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Immunization in Travel Medicine

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KEYWORDS

• Travel medicine • Pretravel consultation • Immunization
• Tropical medicine

Health issues related to travel, conquest, and immigration are not new.[1–3] Imported plagues, including the Black Death, decimated Europe during the Middle Ages, with the resultant practice of quarantine developed in Italy and widely practiced in the ports of fourteenth-century Europe. Smallpox, measles, and other diseases introduced by Europeans ravaged native populations in the Americas. Infections, such as plague and smallpox, have been purposefully introduced to aid conquest of native peoples and subdue enemy combatants. In the last 2 centuries, returning ill travelers, military personnel, and expatriates received treatment in medical facilities specializing in tropical diseases and provided significant impetus to vaccine development.

We live in an increasingly populous and mobile world than experienced by past generations. In the last 2 centuries, the global population has grown from less than 1 billion to more than 6 billion. Population mobility has increased 100-fold since 1960. Travelers can now return to their home country from the most remote locations within 2 days. In 2005, the World Tourism Organization reported 783 million international arrivals per year, with just less than half involving countries outside of Europe. Yearly, 80 million people travel from relatively sanitary, temperate, industrialized nations to the tropical and developing world, increasingly to more remote locations. Travel, increasingly felt to be part of an educated and desirable lifestyle, is available to a wider segment of the population by air and cruise ships. International travel has not shown a significant decline despite economic downturns, increasing fares, and worldwide unrest. The latest available data from 2006 denote Europe to be the leader in annual trip volume, with a total of 475 million travelers internationally, most commonly within Europe (402.1 million), and to a lesser extent to the Americas (24 million), Asia and the Pacific (21.2 million), Africa (16.8 million), and the Middle East (11.2 million) (UN World Tourism Organization: http://www.unwto.org).

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Travelers are frequently unaware of health and safety risks posed by travel and the availability of pretravel consultation.[4,5] Travel-related risks are usually not discussed by travel agents. Immigrant populations increasingly return to their birth countries to visit friends and relatives (VFRs) often not seeking pretravel consultation because of mistaken belief in their continuing immunity to endemic infections.[6]

Reported morbidity among travelers varies considerably; however, some health impairment is reported by up to 75% of short-term travelers to developing countries, with traveler's diarrhea the most common complaint.[7] On a typical 2-week trip, travelers miss an average of 3 days of planned activities because of illness. Approximately 1 in 5 travelers visits a physician on return.[5] Travelers, immigrants, and refugees can rapidly and unexpectedly introduce new and reemerging infections to those who they interact with during return travel and into their home communities. Over the last decade, because of the growth of tourism, humanitarian aid, religious pilgrimages, military deployment, educational and business travel, and immigration and refugee placement, the global health community has increasingly faced the challenges brought on by the emergence and rapid worldwide spread of novel viruses, such as severe acute respiratory syndrome; novel influenza strains, such as H1N1; and other bacterial and parasitic microorganisms, such as *Plasmodium knowlesi* malaria and increasing drug resistance in organisms such as *P falciparum*, *Neisseria gonorrheae*, and *Mycobacterium tuberculosis*.

Only 1% to 3.6% of deaths in travelers are because of infectious diseases; however, the risk of acute and chronic health issues in individual travelers and the risk of global pathogen spread mandate health care provider attention to the prevention, recognition, treatment, and control of these illnesses. Malaria, the most common infectious cause of death among travelers, is easily prevented with appropriate awareness and precautions. Increasingly, issues of special needs must be addressed to travelers, including pregnancy, human immunodeficiency virus, organ transplantation, and physical disabilities. Travel health care providers need to be knowledgeable and experienced when counseling patients regarding relative risk and preventative measures for the wide variety of health and safety issues that they will face during their travel, to ask an appropriate travel and immigration history, and to diagnose and treat illnesses presenting in travelers, immigrants, and refugees.[8,9]

In response to these specialized concerns, a new multidisciplinary medical specialty, travel medicine, emerged in 1988. In 1991, the International Society of Travel Medicine (ISTM; http://www.istm.org) was formed during the Second International Conference in Atlanta, Georgia. In 2010, the 11th International Conference, held in Budapest, Hungary, attracted more than 2000 participants from 65 countries. Travel medicine initially focused on tropical medicine concerns; however, it now encompasses the gamut of travel-related issues, including epidemiology and preventative medicine, wilderness and environmental medical issues, occupational medicine concerns, migrant medicine, medical tourism, international health, and personal safety, as well as the protection of local and global communities in which individuals live, work, and travel. More recently, robust systematically collected data collaboratively obtained by specialized travel/tropical medicine networks, such as TropNet Europe (http://www.tropnet.net), EuroTravNet (http://www.eurotravnet.eu), and GeoSentinel (http://www.geosentinel.org), in conjunction with the European Center for Disease Prevention and Control and the US Centers for Disease Control and Prevention (CDC), have been found to be effective sentinels for early detection and trending of travel-related diseases.[7–9]

