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# Prevention of Infectious Diseases Among International Pediatric Travelers: Considerations for Clinicians

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An estimated 1.9 million children travel overseas annually. Infectious disease risks associated with international travel are diverse and depend on the destination, planned activities, and baseline medical history. Children have special needs and vulnerabilities that should be addressed when preparing for travel abroad. Children should have a pretravel health assessment that includes recommendations for both routine and special travel-related vaccination; malaria chemoprophylaxis, if indicated; and prevention counseling regarding insect and animal exposures, food and water safety, and avoiding injuries. Special consideration should be given to children with chronic diseases. Families should be given anticipatory guidance for management of potential illnesses and information about the location of medical resources overseas.

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## International Travel and Health Risks Abroad

The volume of international travel has increased tremendously during the past decade. Nearly 26.9 million U.S. residents traveled overseas in 2000. Approximately 50 percent of U.S. residents traveled to destinations other than Europe; these destinations included almost 5 million trips to Asia, more than 2.2 million trips to South and Central America, 1.3 million trips to the Middle East, and 500,000 trips to the African continent.<sup>1</sup> An estimated 15 percent to 70 percent of adult travelers report health problems during international travel; 1 percent to 5 percent of travelers seek medical care during travel, 0.1 percent to 1 percent are hospitalized abroad, 0.01 percent to 0.1 percent require emergency evacuation, and 1 in 100,000 die.<sup>2,3</sup> Infectious diseases are a major cause of morbidity among international travelers.<sup>3-7</sup> An

estimated 40 percent of persons traveling annually from industrialized to developing countries develop travelers' diarrhea.<sup>3-9</sup> Malaria is a less frequent but potentially life-threatening problem for travelers; an estimated 30,000 North American and European travelers contract malaria annually.<sup>10</sup> Other infectious diseases reported in travelers include hepatitis A and B, sexually transmitted diseases, animal bites with risk of rabies, typhoid, cholera, legionellosis, human immunodeficiency virus (HIV) infection, and meningococcal disease.<sup>3,11-27</sup>

Less specific information is available on the number of children traveling internationally or living abroad. Extrapolating from overseas travel data for U.S. residents, one can estimate conservatively that at least 1.9 million children travel overseas annually (ie, 7% of the 26.9 million U.S. residents traveling internationally in 2000 reported traveling with children). Information on the causes of serious morbidity and mortality among pediatric travelers is more limited.<sup>28-31</sup> Available data include a 1-year prospective hospital-based study in the United Kingdom of children evaluated for fever who had traveled recently to the tropics.<sup>30</sup> In this study, 31 children with a median age of 4 years (range, 5 months to 15 years) met the study entry criteria. Fourteen of these children had nonspecific, self-limited illnesses of presumed viral origin, and 17 children had conditions requiring hospital management and antimicrobial therapy. Conditions requiring hospital management included four cases of malaria (3 of *Plasmodium falciparum*, and 1 of *Plasmodium vivax* malaria), three cases of bacillary dysentery, two cases each of dengue and

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typhoid fever, and one case each of acute hepatitis A infection, pneumonia (unspecified), *Pneumocystis carinii* pneumonia (in a child with newly diagnosed HIV infection), bacterial lymphadenitis, streptococcal throat infection, and acute myeloid leukemia; no deaths occurred. In another retrospective study of travelers' diarrhea among Swiss children who had visited the tropics or subtropics, Pitzinger and coworkers found incidence rates of 40 percent, 8.5 percent, 21.7 percent, and 36 percent in children aged 2 years or younger, 3 to 6 years, 7 to 14 years, and 15 years and older, respectively.<sup>31</sup> Other authors have reported substantial health risks for pediatric travelers from noninfectious causes such as injuries, including automobile accidents and drowning.<sup>29</sup>

## Pretravel Health Assessment for Pediatric Travelers

Children have special needs and vulnerabilities that should be considered when preparing for travel abroad, and all children should have a pretravel health assessment performed. Depending on the destination and the vaccinations needed, this assessment should be conducted up to 6 months before travel. The pretravel assessment should include an evaluation of the child's medical history and immunization status, as well as a detailed review of the trip itinerary, including travel destinations, planned activities, type of accommodations (eg, hotel chains, residing with local families, camping), extent of contact with the local populations, and exposure to animals. Special consideration should be given to children who have chronic diseases, such as diabetes, cardiac abnormalities, or immunocompromising conditions, in terms of vaccine recommendations and travel risks and precautions. Parents should be advised to carry a summary of their child's medical history, treatment record, and all required prescription medications. During the assessment, the caregiver should ensure the following: 1) the child has received up-to-date and appropriate vaccinations (both routine and special travel-related vaccines); 2) the child has received appropriate malaria and other chemoprophylaxis regimens tailored for use in pediatric travelers; 3) prevention counseling, particularly in the areas of insect barriers, food and water safety, and injury avoidance, has been given; and 4) anticipatory guidance for managing potential illnesses (eg, diarrhea and dehydration) and seeking medical resources overseas has been provided.

### Vaccination for International Travel

Vaccination for international travel is among the most critical and complex components of the pretravel health assessment for children, and a careful review of both recommended routine childhood vaccinations and required and recommended travel-related vaccinations should be undertaken.

#### Routine Childhood Vaccination for Pediatric Travelers

Pediatric travelers must have their routine immunizations brought up-to-date, as many vaccine-preventable diseases (VPDs) are more prevalent in developing countries than in the United States. For example, diphtheria and pertussis are

prevalent in Eastern Europe and many developing countries, and measles still is endemic in much of the developing world. Hepatitis B, *Haemophilus influenzae* type B, *Streptococcus pneumoniae*, and varicella also are endemic in many developing countries. Further, although worldwide polio eradication efforts have decreased the number of countries where travelers are at risk for acquiring polio (with most poliovirus transmission now occurring in 2 large endemic areas in south Asia and sub-Saharan Africa), polio outbreaks still occur; in July 2000, outbreaks of vaccine-derived poliovirus type 1 were reported in the Dominican Republic and Haiti.<sup>32,33</sup> Trip activities also may increase the risk of contracting infectious diseases such as measles; in both 2001 and 2004, epidemiological investigations identified numerous cases of serologically confirmed measles among internationally adopted children and their new parents and siblings, who had traveled to China to accompany them home.<sup>34,35</sup> In addition, travel in large groups on conveyances such as cruise ships can facilitate transmission of VPDs.<sup>36</sup> Parents should check their own immune status because travel with children can increase risk of exposure to VPDs.

