can be done by contacting their primary care provider (or their parents if they are adolescents or young adults). For some diseases (and when there is sufficient time), serological test results may be obtained (e.g., for measles, mumps, rubella, varicella, tetanus, polio, and hepatitis A and B). If documentation cannot be obtained, these persons should be considered to be susceptible, and they should begin an age-appropriate vaccination schedule [68]. Guidelines for accelerated courses and minimal doses for protection are published [64, 65, 68].

Currently, the only vaccine required under IHRs for travel to certain destinations is yellow fever vaccine. Meningococcal vaccine is required by Saudi Arabia for all pilgrims visiting the country for the purpose of Hajj or Umrah. The United States does not require any immunizations for returning residents.

Special consideration must be given to young children, pregnant travelers, and those with special health needs, such as persons with diabetes, persons with chronic renal, cardiac, or pulmonary disease, and persons with HIV infection, malignancy, or another immunodeficiency state. Children should be considered for vaccination against the same diseases as adults, although the specific vaccine product, dose, and administration details may vary [69]. The potential adverse consequences of live vaccines for the fetus during pregnancy or possible dissemination in an immunocompromised host must be carefully assessed when these travelers are seen. An additional problem in immunocompromised persons is their possible failure to develop protective immune responses to vaccine antigens. Specific vaccine recommendations for young children, pregnant women, and immunocompromised travelers are discussed in *Health Information for International Travel* [20], and chapters addressing these topics may be found in textbooks of travel medicine. They will not be addressed in detail in these guidelines.

It is the responsibility of the provider to review the specifics of vaccine administration (provided in package inserts) and to ensure that travelers are not allergic to eggs or other vaccine components, such as preservatives, antibiotics, or latex. In general, persons who can eat eggs or foods prepared with eggs will tolerate egg-based vaccines. Multiple vaccines may be given at the same time at different sites depending upon patient tolerance. Live-viral vaccines should be administered simultaneously or at a 4-week interval to avoid immune interference. It is advisable to delay immunization until a traveler has recovered from moderate-to-severe illness with or without fever to avoid superimposing vaccine adverse effects upon the illness or mistakenly confusing a manifestation of the illness with a vaccine adverse effect [68]. However, it is important to ensure that any delay in administration will not compromise ultimate compliance with receipt of vaccines.

Immune serum globulin (ISG), which is now only occasionally used for hepatitis A prevention, should not be given <3 months before or <2 weeks after measles-mumps-rubella or varicella vaccine to avoid interference with the immune response to these vaccines by antibodies present in ISG. An interrupted course of vaccination does not require restarting the course (except for live, attenuated oral typhoid vaccine), no matter how long the interval [68].

Immunizations Required under IHRs: Yellow Fever

Yellow fever vaccine is regulated by governmental agencies (CDC and State Health Departments in the United States), as required by IHRs [70]. To be certified to administer yellow fever vaccine, clinics must meet certain criteria; these may in-

clude maintenance of the vaccine at the proper temperature, prompt administration after reconstitution, the ability to handle anaphylactic reactions, and proper completion of the WHO International Certificate of Vaccination. State Health Departments will provide clinics that administer yellow fever vaccine with a validation stamp that is used when vaccination is recorded in the International Certificate of Vaccination [71].

At least 4 countries—Canada, England, South Africa, and New Zealand—have made it a requirement that health care personnel who wish to administer yellow fever vaccine receive formal training in travel medicine for their clinic to be certified as a yellow fever vaccinating center. The linkage of yellow fever vaccination with standards and training in travel medicine is an important evolving concept [72, 73].

Travelers to certain areas of countries that are in an endemic zone for yellow fever should receive vaccine (A-III). Endemic zones for yellow fever lie in equatorial South America and ~15 degrees on either side of the equator in Africa. They are regions where conditions are right for yellow fever transmission; the vector is present and the virus may be circulating in nonhuman mammalian hosts. Importantly, human cases can occur among local residents below the level of surveillance detection and, consequently, are not reported. Although previously a distinction had been made between endemic zones and "infected" areas (i.e., areas where yellow fever cases were reported), because of the difficulty in clearly defining the epidemiology of yellow fever, this distinction is no longer being made by either the CDC or the WHO. Information on the endemic zones and specific recommendations for vaccine use can be found in *Health Information for International Travel* [20] and on the CDC Web site (http://www.cdc.gov/travel); vaccination centers in the United States may be found at http://www2.ncid.cdc.gov/travel/yellowfever/ [74]. The CDC has recently estimated that only 10%–30% of Americans traveling to zones in which yellow fever is endemic have been immunized [75].

The yellow fever 17D strain vaccine is live-attenuated and highly effective. IHRs require that it be administered at least 10 days before travel to allow development of protective antibodies. Boosters are required at 10-year intervals for international travel, although vaccination may confer immunity for decades [76].

Recently, severe adverse events, termed yellow fever vaccine–associated viscerotropic and neurologic disease, have been reported in recipients of the vaccine who have no existing yellow fever immunity [77–80]. It is likely that these adverse events are related to altered host response to the vaccine rather than to changes in the vaccine itself. In support of this is the finding that altered thymic function and thymectomy were associated with 4 of 23 cases of viscerotropic disease [81]. These events are rare, in the order of 1 case for every 200,000 doses sold in the United States, and should not dissuade administration of vaccine to travelers who are at risk. However, both viscerotropic and neurologic disease are seen at a rate of ~1 case per 40,000 doses in the population aged 60 years and older, and the rate of other serious vaccine-related adverse events is also higher in this age group [82]. The risks and benefits of vaccination should be discussed with older travelers in the context of their potential exposure to yellow fever. Until further information is available on the risk of vaccine-associated viscerotropic disease, yellow fever vaccine should not be given to persons with a history of thymus disorder or thymectomy [81].

In most circumstances, yellow fever vaccine should not be administered to those who are pregnant or are immunocompromised because of AIDS, leukemia, lymphoma, cancer chemotherapy, receipt of corticosteroids, or other processes, nor to infants who are <9 months of age. It is best for persons in these categories to avoid exposure and to consider altering their travel itinerary. If travel is mandatory, expert advice should be sought to establish whether the individual warrants immunization or should be issued a letter of medical exemption. In all cases, travelers should strictly adhere to measures to prevent mosquito bites, particularly at dusk and dawn, which are the maximum biting times of the principle human vector, the *Aedes* mosquito.

Immunizations for Travel-Related Exposures

Cholera. Cholera vaccine is no longer produced in the United States and has not been required by the WHO for international travel since the early 1980s. Although an oral killed vaccine (Dukoral [SBL Vaccine]) is available in some countries, including Canada, the risk for travelers is extremely low, and immunization is not usually recommended [83].

Hepatitis A. Protection against hepatitis A is indicated for travelers to areas of the world where sanitation and hygiene may be poor and should be considered for all travelers (A-III) [84]. This recommendation is further strengthened by the recent ACIP recommendation that all children in the United States be vaccinated for hepatitis A at 1 year of age [85]. Although hepatitis A is self-limited in most patients and is usually asymptomatic in children under the age of 6 years, illness has accounted for the most time lost from work (1 month) in a study of returned travelers [86] and is associated with a >2% mortality rate among persons >40 years old [87].

Prior to the introduction of ISG and inactivated vaccines in the mid-1990s, hepatitis A occurred at an estimated frequency of 1–10 cases per 1000 travelers for 2–3 weeks of exposure, even among those residing in first-class accommodations [88, 89]. The risk appears to be decreasing secondary to widespread use of vaccines for protection in travelers and changing epidemiology of hepatitis A in destination countries [90–92]. Although it is recommended that individuals receive the full 2-dose series of inactivated vaccine, a single dose of monovalent

hepatitis A vaccine provides high-level protection in 14–28 days. All monovalent, inactivated hepatitis A vaccines are interchangeable. Indirect evidence suggests that immunization immediately prior to potential exposure is effective [93, 94]. ISG, once widely used for passive protection, is seldom indicated except in the very young or in immunocompromised persons who might not respond to the hepatitis A vaccine. Although not approved by the FDA for use in infants, inactivated hepatitis A vaccines are safe, immunogenic, and have some protective effect even in infants with circulating maternal antibody [95–97]

For persons who may have had hepatitis A (individuals who were born or resided in endemic regions or persons who have a history of jaundice), immunity can be ascertained by screening for anti-hepatitis A IgG antibodies, thereby avoiding the cost of the vaccine. Duration of protection following the full course of vaccine is likely to be lifelong [98], and at present, no booster dose is recommended in immunocompetent hosts (A-II).

Japanese encephalitis. Japanese encephalitis is a mosquito-borne, viral disease that is prevalent in most countries of Asia and, with limited risk, in some islands of the Western Pacific and in the Islands of Torres Strait of Australia. The risk to travelers is low. The Japanese encephalitis vaccine is effective, but it carries a risk of hypersensitivity reactions in the order of 0.1–5 cases per 1000 administrations; in rare instances, the hypersensitivity reactions can be severe [99, 100]. Adverse reactions seem to be more common among persons who have allergies to other antigens. A decision to use the vaccine depends upon the destination and the season of travel. In general, travelers having prolonged residence in an endemic country and those with shorter visits but with intense exposure to mosquitoes during transmission seasons in rural areas will be candidates for the vaccine. This latter group might include those engaging in field work and those who are camping or bicycling. Rice fields are a common breeding site for the mosquito vector, and pigs are an important reservoir for the virus. The CDC publishes regions and time-of-year risks for travelers in *Health Information for International Travel* [20]. Three doses of vaccine are given over the course of 1 month, but the schedule can be accelerated to 14 days [101]. Vaccine recipients should be observed for 30 min after vaccination; ideally, they should not travel for 10 days after the last dose because of the risk of a delayed allergic reaction [102].

Meningococcal infection. Vaccination against *N. meningitidis* (with vaccine containing serotypes A/C/Y/W-135) is currently required by Saudi Arabia and recommended by the CDC's ACIP for religious pilgrims traveling to Mecca for the purpose of the Hajj or Umrah. This is a measure to protect against importation and spread of meningococcal disease, as well as to protect individual pilgrims. Meningococcal vaccine is recommended for travelers to the "meningitis belt" in sub-Saharan Africa (generally extending from Senegal to Ethiopia) [103], particularly if they are traveling during the dry season of December through June or will have extensive contact with the local population [104]. Travel to other areas during epidemics warrants vaccination. The CDC (http://www.cdc.gov/travel) and WHO (http://www.who.int/ith/) Web sites can provide information on epidemic disease.

In 2005, a conjugated quadrivalent meningococcal vaccine was approved for use in persons aged 11–55 years [105, 106]. Product licenses for conjugated vaccine products are being sought for children aged 2–10 years. This conjugated vaccine supplements the existing nonconjugated polysaccharide vaccine (table 5). Routine vaccination with meningococcal quadrivalent conjugate vaccine is recommended at the preadolescent visit (at age 11–12 years) [107]. For those not previously vaccinated, the ACIP recommends vaccination at high school entry (i.e., at ~15 years of age). Routine vaccination is also recommended for first-year college students who will live in dormitories. Microbiologists with frequent exposure to *N. meningitidis*, military recruits, persons with terminal complement component deficiencies, and individuals with functional or surgical asplenia should also receive vaccine. Nonconjugated meningococcal polysaccharide vaccines are poorly immunogenic in children under the age of 2 years. Reports of Guillain-Barré syndrome following vaccination with the conjugated vaccine are being evaluated and have not led to a change in recommendations for use of the vaccine [108].

Rabies. Rabies vaccine is recommended for travelers to areas in which rabies is endemic who will have occupational or recreational exposure (e.g., veterinarians, spelunkers, and others with animal contact) [109]. The epidemiology of rabies can be determined by reviewing the rabies information in Health Information for International Travel [20], the CDC Web site (http://www.cdc.gov/travel), and the WHO Global Health Atlas Web site (http://globalatlas.who.int/). Rabies cases in travelers are rare; however, dog or monkey bites are not uncommon. Most cases of rabies in travelers follow a dog bite in areas in which canine rabies is endemic; monkeys, bats, and mongoose are other potentially infected species, as are foxes in Eastern European countries.

It is imperative that all travelers are counseled about dog avoidance (and avoidance of other animals), thorough cleansing of a wound with soap and water in the event of a bite, and the need to obtain prompt postexposure prophylaxis for rabies. A complete course of rabies vaccine prior to travel eliminates the need for rabies immunoglobulin following an exposure. Rabies immunoglobulin of either human or equine origin may be very difficult to obtain in resource-poor regions of the world [110, 111]. Pre-exposure vaccine has the additional theoretical benefit of protecting against unrecognized or unreported ex-

Table 5. Vaccinations for travelers.