Travel medicine providers include tropical medicine specialists, specialized travel medicine services, adult and pediatric general practice providers, occupational medicine practitioners, and pharmacists. In the United States, surveys indicate that 38% of practitioners train in family or general internal medicine, whereas in Canada,

approximately 54% of practitioners train in family medicine.[10] Travel and tropical medicine training has been increasingly embraced in emergency medicine over the last 20 years because of the escalating numbers of immigrants, refugees, and travelers presenting to emergency departments for care.[11] At present, few guidelines regarding certification and qualifications required to practice travel medicine exist. The Glasgow Diploma in Travel Medicine was the first diplomate course (DTM&H) offered by the Communicable Diseases Unit of the University of Glasgow in 1996. Several recognized courses are currently offered worldwide. Since 2003, ISTM has offered a voluntary Certificate of Knowledge Examination, which requires training and/or practice prerequisites. In 2010, the Royal College of Physicians and Surgeons of Glasgow introduced a formal 2-part examination to assess the knowledge of trained and experienced practitioners. Licensure to provide yellow fever vaccine is largely regulated by national or regional health care authorities in Europe and the United States. The CDC publishes the *Health Information for International Travel* (the Yellow Book), which serves as a reference, including updated malaria prophylaxis and treatment guidelines, for those advising international travelers about health risks (http://wwwnc.cdc.gov/travel/content/yellowbook/home-2010.aspx). Similar guidelines are available from several other national health services and specialty societies, such as the Public Health Agency of Canada's Travel Health Guidelines (http://www.phac-aspc.gc.ca/tmp-pmv/) and Health Protection Scotland's Travax Web site (http://www.travax.nhs.uk). Rigorous structured continuing medical education, including outpatient clinic and hospital rounds, didactic lectures, and laboratory work, is provided in many tropical countries worldwide by specialty organizations and tropical medicine consultants. Multiple studies underline the importance of appropriate training, experience, and ongoing education in providing individuals with proper peritravel care.[12–14]

TRAVEL MEDICINE PRACTICE

In general, travel medicine practice involves education and care of the traveler, before, during, and after a trip or more-prolonged stay in another country, to maintain traveler's well-being and safety and avoid importation of infectious agents. As noted, disease surveillance and care of migrants and refugees are becoming increasingly important additions to this practice. The pretravel consultation begins with an evaluation of the health and immunization status of the traveler and concludes with an assessment and a plan based on the itinerary-based risk. A growing number of decision-support resources and tools are available to facilitate this process, including government travel advice sites, Travax, Tropimed, and Gideon. Prevention of individual diseases is addressed by a combination of patient education, vaccination, provision of chemoprophylaxis, use of methods to avoid insect exposure, food and water precautions, provision of medication for self-treatment of certain illnesses, and provision of travel and evacuation insurance if desired. Individual recommendations are based on epidemiologically determined likelihood of injury and disease occurrence in an individual area and the individual traveler's health, experience, health belief model, and tolerance of risk.[15] At times, pretravel consultation may provide a cogent argument for travel postponement, as with pregnant women planning travel to malarial areas.

PRETRAVEL CONSULTATION

Routine medical and dental care should be updated before a trip. Patients are advised to carry a sufficient supply of required medications with them, because those drugs purchased overseas may not be the same drug, may not be manufactured to similar standards as those available in developed countries, or may contain counterfeit

medications or contaminants. Detailed planning, equipment, and medications for large and specialized groups and expeditions are beyond the scope of this article but are readily available from several articles, texts, and on-line information sites provided by both the ISTM and the Wilderness Medicine Society.

Ideally, the initial pretravel consultation should occur at least 4 to 6 weeks before the patient's departure to allow adequate time for serial immunizations and immunizations to take effect, to begin antimalarials that must be started before arrival in endemic areas, and for assessment of potential adverse reactions to vaccinations and medications. If a traveler has less time before travel, it remains important to see a provider for necessary vaccines, antimalarials, other medications, and counseling. Some medications may cause vaccine interactions or interfere with vaccine-derived immune protection. For example, an interval of at least 10 days should be scheduled between a dose of oral cholera vaccine and the initial dose of chloroquine or mefloquine. In general, attenuated live virus vaccines and bacterial vaccines are contraindicated in persons with altered immune competence and during pregnancy.[16–18] Multiple vaccines may be given at different sites during the same visit, limited by the traveler's anticipated tolerance for multiple injections and minor side effects. Up to 6 live virus vaccines may be given on the same day without interfering with immune efficacy; otherwise live virus vaccine doses should be separated by at least 1 month. Some immunizations, such as hepatitis A, may be provided in an accelerated schedule.