If travel to developing countries is planned, assuring immunity is imperative, and accelerated schedules should be considered. Depending on the travel destination and itinerary, routine vaccinations may need to be accelerated to maximize protection, particularly against polio, diphtheria/tetanus/pertussis, and measles (for example, measles vaccination may be recommended for children younger than 12 months of age).<sup>37</sup> Guidelines for standard and accelerated schedules for routine childhood immunizations and special precautions and recommendations for immunocompromised children are available in the American Academy of Pediatrics, "Red Book: 2003 Report of the Committee on Infectious Diseases," and on web sites of the Centers for Disease Control and Prevention (CDC).<sup>37</sup>

#### Common Travel-Related Vaccines for Children

The most recent requirements and recommendations for travel-related vaccinations by specific geographic destinations can be obtained from CDC, "Health Information for International Travelers" (the "Yellow Book"), and from CDC Travelers' Health Internet and other travel-related web sites<sup>32</sup> (see also Table 1, International Travel Health Information Resources for web sites). The United States does not require arriving travelers to have any vaccinations for entry or return into the United States. Some other countries may require proof of vaccination against yellow fever for entry, especially if the traveler is arriving from a country where yellow fever is endemic. Yellow fever vaccine is available only from certified yellow fever vaccination centers; providers can refer to the following CDC yellow fever vaccine registry to locate certified centers in their areas: <http://www2.ncid.cdc.gov/travel/yellowfever>. Saudi Arabia requires meningococcal vaccine for travelers to the Hajj in Mecca. Some countries have required previous vaccination for cholera, but currently no countries require it, and the vaccine is not available in the United States.

Table 2 provides general guidelines and indications for use

Table 1 International Travel Health Information Resources

Resource	Contact Information	Information/Services Provided
Centers for Disease Control and Prevention (CDC) Travelers' Health Information	877-394-8747 (phone) 888-232-3299 (fax) www.cdc.gov/travel/	Recorded information and documents on U.S. recommendations for specific travel destinations; links to other sites, travel advisories, and outbreak notices
CDC "Health Information for International Travel" (Yellow Book)	www.cdc.gov/travel/yellowbook.pdf	General travelers' health information, region- and destination-specific recommendations, including vaccinations and malaria prophylaxis
CDC Malaria Branch	770-488-7788 404-639-2888 (after hours, weekends and holidays)	Information about malaria prophylaxis and treatment, intended for use by health care professionals
CDC MMWR weekly and summaries	www.cdc.gov/mmwr	Outbreak investigations and surveillance summaries
CDC National Immunization Program	www.cdc.gov/nip	Immunization information
American Academy of Pediatrics (AAP)	www.aap.org	Information on pediatric infectious diseases and immunization practices
National Network for Immunization Information (Nnii)	www.immunizationinfo.org	Immunization information for health practitioners and parents
U.S. State Department	877-341-6644 www.travel.state.gov	Information about travel, including safety, visa requirements, links to individual embassies and consulates
World Health Organization (WHO) Infectious Disease Health Topics	www.who.int/health-topics/	Information and maps of travel-related diseases
WHO Yellow Book, "International Travel and Health"	www.who.int/ith/	General travelers' health recommendations; country-specific malarial risks and recommendations
WHO, Outbreak News	www.who.int/disease-outbreak-news/	Monthly newsletter with notifications of recent infectious disease outbreaks
WHO, Weekly Epidemiological Record	www.who.int/wer	Global disease surveillance
Health Canada, Travel Medicine Program	www.travelhealth.gc.ca	Canadian recommendations for travelers health; outbreak information
PROMED (Program for Monitoring Emerging Diseases)	www.promedmail.org	E-mail postings; verified and unverified reports on emerging diseases and outbreaks

of selected common travel-related vaccines, based on U.S. recommendations; World Health Organization (WHO) recommendations may differ.<sup>32,38</sup>

Hepatitis A is endemic in most of the world, and travelers are at risk in any area where sanitation is poor. Vaccination is recommended for pediatric travelers aged 2 years or older who will be visiting countries with intermediate to high endemicity (areas other than the United States, Canada, Australia, New Zealand, Western Europe, and Scandinavia). Studies have demonstrated that protective antibody titers 2 weeks after the patient has received the first dose of Hepatitis A vaccine range from 69 percent to 98 percent; after 4 weeks, protective antibody titers were present in 95 percent to 100 percent of vaccinees. Intramuscular immunoglobulin is recommended for immunoprophylaxis against hepatitis A in children younger than 2 years of age. In addition, for children 2 years of age or older who are departing less than 4 weeks after receiving a vaccination, immunoglobulin and vaccine can be given concurrently at different sites to ensure optimal protection.

Meningococcal disease occurs sporadically worldwide. Epidemic disease has been reported in India, Saudi Arabia,

and sub-Saharan Africa; indeed, recurrent epidemics of meningococcal disease occur in sub-Saharan Africa, mainly from December to June (the dry season). Serogroup A is the most common cause of epidemics outside the United States, but serogroup C and other serogroups have been associated with epidemics. Serogroup W-135 meningococcal infections among travelers returning from Saudi Arabia after visiting Mecca during the Hajj also have been reported recently.<sup>13-15</sup> The meningococcal vaccine available in the United States is the quadrivalent polysaccharide A/C/Y/W-135, which is recommended for pediatric travelers 2 years or older who are visiting sub-Saharan Africa during the dry season, or any country where an epidemic caused by a vaccine serogroup is occurring. The vaccine can be administered to children younger than 2 years of age, but their immunologic response may be limited to serogroup A only.<sup>37</sup>

Yellow fever occurs year-round in predominately rural areas of Sub-Saharan Africa and South America; in recent years, outbreaks have been increasing. Recently, yellow fever has reemerged in Brazil, raising concern about increased risk in other areas of Latin America and raising the possibility of transmission of yellow fever in urban areas.<sup>39</sup> Although a rare