Vaccine	Type (route and dose)[a]	Schedule[a]	Indications[a]	Precautions and contraindications[b]	Adverse effects[b]
Toxoids					
Tetanus-diphtheria	Adsorbed toxoids (im, 0.5 mL)	Primary: 3 doses; first 2, 4–8 weeks apart; 3rd dose after 6–12 months; booster: every 10 years; alternatively, a single dose may be given at age 50 years for persons who have completed full pediatric series, including teenage booster. A new Tdap vaccine should be used to provide single booster.	For children ⩾7 years old and adults	SAR after a previous dose or to a vaccine component; Guillain-Barré syndrome ⩽6 weeks after previous dose	LRs are common; occasional systemic symptoms; Arthus-like reactions in persons with multiple previous boosters; anaphylaxis or other allergic reactions are rare
Tdap (Boostrix [GlaxoSmithKline] for ages 10–18 years and Adacel [Sanofi Pasteur] for ages 11–64 years)	Combination toxoids of diphtheria and tetanus with acellular pertussis (im, 0.5 mL)	Primary: not used for this purpose; booster: single dose for adolescents age 11–12 years who have completed childhood DTP/DTaP course and single dose for adults 19–64 years	For adolescents and adults aged 11–64 years who need boosting for any of the 3 antigens	SAR to a vaccine component; encephalopathy within 7 days of receipt of vaccine with pertussis component; progressive neurologic disorder; Guillain Barré syndrome ⩽6 weeks after previous dose of tetanus toxoid-containing vaccine; history of Arthus reaction after tetanus or diphtheria toxoid-containing vaccine administered <10 years previously	LRs include erythema, swelling, and pain and are common; systemic reactions include fever, headache, fatigue, and gastrointestinal symptoms
DTaP (multiple preparations available)	Combination toxoids of diphtheria and tetanus with acellular pertussis (im)	Primary: first at 2 months, 2nd and 3rd at 4–8-week interval; 4th at 15–18 months of age; 5th at 4–6 years of age. Fifth dose not needed in children given primary series at 4 years of age	For infants and children ⩽7 years old	SAR after a previous dose or to a vaccine component; encephalopathy within 7 days of previous dose; progressive underlying neurologic disorder; high fever (temperature, ⩾40.5°C), seizure, or inconsolable crying after previous dose (relative contraindications)	LRs include erythema, induration, and tenderness; mild systemic reactions, including fever (temperature, >38.3°C) in 3%–5% of DTaP recipients; high fever, seizures, and persistent crying reactions are less common with DTaP than with older diphtheria and tetanus whole-cell P vaccine; anaphylactic and other SARs are rare
Inactivated bacteria vaccines					
Hib	Conjugated polysaccharide (im)	Primary: 3 doses at 2, 4, and 6 months; 4th dose at 12–15 months; schedule may vary depending upon product	All infants and children ⩽ 5 years old	SAR after a previous dose or to a vaccine component; age <6 weeks	LRs; allergic reactions
Pneumococcal polysaccharide	Polysaccharide, 23 serotypes (sc or im, 0.5 mL)	Primary: single dose; booster: high-risk patients after 5 years	Persons ⩾ 5 years at increased risk of pneumococcal disease and its complications; healthy adults ⩾65 years old	SAR after a previous dose or to a vaccine component; moderate or severe acute illness with or without fever	Approximately 50% of patients have mild erythema and pain at injection site; systemic reaction in <1% of patients; Arthus-like reaction with booster doses
Pneumococcal conjugate vaccine	Conjugated 7-valent polysaccharide (im)	Primary: 3 doses at 2, 4, and 6 months; 4th dose at 12–15 months	All children aged 2–23 months; children 24–59 months old if at risk	SAR after a previous dose or to a vaccine component	LRs; allergic reactions
Meningococcal	Polysaccharide (MPSV4) containing the 4 serotypes A, C, Y, and W-135 (sc, 0.5 mL)	Primary: single dose; booster: 5 years in adults and children ⩾4 years old; boosted at 2–3 years in children 2–4 years old	Travelers to areas with epidemic meningococcal disease; religious pilgrims to Saudi Arabia; college freshmen; microbiologists exposed to *Neisseria meningitidis;* asplenia or certain complement-deficiency conditions	SAR after a previous dose or to vaccine component; can be considered in pregnancy	Mild LRs in 4%–56% of cases; anaphylaxis and neurologic reactions are rare
Meningococcal conjugate	Conjugated polysaccharide containing the 4 serotypes A, C, Y, and W-135 (im, 0.5 mL)	Primary: single dose; booster: not currently determined	As per MPSV4 PLUS, children aged 11–12 years and children aged 15 years not previously vaccinated	SAR after a previous dose or to vaccine component; can be considered in pregnancy	LRs in 10%–60% of cases; occur more frequently than with nonconjugated polysaccharide vaccine; systemic reactions of fever, headache, and malaise
Typhoid	Polysaccharide Vi antigen (im, 0.5 mL)	Primary: single dose for age ⩾2 years; booster: every 2 years	Risk of exposure to typhoid fever	Safety in pregnancy is unknown; SAR after a previous dose or to a vaccine component	Local pain and induration in 7% of cases; headache in 16%; fever in <1%

Attenuated live bacterial vaccine					
Typhoid	Attenuated Ty21a mutant of *Salmonella* Typhi (po)	Primary: 1 capsule every other day for 4 doses; booster: every 5 years	Risk of exposure to typhoid fever in persons ≥6 years old	Safety in pregnancy is unknown; AIC[c]; persons with acute febrile or gastrointestinal illness; persons taking antibiotics; if taking mefloquine, separate doses by 24 h; refrigerate capsules	Infrequent gastrointestinal upset or rash
ALV vaccines[d]					
Influenza (Flumist [MedImmune Vaccines])	Attenuated trivalent live virus (intranasal, 0.5 mL; dose will vary depending upon age)	Primary: age 5–8 years (no prior dose), day 0, and day 60; age 5–8 years (prior dose), 1 dose per season; age 9–49 years, 1 dose per season	Alternative vaccine to inactivated product; recommended for persons 5–49 years old; international travelers	History of hypersensitivity to prior dose or components, including eggs; children 5–17 taking aspirin; history of Guillain-Barré syndrome; AIC[c]; history of asthma; safety not assessed during pregnancy	Mild upper respiratory symptoms, including rhinitis, nasal stuffiness, and congestion
Measles	ALV, available in monovalent form or combined with rubella and mumps (i.e., MMR) (sc, 0.5 mL)	Primary: 2 doses; 1st at 12–15 months of age, 2nd at 4–6 years; for adults, 2 doses separated by at least 1 month; booster: none	Persons born after 1956 who have not had documented measles nor received 2 doses of live vaccine	Pregnancy; AIC[c]; history of anaphylaxis to gelatin or neomycin; administration of Ig used for hepatitis A prevention within 3 months	Temperature of ≥ 39.4°C 5–21 days after vaccination in 5%–15% of cases; transient rash in 5% of persons previously immunized with killed vaccine (during 1963–1967), 4%–55% have a LR; rare (with MMR) SARs, thrombocytopenia, and CNS conditions
Mumps	ALV (sc, 0.5 mL)	Primary: 1 dose, usually given as part of MMR vaccine; booster: none	Persons born after 1956 who have not had documented mumps or mumps vaccine	Pregnancy; AIC[c]; history of anaphylaxis to gelatin or neomycin; administration of Ig used for hepatitis A prevention within 3 months	Mild allergic reactions are uncommon; parotitis is rare
Rotavirus	ALV (po)	Primary: 3 doses at 2, 4, and 6 months; complete series before 32 weeks of age	All infants	Severe hypersensitivity to vaccine component or previous dose of vaccine; AIC[c]; delay vaccination in those with moderate to severe gastroenteritis	Slight increase in vomiting and diarrhea, compared with placebo recipients
Rubella	ALV (sc, 0.5 mL)	Primary: 1 dose, usually given as part of MMR; booster: none	All persons, particularly women of childbearing age, without documented illness or live vaccine on or after first birthday	Pregnancy; AIC[c]; history of anaphylaxis to neomycin; administration of Ig used for hepatitis A prevention within 3 months	Up to 25% of postpubertal women have joint pains, transient arthralgias, beginning 3–25 days after vaccination, persisting 1–11 days; frank arthritis in <2% of recipients; transient lymphadenopathy
Varicella	ALV (sc, 0.5 mL)	Primary: 2 doses; first at 12–15 months of age, second at 4–6 years; unvaccinated older children and adults, 2 doses at 4–8 week interval	Persons ≥12 months old who have not had varicella	Pregnancy; AIC[c]; potential for rare transmission of vaccine virus to susceptible hosts; administration of Ig within 3 months; SARs to gelatin or neomycin	Local pain and induration in ~20% of cases; fever, ~15%; localized or mild systemic varicella rash, ~6%
Yellow fever	ALV (sc, 0.5 mL)	Primary: single dose 10 days to 10 years before travel; booster: every 10 years	As required by individual countries or travel in regions of yellow fever endemicity	Avoid in pregnant women, unless high-risk travel; infants <9 months old; AIC[c]; hypersensitivity to eggs; persons with thymus disorders; caution in persons ≥60 years old	Mild headache, myalgia, fever 5–10 days after vaccination in 25% of cases; immediate hypersensitivity is rare; viscerotropic or neurologic disease is rare
Inactivated virus vaccines					
Hepatitis A (Havrix [GlaxoSmithKline] and Vaqta [Merck][e])	Inactivated virus (im, adult and pediatric formulations)	Primary: 2 doses, 2nd dose after 6–18 months provides possibly lifelong protection; booster: not currently recommended	Travel to developing countries; all children ≥12 months old; persons with clotting disorders or chronic liver disease; men who have sex with men; some persons may benefit from prevaccine hepatitis A serological testing	Safety in pregnancy is unknown; SAR after a previous dose or to a vaccine component	LRs with pain and tenderness in <56% of cases; occasional fever in <5%; headache in 16%
Hepatitis B (Recombivax HB [Merck] and Engerix [GlaxoSmithKline])	Recombinant-hepatitis B surface antigen (im, adult and pediatric formulations)	Primary: 3 doses at 0, 1–2, and 4–6 months of age; can accelerate vaccination; booster: not routinely recommended	Health care workers in contact with blood; persons residing in areas of intermediate to high endemicity for hepatitis B; others at risk for contact with blood, body fluids, or blood-contaminated medical or dental instruments	Pregnancy is not a contraindication in persons at high risk; SAR after a previous dose or to a vaccine component	Mild, LR in 3%–29% of cases; fever in 1%–6%

Hepatitis A and B antigens combined (Twinrix [GlaxoSmithKline])	Inactivated hepatitis A virus plus recombinant hepatitis B surface antigen, (im, 1.0 mL)	Primary: 3 doses at 0, 1, and 6 months; accelerated schedules exist	Travelers ⩾18 years old at risk for both hepatitis A and B; give at least 2 doses of vaccine prior to departure to provide protection against hepatitis A	Safety in pregnancy is unknown; SAR after a previous dose or to a vaccine component	LRs in ~56% of cases; systemic symptoms of headache and fatigue, similar to single antigen preparations
Poliomyelitis	Killed poliomyelitis virus, trivalent, (sc or im, 0.5 mL)	Primary: 3 doses, first 2 at a 4- to 8-week interval; 3rd dose 6–12 months after 2nd dose; booster: 1 adult, lifetime dose with travel to regions of endemicity	Only formulation of polio vaccine used in United States; travel to countries where polio is endemic	SAR after a previous dose or to a vaccine component; pregnancy is a relative contraindication	Mild LRs
Influenza	Inactivated whole and split influenza A and B virus (im, 0.5 mL)	Annual vaccination with current vaccine	Persons ⩾ 6 months old with high-risk conditions; persons with chronic diseases; healthy adults ⩾50 years old; healthy children aged 6–23 months; health care workers; travelers at risk; pregnant women in 2nd or 3rd trimester during flu season; others wishing vaccination	SAR after a previous dose or to a vaccine component, including egg protein	Mild LRs in <33% of cases; occasional systemic reaction of malaise or myalgia, beginning 6–12 h after vaccination and lasting 1–2 days; rare allergic reaction
Japanese B encephalitis	Inactivated virus (sc, 1.0 mL)	Primary: 3 doses at days 0, 7, and 30; booster: 1 dose at 24-month interval (however, duration of protection is not known)	Travelers to area of risk with rural exposure or prolonged residence	Pregnancy; history of multiple allergies, especially anaphylaxis or urticaria; history of allergic response to Japanese encephalitis or other mouse- derived vaccines; because of delayed allergic reactions, recipients should be observed for 30 min after each dose and the series completed ⩾10 days before departure	Local, mild reactions lasting 1–3 days (in 20% of cases) or mild systemic reactions of fever, myalgia, headache, or gastrointestinal upset (10%); allergic reactions of urticaria, rash angioedema, or respiratory distress (~6 cases per 1000 patients); sudden death or encephalomyelitis is rare
Rabies	Inactivated virus in HDCV, PCEC, or RVA[f] (im, 1.0 mL)	Preexposure: 3 doses at days 0, 7, and 21 or 28; booster: depends on risk category and is based on serological test results; postexposure prophylaxis: rabies Ig day 0 and vaccine given days 0, 3, 7, 14, and 28	Itineraries and activities that place the traveler at risk for rabies; dogs are primary threat in developing regions; medical workers in areas of endemicity	Allergy to previous doses; may be given in pregnancy if indicated	LRs: pain, erythema, swelling, and itching; mild systemic reactions: headache, nausea, aches, and dizziness; occasional (in 6% of patients) immune complex-like reactions with booster dose of HDCV occurring 2–21 days after vaccination
Passive prophylaxis					
Ig	Fractionated Igs, primarily IgG (im)	Travel of <3 months duration: 0.02 mL per kg of body weight; travel of >3 months duration: 0.06 mL per kg of body weight every 4–6 months	For prevention of hepatitis A; some travelers may benefit from pretravel hepatitis A antibody testing	Should not be given <2 weeks after or 3 months before measles, mumps, rubella, or varicella vaccines	Local discomfort; rare systemic allergy

NOTE. The table is based on *Health Information for International Travel 2005–2006,* (available at http://www.cdc.gov/travel/yb/index.htm) [20] and other national guidance [66–68]. AIC, altered immunocompetence; ALV, attenuated live virus; DTaP, diphtheria, tetanus, and acellular pertussis; DTP, diphtheria, tetanus, and pertussis; HDCV, human diploid cell rabies vaccine; Hib, *Haemophilus influenzae* type b; id, intradermally; Ig, immunoglobulin; LR, local reaction; MMR, measles, mumps, and rubella vaccine; PCEC, purified chick embryo cell; RVA, rabies vaccine adsorbed; SAR, severe allergic reaction; Tdap, tetanus, diphtheria, and acellular pertussis for adolescents and adults.