Pretravel History

The individual's medical history, current medications and allergies, and immunizations are reviewed because these influence vaccine indications and potential contraindications.[18] For example, individuals with egg allergies have a potential contraindication to the vaccination for measles, mumps, rubella, yellow fever, influenza, and rabies. The pretravel history includes exploration and documentation of the individual's purposes for travel, specific travel itinerary, and duration, including discussion of planned or possible stopovers and side trips, with attention to seasonal and locale-specific variances in risk of infection and injury. For example, an individual traveling on business to Rio de Janeiro might wish to take a side trip to the Amazon, which will require additional counseling, vaccinations, and prophylaxis. The types of accommodation and likely styles of eating and drinking during the trip should be discussed relative to risk. Planned activities should also be reviewed relative to risk, for example, spelunking, white water rafting, fresh water and salt water swimming and diving, trekking in remote areas, and potential domestic and wild animal exposure. What degree of interaction will the traveler have with local populations? Will the traveler be engaged in agriculture, wildlife biology, construction, or local medical or humanitarian work? Will the individual travel to an area of unrest or conflict? Current outbreaks of disease and areas of violence and conflict, described on State Department, World Health Organization (WHO), CDC, Pan American Health Organization, and ProMed sites, also play important roles in pretravel counseling.

Immunizations

Immunization is the most common reason that patients seek pretravel consultations. Travelers to tropical and developing countries from Western Europe and North America are exposed to communicable diseases infrequently seen in their home countries because of generally high sanitation standards and mandatory childhood immunization. Appropriate immunization has been shown to increase the likelihood of a traveler remaining healthy. The CDC currently divides travel immunizations into 3 categories: routine, recommended, and required. First-time travelers may be dismayed at the

number of vaccines recommended, the route of administration, and the cost. Because many vaccines are not covered by regular health insurance, vaccines and the relative risk of travel-related illness are prioritized for the traveler. Travelers may elect to obtain routine vaccinations from their primary care provider to maximize insurance coverage. All immunizations administered to travelers are recorded in a copy of the yellow booklet, *International Certificates of Vaccination*, recognized by the WHO, which should be kept with the individual's passport. A specific page validates yellow fever vaccination.

Routine immunizations before travel

Routine immunizations, such as those for tetanus, diphtheria, pertussis, measles, mumps, rubella, varicella, pneumococcus, and influenza, should be reviewed and updated as warranted. Travelers are counseled about the potential differences in influenza risk and likelihood of vaccine efficacy when traveling in semitropical and tropical areas than in temperate areas and between the northern and southern hemispheres. Because of the infrequent but continued presence of wild poliovirus and clinical polio in developing countries, the CDC currently recommends that adult travelers who have received a primary polio vaccination series with either inactivated poliovirus vaccine (IPV) or oral polio vaccine (OPV) should receive a single lifetime additional dose of IPV.[19] The CDC currently recommends that all adults (younger than 65 years) should receive 1 dose of Tdap (tetanus-diptheria-pertussis vaccine) as one of their recommended 10-year boosters, which is particularly relevant to the traveler because of the increased likelihood of exposure to diphtheria and pertussis in developing countries. Individuals born before 1958 are generally considered immune to measles and mumps. All individuals born after 1957 should have documentation of 1 or more doses of measles-mumps-rubella (MMR) vaccine unless they have medical contraindication, laboratory evidence of immunity to each of the 3 diseases, or documentation of provider-diagnosed measles or mumps. Individuals who received inactivated (killed) measles vaccine or measles vaccine of unknown type during the period from 1963 to 1967 should be revaccinated with 2 doses of measles vaccine. Because of a significant risk of measles exposure, a second MMR vaccine, administered a minimum of 28 days after the first, is recommended for adults who work in outbreak settings or in health care settings in developing countries or plan to travel internationally.[20]

Recommended vaccines before travel

Recommended vaccines include those that help to protect travelers from contracting illnesses present in other parts of the world and to prevent the importation of infectious diseases across international borders. Which vaccinations an individual will need depends on several factors, including the traveler's age and health status, previous immunization, the destination, the season of the year the individual will be traveling, the length of time an individual will spend in a specific area, whether a traveler will be spending time in rural areas, what activities the individual will engage in,[21–23] and whether the destination is currently experiencing disease outbreaks. For example, rabies preexposure prophylaxis is recommended for those travelers who will spend a significant time outdoors, especially in rural areas, or who anticipate activities such as spelunking, cycling, camping, or hiking. Rabies vaccination is also recommended for travelers with significant occupational risk (such as veterinarians); for long-term travelers and expatriates living in areas of significant exposure risk; and for travelers involved in any activities that might bring them into direct contact with bats, carnivores, and other mammals. Children are considered at higher risk for rabies exposure because they tend to interact with animals, may receive more bites, and may not report bites or exposures. See **Table 1** for a list of recommended vaccinations for travel to certain countries.