**Table 2** Common Travel-Related Vaccines for Children

<b>Vaccine</b>	<b>Vaccine Type</b>	<b>Route</b>	<b>Minimum Age</b>	<b>Primary Series*</b>	<b>Booster/ revaccination†</b>	<b>Protection</b>	<b>General Indications for Use‡</b>
Hepatitis A§	Inactivated virus	im	2 years	2 doses at 0, 6–12 month intervals	Unknown	4 weeks after dose 1 Dose 1: Protective antibody titers after 2 weeks: 69–98% Dose 2: Protective antibody titers after 4 weeks: 94–100%	Use for travel to Latin America, Africa, Asia (except Japan), Oceania (except Australia, New Zealand), Middle East, and some parts of Europe  Recommended routinely for children >2 years living in selected areas of United States
Meningococcal (quadrivalent A,C,Y, W135; bivalent A, C)¶	Polysaccharide inactivated bacterial components	sc	2 years	1 dose	3–5 years, Booster after 2–3 years for children vaccinated at age <4 years	7–10 days after dose	Required for travelers to annual Hajj in Mecca Use for travel to sub-Saharan Africa during dry season (December through June) and any country where an epidemic is occurring
Yellow fever	Live attenuated virus	sc	9 months	1 dose	10 years	10 days after dose	Use for travelers to areas of Africa and South America Children ages 6–9 months: seek expert consultation to determine risk-benefits Recent reports of rare serious adverse events of multiorgan system failure after vaccination
Japanese encephalitis	Inactivated virus	sc	1 year	3 doses at 0, 7 and 14 or 30 days	2–3 years Booster: 1 dose	10–14 days after dose 3	Use for travel to selected areas of Asia, Oceania (Australia and Papua New Guinea), Russia, especially travelers to rural areas or epidemic regions during seasonal transmission (usually May to September) Severe allergic reactions (including anaphylaxis) occur in ~0.6% of persons. Anaphylaxis can occur up to 10 days after vaccination; all vaccine doses should be administered ≥10 days prior to travel
Rabies	Inactivated virus; cell culture derived	im, id (HDCV only)	US: None	3 doses at 0, 7 and 21 or 28 days	6 months–3 years	14 days after dose 3	Use for travelers to rabies-endemic countries

Human diploid cell vaccine (HDCV) Rabies vaccine adsorbed (RVA) Purified chick-embryo cell culture vaccine (PCEC)					Based on risk or serology Booster: 1 dose		Recommended for long-term travel in rural areas, or areas with limited access to health care, or short-term travel with extensive rural exposures. Post-exposure in vaccinated person: 2 doses at 0, 3 days (no rabies immune globulin required). Postexposure in unvaccinated person: rabies immune globulin (20 IU/kg) plus vaccination with 5 doses at 0, 3, 7, 14, and 28 days.
Typhoid (ViCPS)	Capsular polysaccharide	sc	2 years	1 dose	2 years	14 days after dose	Use for travel to Africa, Asia, and Latin America for long-term stays, or travel outside tourist destinations Protective efficacy: 50–74% in endemic areas
Typhoid oral (Ty21a)	Live attenuated bacteria	oral	6 years	4 doses at 0, 2, 4, 6 days	5 years	7–10 days after last dose	See indications for Typhoid ViCPS Protective efficacy: 60–85% in endemic areas Not for administration within 24 hours of mefloquine, atovaquone/proguanil, doxycycline or any other antibiotic
Influenza	Inactivated virus	im	6 months	Children <9 yrs: 1 or 2 doses, depending on vaccination status Children ≥9 yrs: 1 dose	1 year	14 days after completed age-dependent series	Consider for those at high risk for influenza complications for travel to 1. Tropics any time of year 2. Southern hemisphere (April–September), 3. Destinations with large groups of tourists 4. Destination with influenza outbreaks Contraindication: severe anaphylaxis to eggs
BCG	Live attenuated bacteria	id, sc	birth	1 dose	None	2 months after dose (WHO)	Consider use in long-term pediatric travelers <1 yr residing in high risk areas

\*Number of doses and recommended ages and intervals (Note: interval represents time from dose)

†Number of doses and recommended ages and intervals

‡Contraindications: anaphylactic reaction to prior dose or any vaccine component and/or moderate to severe acute illness is a contraindication for all vaccines

§Combination hepatitis A-hepatitis B (Twinrix®) is now available for use in persons ≥18 years of age. The vaccine, which is composed of inactivated viral components, is administered intramuscularly. The schedule involves 3 doses at 0, 1, 6 months. It can be administered at an accelerated schedule of 4 doses at 0, 7, 21 days, and 1 year.

¶Meningococcal vaccine: Quadrivalent vaccine can be administered to children younger than 18 months but may have limited immunologic response; serogroup A is immunogenic in children 3 months of age or older. Responses to other serogroup components are poor or unknown in children 2 years of age or younger. Group A meningococcal vaccine can be administered to children under 18 months; it is administered as 2 doses separated by a 3-month interval. Bivalent A, C vaccine is available outside of United States.

occurrence, yellow fever continues to be reported among travelers, particularly unvaccinated travelers, and can be fatal. Prevention measures against yellow fever should include the use of personal protection measures against mosquitoes and vaccination.

Yellow fever vaccine is considered a relatively safe and effective vaccine. However, the vaccine has been found to be associated with an increased risk of developing encephalitis and other severe reactions in young infants.<sup>37</sup> The vaccine should not be used in children younger than 6 months of age. It should be used with caution in children 6 to 9 months of age, and after discussion with a travel medicine expert to weigh risks and benefits.<sup>37</sup> Medical waivers can be given to children who are too young for vaccination and to those who have other contraindications to vaccination, such as immunodeficiency. Recently, reports have raised concern about possible rare instances of yellow-fever vaccine-associated neurotropic and viscerotropic disease, and these adverse events are being investigated.<sup>40-43</sup> In the interim, CDC has stated that given the risk of serious illness and death caused by yellow fever, evidence of increasing transmission of the disease, and the known effectiveness of the vaccine, clinicians should continue to use yellow fever vaccine to protect travelers. However, CDC recommends that healthcare providers carefully review travel itineraries to ensure that yellow fever vaccine be given to only people traveling to areas where yellow fever is endemic or areas where there is reported yellow fever activity.<sup>42,43</sup>