[a] Manufacturer's full prescribing information should be consulted. Doses given are generally for adults; pediatric doses may vary.

[b] Only major precautions, contraindications, and adverse effects are listed. Moderate or severe acute illness with or without fever is a contraindication to all vaccines.

[c] Persons immunocompromised because of congenital immunodeficiency diseases, leukemia, lymphoma, generalized malignancy, and HIV infection or AIDS or persons immunosuppressed as a result of therapy with corticosteroids, alkylating agents, antimetabolites, or radiation. Persons with a history of thymectomy, thymus disease, or myasthenia gravis should not receive yellow fever vaccine.

[d] Attenuated live viral vaccines should be given simultaneously or separated by at least 4 weeks.

[e] Different vaccine products are interchangeable and may be used to complete or boost a series begun with a different product.

[f] As of March 2006, only PCEC vaccine is available.

posures. This may occur in children who are afraid to tell parents that they were bitten. In general, a pre-exposure course should be completed with the same vaccine product, because there are no studies that examine efficacy when the series is completed with a second product. All travelers who have had an exposure, regardless of their pretravel rabies vaccine history, require postexposure prophylaxis: those who have had pretravel vaccine require an additional 2 doses, and those who have received no prior rabies vaccine require a complete course of vaccine (5 doses by US standards) plus rabies immunoglobulin [112]. Postexposure and boosting doses of rabies vaccine do not have to be administered using the original vaccine product.

Tick-borne encephalitis. This viral encephalitis is prevalent in rural forested areas of Eastern and Central Europe, Scandinavia, and Siberia in spring and summer months [113]. It is most commonly transmitted by *Ixodes* ticks, but it may also be contracted by ingesting unpasteurized dairy products in areas of endemicity. There are 2 inactivated vaccines (FSME-Immun [Baxter AG] and Encepur [Chiron]), but neither of these is licensed in the United States or Canada, and they require 3 doses administered over the course of a year to obtain full protection. Although accelerated schedules exist, these are not practical for most travelers, because the vaccine would need to be administered in the destination country. Travelers to areas of disease risk should exercise tick precautions by wearing protective clothing, applying repellents, using residual insecticides, and performing a careful check for ticks after being in infested areas. Expatriates can consider obtaining vaccine during their overseas residence.

Typhoid fever. The risk of typhoid is ~1 order of magnitude less than the risk of hepatitis A: 1–10 cases per 100,000 travelers, depending upon the destination [114]. Travelers to the Indian subcontinent, particularly VFRs, are at greatest risk [49, 115–117]. Typhoid immunization is indicated for travelers to areas of endemicity in Central and South America, Asia, and Africa who will be consuming food and drink in conditions of poor sanitation and hygiene. Duration of travel is less important as an indicator of risk when persons travel to high-risk destinations [49, 118]. Increasing antibiotic resistance among *Salmonella enterica* serovar Typhi is another reason to consider vaccination [119]. In the United States, there are 2 vaccines available for protection against *S.* Typhi: a live-attenuated oral vaccine (Vivotif Berna [Berna Products]) and an injectable Vi capsular polysaccharide vaccine (Typhim Vi [Sanofi Pasteur]). They are of comparable efficacy, providing protection levels of 50%–70% [120]. Because typhoid vaccines provide incomplete protection and do not protect against *S. enterica* serovar Paratyphi, travelers need to remain cautious about food and beverage ingestion.

Other vaccines. Anthrax and smallpox vaccines are not currently recommended or available for civilian travelers. Although smallpox vaccine has been administered since early 2003, its use is restricted to programs of bioterrorism preparedness [121].

Tuberculosis skin testing should be performed for those with anticipated exposure to tuberculosis or long-term stays in developing areas or when requested by the traveler because of concern about exposure (B-III). It is usually performed before travel and 3 months after return. The need for testing is particularly important for health care workers in countries of endemicity, for whom the risk for infection may be as high as 7.9 cases per 1000 person-months [122]. Bacille Calmette-Guérin vaccine is incorporated into routine childhood immunization programs in many countries. Although Bacille Calmette-Guérin vaccine (BCG Vaccine [Organon USA]) may be obtained in the United States by request, it is rarely indicated [123]. It may be considered on an individual basis for children <5 years of age who will be continually and unavoidably exposed to a person with infectious pulmonary tuberculosis [123].

Special Indications for Vaccines Routinely Used in North America

H. influenzae *type B.* The indications for traveling children are the same as for residents in the United States.

Hepatitis B. Consideration should be given to immunizing all North American adults against hepatitis B, whether or not they travel. Although the risk to short-term travelers may be low, any traveler with potential contact with blood or body fluids though sex, medical work, or other activities should be immunized. If medical care is obtained overseas, injections should be avoided, particularly in developing regions, where up to 75% of injections are administered with reused, unsterilized equipment [124]. Long-term travelers or those that make repeated trips should also be immunized. An accelerated schedule over 2 months has been approved in the United States with one of the hepatitis B vaccines (Engerix-B [GlaxoSmithKline]) to achieve protection in travelers who are departing prior to completion of the 6-month normal schedule [125]. A further accelerated schedule over 3 weeks has been studied and results in 65% seroconversion at 1 month [126]. This schedule is approved in the European Union and Canada, but is not FDA-approved for the United States. In both accelerated schedules, an additional dose should be given at 12 months to confer long-term protection.

A recent report suggested an association of hepatitis B vaccination with the subsequent development of multiple sclerosis [127]. Although this report indicated that hepatitis B vaccine may be one of many factors associated with development of multiple sclerosis, it stands in contrast to other analyses that have concluded there is no link (e.g., Ascherio et al. [128] and articles cited by Naismith and Cross [129] in their review) and has not led to changes in vaccine indications.

Combination hepatitis A and B. A combined vaccine may be used in travelers aged ⩾18 years when protection against both antigens is desired. Two doses of vaccine must be given 1 month apart to achieve protection against hepatitis A, because a lower dose of antigen is used in this preparation, compared with single-antigen hepatitis A vaccines. This vaccine has also been approved in Europe for use in a 3-week accelerated schedule, with a fourth dose administered at 12 months [130].

Influenza. Influenza is a year-round concern for travelers, particularly when they are brought together from all parts of the world in crowded conditions, such as on cruise ships [131]. Recent data indicate that influenza may be the most frequently acquired vaccine-preventable illness, with ~1% of travelers acquiring influenza during travel [132] . Therefore, influenza can be considered to be a travel-related infection that should be prevented [133, 134]. North Americans traveling during winter months in the Northern Hemisphere, to the Southern Hemisphere from April to September, or to the tropics throughout the year, are at potential risk. The efficacy of the vaccine depends on its antigen composition, which is based yearly on projections of influenza activity in North America [135]; the vaccine may not protect against strains circulating elsewhere in the world. The annual seasonal influenza vaccine is often not available in the United States during the late spring, summer, and early fall, when some travelers might need it.

Influenza vaccine is not protective against highly pathogenic avian influenza A/H5N1, which has caused outbreaks of avian influenza in birds in Asia, Europe, the Middle East, and Africa since December 2003 and has resulted in >250 human cases in Viet Nam, Thailand, Indonesia, China, Cambodia, Turkey, Iraq, Azerbaijan, and Djibouti with a 58% case-fatality rate [136, 137]. Current recommendations for decreasing the risk of acquiring avian influenza while traveling in regions with bird infection include avoiding contact with live poultry and wild birds, not visiting live animal markets and poultry farms, avoiding contact with surfaces contaminated with animal feces, not eating or handling undercooked or raw poultry, egg, or duck dishes, exercising good personal hygiene with frequent hand washing, and monitoring one's health for 10 days after return [138]. It is generally not recommended that travelers carry with them a self-treatment course of oseltamivir for avian influenza. Health advisers should visit the CDC and WHO avian influenza sites (http://www.cdc.gov/flu/avian/ and http://www.who.int/csr/disease/avian_influenza/en/index.html, respectively) for the latest information concerning the risk of avian influenza.

Measles. Measles is no longer considered to be endemic in the United States, and most cases are related to international importation [139]; therefore, all travelers should be protected. Two doses of measles vaccine are recommended in childhood. Children aged 6–11 months of age who are at risk during travel should receive a single dose of a measles-containing vaccine and then resume the vaccine schedule with the measles-mumps-rubella vaccine at age 12–15 months. All travelers born after 1956 who had a single early childhood dose should receive a second dose of a measles-containing vaccine, preferably measles-mumps-rubella vaccine. Travelers with no history of measles or immunization should receive 2 doses at least 1 month apart. Two doses of measles vaccine are now required by many colleges.

Pertussis. Protection against pertussis is usually achieved during childhood by administering 1 of the combination pediatric vaccines containing acellular pertussis antigen [67]. It is important to maintain widespread childhood immunity to pertussis to help prevent cases of disease in young infants prior to their vaccination and cases in older persons with waning immunity [140].

To address an increase in pertussis cases, in May and June of 2005, 2 new combined tetanus toxoid, diphtheria toxoid, and acellular pertussis vaccines (Tdap) were approved by the FDA, 1 for use in adolescents and the other for use in both adolescents and adults [141, 142]. These vaccines should be used in persons aged 11–64 years as a booster against tetanus, diphtheria, and pertussis [141, 142].

Pneumococcal vaccine. The indications for travelers are the same as those for residents of North America.

Poliomyelitis. All travelers should have completed a primary course of polio vaccine. One additional lifetime dose of the inactivated polio vaccine should be given to adults (i.e., those aged ⩾18 years) who are traveling to regions of the world that remain a risk for polio transmission (primarily countries in Africa and Asia). The WHO has declared 3 regions of the world to be polio-free: the Western Hemisphere, the European Region, and the Western Pacific. However, regional spread of polio, as well as importation of wild-type strains of the virus into countries that have eradicated disease, has occurred since 2003, following the suspension of polio vaccination campaigns in the north of Nigeria [143, 144]. In the second half of 2005, the following countries reported circulation of imported poliovirus: Angola, Chad, Ethiopia, Indonesia, Nepal, Niger, Somalia, and Yemen, and as of early 2006, 4 countries remained endemic for indigenous polio: India, Pakistan, Afghanistan, and Nigeria [145].

In addition, small outbreaks of paralytic polio have occurred secondary to circulating vaccine-derived polioviruses when the vaccine strain undergoes mutation and reversion to virulence [146]. Such outbreaks have occurred in recent years in Haiti, the Dominican Republic, the Philippines, and Madagascar. For the latest information about the status of polio, the WHO Global Polio Eradication Initiative Web site should be consulted (http://www.polioeradication.org/).

Rotavirus. Rotavirus is an important cause of gastrointestinal illness in children throughout the world. Recently, 2 oral

live-attenuated vaccines have been developed against rotavirus and have demonstrated good protective efficacy, particularly in preventing severe disease [147, 148]. There is no evidence of an increased risk of intussusception with either vaccine, a problem that led to the withdrawal in 1999 of the previously licensed rotavirus vaccine, Rotashield [Wyeth-Ayerst] [149]. One of the vaccines, RotaTeq (Merck), has received US licensure for prevention of rotavirus in infants in a 3-dose schedule beginning at age 2 months [149]. The other product, RotaRix (GlaxoSmithKline), has licensure in the European Union and some countries in Africa, Latin America, and Asia. RotaTeq contains 5 human-bovine reassortant rotaviruses; 4 express 1 of the human outer capsid proteins and a bovine attachment protein, and the fifth expresses a bovine outer capsid protein and a human attachment protein. RotaRix is a monovalent vaccine using an attenuated human rotavirus strain. Infants who are traveling should be immunized against rotavirus according to the approved schedule.

Tetanus and diphtheria. Previously immunized adults should be boosted at 10-year intervals independent of travel. With respect to tetanus, consideration may be given to boosting travelers after 5–10 years if they will be at risk for tetanus-prone injuries in isolated areas and unable to access a tetanus booster if exposed (B-III). Travelers to countries where diphtheria poses a risk (most countries of Africa, Asia, the Middle East, Eastern Europe, and Northern Asia, as well as focal areas of Latin America) should be up to date on diphtheria vaccination. Boosting for tetanus and diphtheria in adolescents and adults should be done with the new combined vaccine, Tdap (table 5).

Varicella (chicken pox). Travelers without a history of chicken pox may be evaluated for previous infection by antibody testing against varicella zoster virus. Travelers who are found not to be immune should be offered vaccination.