Table 1
Travel vaccines

Vaccine	Type	Administration	Booster Interval	Indications	Efficacy	Contraindications	Precautions	Comments	Side Effects
Cholera (OCV)-CVD 103-HgR (Orochol-E; Berna Biotech, Bern, Switzerland)	Live attenuated, derived from reference strain 569B (classical, O1, Inaba)	Oral, 1 dose	6-mo intervals for continued risk	No WHO regulation. 2 available that are considered safe and efficacious. Consider for long-term travel to endemic areas or to areas with active outbreaks	60%–90% in clinical studies	Not recommended for children younger than 2 y. Not recommended in pregnancy. Not recommended in immune deficiency and immuno-suppressive or antimitotic drugs	Travelers should still follow food and water precautions. Travelers with underlying gastric hypochlorhydria or partial resection or who take medications that block gastric acid production may have increased susceptibility to cholera.	Earliest onset of protective immunity 8 d after immunization Does not protect against *V cholerae* O139	Rare gastrointestinal
WC/rBS (Dukoral; SBL Powderject, Stockholm, Sweden)	Killed whole unit B subunit	Oral, 2 doses 10–14 d apart	6-mo intervals for continued risk	No WHO regulation. 2 available that are considered safe and efficacious	50%–86%	Not recommended for children younger than 2 y	Travelers should still follow food and water precautions. Travelers with underlying gastric hypochlorhydria or partial resection or who take medications that block gastric acid production may have increased susceptibility to cholera.	Earliest onset of protective immunity 10 d after the second dose Not available in United States. Available in Canada, Western Europe, South America, and Asia. Offers some protection against traveler's diarrhea because of cross-reactivity with heat-labile toxin. Does not protect against *V cholerae* O139 A variant WC/rBS is licensed in	Rare gastrointestinal

							Vietnam which contains no recombinant B-subunit, also administered in 2 doses, 1 wk apart	
Hepatitis A (HAV) (Havrix; GlaxoSmith-Kline Biologicals, Pittsburgh, PA, USA)	Inactivated HAV, derived from HM-175 viral strain	Intramuscular (IM) deltoid, 2 doses	0 and 6–12 mo (delay in booster dose up to 66 mo in testing did not seem to influence anamnestic immune response to the booster dose	Hepatitis A is a serious viral infection with fecal oral transmission, which is the leading cause of vaccine-preventable illness occurring among nonimmune international travelers. The incidence rate can be as high as 20 cases/1000 travelers/mo during adventure or rural travel, and 3–6 cases/1000 travelers/mo in those going to tourist areas and resorts, in developing countries.	90%–100% seropositivity rate	Not recommended for children younger than 1 y. Sensitivity to aluminum, aluminum hydroxy, or 2-phenoxy-ethanol	Available worldwide Protective immunity 2–4 wk following receipt 1st dose. 2nd dose confers lasting immunity >10y. Now included among routine immunizations in US for children Updated recommen-dations no longer call for dose IG when hepatitis A is given <2 wk before departure	Severe allergic reaction (eg, anaphylaxis) after a previous dose of any hepatitis A–containing vaccine, or to any component of HAVRIX, including neomycin. The most common adverse events are injection-site soreness (56% adults, 21% children) and headache (14% adults, <9% children)
HAV (VAQTA; Merck & Co, Inc, Whitehouse	Inactivated HAV, derived from CR-326F strain	IM deltoid, 2 doses	0 and 6–12 mo (delay in booster dose up to 66 mo in testing did not	Hepatitis A is a serious viral infection with fecal oral transmission,	90%–100% seropositivity rate	Not recommended for children younger than 1 y. Sensitivity to aluminum or	Available Worldwide Protective immunity 2–4 wk after receipt	Severe allergic reaction (eg, anaphylaxis) after a previous dose of any

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Table 1
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Vaccine	Type	Administration	Booster Interval	Indications	Efficacy	Contraindications	Precautions	Comments	Side Effects
Station, NJ, USA)			seem to influence anamnestic immune response to the booster dose	which is the leading cause of vaccine-preventable illness occurring among nonimmune international travelers. The incidence rate can be as high as 20 cases/1000 travelers/mo during adventure or rural travel, and 3–6 cases/1000 travelers/mo in those going to tourist areas and resorts, in developing countries.		aluminum hydroxyl		of the first dose. Second dose confers lasting immunity for more than 10 y. Now included among routine immunizations in the United States for children Updated recommendations no longer call for dose IG when hepatitis A is given less than 2 wk before departure	hepatitis A–containing vaccine The most common adverse events are injection-site soreness and headache
HAV (AVAXIM; Sanofi Pasteur, Swiftwater, PA, USA)	Inactivated HAV, derived from GBM viral strain	IM deltoid, 2 doses	0 and 6–12 mo (delay in booster dose up to 66 mo in testing did not seem to influence anamnestic immune response to the booster dose	Hepatitis A is a serious viral infection with fecal oral transmission, which is the leading cause of vaccine-preventable illness occurring among non-immune international travelers. The incidence rate can be as high	90%–100% seropositivity rate	Not recommended for children younger than 1 y		Available in Europe Protective immunity 2–4 weeks after the receipt of first dose. Second dose confers lasting immunity for more than 10 y. Now included among routine immunizations in the United States for children	Severe allergic reaction (eg, anaphylaxis) after a previous dose of any hepatitis A–containing vaccine The most common adverse events are injection-site soreness and headache