Japanese encephalitis (JE) is a viral infection transmitted by *Culex* mosquitoes, which bite from dusk to dawn. JE occurs year-round in tropical regions, and primarily from May through October in temperate zones. Risk is greatest for travelers to rural Asia, where the mosquito breeds in rice fields and other agricultural areas. JE is associated with a high case-fatality rate and severe neurological sequelae, especially among young children and the elderly. Vaccination should be considered for pediatric travelers who are 1 year of age or older and who will visit and reside in areas where JE is endemic or epidemic, especially during transmission season, or for pediatric travelers whose activities include trips to rural farming areas. Short-term travelers (<30 days) who visit only major urban areas are at lower risk for acquiring JE and generally do not need to be vaccinated.<sup>32</sup>

Rabies occurs worldwide. In certain areas of the world, including parts of Brazil, Bolivia, Colombia, Ecuador, El Salvador, Guatemala, India, Mexico, Nepal, Peru, the Philippines, Sri Lanka, Thailand, and Vietnam, canine rabies remains highly endemic. Rabies also occurs in other wild animals, including bats. Rabies vaccine should be considered for children visiting rabies-endemic countries for longer than 1 month; undertaking extensive outdoor activities, such as backpacking or camping; or traveling to areas where access to health care is limited. To reduce the risk of acquiring rabies, children and their families should be counseled to stay away from stray dogs and other animals, especially if traveling to Latin America, Asia, or Africa.<sup>32</sup>

Typhoid vaccine is recommended for pediatric travelers visiting developing countries, especially for prolonged peri-

ods of time, or traveling outside the usual tourist destinations. Parents should be cautioned, however, that vaccination is not 100 percent effective, and safe food and water precautions should be followed.

Influenza vaccine should be considered for children with chronic diseases and others at increased risk for developing complications of influenza if they are traveling to the tropics or to the Southern hemisphere from April through September. In addition, influenza risk has been shown to be increased in destinations and on conveyances having large groups of tourists and in destinations with influenza outbreaks occurring, and, therefore, vaccination also should be considered in these circumstances.<sup>44</sup> Lastly, Bacille Calmette-Guerin (BCG) vaccine is a live vaccine prepared from attenuated strains of *Mycobacterium bovis*; BCG is used primarily in young infants to prevent disseminated and other forms of life-threatening diseases caused by tuberculosis (TB), such as tuberculous meningitis. BCG is recommended by the WHO for administration at birth; in the United States, BCG is recommended only in limited circumstances, such as unavoidable risk of exposure to *M. tuberculosis*. Vaccination of a young pediatric traveler (non-HIV-infected and with negative TB skin test) might be considered, therefore, if travel is planned for a long-term stay in a country with high TB prevalence and prolonged contact with active TB cases is considered a potential problem.<sup>37,45</sup> BCG vaccine can be obtained from the Canadian subdivisions of Aventis Pasteur or Organon. More generally, children traveling to countries with high prevalence of TB should be given a skin test before and after travel to document possible exposure to TB. U.S. children who had traveled within the previous 12 months to countries with a high prevalence of TB were reported to be 3.9 times more likely to have positive TB skin tests than were children who lived in the same U.S. areas but had not traveled.<sup>46</sup>

## Prevention of Malaria

### Malaria Epidemiology

(For global epidemiology and disease, refer to the malaria review in this issue by Crawley and Nahlen). In the United States, 5794 cases of malaria among U.S. civilians were reported to the CDC from 1992 through 2000. Of 5662 U.S. civilian cases with information about country of acquisition, 3289 (58%) were acquired in Africa, 1054 (19%) in Asia, 1059 (19%) in Latin America or the Caribbean, and 260 (4%) in Oceania. During this period, 976 (17%) of the cases occurred in children younger than 18 years of age. Among children with malaria, 343 (35%) were ages 1 month to 5 years; 215 (22%) were ages 6 to 9 years; 226 (23%) were ages 10 to 14 years; and 192 (20%) were ages 15 to 17 years. (CDC, unpublished data). In 2002, CDC received 1337 case reports of malaria occurring among persons in the United States.<sup>47</sup> A recent review of malaria cases among U.S. civilians (adults and children) reported that the largest percentage of cases (38.5%) occurred among persons who were visiting friends or relatives in malarious areas.<sup>48</sup> Retrospective reviews of malaria in children also have found that a substantial

proportion of cases occurred among recent immigrants and among children of former immigrants who had traveled to visit their family's country of origin.<sup>28,49</sup>

### Preventing Malaria in Pediatric Travelers

Young children and nonimmune persons of any age are at greater risk for the development of severe complications from malaria; the substantial proportion of U.S. malaria cases reported in children underscores the importance of having strategies for the prevention of malaria. The prevention of malaria in pediatric travelers depends first on obtaining current and accurate information about the risk of contracting malaria in proposed travel destinations and determining if planned activities and season of travel place the traveler at increased risk of exposure. Information on geographic and country-specific risks regarding malaria is available from multiple sources (see Table 1, International Travel Health Information Resources).

Prevention strategies for pediatric travelers are two-fold: personal protection measures against mosquitoes and antimalarial chemoprophylaxis. The first mainstay of prevention is appropriate and effective use of personal protection measures to avoid being bitten by *Anopheles* mosquitoes, which typically are evening and nighttime feeders. These measures include wearing clothing that reduces the amount of exposed skin (such as long-sleeved shirts, long pants tucked into socks, and hats) and, whenever possible, remaining in well-screened or enclosed air-conditioned areas. Travelers staying overnight in facilities without air conditioning or screens should use insecticide-treated mosquito nets over the beds.<sup>50</sup> During the evening, insecticide also can be sprayed inside rooms. Another important measure of personal protection is appropriate use of insect repellent, such as *N,N*-diethylmetatoluamide (DEET), on exposed skin. The American Academy of Pediatrics has recommended using repellents with less than 30 percent DEET for infants and children.<sup>51</sup> DEET should not be used in children younger than 2 months of age or applied to hands, mouth, or near the eyes of young children. Despite the demonstrated efficacy of these measures, studies have found only 17 percent of adult travelers with malaria reported using insect protection methods, and only 11 percent took recommended chemoprophylaxis.<sup>52</sup>

The second mainstay of preventing the acquisition of malaria is chemoprophylaxis. The selection of the appropriate drug for antimalarial chemoprophylaxis must be based on numerous factors, including the most recent information available about the prevalence of malaria in the proposed travel destinations; trip itinerary; age, weight, and medical history of the traveler; personal preference regarding frequency of dosing and duration of chemoprophylaxis on trip return; and cost of medication. CDC provides resources with guidance on appropriate use and recommended regimens for antimalarial chemoprophylaxis (see Table 1, International Travel Health Information Resources).