TRAVELER'S DIARRHEA: PREVENTION AND MANAGEMENT

Traveler's diarrhea is the most common illness in persons traveling from resource-rich regions of the world to resource-poor regions [150, 151]. By formal criteria, it is characterized by $\geqslant 3$ loose stools over a 24-h period, accompanied by an enteric symptom, such as fever, nausea, vomiting, and abdominal cramping. However, from the traveler's perspective, the sudden onset of uncomfortable diarrhea during or shortly after travel may be considered traveler's diarrhea. Tenesmus and bloody stools are uncommon. Most illness will resolve spontaneously over a 3–5-day period; however, as many as one-quarter of travelers will have to change their planned activities, and some will be left with a postinfectious irritable bowel syndrome [152–154]. The rates of diarrhea are in the order of 40%–60% over a 2–3-week vacation for persons from industrialized countries traveling to developing regions [151, 155].

The disease is predominately caused by bacterial enteropathogens: enterotoxigenic *Escherichia coli* (ETEC), enteroaggregative *E. coli*, *Salmonella* species, *Campylobacter* species, and *Shigella* species; ETEC is the most common pathogen, accounting for up to one-third of etiologies [155], and enteroaggregative *E. coli* are increasingly recognized [156]. Noncholerae vibrios, *Aeromonas* species, and *Plesiomonas* species are less common bacterial etiologies. Viral causes include noroviruses and rotavirus. Noroviruses have been a particular problem in cruise ship–associated enteric outbreaks [157]. Parasites are less common and are usually seen in long-term travelers. Of the enteric protozoa *(Giardia lamblia, Cryptosporidium hominis, Cyclospora cayetanensis,* and *Entamoeba histolytica), G. lamblia* is the most common.

Prevention: Food and Beverages

Drinking contaminated water accounts for the acquisition of a proportion of enteropathogens, notably some viruses and parasites, but ingesting contaminated food appears to be the most common mode of acquisition. Analysis of the literature in reviews and a recently published book [158–161] suggests that inadequate public health practices in locations of food and beverage consumption might be a more important risk than contamination of specific food and beverage items [162]. This can make it difficult for the traveler to exert control over his or her environment and be successful in preventing diarrhea. In addition, educating travelers about safe beverage and food choices has often failed to effect either behavioral change or protection from diarrhea [163], and sampling the local cuisine is often an integral part of the enjoyment of travel. Nevertheless, although avoidance measures may not be entirely effective, it remains important to advise the traveler about how to prevent diarrhea (A-III). Common-sense measures may help and are likely to decrease the chance of acquiring other, more-serious fecal-oral transmitted enteric infections, such as typhoid fever, larval cestode infections (e.g., cysticercosis), and intestinal helminths (B-III).

Travelers should seek restaurants and other locations of food consumption that have an excellent reputation for safety. Piping hot, thoroughly cooked food, dry food, and fruits and vegetables peeled by the traveler are generally safe. Tap water, ice cubes, fruit juices, fresh salads, unpasteurized dairy products, cold sauces and toppings, open buffets, and undercooked or incompletely reheated foods should be avoided.

Prevention: Vaccines

There is currently no vaccine against the general syndrome of traveler's diarrhea. The inactivated, oral, *Vibrio cholerae* whole cell/B subunit vaccine (Dukoral [SBL Vaccine]) confers limited

protection against heat-labile enterotoxin–producing *Escherichia coli* in persons who live in endemic regions [164]. However, the level of protection in travelers has been variable [165–167]. Conservative calculations that take into account the incidence of heat-labile enterotoxin–producing *E. coli* disease throughout the world and vaccine effectiveness estimate that ⩽7% of travelers might benefit from receipt of this vaccine [83]. Although the vaccine is licensed in Canada, it is not available in the United States. A decision to use it depends upon balancing the cost, adverse effects, and limited efficacy of the vaccine against the known effectiveness and costs of self-treatment.

Chemoprophylaxis

Both nonantibiotics, such as bismuth subsalicylate–containing formulations (e.g., Pepto Bismol [Proctor and Gamble]) [168–170] and antibiotics [13, 171–175, 196–200], have been proven effective in preventing traveler's diarrhea (A-I) (table 6). Probiotics, such as lactobacillus, have not demonstrated sufficient efficacy to be recommended [201–203]. Bismuth subsalicylate in tablet and liquid form has afforded 62%–65% protective efficacy against traveler's diarrhea [168, 169]; however, a regimen of chewing 2 tablets or drinking 2 oz 4 times per day may be inconvenient for many travelers. Black tongue and stools caused by the formation of insoluble bismuth salts may occur, and simultaneous ingestion of bismuth subsalicylate with doxycycline may lead to decreased absorption of doxycycline [204].

Throughout the 1970s and 1980s, antibiotics were extensively studied in the prevention of traveler's diarrhea and were found to be effective in short-term travelers (those traveling for 3 weeks or less) [205]. Doxycycline and trimethoprim-sulfamethoxazole (TMP-SMX) were most commonly used, but widespread drug resistance renders them no longer useful. When fluoroquinolones were introduced, they afforded 84% protection in a chemoprophylaxis study [174]. Their efficacy may be lower in regions of the world such as Southeast Asia and India, where fluoroquinolone resistance is on the rise [206–208].

Enthusiasm for chemoprophylaxis began to wane as studies demonstrated that self-treatment was effective in rapidly improving illness. Chemoprophylaxis can contribute to development of resistant enteric bacteria and potentially predispose the traveler to infection with other deleterious pathogens, such as *Clostridium difficile*. Experts also questioned the rationale for taking antibiotics to prevent what was usually a mild illness.

Table 6. Recommended agents for traveler's diarrhea.

Use, agent	Dosage	References
Prophylaxis[a]		
Bismuth subsalicylate (Pepto Bismol)	Two tablets chewed 4 times per day	[168–170]
Norfloxacin[b]	400 mg po daily	[171–173]
Ciprofloxacin[b]	500 mg po daily	[174, 175]
Rifaximin	200 mg qd or bid	[176]
Symptomatic treatment[c]		
Bismuth subsalicylate (Pepto Bismol)	1 oz po every 30 min for 8 doses	[177]
Loperamide	4 mg po then 2 mg after each loose stool not to exceed 16 mg daily	[15, 178–180]
Antibiotic treatment[d]		
Fluoroquinolones		
Norfloxacin	400 mg po bid	[181–183]
Ciprofloxacin	500 mg po bid	[184–190]
Ofloxacin	200 mg po bid	[191–193]
Levofloxacin	500 mg po qd	[16]
Azithromycin	1000 mg po once	[16, 194]
Rifaximin[e]	200 mg po tid	[17, 184, 195]

[a] There is currently no antibiotic with demonstrated efficacy in prophylaxis against *Campylobacter* species. *Campylobacter* species is more frequent as an etiology of traveler's diarrhea in South and Southeast Asia. No antibiotic has US Food and Drug Administration approval for use in prophylaxis for traveler's diarrhea.

[b] Other fluoroquinolones are likely to be effective but have not been studied in prophylaxis.

[c] See Treatment for other agents that either have limiting adverse effects, are not very efficacious, or have not been studied in traveler's diarrhea.

[d] See Duration of Therapy and Combination Therapy for discussion of duration of therapy and adjunctive therapy with loperamide.

[e] Although the US Food and Drug Administration–approved dose is 200 mg po tid, 1 study demonstrated efficacy with 400 mg po bid. Rifaximin is approved by the US Food and Drug Administration for the treatment of traveler's diarrhea caused by noninvasive strains of *Escherichia coli* in persons ⩾12 years old.

When these issues were taken into consideration, a consensus panel in the mid-1980s recommended against routine use of antibiotic prophylaxis for traveler's diarrhea [209], a position supported by this panel.

Chemoprophylaxis may be considered in healthy travelers for whom staying well is critical and in special-needs travelers in whom the risk for diarrhea is increased or the consequences of a diarrheal episode may be severe (B-III). Hosts at increased risk for acquiring diarrhea include those with achlorhydria, such as patients with late-stage AIDS, and those with immunodeficiency secondary to malignancy, transplantation, chemotherapy, or hypogammaglobulinemia [210]. Travelers at risk for complications of diarrhea are those with underlying chronic gastrointestinal disease (e.g., Crohn disease, ulcerative colitis, or chronic diarrhea), those with renal insufficiency or diabetes mellitus, or those who have advanced HIV infection, for whom an episode of *Campylobacter* species or *Salmonella* species diarrhea could be more severe [211]. Persons with ileostomies or colostomies may also have difficulty managing an episode of watery diarrhea in a resource-poor region. Although the very young, elderly individuals, and pregnant women might be considered to be at high risk, no data support the use of chemoprophylaxis, and the choice of an agent during infancy or pregnancy is difficult.

In healthy travelers, the importance to the traveler of staying well may be considered in deciding whether to suggest chemoprophylaxis. Critical travel might include certain business or political travel, select athletic events, and extreme travel. In some instances when there are large groups (e.g., Olympic teams), traveling with safe food and a dedicated cook might be preferable to the use of chemoprophylaxis.

When considering chemoprophylaxis, fluoroquinolone antibiotics remain the first choice (A-I). Antibiotics that are poorly absorbed or not absorbed are of interest, because they are generally well tolerated and do not have systemic adverse effects. Rifaximin is a poorly absorbed antibiotic that was released in the United States in 2004 for treatment of traveler's diarrhea caused by *E. coli* [212, 213]. There is limited data from Mexico demonstrating 72% protective efficacy in chemoprophylaxis [176], but it, as well as other antibiotics, have not been approved by the FDA for this indication.

Regimens for chemoprophylaxis of traveler's diarrhea (when it is indicated) are shown in table 6. If prescribed, chemoprophylaxis should be recommended for no more than 2–3 weeks, the time period studied in trials and a period short enough to minimize the risk of an adverse event caused by the antibiotic.

Treatment

Fluid replacement and diet. Given the difficulty in changing behavior to decrease the frequency of diarrhea during travel [163], the limited role of chemoprophylaxis, and the challenge of finding quality medical care in many resource-poor regions of the world, self-treatment has become the management paradigm of choice for travelers. Replacement of fluid losses has classically been the cornerstone of diarrhea treatment. However, traveler's diarrhea in adults is not usually dehydrating. When adult patients were treated with the antisecretory-antimotility drug loperamide (Imodium [McNeil]), the addition of oral rehydration solution to the regimen conferred no additional benefit, compared with the taking of fluids ad libitum [214]. This study did not address very young or elderly travelers or travelers in remote areas far removed from medical care for whom the risk of dehydration might be a more important consideration. Dehydrated infants and young children can restore hydration and maintain electrolyte balance by drinking fluids prepared with oral rehydration salts. These solutions may be obtained commercially throughout the world. In adults, a diet restricted to liquids and bland foods may not offer additional treatment benefit when diarrhea is also being treated with antibiotics [215].

Symptomatic therapy. Currently recommended medications for symptomatic relief of traveler's diarrhea are listed in table 6. Bismuth subsalicylate reduces the number of stools passed in traveler's diarrhea by ~50% [177, 216, 217]. It may be recommended in mild cases of diarrhea, but better agents exist for moderate-to-severe disease (B-I) [178]. When compared directly with loperamide for traveler's diarrhea, it has a longer onset of action, but it is more effective in treating nausea [178].

The opiates and diphenoxylate are effective as antimotility agents [218–220], but their use may be associated with CNS and other adverse effects, and they may be poorly tolerated in elderly persons. Therefore, loperamide has become the antimotility agent of choice (A-I) [178, 179, 220, 221]. Loperamide is more efficacious in controlling diarrhea than bismuth subsalicylate [178] and has an onset of action within the first 4 h after ingestion. When it is used in combination with an antibiotic, there may be rapid improvement of traveler's diarrhea [191, 192, 216, 222]. It appears to be safe in most types of diarrhea, as long as it is not used above the recommended dose, although we do not recommend using it when there is gross blood in the stool or temperature >38.5°C (e.g., in cases of dysentery) or in young children [179, 223, 224].

Agents that offer little or no relief are the kaolin pectin adsorbents and probiotics, such as *Lactobacillus* species [179, 225].

Antibiotics. Antibiotics are effective in the treatment of traveler's diarrhea and can reduce the average duration of disease from several days to ~1 day [160, 226]. Antibiotics that are recommended are listed in table 6 (A-I). Antibiotics that are no longer recommended because of drug resistance worldwide are the sulfonamides, neomycin, ampicillin, doxycycline,

tetracycline, trimethoprim alone, and TMP-SMX. Fluoroquinolones remain predictably active for empiric therapy in most parts of the world and remain the drugs of first choice. However, clinically important levels of resistance to fluoroquinolones among *Campylobacter* species and, to a lesser extent, among other enteropathogens have occurred, notably in Southeast Asia and the Indian subcontinent [206–208] but also in other regions [227–229]. This issue needs to be considered when prescribing self-treatment. Although there is some concern that fluoroquinolones, such as ciprofloxacin, are associated with transient musculoskeletal adverse effects in children [230], a growing body of evidence supports the pediatric use of ciprofloxacin, particularly for short-course treatment [231, 232]. In addition, ciprofloxacin has been approved by the FDA for use to treat complicated urinary tract infections in young children.

An alternative for the treatment of traveler's diarrhea in all destinations, and particularly for treatment in areas of fluoroquinolone resistance, is azithromycin (B-I). This drug is effective against *Campylobacter* species, as well as against the broad range of bacterial pathogens that cause traveler's diarrhea [16, 194, 233, 234]. Azithromycin is safe to use in children and pregnant women, although dosing data for the treatment of diarrhea in children are lacking, and the drug has not been studied specifically for this indication in pregnancy.