				as 20 cases/1000 travelers/mo during adventure or rural travel, and 3–6 cases/1000 travelers/mo in those going to tourist areas and resorts, in developing countries.				Updated recommendations no longer call for dose IG when hepatitis A is given less than 2 wk before departure	
HAV (Epaxal Berna; Berna BioTech, Bern, Switzerland)	Inactivated virosomal HAV, derived from RG-SB viral strain	IM deltoid, 2 doses	0 and 6–12 mo (delay in booster dose up to 66 mo in testing did not seem to influence anamnestic immune response to the booster dose	Hepatitis A is a serious viral infection with fecal oral transmission, which is the leading cause of vaccine-preventable illness occurring among nonimmune international travelers. The incidence rate can be as high as 20 cases/1000 travelers/mo during adventure or rural travel, and 3–6 cases/1000 travelers/mo in those going to tourist areas and resorts, in	90%–100% seropositivity rate	Not recommended for children younger than 1 y		Available in Europe Protective immunity 2–4 wk after the receipt of first dose. Second dose confers lasting immunity for more than 10 y. Now included among routine immunizations in the United States for children Updated recommendations no longer call for dose IG when hepatitis A is given less than 2 wk before departure	Severe allergic reaction (eg, anaphylaxis) after a previous dose of any hepatitis A–containing vaccine The most common adverse events are injection-site soreness and headache

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Vaccine	Type	Administration	Booster Interval	Indications	Efficacy	Contraindications	Precautions	Comments	Side Effects
				developing countries.					
Hepatitis B (HBV) (Engerix B; GlaxoSmith-Kline Biologicals, Pittsburgh, PA, USA)	Recom-binant HBV	IM deltoid, 3 doses	0, 1, and 6 mo (standard schedule) 0, 1, and 2 mo (accelerated schedule) Need for booster not determined	In many parts of Asia and Africa, up to 15% of the general population may be asymptomatic carriers of hepatitis B virus. Those who will live and work among the local population, and those who might have intimate contact or sexual contact with the local population, should consider immunization. Inadvertent exposures can occur during medical procedures and personal grooming/ esthetic activities (shaving, manicures and pedicures, piercings, tattoos, etc)	90%–100% seropositivity rate			Included in the recommended childhood immunization schedule since 1990 In travelers at high risk, the possibility of nonsero-conversion among vaccine recipients should be considered. Risk factors include age more than 30 y, chronic medical conditions, smoking, obesity, male gender, and vaccine administration in buttock. Anti-HBs testing should be performed 1–6 mo after the last dose of vaccine. If no seroconversion has occurred, 1 additional dose of hepatitis B vaccine should be given and the titer rechecked 4–12 wk later. If no conversion has	Severe allergic reaction (eg, anaphylaxis) after a previous dose of any hepatitis B–containing vaccine or to any component of ENGERIX B, including yeast. The most common adverse events are injection-site soreness and tiredness.

						occurred, the second series is completed with 2 additional doses given at monthly intervals. Limited data from clinical studies show that titers and protection do not always correlate closely, even those with low or nondetectable titers may still be protected after immunization.	
HBV (Recombivax; Merck & Co, Inc, Whitehouse Station, NJ, USA)	Recombinant noninfectious subunit viral vaccine, derived from HBsAg produced in yeast cells	IM deltoid, 3 doses	0, 1, and 6 mo (standard schedule)	In many parts of Asia and Africa, up to 15% of the general population may be asymptomatic carriers of hepatitis B virus. Those who will live and work among the local population, and those who might have intimate contact or sexual contact with the local population, should consider immunization.	90%–100% seropositivity rate	Included in the recommended childhood immunization schedule since 1990. In travelers at high risk, the possibility of nonsero-conversion among vaccine recipients should be considered. Risk factors include age more than 30 y, chronic medical conditions, smoking, obesity, male gender, and vaccine	Severe allergic reaction (eg, anaphylaxis) after a previous dose of any hepatitis B–containing vaccine. The most common adverse events are injection-site soreness and tiredness.