Figure 1 outlines an algorithm for determining appropriate antimalarial chemoprophylaxis regimens for pediatric travelers. Because the distribution of drug-resistant malaria is evolving constantly, clinicians should obtain the most recent

information about the risk of malaria and zones of drug resistance before prescribing chemoprophylaxis for malaria. The first decision point in selecting appropriate antimalarial chemoprophylaxis is whether travel is occurring in a region of chloroquine-sensitive or -resistant malaria. For travel to areas with chloroquine-sensitive malaria, chloroquine is the drug of choice for antimalarial chemoprophylaxis. *Plasmodium ovale*, *Plasmodium malariae*, and most *P. vivax* are widely sensitive to chloroquine; however, chloroquine-resistant *P. vivax* is an emerging problem and has been reported from Guyana, New Guinea, India, Myanmar (Burma), and areas of Indonesia.<sup>53</sup> In addition to chloroquine-resistant *P. vivax*, chloroquine-resistant *P. falciparum* has been reported from these areas, and, consequently, chloroquine would not be recommended for chemoprophylaxis for travelers to these regions.

If the traveler is visiting a region with chloroquine-resistant malaria, the next decision point is whether travel will include regions with chloroquine-resistant malaria only or both chloroquine- and mefloquine-resistant malaria. Chloroquine-resistant *P. falciparum* is widespread and exists in all malaria-endemic areas except Mexico, the Caribbean, Central America west of the former Panama Canal zone, Argentina, and parts of the Middle East and China.<sup>32</sup> In some regions, *P. falciparum* may be resistant to both chloroquine and mefloquine; these areas currently are limited to the borders of Thailand with Myanmar (Burma) and with Cambodia, in the western provinces of Cambodia, and in the eastern states of Myanmar.<sup>32,53</sup> For travel to areas with chloroquine-resistant malaria, currently the three antimalarial chemoprophylaxis options are: mefloquine (Lariam; Hoffman-LaRoche, Nutley, NJ), atovaquone-proguanil (Malarone; Glaxo Wellcome, Research Triangle Park, NC), or doxycycline. CDC no longer recommends the use of chloroquine/proguanil for chemoprophylaxis for chloroquine-resistant areas. For travel to areas with chloroquine- and mefloquine-resistant malaria, either atovaquone-proguanil or doxycycline can be used.

When antimalarial chemoprophylaxis options are being evaluated, each medication should be reviewed for contraindications and weight and age restrictions (see Table 3, Antimalarial Chemoprophylaxis Regimens for Pediatric Travelers). Chloroquine is relatively well tolerated in children. In the United States, chloroquine is available in tablet form; in Europe and other countries, it also is available as a syrup. Mefloquine can be used safely in children weighing less than 15 kilograms and may be useful for longer trips because it is administered once weekly. However, it must be continued for 4 weeks after leaving the malarious area, and no liquid preparation is available. Doses for children are one-quarter, one-half, and three-quarters of a tablet, depending on weight. Few data are available on the use of atovaquone-proguanil in children weighing less than 11 kilograms; however, studies are in progress. For children weighing more than 11 kg at risk for acquiring chloroquine-resistant *P. falciparum* infection, atovaquone-proguanil can be advantageous for short trips because it is started 1 to 2 days before the trip and can be stopped 7 days after the trip. It is available in pediatric tablet form. Doxycycline is contraindicated in children younger



**Table 3** Antimalarial Chemoprophylaxis Regimens for Pediatric Travelers

Medication	Regimen	Dose	Contraindications/ Precautions	General Indications/Information
Chloroquine (Aralen®)	Weekly starting 1–2 weeks before trip; continue weekly during trip and for 4 weeks after trip	5 mg base/kg (8.3 mg salt/kg) up to 300 mg base (500 mg salt) <i>Tablets: 300 mg base (500 mg salt)</i>	Prior retinal or visual field changes Psoriasis (may be exacerbated)	Use only in areas of chloroquine-sensitive malaria Retinal damage at high doses* Bitter taste
Mefloquine (Lariam®)	Weekly starting 1 week before trip; continue weekly during trip and for 4 weeks after trip	≤15 kg: 4.6 mg/kg base (5 mg/kg salt) 15–19 kg: _ tablet 20–30 kg: _ tablet 31–45 kg: _ tablet ≥46 kg: 1 tablet <i>Tablets: 228 mg base (250 mg salt)</i>	Psychiatric conditions, cardiac conduction and seizure disorders, hypersensitivity to mefloquine Do not take with quinine-like drugs	Use in areas with chloroquine-resistant malaria Occasional serious adverse effects: seizures, nightmares, depression, anxiety, psychosis, especially in persons with these preexisting medical conditions Bitter taste
Atovaquone/proguanil (Malarone™)	Daily starting 1–2 days before trip; continue daily during trip and for 7 days after trip	11–20 kg: 1 pediatric tablet (62.5 mg/25 mg) 21–30 kg: 2 pediatric tablets (125 mg/50 mg) 31–40 kg: 3 pediatric tablets (187.5 mg/75 mg) ≥40 kg: 1 adult tablet (250 mg atovaquone and 100 mg proguanil hydrochloride) <i>Pediatric tablets: 62.5 mg atovaquone and 25 mg proguanil hydrochloride</i> <i>Adult tablets: 250 mg atovaquone and 100 mg proguanil hydrochloride</i>	Contraindicated in severe renal failure. Not recommended for children <11 kg, pregnant or lactating women. Do not take with tetracycline, metoclopramide, rifampin or rifabutin (all reduce concentrations of atovaquone).	Use in areas with chloroquine-resistant or mefloquine-resistant malaria For short-term traveler, advantageous because can stop prophylaxis 1 week after leaving malarious area Available in pediatric tablets Take with food or milk
Doxycycline	Daily starting 1–2 days before trip; continue daily during trip and for 4 weeks after trip	2 mg/kg up to 100 mg daily <i>Tablets: 50 mg, 100 mg</i>	Do not use for children younger than 8 years of age, pregnant or lactating women	Use in areas with chloroquine-resistant and mefloquine-resistant malaria GI symptoms, photosensitivity May decrease the effectiveness of oral contraceptives

\*Despite the use of chloroquine as an antimalarial chemoprophylaxis agent for decades and the use of high-dose chloroquine for certain chronic diseases, the literature is inconclusive regarding the potential risk of retinopathy associated with long term use of chloroquine for antimalarial prophylaxis. Retinopathy rarely has been reported in patients on weekly prophylaxis. Retinopathy appears to be related to dosage and accumulated dosage.