Rifaximin is an alternative to fluoroquinolones in the treatment of persons with afebrile, nondysenteric traveler's diarrhea [17, 184, 195, 212, 213, 235]. Attributes that make it attractive for use in diarrhea include limited absorption (<0.5% of an oral dose), a good safety record [235, 236], activity against a wide range of enteropathogens (especially when stool concentrations are compared with MICs) [237], and no other uses other than for enteric diseases. It is as effective as ciprofloxacin in the treatment of traveler's diarrhea when the predominant enteropathogen is ETEC [184]. However, rifaximin is not approved for the treatment of persons with diarrhea associated with fever or passage of bloody stools or when *Shigella, Salmonella,* or *Campylobacter* species are suspected pathogens [212].

Duration of Therapy

Although many clinical trials have studied 3 or more days of therapy with an antibiotic for the treatment of traveler's diarrhea, a single dose has been shown to be effective [16, 238], and in several head-to-head comparisons, has been shown to have equivalent efficacy to a 3-day course of antibiotics [15, 191, 192, 222, 239]. Concern has been raised, however, that severe diarrhea might be better treated with 3 days of therapy than with a single dose. With no firm data to guide the issue, we recommend providing travelers with 3 days of treatment and having them reevaluate themselves 24 h after beginning therapy (B-I). If patients are not totally well at 24 h, they are advised to complete a 3-day course of therapy or stop sooner if they are well.

Combination Therapy

The combination of an antibiotic with loperamide has been studied in a number of clinical trials to understand whether such a combination would decrease the duration of diarrhea, compared with single-agent treatments. A study of loperamide and TMP-SMX [15] demonstrated a 1-h median duration of diarrhea in the combination-treated group, compared with a 34-h median duration in those treated with TMP-SMX alone. Similar results were noted in a subsequent study of loperamide plus TMP-SMX [222], and the observation was extended to the combination of loperamide plus ofloxacin [191, 192]. There was no significant benefit of the combination loperamide plus ciprofloxacin when the placebo-treated comparison arm experienced relatively mild disease [185]. However, a strong trend favored the benefits of combination therapy in enterotoxigenic *E. coli* diarrhea early in the clinical course. Another study in which a *Campylobacter* species was the prevalent pathogen failed to reveal any benefit of combination therapy with loperamide and ciprofloxacin [186].

Practical Approach to Treatment of Traveler's Diarrhea

Opinions vary as to how travelers should use the available therapeutic agents. Because traveler's diarrhea is usually self-limiting, the cautious approach is to focus on fluid replacement and maintaining hydration as the cornerstone of therapy. Travelers can be instructed to use symptomatic treatment (e.g., antimotility therapy) when rapid control of symptoms is desired (e.g., during a lengthy ride on a bus without a toilet) and specific antimicrobial therapy when disease is moderate-to-severe or symptoms suggest an invasive pathogen. This committee prefers to offer older children and adults the option of treating disease with loperamide and an antimicrobial agent when there is no fever or blood in the stool (B-III). This regimen may lead to a rapid response and substantial reduction in the duration of diarrhea, an important goal for many travelers. Furthermore, available data suggest that most travelers will receive maximum benefit by a single dose of an antibiotic that may lessen the likelihood of adverse reactions to therapy. If combination therapy does not improve symptoms within a 48-h period or if symptoms worsen despite empiric therapy, travelers should seek medical consultation.

PREVENTION OF MALARIA IN TRAVELERS

Malaria is the most common preventable infectious cause of death among travelers and is the most frequent cause of fever in the returned traveler [240–242]. Approximately 1350 cases of malaria—more than one-half of which are due to the most

Table 7. Malaria chemosuppressive regimens according to geographic area.

Geographic area or country	Drug(s) of choice	Alternatives
Central America (west of the former Panama Canal Zone), Mexico, Haiti, Dominican Republic, most of the Middle East (chloroquine resistance reported in Iran, Oman, Saudi Arabia, and Yemen), states of the former Soviet Union, northern Africa, Argentina and Paraguay, and parts of China. These areas will have chloroquine-susceptible *Plasmodium falciparum.*	Chloroquine	Atovaquone-proguanil, doxycycline, mefloquine, primaquine, hydroxychloroquine
South America, including Panama east of the former Panama Canal Zone (except Argentina and Paraguay), Asia, Southeast Asia, sub-Saharan Africa, and Oceania. These areas will have chloroquine-resistant *P. falciparum.*	Atovaquone-proguanil, doxycycline, mefloquine	Primaquine
Rural, forested areas of the Thailand-Burma and Thailand-Cambodia borders; western provinces of Cambodia. These areas will have multidrug-resistant *P. falciparum.*	Doxycycline, atovaquone-proguanil	Primaquine

NOTE. See *Health Information for International Travel 2005–2006* [20] and the Centers for Disease Control and Prevention Traveler's Health malaria epidemiology site (http://www.cdc.gov/travel/regionalmalaria/) for details of risk areas. Risk may be focal in many countries.

severe form *P. falciparum*—and several deaths are reported annually to the CDC [9, 48, 243]. Most travelers who develop malaria do so because they use ineffective or no chemoprophylaxis or are not adherent to an appropriate chemoprophylactic drug regimen [9, 31, 48, 244, 245]. More than 75% of US civilians who developed malaria from 1999 through 2003 had taken no or inappropriate chemoprophylaxis [44–48]. In addition, travelers frequently fail to use personal protection measures. VFRs contribute extensively to imported malaria [246, 247], leading to a disproportionate incidence of malaria in this travel population [48]. Lastly, the past 2 decades have seen a deterioration in malaria control in many areas of endemicity, escalating drug resistance, and increasing reports of real or perceived adverse effects from antimalarials. Each of these issues contributes to the difficulties in adequately protecting travelers.

Travelers to malarious areas need to be aware of the risk of malaria and to understand that it is a serious infection, to know how to prevent it by avoiding mosquito bites and complying with antimalarial drug regimens, and to seek medical attention urgently should they develop a fever during travel or within several months to 1 year or more after return. This approach has been termed the A, B, C, D of malaria prevention: A for awareness of risk, B for bite avoidance, C for compliance with chemoprophylaxis, and D for prompt diagnosis [248]. When considering prevention, most efforts are aimed at preventing *P. falciparum* malaria, because this species causes the most clinically severe disease, may progress to a life-threatening condition within hours, and is associated with widespread drug resistance.

Risk assessment. Risk assessment for malaria requires a detailed knowledge of the traveler's itinerary. The risk depends on the geographic area to be visited (table 7 and figures 1 and 2), the type of accommodation (e.g., open air, tented, air conditioned, or screened), duration of stay, season (rainy vs. dry), elevation, and efficacy of and adherence to preventive measures.

Prevention of mosquito bites. All travelers to areas in which malaria is endemic should be instructed regarding methods to prevent bites from *Anopheles* mosquitoes, which feed between dusk and dawn [249]. Such measures include using insect repellents containing DEET [250], staying in well-screened or air-conditioned rooms, sleeping within insecticide (e.g. permethrin)–impregnated bed nets [251], and wearing clothing that reduces the amount of exposed skin. DEET, when used appropriately, is safe for infants and children over the age of 2 months. Percentages of DEET considered by this committee to provide a sufficient duration of protection are 20%–50% and should protect travelers for $\geq$4 h (B-II); lower percentages will provide a shorter duration of protection. Picaridin, a synthetic repellent, has been shown to be effective and often comparable to DEET in clinical trials [252–255]. A 7% formulation of picaridin was recently released in the United States; however, this is a lower concentration than that employed in most of the trials (~20%) [256]. Clothing may be treated with residual insecticides, such as permethrin [249]. Mosquito coils may be burned or vaporizing mats employed in enclosed spaces. The efforts made to prevent the bites of *Anopheles* mosquitoes will also be effective in reducing bites from other mosquito species, sandflies, and ticks.

Use of antimalarial chemoprophylaxis. When considering antimalarial drugs, their potential adverse effects must be weighed against the risk of acquiring malaria and the traveler's

Figure 1. Map of malaria epidemiology in the Americas. Delineation is made between areas with chloroquine-susceptible *Plasmodium falciparum* malaria and chloroquine-resistant *P. falciparum* malaria. The map is courtesy of the Centers for Disease Control and Prevention and is used with permission.

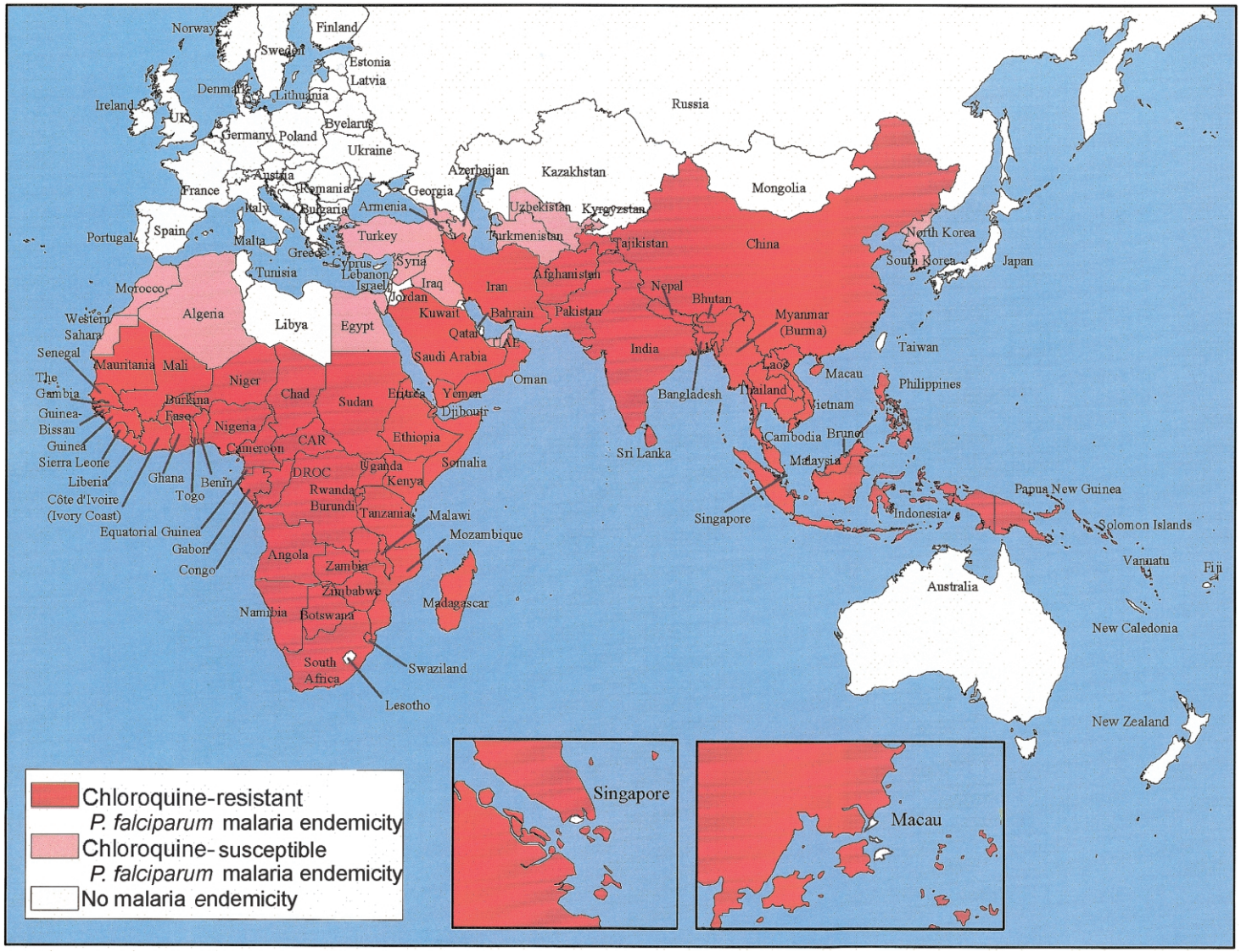

Figure 2. Map of malaria epidemiology in Africa, the Middle East, and Asia. Delineation is made between areas with chloroquine-susceptible *Plasmodium falciparum* malaria and chloroquine-resistant *P. falciparum* malaria. Areas with multidrug-resistant *P. falciparum* malaria may be found in the forested regions of Thailand that border Burma and Cambodia and in the western regions of Cambodia. The map is courtesy of the Centers for Disease Control and Prevention and is used with permission.

access to prompt, reliable medical care. Therapy with antimalarial drugs should be started prior to travel, and the drugs should be taken regularly during exposure and for a period of time after leaving an area in which malaria is endemic. The following questions must be addressed before prescribing an antimalarial drug:

- Is the traveler at risk of malaria?
- Is travel in an area with drug-resistant *P. falciparum* malaria?
- Will the traveler have access to reliable medical care in the event that symptoms of malaria occur?
- Are there any contraindications to the use of a particular antimalarial drug?

With careful discussion of these topics with the traveler, a safe and effective drug can usually be chosen.

Travelers to the following areas should generally take an antimalarial drug (table 7 and figures 1 and 2): urban and rural risk areas of sub-Saharan Africa (except most of South Africa) and Oceania (including Papua [Indonesian New Guinea], Papua New Guinea, and Vanuatu), India, Bangladesh (except Dhaka), Pakistan, Nepal (Terai region), and Haiti; travelers with evening or overnight exposure in rural, nonresort areas of Southeast Asia, Central and South America, and certain parts of Mexico, North Africa, and the Dominican Republic should also take an antimalarial drug. Because of the variation in malaria risk within regions and countries, the specific itineraries should be examined using maps, CDC publications [20], and the CDC Web site (http://www.cdc.gov/travel/).