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Vaccine	Type	Administration	Booster Interval	Indications	Efficacy	Contraindications	Precautions	Comments	Side Effects
				Inadvertent exposures can occur during medical procedures and personal grooming/ esthetic activities (shaving, manicures and pedicures, piercings, tattoos, etc)				administration in buttock. Anti-HBs testing should be performed 1–6 mo after the last dose of vaccine. If no seroconversion has occurred, 1 additional dose of hepatitis B vaccine should be given and the titer rechecked 4–12 wk later. If no conversion has occurred, the second series is completed with 2 additional doses given at monthly intervals. Limited data from clinical studies show that titers and protection do not always correlate closely, even those with low or nondetectable titers may still be protected after immunization.	
Hepatitis A/B (Twinrix; GlaxoSmith-Kline	720 enzyme-linked immuno-sorbent assay units hepatitis	IM deltoid, 3 doses	0, 1, and 6 mo (standard schedule)	See above comments for hepatitis A and hepatitis B	100% seropositivity rate after first dose A, 82%			A pediatric formulation of the combined vaccine is not	Adverse reactions with Twinrix are similar to those

Biologicals, Pittsburgh, PA, USA)	A antigen and 20 μg hepatitis B antigen		0, 7, and 21–30 d (accelerated schedule) Need for booster not determined after standard schedule, a fourth dose is recommended 12 mo after the first dose to assure long-lasting immunity		after first dose B, 86% after second dose B, and 97% after third dose B		available in the United States but is available in other countries	experienced with the monovalent components. The most common adverse events are injection-site soreness, headache, and tiredness.
Immune globulin (IG)	Purified human IG	IM, deep Gluteus Maximus, 1 dose of 2 mL for 3-mo protection or 1 dose of 3 mL for 5-mo protection		Those unable to receive hepatitis A vaccination			Hepatitis A protection via passive transfer of preformed antibodies against hepatitis A (at least 100 IU/mL)	
Japanese encephalitis (JEV Vax, Biken; Sanofi Pasteur, Swiftwater, PA, USA)	Inactivated Japanese encephalitis virus (JEV) derived from infected mouse brains, with the final product containing less than 2 ng of myelin base protein per milliliter	Subcutaneous (SC), 3 doses	0, 7, and 30 d. Booster dose may be given after 2 y	Low risk of travel-associated JEV disease but high morbidity and mortality of disease. Not considered a risk for short-term travelers visiting usual tourist destinations in urban areas and developed resort areas. Visitors going to endemic rural areas during the transmission season face an estimated risk	88%–100% adults from nonendemic settings developed neutralizing antibodies after receiving 3 doses of vaccine	Not recommended for children younger than 1 y	Production was discontinued in 2006, but stockpiles of vaccine will be in use for children aged 1–16 y until depleted 2010/2011	Local pain, swelling, and redness at injection site in approximately 20% recipients. Systemic symptoms of fever, headache, and malaise in approximately 10% recipients. Hypersensitivity reactions, most commonly urticaria, angioedema, or both, in 15–62/10,000 vaccinated individuals

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Vaccine	Type	Administration	Booster Interval	Indications	Efficacy	Contraindications	Precautions	Comments	Side Effects
				during a 1-mo period of 1:5000 or 1:20,000/wk. The risk of infection is decreased by personal protective measures to prevent mosquito bites. Japanese encephalitis has been acquired by short-term travelers to endemic rural areas, as such it should be offered to travelers going on trips of any length to rural areas during transmission season; travelers to an area of JEV outbreak; and expatriate workers, students, and missionaries who plan to travel, live, or work in urban, suburban, or farming communities in endemic areas.				almost immediately after or up to 2 wk after the first, second, or third dose of vaccine. The CDC recommends that vaccinated individuals be directly observed for 30 min after vaccine receipt and that they do not depart until 10 d after the last JEV dose.