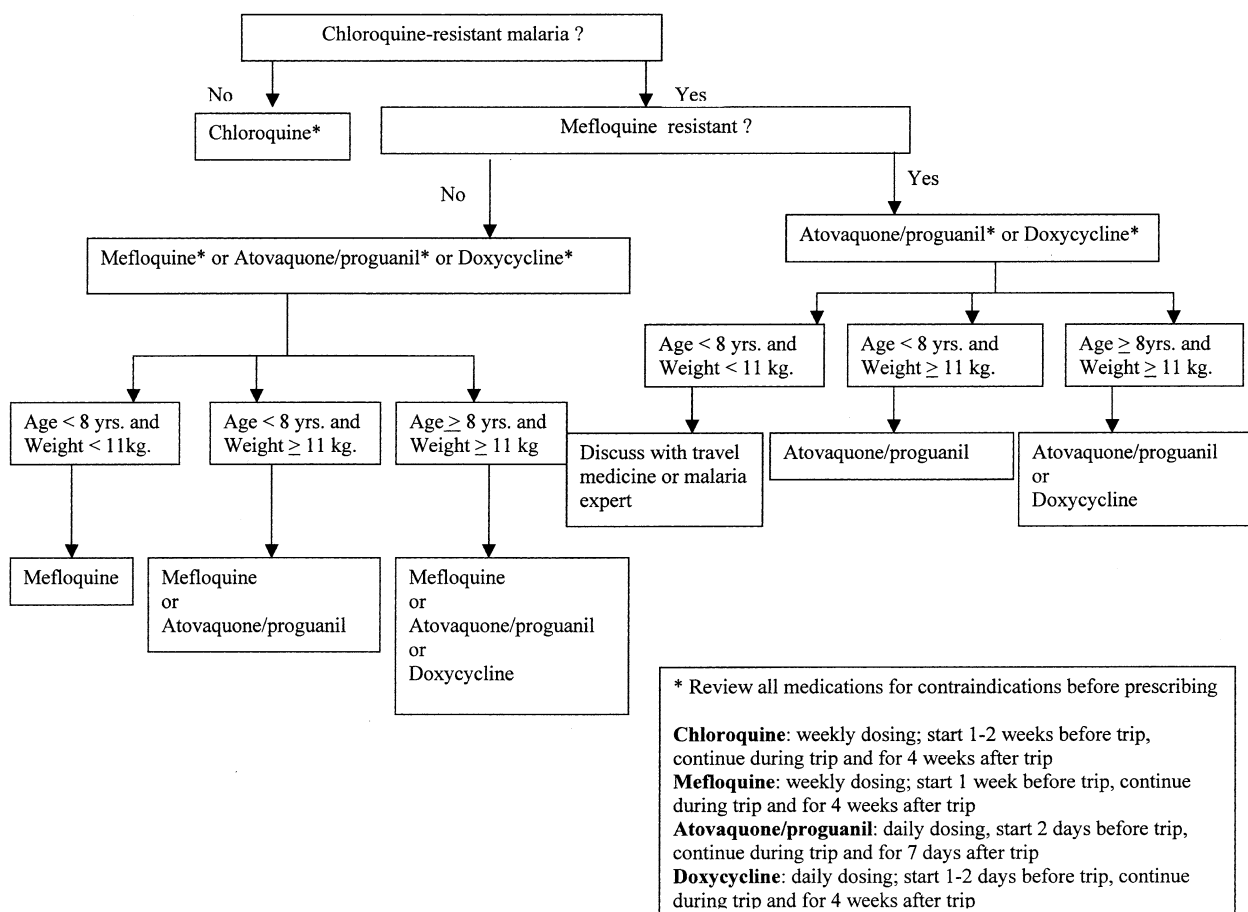


Figure 1 Algorithm for determining appropriate antimalarial chemoprophylaxis regimens for pediatric travelers.

than 8 years of age because of concerns about the propensity of tetracycline to stain growing teeth or potentially to affect developing bones. For older children, doxycycline must be administered daily and continued for 4 weeks after departing the malarious area.

Primaquine may be used as an option for primary prophylaxis in special circumstances. Clinicians should contact CDC Malaria Branch for additional information (see Table 1). Primaquine also can be used for terminal prophylaxis to decrease the risk of occurrences of relapses of *P. vivax* and *P. ovale*.<sup>32,54</sup> Another aminoquinoline, tafenoquine, which is a long-acting primaquine analog, is undergoing investigation and may become approved for malaria chemoprophylaxis indications in the future.<sup>53</sup>

The importance of recommending appropriate antimalarial chemoprophylaxis regimens for travelers cannot be over-emphasized. A review of malaria cases among U.S. civilians in 1998 found that close to 60 percent had not taken any chemoprophylaxis and another 13 percent had not taken the CDC-recommended drug for the area visited.<sup>48</sup> In retrospective reviews of pediatric malaria cases, between 75 and 100 percent of cases had received no or inadequate chemoprophylaxis.<sup>49,55</sup> Indeed, the inappropriate use of antimalarial chemoprophylaxis has been shown to be an important cause of mortality and serious morbidity among travelers. From 1992 through early 2001, CDC received reports of seven U.S.

travelers who died from malaria after using inappropriate chemoprophylaxis. All these travelers had received prescriptions for chloroquine for travel to areas with widespread chloroquine resistance. Among 4685 cases of imported malaria with information about chemoprophylaxis during 1992 through early 2001, 2616 (56%) took no chemoprophylaxis, and 893 (19%) took an inappropriate chemoprophylaxis regimen.<sup>56</sup> In addition to being given preventive therapy, parents should be counseled in signs and symptoms of malaria infection in children, such as fever, headaches, vomiting, diarrhea, and myalgias. Delays in recognition and treatment of malaria are associated directly with increases in morbidity and mortality rates; therefore, prompt and appropriate initiation of effective therapy is paramount.