Chloroquine-resistant *P. falciparum* (CRPF) malaria is now widespread in all areas of the world in which malaria is endemic, except for Mexico, Hispaniola (Haiti and the Dominican Republic), Central America west and north of the Panama Canal, and parts of North Africa, the Middle East, and China (figures 1 and 2). *P. falciparum* strains resistant to chloroquine, mefloquine, and sulfonamides are rare and confined to the regions of Thailand that border Burma and Cambodia, the eastern provinces of Burma, and the western provinces of Cambodia. Travelers infrequently visit these areas, except for Siem Reap in Cambodia. Chloroquine-resistant *Plasmodium vivax* is widespread in Papua and Papua New Guinea and has been documented in Vanuatu, Burma, Colombia, and Guyana [257–262].

Table 8 delineates antimalarial drugs according to geographic area.

Early diagnosis and treatment if fever develops during or after travel. Because many health care providers in industrialized countries are unfamiliar with the diagnosis and management of malaria, all travelers should be well informed about the disease and become advocates for their own care. They should understand that no antimalarial drug guarantees complete protection and that fever during or after travel (particularly in the first 2 months after travel, but as long as 6 months to 1 year after return) is a medical emergency requiring urgent assessment by a health care practitioner. Travelers should understand that, in the case of fever, they should be evaluated and tell the health care provider about their travel (if they are being seen after return). Ideally, they should have thick and thin blood films repeated twice (12–24 h apart) if the initial films have negative results. Long-stay travelers, in particular, should be made aware that local laboratories in developing countries, especially in Africa, have an unduly high rate of false-positive malaria diagnoses [263]. A traveler who develops malaria during a trip should be advised to immediately seek expert medical advice concerning therapy. Travelers will need to continue prophylaxis if they remain in malarious areas. Because chemoprophylactic agents (with the exception of primaquine) do not eradicate the dormant hypnozoites of relapsing malaria (*P. vivax* and *Plasmodium ovale*), it is not uncommon for these species to present many months after departure from a malarious area, in spite of adherence to standard regimens [264]. Although <1% of cases of *P. falciparum* malaria will occur >6 months after return, nearly 15% of cases of *P. vivax* malaria occur after this interval [48].

Chemoprophylactic Regimens: Standard Antimalarial Drugs

Chloroquine. Chloroquine is the drug of choice for travel to areas in which chloroquine resistance has not been described or is minimal. Except for its bitter taste, it is usually well tolerated; it may cause nonallergic generalized pruritus in individuals of African descent [265]. It is safe to use in pregnancy. US authorities no longer recommend the addition of daily proguanil to a weekly regimen of chloroquine, because the efficacy of this combination for treating CRPF malaria is inferior to that of alternative regimens [266–268]. Mouth ulcers may occur in more than one-third of chloroquine-proguanil users [269].

Atovaquone-proguanil. Atovaquone-proguanil (Malarone [GlaxoSmithKline]) is one of 3 drugs of choice for travelers to regions with CRPF malaria; the other 2 are doxycycline and mefloquine [20]. Atovaquone [270], a ubiquinone analog that selectively inhibits parasite mitochondrial electron transport, acts synergistically with proguanil (a dihydrofolate reductase inhibitor) against chloroquine-susceptible, chloroquine-resistant, and multidrug-resistant *P. falciparum* isolates (such as may be found in forested border areas of Thailand, western Cambodia, and eastern Burma), as well as other malaria species. Both proguanil and atovaquone are causally prophylactic (acting on the pre-erythrocytic hepatic phase) for all species of malaria, but they do not prevent hypnozoite formation by *P. vivax* or *P. ovale* [271–273].

Atovaquone-proguanil has been formulated as a fixed drug combination with both adult and pediatric preparations (table 8). The drug is taken daily beginning 1–2 days prior to exposure, during exposure, and for 1 week after exposure.

Early prevention trials demonstrated almost 100% protective

Table 8. Antimalarial drugs for prophylaxis and self-treatment.

Generic name	Trade name	Tablet size	Adult dosage	Pediatric dosage	Adverse effects
Prophylaxis					
Chloroquine phosphate	Aralen[a]	500 mg salt (300 mg base)	One tablet orally once per week; begin 1 week before travel and continue for 4 weeks after travel	8.3 mg per kg of body weight salt (5 mg per kg of body weight base) orally once per week	May exacerbate psoriasis; common adverse effects include bitter taste, headache, pruritus in persons of African descent; occasional adverse effects include skin eruptions, reversible corneal opacity, transient visual blurring, and partial alopecia; rare adverse events include retinopathy (>100 g base total dose), blood dyscrasias, nail and mucous membrane discoloration, nerve deafness, myopathy, and photophobia
Hydroxychloroquine	…	200 mg salt (155 mg base)	2 tablets orally once per week, as for chloroquine	6.5 mg per kg of body weight salt (5 mg per kg of body weight base) orally once per week (maximum 310 mg base)	As for chloroquine
Atovaquone-proguanil	Malarone[b]	250 mg atovaquone and 100 mg proguanil (adult tablet); 62.5 mg atovaquone and 25 mg proguanil (pediatric tablet)	One tablet orally once daily; begin 1–2 days before travel and continue for 7 days after travel	Body weight 11–20 kg, 1 pediatric tablet daily; body weight 21–30 kg, 2 pediatric tablets daily; body weight 31–40 kg, 3 pediatric tablets daily; body weight ⩾41 kg, 1 adult tablet daily	Take with food; do not use in persons with creatinine clearance <30 mL/min; common adverse events include nausea, abdominal pain, and headache; occasional adverse events include transient increase in transaminase levels with treatment doses; rare adverse events include rash
Doxycycline	…	100 mg	One tablet orally once daily; begin 1–2 days before travel and continue for 4 weeks after travel	⩾8 years old, 2 mg per kg of body weight orally once daily (maximum dosage, 100 mg/day)	Stains teeth in children <8 years old and fetuses; should be taken in upright position to avoid esophageal irritation; common adverse events include GI upset, photosensitivity, and *Candida* vaginitis; rare adverse events include allergic reactions, blood dyscrasias, azotemia in renal disease, and esophageal ulceration
Mefloquine	Lariam[c]	250 mg salt (228 mg base)	One tablet orally once per week; begin 1 week before travel and continue for 4 weeks after travel	Body weight ⩽9 kg, 5 mg salt per kg weekly; body weight 10–19 kg, one-quarter tablet; body weight 20–30 kg, one-half tablet; body weight 31–45 kg, three-quarters tablet; body weight ⩾46 kg, 1 tablet	Contraindicated in patients with active depression, history of psychosis, seizure disorder, or cardiac conduction abnormality; common adverse events include dizziness, nausea, diarrhea, headache, nightmares, insomnia, and mood alteration; rare adverse events include seizures and psychosis
Primaquine	…	26.3 mg salt (15 mg base)			Hemolysis with G6PD deficiency; take with food; common adverse events include GI upset
For presumptive antirelapse therapy (terminal prophylaxis)			2 tablets orally once daily for 14 days	0.8 mg per kg of body weight salt (0.5 mg per kg of body weight base) orally once daily for 14 days	
For primary prophylaxis			2 tablets orally once daily; begin 1–2 days before travel and continue for 7 days after travel	0.8 mg per kg of body weight salt (0.5 mg per kg of body weight base) orally; begin 1–2 days before travel and continue for 7 days after travel	
Self-treatment					
Atovaquone-proguanil	Malarone[b]	250 mg atovaquone and 100 mg proguanil (adult dose)	4 tablets orally once daily (can be divided into 2 doses) for 3 days	body weight 5–8 kg, 2 pediatric tablets for 3 days; body weight 9–10 kg, 3 pediatric tablets for 3 days; body weight 11–20 kg, 1 adult tablet for 3 days; body weight 21–30 kg, 2 adult tablets for 3 days; body weight 31–40 kg, 3 adult tablets for 3 days; body weight ⩾ 41 kg, 4 adult tablets for 3 days	Take with food; do not use in persons with creatinine clearance <30 mL/min; common adverse events include nausea, abdominal pain, and headache; occasional adverse events include transient increase in transaminase levels; rare adverse events include rash

NOTE. G6PD, glucose-6-phosphate dehydrogenase; GI, gastrointestinal.

[a] Abbott Laboratories.
[b] GlaxoSmithKline.
[c] Roche.

efficacy against *P. falciparum* in semi-immune children and adults in Kenya, Zambia, and Gabon [274–277]. In 2 tolerability studies in nonimmune travelers, atovaquone-proguanil was found to be very effective by the use of surrogate markers [278, 279]. The efficacy in nonimmune hosts has been corroborated by other studies [280–282].

Atovaquone-proguanil has an excellent safety profile and is well tolerated [283]. In the tolerability studies involving nonimmune travelers, the drug was well tolerated; it was discontinued because of adverse effects significantly less often than was mefloquine (0.2%–1.2% for atovaquone-proguanil vs. 5% for mefloquine) [278, 279]. The most frequent adverse effects of atovaquone-proguanil during trials among travelers were gastrointestinal upset, insomnia, headache, rash, and mouth ulcers [278, 279, 284]. Atovaquone-proguanil is contraindicated in those with renal insufficiency and a creatinine clearance <30 mL per min, and it is not recommended for use in pregnant women.

Mefloquine. Mefloquine is effective in preventing malaria of all species, including CRPF; however, it will not prevent multidrug-resistant *P. falciparum* malaria. In chemosuppressive doses, mefloquine is usually well tolerated; however, adverse neuropsychiatric reactions are well recognized. The FDA, in cooperation with the manufacturer of mefloquine, Roche Pharmaceuticals, has mandated that a drug information document be provided to all travelers who are prescribed mefloquine [285].

Between 25% and 40% of travelers experience adverse effects from mefloquine; most of the adverse effects are mild, self-limited, and do not require discontinuation of the drug [266, 267, 284, 286, 287]. The most frequent mild adverse effects are gastrointestinal upset, strange dreams, mood changes, insomnia, and headache. Troublesome, disabling neuropsychiatric adverse events (e.g., anxiety, depression, nightmares, paranoid ideation, and dizziness) requiring discontinuation of treatment with the drug and medical attention are reported in ~5% of users [284, 288, 289]. One recent study demonstrated that the rate of discontinuation of mefloquine prophylaxis was similar to that for other recommended antimalarials [284]. Severe neuropsychiatric reactions (e.g., seizures and psychosis) are rare, and they have been reported in 1 individual per 10,000–13,000 patients receiving mefloquine [266, 267, 290]. Adverse effects appear to be more common among women and less frequent among children [291, 292]. Excessive alcohol use has been implicated as a cofactor in 1 case report [293].

Most adverse effects that might require discontinuation of prophylaxis with the drug occur within the first 3 doses. Approximately 40% of adverse events will occur following the first dose, and nearly 80% of adverse events will have occurred after the third dose [294, 295]. When there is a question as to whether mefloquine will be tolerated, prophylaxis with the drug may be initiated several weeks prior to exposure to allow for a change to a suitable alternative, if necessary.

Contraindications to mefloquine include known hypersensitivity to the drug, a history of convulsions or a major psychiatric disorder, and a recent history of depression or anxiety reaction [296]. It should be used with caution in persons with cardiac conduction disorders. Mefloquine is a category C drug for pregnant women; however, if travel to areas where CRPF is found cannot be avoided during pregnancy, based on limited data [297–301], the drug may be administered safely during the second and third trimesters and can probably also be administered during the first trimester (B-III).

For travelers who are departing on short notice, mefloquine has been given with a loading dose of 250 mg per day for 3 days followed by weekly administration [286, 302]. This loading dose rapidly achieves steady-state blood levels, but it may not be well tolerated, is not widely used, and is an off-label use in the United States [286, 303].

Doxycycline. Doxycycline is effective in preventing all species of malaria and, like atovaquone-proguanil, prevents multidrug-resistant *P. falciparum* infection [304]. Doxycycline has equivalent efficacy to mefloquine in comparative trials in Papua and Africa [268, 305]. Treatment with the drug is initiated 1–2 days before exposure and is administered daily thereafter until 4 weeks after departure from a malarious area. Noncompliance with this daily regimen is an important reason for doxycycline prophylaxis failure [306].

Doxycycline is usually well tolerated, but it may be associated with gastrointestinal upset (with esophageal ulceration in rare cases), an idiosyncratic photosensitivity reaction due to ultraviolet A radiation, and vaginitis due to *Candida* species [284, 307–309]. The drug should be taken while upright with fluids and food and, preferably, not taken just prior to reclining at bedtime; a sunscreen that blocks UV rays should be used when there is sun exposure. Women at risk for *Candida*-associated vaginitis should carry antifungal self-treatment, such as fluconazole (administered in a single 150-mg dose). Doxycycline is contraindicated in pregnant women and in children <8 years of age because of effects on teeth.