Japanese encephalitis (JEV IXIARO; Intercel Biomedical, Livingston, UK, distributed by Novartis Vaccines, Cambridge, MA, USA)[47–49]	Inactivated, cell culture derived	IM, 0.5 mL, 2 doses	0 and 28 d. Approved on 2009, as such need for and timing of booster doses have not yet been determined		96% adults developed protective neutralizing antibodies	Not licensed in the United States for travelers younger than 17 y	Immunization should be completed at least 2 wk before traveling to endemic area. There are no data for the interchange-ability of JE vaccines or the use of IXIARO as a booster dose after a primary series with JE-VAX. It is currently recommended that those who previously received JE-VAX and require further vaccination should receive either a booster dose with JE-VAX or a primary series of 2 doses of IXIARO.	Contains protamine sulfate. The most common (≥10%) systemic adverse events were headache and myalgia. The most common (≥10%) injection-site reactions were pain and tenderness. Safety and effectiveness have not been established in pregnant women and nursing mothers.
Meningococcus (A/C/Y/W-135) (MCV4) (Menactra; Sanofi Pasteur, Swiftwater, PA, USA)	A, C, Y, W135 polysaccharides conjugated to diphtheria toxin protein	IM, 1 dose	Booster interval has not been determined, with estimated protective immunity lasting 7 y or more Individuals who received the MPSV4 vaccine in the past can be boosted with MCV4 if	[a]Due to outbreaks of meningococcal disease among Hajj pilgrims with secondary spread to family and friends after the pilgrims returned home, Saudi Arabia mandated vaccine		Licensed for use among individuals aged 11–55 y	The Advisory Committee on Immunization Practices routinely recommends vaccination with quadrivalent meningococcal conjugate vaccine for individuals 11–18 y old and	The most frequently reported adverse effects reported with MCV4 (Menactra) in children 2–10 y of age were local effects at the injection site (eg, pain) and irritability. Diarrhea,

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Vaccine	Type	Administration	Booster Interval	Indications	Efficacy	Contraindications	Precautions	Comments	Side Effects
			they remain at risk for exposure	requirement in 2003 for all persons traveling to Saudi Arabia during the annual Hajj, and either quadrivalent vaccine will fulfill the requirement. In some countries, bivalent meningococcal polysaccharide vaccine or conjugate vaccines vs A and C are commonly available; however, outbreaks involving Y and W-135 have occurred during some Hajj outbreaks. Vaccine is also recommended for travelers going to live or work in certain areas of South America and sub-Saharan Africa and other areas where meningococcal disease is epidemic or				incoming college freshman who will live in large residence halls on campus. Some colleges require vaccination before matriculation. It is also recommended for individuals at increased risk for disease, including microbiologists routinely exposed to strains, military recruits, individuals with terminal complement component deficiencies, and persons with anatomic or functional asplenia. Enables enhanced immunity through activation of a strong T-cell response	drowsiness, and anorexia were also common in this age group. The most common adverse effects reported with MCV4 (Menactra) in adolescents and adults 11–55 y of age were local effects at the site of injection (eg, pain), headache, and fatigue. In the clinical studies comparing safety and efficacy of MCV4 (Menactra) and MPSV4 (Menomune), adverse local effects were reported more frequently with MCV4 (Menactra) than with MPSV4 (Menomune); however, the incidence of systemic adverse effects reported with the conjugated vaccine was

				hyperendemic among the local residents.		similar to that reported with the unconjugated vaccine.
Meningococcus (A/C/Y/W-135) (MPSV4) (Menimmune; Sanofi Pasteur, Swiftwater, PA, USA)	Polysaccharide vaccine	SC, 1 dose	Estimated protective interval 3–5 y A second dose is recommended after 2–3 y in children living in high-risk areas who received their first dose at younger than 4 y	Due to outbreaks of meningococcal disease among Hajj pilgrims with secondary spread to family and friends after the pilgrims returned home, Saudi Arabia mandated vaccine requirement in 2003 for all persons traveling to Saudi Arabia during the annual Hajj, and either quadrivalent vaccine will fulfill the requirement. In some countries, bivalent meningococcal polysaccharide vaccine or conjugate vaccines vs A and C are commonly available; however, outbreaks involving Y and W-135 have occurred		The most frequently reported adverse effects reported with MCV4 (Menactra) in children 2–10 y of age were local effects at the injection site (eg, pain) and irritability. Diarrhea, drowsiness, and anorexia were also common in this age group. The most common adverse effects reported with MCV4 (Menactra) in adolescents and adults 11–55 y of age were local effects at the site of injection (eg, pain), headache, and fatigue. In the clinical studies comparing safety and efficacy of MCV4 (Menactra) and MPSV4 (Menomune), adverse local

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Vaccine	Type	Administration	Booster Interval	Indications	Efficacy	Contraindications	Precautions	Comments	Side Effects
				during some Hajj outbreaks. Vaccine is also recommended for travelers going to live or work in certain areas of South America and sub-Saharan Africa and other areas where meningococcal disease is epidemic or hyperendemic among the local residents.					effects were reported more frequently with MCV4 (Menactra) than with MPSV4 (Menomune); however, the incidence of systemic adverse effects reported with the conjugated vaccine was similar to that reported with the unconjugated vaccine.
Plague	Killed bacterial vaccine	IM, 1 mL, 3 doses	0, 1, and 4–7 mo Boost if risk exposure persists. First 2 booster doses (0.1–0.2 mL) 6 mo apart, then 1 booster dose at 1- to 2-y intervals	International travelers going on standard tourist itineraries to countries of Asia, Africa, and the Americas where plague is reported unlikely to be at risk. Those at high risk include field biologists and those who will reside or work in areas where avoidance of rodents and fleas is difficult.	Poorly documented protective effect	Not commercially available			Pain, redness, and induration at the site of injections. Systemic symptoms include headache, fever, and malaise after repeated doses.