### Preventing Other Infectious Diseases in Pediatric Travelers

Because the epidemiology of many diseases is evolving, prevention hinges on clinicians' knowledge about current information regarding risks and outbreaks in travel destinations. A variety of pathogens are being recognized increasingly as emerging infectious diseases among travelers. In addition to malaria, other vector-borne infectious diseases are among the important diseases for consideration in travelers.

Dengue is one of the most important vector-borne viral

infections worldwide and is endemic in Asia, the South Pacific, Africa, Latin America, and the Caribbean. Epidemics of dengue hemorrhagic fever, the more severe clinical form of dengue fever, occur every 3 to 5 years in Southeast Asia and are an emerging problem in Latin America. Recently, outbreaks of dengue fever occurred in Hawaii and along the U.S. and Mexico border.<sup>57-59</sup> Worldwide, an estimated 50 to 100 million cases of dengue fever occur annually; of these cases, 200,000 to 500,000 are dengue hemorrhagic fever. Every year, cases of dengue fever among U.S. travelers are reported to CDC. Dengue is transmitted primarily by day-biting *Aedes aegypti* mosquitoes, which breed in flower vases, barrels, and discarded tires that collect water. Transmission occurs in rural and urban areas, but the risk is greatest in urban areas. Prevention should focus on protection against mosquito bites. Travelers to risk areas should be counseled to apply repellent during the day, even while visiting cities. No vaccine is available, and prior infection with one of the four serotypes does not protect against infection with another serotype. The risk of developing dengue hemorrhagic fever actually may increase with subsequent infection with a different serotype.<sup>60</sup>

Infections with African trypanosomiasis (sleeping sickness), a parasitic infection transmitted by the bite of a tsetse fly, occasionally have been reported among travelers. Infection can result in severe neurological sequelae and is 100 percent fatal if untreated. In 2001, significant increases in the number of cases were reported among U.S. and European travelers to game parks in Tanzania and Kenya. Between 1967 and 2000, an imported case occurred on average every 1 to 2 years; however, in 2001, seven cases were reported among U.S. travelers.<sup>61,62</sup>

Schistosomiasis, another parasitic infection caused by flukes that live part of their life cycle in fresh water snail hosts, affects more than 200 million people worldwide. Schistosomiasis has been reported among travelers to endemic areas of the Africa, Asia, South America, and the Caribbean who participated in high-risk activities, such as swimming or wading in fresh water.<sup>32,63,64</sup> Children and their families should be counseled against swimming or wading in fresh water in risk areas.

Tick-borne encephalitis is transmitted primarily by the bite of *Ixodes* ticks. It also can be transmitted by ingestion of unpasteurized dairy products from infected livestock. Transmission occurs during summer months in western and central Europe, Scandinavia and parts of the former Soviet Union. Persons who will be traveling for longer than 3 weeks in endemic rural areas or travelers who will be engaging in high-risk activities, such as camping, should be considered for vaccination. The vaccine is not available in the United States but can be obtained in Europe.<sup>32</sup>

Examples of recent outbreaks or cases of unusual pathogens affecting travelers include fungal organisms (such as histoplasmosis and coccidioidomycosis), leptospirosis, and leishmaniasis. Histoplasmosis is a fungal infection acquired by inhalation of spores, usually through exposure to bat, bird, or chicken droppings in barnyards and caves. The organism is endemic in the United States, Latin Amer-

ica, eastern Asia, parts of Europe, Africa, and Australia. Coccidioidomycosis, a fungal infection associated with inhalation of soil from high-risk areas, is endemic in the southwestern United States and Latin America. Both infections can cause a spectrum of illnesses from asymptomatic infection to acute pulmonary infection to severe, disseminated disease, especially in immunocompromised persons. Several outbreaks of histoplasmosis have been reported among groups of U.S. visitors who entered a cave with bats in Costa Rica (CDC, unpublished data),<sup>65</sup> Ecuador,<sup>66</sup> Peru,<sup>67</sup> and Nicaragua.<sup>68</sup> Recently, more than 200 college students became infected with histoplasmosis during a spring break trip to Acapulco, Mexico.<sup>69</sup> Two outbreaks of coccidioidomycosis have been reported among youth missionary groups involved in construction work in Mexico.<sup>70,71</sup> Most of these fungal outbreaks have two common features: high-risk, group activities and high attack rates, even in young, nonimmunocompromised individuals. Because no vaccine is available, prevention involves counseling travelers to avoid exposure or to use special masks for high-risk individuals who cannot avoid exposure.<sup>72</sup>

Leptospirosis is a zoonotic infection that is transmitted by exposure to water or soil contaminated with organisms excreted by domestic and wild animals. Outbreaks have been reported among whitewater rafters in Costa Rica and among athletes from 26 countries who participated in the Eco-Challenge multisport expedition race in Borneo, Malaysia in 2000.<sup>73</sup> Because no vaccine against leptospirosis exists, persons engaging in high-risk activities should be counseled to avoid exposure to water that may be contaminated or to wear protective clothing.

Leishmaniasis, a parasitic infection transmitted by the bite of a sand fly, can lead to cutaneous or visceral infection. It has been reported among students who traveled to the rain forest in Costa Rica and among other travelers.<sup>74</sup> The appropriate use of insect repellent and other personal protection measures against sand fly bites is the only prevention tool that is available.

In 2003, we experienced the global spread of a novel coronavirus, SARS CoV, which causes severe acute respiratory syndrome (SARS); in many locations, the introduction of disease by ill travelers was followed by spread to healthcare workers and household contacts.<sup>75</sup> During the course of approximately 6 months, more than 8000 persons were infected with the virus and more than 800 persons died. The majority of cases occurred in adults, and pediatric patients appeared to have a milder clinical course.<sup>76,77</sup> The United States was relatively spared during the outbreak, reporting a total of 75 suspect or probable cases, with only eight laboratory-confirmed cases and no attributable deaths. However, during the SARS outbreak, at least 17 suspect or probable SARS cases were investigated in the United States among children recently adopted from China and their family members. Although none of these cases ultimately was laboratory-confirmed, these findings demonstrate unique risks for pediatric travelers and their families and highlight the need for

clinicians to be knowledgeable of emerging infectious diseases and recommended travel precautions.