Chemoprophylactic Regimens: Alternative Antimalarial Drugs

Primaquine. Primaquine is an 8-aminoquinoline that has been used for decades to prevent relapses from the hypnozoite form of *P. vivax* and *P. ovale,* either during treatment of clinical cases (radical cure) or as presumptive antirelapse therapy (terminal prophylaxis) following heavy exposure to these parasites. Recent studies have demonstrated primaquine to be a very effective and safe (in individuals with normal glucose-6-phosphate dehydrogenase [G6PD] levels) chemoprophylactic agent (reviewed in [310] and [311]). It is a causal prophylactic that has activity against the exoerythrocytic tissue stage of malaria,

eliminating *Plasmodium* infections during their development phase in the liver and, thereby, preventing symptomatic infection. It is effective against CRPF. In randomized, double-blind, placebo-controlled trials involving both partially immune and nonimmune subjects for up to 50 weeks, primaquine showed protective efficacy of 85%–95% against *P. falciparum* and *P. vivax* infections in Kenya, Indonesia, and Colombia [268, 312–314].

The limited effectiveness of a 15-mg dose (base) of primaquine in achieving radical cure or as effective, presumptive antirelapse therapy for infection due to *P. vivax* is now well recognized [310, 315] and has led to an increase in the dose of primaquine to 30 mg per day for adults [20, 311]. Treatment with the drug should be initiated 1 day before exposure, administered daily during exposure, and may be discontinued 7 days after departure from a malarious area. The drug is generally well tolerated but may cause gastrointestinal upset that can be decreased by taking it with food. Because primaquine can cause oxidant-induced hemolytic anemia in those with G6PD deficiency, a G6PD level must be determined for all persons prior to being prescribed this drug. If the patient has G6PD deficiency, the drug should not be used. The drug is contraindicated during pregnancy, as the G6PD status of the fetus cannot be determined.

Tafenoquine. Tafenoquine is a new investigational 8-aminoquinoline with a prolonged half-life that is in clinical trials both as a weekly and as a monthly dosed chemoprophylactic agent [316, 317]. Although the drug appears to be well tolerated and, compared with primaquine, has the advantage of a longer dosing interval when taken for prophylaxis, it is a potent oxidizing agent and must not be given to persons with G6PD deficiency. It is currently not available for clinical use in any country.

Self-Diagnosis

Over the past decade, rapid diagnostic tests for malaria, based on *Plasmodium* lactate dehydrogenase and histidine-rich protein II plasmodial antigens, have been shown to be highly sensitive (90%–100%) and specific (95%–100%) [318]. However, when these tests have been used by travelers for self-diagnosis in the field, the rate of false-negative results has been unacceptably high [319]. This is likely due to the complexity of the test procedure, inadequate instructions, and the difficulty in performing the test in the field while ill. Clearer instructions result in improved sensitivity and specificity when the test is performed by travelers under controlled conditions [320]. Rapid diagnostic tests for malaria are not approved in the United States but are available in Canada and in some countries of Europe. Nevertheless, they are not currently recommended for use by travelers for self-diagnosis.

Stand-By Self-Treatment

In a number of European countries, notably Switzerland and Germany, chemoprophylaxis may not be recommended for low-risk malarious areas, such as India, Thailand, and parts of Latin America. European experts argue that, in these situations, the risk of adverse events from antimalarials is greater than the risk of malaria [321, 322]. Instead, antimalarial prophylaxis is not employed, and a self-treatment regimen of atovaquone-proguanil or artemether-lumefantrine is recommended when a febrile illness occurs and medical care is not available within 24 h. Because of the inconsistent and inappropriate use of self-treatment regimens, the North American approach is to recommend antimalarial prophylaxis whenever there is a risk of malaria, and this approach is supported by this committee (A-III) [20, 302]. When consideration is given to self-treatment alone, expert opinion should be sought.

OTHER CONSIDERATIONS

Access to Medical Care

It is not uncommon for illness to occur overseas, and as many as 8% of travelers will seek medical care for these events [56, 86]. Accessing medical care can be difficult, and travelers should be given guidelines as to how to locate reliable care. US embassies and consulates, although not facilitating medical care, can provide a list of recommended physicians. Several of the commercial database programs will list health care facilities, and there are services to which travelers can subscribe that will list overseas health professionals. Travel health insurance companies will often have preferred providers in foreign countries, and they can arrange for payment for medical services and air evacuation, if necessary. Travelers should be encouraged to take out supplemental travel health and evacuation insurance. The Appendix gives suggested resources, and the US Department of State lists doctors and hospitals abroad (http://www.travel.state.gov/travel/tips/health/health_1185.html). Travelers who have a history of anaphylaxis to medications, foods, or insect bites should carry with them antihistamine preparations and an injectable epinephrine product.

Safety, Behavior, and Injury Prevention

Injuries are the leading cause of preventable death among travelers and are among the leading causes of death and disability worldwide; road traffic accidents account for the majority of injury-related deaths [240, 323–325]. Male travelers 15–44 years old are at particularly high risk for injury. Road traffic injuries also involve pedestrians; in fact, 65% of traffic-related deaths and injuries occur among pedestrians [326]. Countries in SE Asia account for more than one-third of deaths from road traffic injuries, and Africa has the highest case rate: 28 deaths per 100,000 population [325, 327]. Travelers should be aware of the difficulties of driving overseas, where there may be dif-

ferent traffic patterns, poorly maintained roads, and lack of vehicle safety features, such as seat belts and child restraints [328–330]. They should avoid road travel at night and mixing alcohol with driving; they should wear helmets when riding bicycles or mopeds and motorcycles. Injuries caused by fire, falls, poisoning, drowning, and animal bites are also important causes of travel-related morbidity.

Intentional injuries caused by violence, political and civil conflicts, and terrorist activities should be discussed with all travelers [331]. Being vigilant, avoiding risk situations, and accessing up-to-date safety information from the US Department of State Web site (http://travel.state.gov/) concerning risk destinations are helpful measures.

Because of the risk of acquiring STIs (including HIV infection) from sexual experiences overseas, travelers should be either abstinent or use barrier protection, realizing that barrier methods are not 100% effective (A-III) [332]. Travelers who anticipate having sex should carry their own condoms, because the quality of condoms in some destinations may be substandard [333]. Alcohol remains a key risk factor, both for the occurrence of accidents and injuries and for engaging in unsafe sexual practices. In addition, use of alcohol or illegal substances may increase the risk of assault or arrest and incarceration.

Travelers need to be aware of the risks of blood-borne infections (e.g., HIV, hepatitis B virus, and hepatitis C virus infections) from unprotected sexual contact and from the use of contaminated needles [124], syringes, and other medical or dental devices (e.g., as the result of emergency dental care, injections, tattooing, facial and head shaving, and transfusions).

Travel and Environmental Illness

Travelers should apply sunscreens with a sun protection factor of at least 15 prior to sun exposure and in sufficient quantities to achieve protection [334]. If sun exposure is ongoing, sunscreens should be reapplied at ~2 h intervals and also after swimming or profuse sweating.

Medications to prevent motion sickness are best taken prior to beginning a journey. For long-term control, such as might be needed on a sailing expedition or when frequent bus trips are taken, sustained release, transdermal scopolamine (Transderm Scop [Novartis]) may be applied. Oral scopolamine preparations are also available [335]. Scopolamine can cause drowsiness and drying of mucous membranes; it is contraindicated in persons with glaucoma or urinary obstruction. Medications for short-term prevention are dimenhydrinate and meclizine. Phenergen may be taken for severe nausea but is highly sedating.

Jet lag, which is associated with travel across multiple times zones (usually ⩾5 time zones), occurs because the normal circadian rhythm is disrupted. It is characterized by symptoms of fatigue, impaired sleep, loss of concentration, and impaired performance [336]. Generally, travel eastward is associated with more symptoms and takes longer to adapt to than westward travel. Several methods have been used to alleviate symptoms and to allow adjustment to the new time zone more rapidly than the typical adjustment time of 1 day per h of time zone change. Exposure to bright light, short-acting hypnotics, and melatonin have each been advocated. If hypnotics, such as the benzodiazepines or benzodiazepine receptor agonists (e.g., zolpidem [337]), are used, they should be tried before travel and taken in the lowest effective dose. They may be taken for the first few nights in the new time zone and may help to alleviate the exhaustion from failure to sleep. In general, sedatives should be avoided during flight, unless the traveler can be assured of uninterrupted rest throughout the duration of drug activity.

Several randomized, controlled trials have demonstrated the efficacy of melatonin (reviewed in [338]). It may be taken at bedtime (10 P.M. to midnight) in a dose of 2–5 mg beginning on the night of arrival and for several nights thereafter. However, because it is listed as a "dietary supplement" and not a drug, it is not subject to the FDA approval process, and over-the-counter preparations may be contaminated with impurities [339]. Its use is not advocated by all authorities [336].

The concept of "fitness to fly" is an emerging one that balances the medical risks of air travel with an assessment of whether an individual can safely undertake a flight [336, 340, 341]. Of medical risks during travel, DVT, with the risk for fatal pulmonary embolism, has been an increasingly recognized complication of long-haul flights that typically last for 6–10 h or more. DVT appears to occur most commonly among individuals with additional risk factors [342]. DVT may affect as many as 3% of travelers with cardiovascular risk factors [343]; the use of oral contraceptive pills [344], recent surgery, and active malignancy may also increase risk [345]. Pulmonary embolism occurs in 1–2 cases per million flights >5000 km [346].

Sensible measures to decrease risk include avoiding prolonged immobility, not wearing constrictive clothing around the waist or lower extremities, exercising the calf muscles, maintaining hydration, and limiting alcohol ingestion (A-III) [345]. The use of below-the-knee support stockings may help to decrease the risk of DVT in those who are predisposed to the condition (B-II) [343, 347]. Aspirin is not felt to provide sufficient reduction in the incidence of DVT, compared with its potential for dangerous adverse effects, and, therefore, is not recommended [336, 345]. Low molecular weight heparin may decrease the incidence of DVT among high-risk travelers (B-I) [336, 348], but its use should be carefully considered on an individual basis.

High altitude illness. Travel to destinations more than 2500–3500 m (8200–11,500 feet) in altitude, such as Cusco, Peru (3300 m), La Paz, Bolivia (3450 m), Lhasa, Tibet (3750 m), the Everest base camp in Nepal (5500 m), or Aspen, Col-

orado (2400 m), carries the risk of altitude illness. This disease can be divided into 3 syndromes: acute mountain sickness (AMS), high-altitude cerebral edema (HACE), and high-altitude pulmonary edema (HAPE). There appears to be individual susceptibility to developing altitude illness, but it is not possible to predict who will have problems in the absence of previous travel to altitude. Travelers with underlying cardiac, pulmonary, or hematologic disease should be carefully evaluated for their ability to travel safely to high altitude destinations.

There are several factors that can contribute to developing high-altitude illness: rate of ascent, altitude achieved, and altitude at which the traveler sleeps. Thus, rapid ascent above 3000 m with failure to adequately acclimatize as further altitudes are reached carries a high likelihood of illness. Overall, ~25% of those who ascend to moderate altitude (1900–3000 m) [349], ~50% of trekkers who walk to altitudes >4000 m in 5 days [350], and as many as 80% of those who fly directly to destinations >3750 m in altitude [351] will develop AMS.

AMS usually occurs within the first 12 h at high altitude and is characterized by headache with anorexia, fatigue, dizziness, and sleep disturbance. These symptoms may resolve spontaneously over a few days if further ascent is not attempted. AMS can progress to more-severe manifestations—HACE and HAPE—which can be fatal if not treated promptly. HACE is usually preceded by AMS; persons with HACE have poor concentration and lethargy, progressing to ataxia, altered consciousness, and coma, with death resulting from brain herniation. HAPE is heralded by dry cough and shortness of breath with exertion, progressing to shortness of breath at rest and production of pink, frothy sputum as pulmonary edema occurs.

The key to prevention of AMS is acclimatization: spending a few days at an intermediate altitude of <3000 m and then gradually ascending >3000 m with the increase in sleeping elevation not exceeding 300–500 m (1000–1500 feet) per night [352–354]. For every 1000 m ascended, an extra night should be spent at the same elevation.

The most studied drug for prevention has been acetazolamide (Diamox [Lederle]), a carbonic anhydrase inhibitor that may facilitate acclimatization by increasing ventilation (particularly at night), increasing bicarbonate diuresis following the respiratory alkalosis at altitude, and increasing arterial oxygen levels. Although there is no agreement on the optimal dosage [355], many practitioners accept a dose of 125–250 mg twice daily, begun 1 day before ascent and continued for at least 2 days at the highest altitude (B-I) [353, 354, 356–358]. Those taking acetazolamide may experience circumoral and finger paraesthesias and a mild diuresis; carbonated beverages may have a poor taste. The drug should not be used in persons allergic to sulfonamides.

Dexamethasone should usually be reserved for treatment of severe cases of altitude illness [359]. Nifedipine may be effective in preventing a recurrence of HAPE, but it should only be used by experienced practitioners [360, 361]. There are limited data on the efficacy of *Ginkgo biloba* (reviewed in [353]), and a recent trial did not demonstrate a benefit of prophylactic use in high-altitude (to nearly 5000 m) trekkers in Nepal [358]. In a small study, sildenafil increased maximum workload and cardiac output at high altitude, but at present, there is insufficient experience with the drug to currently recommend it [362].

For mild AMS, one should avoid further ascent and see if symptoms resolve. Oral analgesics may be helpful, and acetazolamide in a dose of 250 mg twice daily has been effective [363]. In the absence of improvement or with progression to HACE or HAPE, the first response should be to descend; sometimes a descent of as little as 500–1000 m may be life-saving. Although oxygen, hyperbaric chambers, acetazolamide, dexamethasone, and nifedipine have been used for the various conditions of high altitude illness, none of these are a substitute for descent, and they should only be prescribed by experienced practitioners in consultation with their mountaineer travelers.