## Prevention and Management of Diarrhea in Pediatric Travelers

One of the most difficult tasks faced by international travelers of any age is ensuring the safety of food and water. Travelers' diarrhea, caused by ingestion of contaminated food and water, affects between approximately 20 to 50 percent of adult travelers, and it is the most frequent health problem reported by travelers to developing countries.<sup>8</sup> In terms of children, a retrospective study conducted by Pitzinger and coworkers among Swiss children who had visited the tropics or subtropics reported similar incidence rates of traveler's diarrhea in children: 40 percent, 8.5 percent, 21.7 percent, and 36 percent in children aged 0 to 2 years, 3 to 6 years, 7 to 14 years, and 15 years and older, respectively.<sup>31</sup> In this study, the authors also found that small children (0 to 2 years) most frequently were affected with travelers' diarrhea and that the clinical course tended to be more severe and prolonged when compared with older pediatric age groups. Overall, children were found to have longer-lasting illness than that in adults, with an average duration of 11 days for all children combined and 29 days for small children. Enteric pathogens typically are isolated from approximately 50 to 75 percent of stool specimens from adult travelers with diarrhea; in the remainder, usually no pathogen is isolated. *Escherichia coli*, especially enterotoxigenic *E. coli* (ETEC), is the most common overall cause of travelers' diarrhea (although incidence can vary by destination), followed by *Camplobacter* spp., *Salmonella* spp., and *Shigella*. Other etiologic agents include pathogenic bacteria such as *Aeromonas* and *Plesiomonas*, protozoa (eg, *Giardia lamblia*, *Entamoeba histolytica*, *Cryptosporidium* spp., and *Cyclospora cayetanensis*), viruses such as rotavirus or Norwalk-like viruses, and rarely helminthes.<sup>78</sup> Numerous risk factors for traveler's diarrhea also have been identified and include the consumption of certain high-risk foods (raw foods such as meats, seafood, and vegetables, unpasteurized dairy products, and ice and tap water) and travel to certain destinations.<sup>6,8</sup> Destinations generally considered to have a high risk for travelers' diarrhea include Latin America, Africa, Asia, and the Middle East; low-risk travel destinations include North America, Northern Europe, Australia, and New Zealand.<sup>32</sup> Location of food preparation also is a recognized risk factor for traveler's diarrhea, with a higher risk shown for travelers eating from street vendors and in local restaurants and a lower risk for those eating in luxury hotels and private homes.

Counseling about food and water precautions to prevent traveler's diarrhea and anticipatory guidance to assure successful management of diarrhea are important parts of the pediatric pretravel assessment. In areas where access to bottled water is poor, water may be boiled for 1 minute (or for 3 minutes at altitudes greater than 2000 m [6562 feet]). These procedures will kill bacterial, parasitic, and viral pathogens. Chemical disinfection with iodine is an alternative method for water treatment when it is not possible to boil water;

however, this method cannot be relied on to kill *Cryptosporidium* unless the water stands for 15 minutes before drinking. Chlorine also can be used for chemical disinfection, but its germicidal activity varies with pH, temperature, and the organic content of the water; it can, therefore, provide less consistent levels of disinfection in many types of water. Portable filters are available and provide various degrees of protection against microbes.

Parents of pediatric travelers also should be counseled on the importance of advance planning for food and beverage items, especially for infants and young children. Breast-feeding infants are considered relatively safe from travelers' diarrhea; for infants receiving formula, formula concentrate and powdered forms are the most convenient for travel, but a clean water supply must be available, or water must be boiled or chemically disinfected before preparation. For feeding toddlers and for older children, the travel adage of "boil it, cook it, peel it, or forget it" applies. Travelers should avoid eating dairy products, including cheese and ice cream, because they often are unpasteurized.

When a pediatric traveler develops diarrhea, oral rehydration solution to maintain hydration is the treatment of choice. Parents also should be educated about the signs of mild, moderate, and severe dehydration and instructed in management of diarrhea, especially oral rehydration therapy. Antimotility agents, such as Lomotil (active ingredient, diphenoxylate; Pfizer Inc, New York, NY) and Imodium (active ingredient, loperamide; McNeil-PPC, Inc., Ft Washington, PA), are not recommended in children because of potential toxic megacolon and toxicity (extrapyramidal symptoms with diphenoxylate). Empiric treatment of traveler's diarrhea with antimicrobial agents, typically ciprofloxacin, because of resistance to other agents such as trimethoprim-sulfamethoxazole, is used for adults. Few studies of empiric antimicrobial treatment have been performed in children, and it is not a routinely recommended intervention for children. Parents should be advised that severe diarrhea requires urgent medical attention, especially in younger pediatric travelers. Prophylaxis for travelers' diarrhea with medications such as bismuth subsalicylate (the active ingredient in Pepto-Bismol; Proctor & Gamble, Cincinnati, OH) is not recommended because of the potential accumulation of salicylate. Prophylactic regimens with antimicrobial agents also are not recommended in children; the benefits usually are outweighed by potential risks, including allergic drug reactions, antimicrobial-associated colitis, and emergence of antibiotic-resistant strains. Moreover, limited information is available about destination-specific antimicrobial resistance patterns.<sup>37</sup>

## International Travel Information Resources

Clinicians need to provide pediatric travelers and parent(s) with up-to-date and accurate international travel health information and recommendations for preventing illness. Increasingly, the Internet and computer-based travel resources are being used by practitioners and consumers alike because they provide current information that can be used to counsel and treat international travelers appropriately and effectively.

ly.<sup>79</sup> A summary of some selected travel health resources that can be useful for providing information on health risks in specific travel destinations and current travel health recommendations (including immunizations and chemoprophylaxis) is provided in Table 1. In addition, if health care provided overseas is not covered by a family's health insurance company, insurance can be purchased from several companies and can include airlift/medical evacuation. The U.S. Embassy or consulate can provide names and addresses of English-speaking healthcare providers in the travel destination if medical evaluation is needed abroad. This information can be obtained before departure from Embassy Internet sites or by calling the embassy. In addition, names of physicians abroad also can be obtained from some worldwide directories, including those of the International Society of Travel Medicine, at [www.istm.org](http://www.istm.org).

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