POST-TRAVEL MEDICAL CARE

Travel medicine practitioners may frequently evaluate ill returned travelers. Both the consensus statement by Canadian travel medicine experts [33] and the body of knowledge developed by the ISTM [42] state that an extensive knowledge of tropical disease is not required to practice travel medicine. The Canadian panel recommended that "all post-travel consultations should be managed by a physician and should include the following: recognition of any travel-related illness, and timely medical assessment, with referral if required" [33, p.4]. Therefore, all practitioners should be able to recognize key syndromes in the returned traveler. For those without the required expertise to treat ill returned travelers, it is important that they have pre-established referral links with qualified specialists and specialty diagnostic services that will expedite care of patients in need of prompt evaluation.

The most common syndromes in returned travelers are diarrhea, respiratory tract illness, skin conditions, and fever [56, 86]. In a study of nearly 800 returned US travelers, diarrhea occurred in 13%, upper respiratory tract infections in 10%, skin rash in 3%, and fever in 2% [56]. Sixty-five percent of illnesses had their onset after return, and overall, 12% of travelers sought medical care for them after arriving home.

The following should be considered when formulating a differential diagnosis: the geographic location(s) visited, the traveler's activities, the frequency of specific diseases in the region(s), the incubation periods of potential pathogens, and the vaccines and other prophylactic measures that were used [41, 364–366]. Many common bacterial and viral infections have short incubation periods and will have their onset either abroad or within the first week or 2 of return. Diseases with longer

incubation periods, such as giardiasis and amebiasis, viral hepatitis, malaria, and tuberculosis, may present weeks to months after return.

A recent study from the GeoSentinel surveillance network examined illness in travelers who had returned from widely dispersed global destinations and presented to tropical and travel medicine centers throughout the world [5]. In addition to defining the most common syndromes in travelers who present for medical evaluation (fever, acute and chronic diarrhea, skin disorders, and respiratory illness), their study also helped to elucidate region-specific diagnoses; travelers often act as a window into the diseases endemic in their countries of travel [367]. Thus, *P. falciparum* malaria in travelers tends to originate from sub-Saharan Africa (particularly West Africa), rickettsial illness (African tick-bite fever) from southern Africa, dengue from the Caribbean and southeast Asia, cutaneous leishmaniasis from Central and South America, and typhoid fever from South Asia. Knowing which diseases are most common among travelers visiting specific destinations can help narrow a differential diagnosis.

Both general and disease-specific testing will need to be performed to establish a diagnosis in many cases. Most travelers with systemic syndromes will need a complete blood cell count (with an eosinophil count that may indicate systemic helminth infection), liver enzyme tests, and a test of renal function. If there are respiratory complaints, a chest radiograph may be indicated. Certain travelers with respiratory symptoms may also merit a tuberculin skin test, particularly long-stay travelers returning from areas in which disease is endemic and health care workers [122]. Many cases of diarrhea in returned travelers may be treated empirically; however, in other cases, diarrheal stools should be tested for blood and cultured for enteropathogens, particularly when patients present with fever, tenesmus, or gross blood in the stool. In these cases, empiric treatment with a fluoroquinolone or azithromycin can be considered while awaiting stool culture results and adjusted as necessary when culture results are received. If diarrhea has lasted for 10 days to 2 weeks or longer, antigen detection for *Giardia* and *Cryptosporidium* species and, depending upon the clinical history, examination of stool samples for ova and parasites is appropriate. Some travelers with prolonged diarrhea will no longer have an infectious etiology but will have developed a postinfectious irritable bowel syndrome [153, 154, 368].

Febrile illness warrants immediate attention, because it may be due to malaria or another potentially life-threatening pathogen. Common factors contributing to death from malaria are failure of the patient to comply with the correct chemoprophylaxis and failure of the physician to consider the diagnosis early in the course [9]. Persons who present with fever who have visited regions in which malaria is endemic should be evaluated with thick and thin blood smears; if available, antigen detection assays may be used to supplement the diagnosis. If initial smear results are negative and the diagnosis remains a consideration, the blood smears should be repeated. Other etiologies for febrile syndromes include dengue, acute HIV syndrome, leptospirosis, acute schistosomiasis, and enteric fever caused by *S.* Typhi or *S.* Paratyphi. Obtaining an acute-phase serum sample for testing at a later date may be helpful in characterizing illness.

Skin problems may present as discrete lesions (e.g., cutaneous leishmaniasis, cutaneous larva migrans, tungiasis, myiasis, or pyoderma following infection of insect bites) [369, 370]. A skin lesion may also indicate a systemic syndrome: an eschar can herald African tick typhus (caused by *Rickettsia africae*), or a chancre can indicate East African trypanosomiasis caused by *Trypanosoma brucei rhodesiense.* Systemic rashes may be seen with dengue, chikungunya virus, acute HIV infection, and measles.

Travelers with respiratory illness will usually complain of nonspecific upper respiratory symptoms or pharyngitis [371]. However, some will have lower respiratory tract infections with pneumococcal pneumonia, legionellosis, influenza, and tuberculosis. In the current global situation of avian influenza, travelers who return from areas of endemicity with fever and respiratory symptoms and have had an exposure within 10 days to diseased birds or persons with possible avian influenza should be evaluated by specific protocols that can be found on the CDC avian influenza Web site (http://www.cdc.gov/flu/avian/).

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APPENDIX

Travel medicine textbooks and print resources:

Auerbach PS, ed. Wilderness medicine. 4th ed. St. Louis, MO: C.V. Mosby, **2001**

Bia FJ, ed. Travel medicine advisor. Atlanta: American Health Consultants, **2006**

Bia FJ, Hill DR, eds. Travel and tropical medicine. Infect Dis Clin North Am **2005**; 19:1

DuPont HL, Steffen R, eds. Textbook of travel medicine and health. 2nd ed. Hamilton, Ontario: B.C. Decker, **2001**

Ericsson CD, DuPont HL, Steffen R, eds. Traveler's diarrhea. Hamilton, Ontario, Canada: B.C. Decker, **2003**

Freedman DO, ed. Travel medicine. Infect Dis Clin N Amer **1998**; 12:2

Jong E, Zuckerman J, eds. Traveler's vaccines. Hamilton, Ontario: B.C. Decker, **2004**

Jong E, McMullen R, eds. The travel and tropical medicine manual. Philadelphia, PA: Saunders, **2003**

Keystone JS, Kozarsky PE, Nothdurft HD, Freedman DO, Connor BA, eds. Travel medicine. New York: Mosby, **2004**

Plotkin SA, Orenstein WA, eds. Vaccines. 4th ed. Philadelphia: Saunders, **2004**

Schlagenhauf P, ed. Traveler's malaria. Hamilton, Ontario: B.C. Decker, **2001**

Zuckerman JN, ed. Principles and practice of travel medicine. New York: John Wiley & Sons, **2001**

Table A1. Travel medicine Web sites.

Category, Web site	Web site address
Authoritative travel medicine recommendations	
WHO On-line International Travel and Health (The Green Book)	http://www.who.int/ith/
US CDC Traveler's Health Home	http://www.cdc.gov/travel/index.htm
US CDC Online Health Information for International Travel (The Yellow Book)	http://www.cdc.gov/travel/yb/index.htm
US CDC Malaria page (Information on all aspects of malaria)	http://www.cdc.gov/malaria/
Health Canada Travel Medicine Program Information for Professionals	http://www.phac-aspc.gc.ca/tmp-pmv/prof_e.html
National Travel Health Network and Centre (United Kingdom)	http://www.nathnac.org
Travel warnings and consular information	
US Department of State: Travel Warnings and Consular Information	http://www.travel.state.gov/travel/cis_pa_tw/cis_pa_tw_1168.html
US Department of State: Medical Information for Americans Traveling Abroad	http://www.travel.state.gov/travel/tips/health/health_1185.html
UK Foreign and Commonwealth Office; Country Advice	http://www.fco.gov.uk/servlet/Front?pagename=OpenMarket/Xcelerate/ShowPage&c=Page&cid=1007029390590
Canada Consular Affairs Bureau	http://www.voyage.gc.ca/consular_home-en.asp
Australia Department of Foreign Affairs and Trade; Travel Advice by Country	http://www.smartraveller.gov.au/zw-cgi/view/Advice/
Vaccine resources	
US Advisory Committee on Immunization Practices: Vaccine-specific guidelines	http://www.cdc.gov/nip/ACIP/
US Vaccine Information Statements for Patients	http://www.cdc.gov/nip/publications/VIS/default.htm
Epidemiology and Prevention of Vaccine Preventable Diseases (The CDC Pink Book)	http://www.cdc.gov/nip/publications/pink/
Immunization Action Coalition	http://www.immunize.org/index.htm
Mulitsource destination-specific database programs (for health care providers)[a]	
Exodus	http://www.exodus.ie
Global Infectious Diseases Epidemiology Network (GIDEON)	http://www.gideononline.com
SOS Travelcare	http://www.internationalsos.com/online/
Travax and Travax Encompass (United States)	http://www.shoreland.com
Travax (Health Protection Scotland, unrelated to US site)	http://www.travax.scot.nhs.uk
TropiMed	http://www.tropimed.com/ANG/home.htm
Mulitsource destination-specific database programs (for travelers)	
Shoreland's Travel Health On-Line (derived from US Travax)	http://www.tripprep.com
Fit for Travel (derived from the Health Protection Scotland Travax)	http://www.fitfortravel.scot.nhs.uk
Fit for Travel from the University of Munich (unrelated to Scottish site)	http://www.fit-for-travel.de/en/default.asp
The TravelDoctor TMVC Australia Trip Planner	http://www.traveldoctor.com.au/
International Association for Medical Assistance to Travelers (IAMAT): Global Physician's Directory and Malaria and Immunization Guides	http://www.iamat.org
International SOS Online Country Guides[a]	http://www.intsos.com
Travel Medicine	http://www.travmed.com/
Emerging diseases and outbreaks	
ProMED-mail: The ISID Program for Monitoring Emerging Infectious Diseases	http://www.promedmail.org
WHO Communicable Disease Surveillance and Response (CSR) Homepage	http://www.who.int/csr/en/
WHO Disease Outbreak News	http://www.who.int/csr/don/en/
Surveillance and epidemiological reports	
Weekly Epidemiological Record (WHO)	http://www.who.int/wer/en/
EuroSurveillance (European information on communicable disease surveillance and control)	http://www.eurosurveillance.org/

(continued)

Table A1. ***(Continued.)***

Category, Web site	Web site address
Morbidity and Mortality Weekly Report (US CDC)	http://www.cdc.gov/mmwr
Canada Communicable Disease Report	http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/index.html
WHO Global Health Atlas	http://globalatlas.who.int/
Geosentinel (the global surveillance network of the ISTM and CDC)[a]	http://www.istm.org/geosentinel/main.html
TropNet Europ (European Network on Imported Infectious Diseases Surveillance)[a]	http://www.tropnet.net
General travel medicine advice for travelers	
Health Canada Travel Medicine Program Information for Travelers	http://www.phac-aspc.gc.ca/tmp-pmv/pub_e.html
Training in travel medicine	
HealthTraining.org Database of Training Opportunities	http://www.healthtraining.org
TropEd Europ List of Accredited Programs	http://www.troped.org/
TrainingFinder Public Health Foundation; Database of postgraduate training opportunities in international health	http://www.trainingfinder.org/
International Society of Travel Medicine Certification Process (follow links under "Travel Medicine Education")	http://www.istm.org
American Society of Tropical Medicine and Hygiene Certification Process	http://www.astmh.org/certification/index.cfm
Health Protection Scotland: Multidisciplinary Courses in Travel Medicine	http://www.travelcourses.scieh.scot.nhs.uk/diploma.asp
Professional societies	
International Society of Travel Medicine	http://www.istm.org
American Society of Tropical Medicine and Hygiene	http://www.astmh.org
Royal Society of Tropical Medicine and Hygiene	http://www.rstmh.org
Wildnerness Medical Society	http://www.wms.org
Divers Alert Network	http://www.diversalertnetwork.org/
American College of Occupational and Environmental Medicine	http://www.acoem.org/
American Association of Occupation Health Nurses	http://www.aaohn.org/
Vendors of travel health products	
Chinook Medical	http://www.chinookmed.com
Travel Medicine	http://www.travmed.com
Magellan's	http://www.magellans.com
Medical Advisory Services for Travellers Abroad: United Kingdom (MASTA UK)	http://www.masta.org/travel-shop.aspx?page_id=2#
Listserv Discussion Groups	
TravelMed (discussion group of the ISTM; follow links to "TravelMed listserv")[a]	http://www.istm.org
TropMed (discussion group of the ASTMH)[a]	http://www.astmh.org/clinicians/acctmth.cfm

NOTE. Inclusion of commercial products and sites does not imply that other sites or products do not have merit. ASTMH, American Society of Tropical Medicine and Hygiene; CDC, Centers for Disease Control and Prevention; ISID, International Society of Infectious Diseases; ISTM, International Society of Travel Medicine; WHO, World Health Organization.

[a] Access to all or part of these sites may be restricted to fee-paying subscribers and members or to specific professional groups. Sample material is usually available.

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