Rabies (HDCV) (HDCV Imovax; Sanofi Pasteur, Swiftwater, PA, USA) or rabies vaccine absorbed (RVA; GlaxoSmith-Kline Biologicals, Pittsburgh, PA, USA) or purified chick embryo vaccine (PCEC) (RabAvert; Chiron, Emeryville, CA, USA)	Inactivated virus vaccine. RVA and PCEC are derived from virus grown in tissue culture cells in a medium clear of human albumin.	IM, 1 mL, 3 doses	0, 7, and 21 or 28 d Boost after 2 years if continued risk of exposure or test serum antibody level	Animal bites, especially dog bites, present a potential rabies hazard to those who travel to urban and rural areas in Central and South America, the Middle East, Africa and Asia. Preexposure rabies immunization is recommended for rural travelers, especially adventure travelers, who go to remote areas, and for expatriate workers, missionaries, and their families living in countries where rabies is a recognized risk. Preexposure prophylaxis simplifies the postbite medical care of a person following an exposure in a high-risk area.		The 3 vaccine products may be used inter-changeably in preexposure rabies immunization given IM. RVA and PCEC vaccines may only be given IM.	Mild local reactions are common, including erythema, pain, and swelling at the injection site. Mild systemic symptoms including headache, dizziness, nausea, abdominal pain, and myalgias may develop in some recipients. In approximately 5% of individuals receiving booster doses of HDCV for preexposure prophylaxis, a serum sickness–like illness characterized by urticaria, fever, malaise, arthralgias, arthritis, nausea, and vomiting may develop 2–21 d after the vaccine dose is administered.

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Vaccine	Type	Administration	Booster Interval	Indications	Efficacy	Contraindications	Precautions	Comments	Side Effects
Rabies (HDCV), Imovax intradermal administration	Inactivated virus vaccine	Intradermal, 0.1 mL, 3 doses	0, 7, and 21 or 28 d Boost after 2 years if continued risk of exposure or test serum antibody level	Animal bites, especially dog bites, present a potential rabies hazard to those who travel to urban and rural areas in Central and South America, the Middle East, Africa, and Asia. Preexposure rabies immunization is recommended for rural travelers, especially adventure travelers, who go to remote areas, and for expatriate workers, missionaries, and their families living in countries where rabies is a recognized risk. Preexposure prophylaxis simplifies the postbite medical care of a person following an exposure in a high-risk area.				The efficacy of the intradermal vaccine series is compromised if chloroquine prophylaxis against malaria is started within 3 wk after the third dose of intradermal vaccine.	

Tick borne encephalitis (Encepur; Chiron, Behring, Germany), standard schedule	IM, 3 doses	0, 28, and 300 d Boost 3 years after last dose	Tick borne encephalitis is caused by infection with either Central European encephalitis virus (CEEV) in Europe or Russian Spring Summer encephalitis virus (RSSEV) in the Common-wealth of Independent States, transmitted by Ixodes ticks in endemic areas from April through August or ingestion of unpasteurized dairy products from infected cows, goats, or sheep.	Vaccination is currently not available in the United States Vaccines are interchangeable Because vaccine is not available in the United States, travelers will need to rely on personal protective measures against insect exposure, including protective clothing, DEET on all exposed areas of skin, and treating outdoor clothing with permethrin-containing insecticide. All travelers to these areas are advised not to eat unpasteurized dairy products.
Tick borne encephalitis (Encepur; Chiron, Behring, Germany), rapid schedule	SC, 3 doses	0,7, and 21 d First booster dose at 15 mo after first vaccine dose, second booster dose at 36 mo after the first booster	Tick borne encephalitis is caused by infection with either CEEV in Europe or RSSEV in the Common-wealth of Independent States, transmitted by Ixodes ticks in endemic areas from April through	Vaccination is currently not available in the United States Vaccines are interchangeable Because vaccine is not available in the United States, travelers will need to rely on personal protective measures against insect exposure, including protective clothing, DEET on all exposed areas of skin, and

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Vaccine	Type	Administration	Booster Interval	Indications	Efficacy	Contraindications	Precautions	Comments	Side Effects
				August or ingestion of unpasteurized dairy products from infected cows, goats, or sheep.			treating outdoor clothing with permethrin-containing insecticide. All travelers to these areas are advised not to eat unpasteurized dairy products.		
Tick borne encephalitis (FSME; Immuno, Vienna, Austria), standard schedule	Chick embryo cell cultures	SC, 3 doses	0, 1–3, and 9–12 mo after dose 2 Boost 3 years after last dose	Tick borne encephalitis is caused by infection with either CEEV in Europe or RSSEV in the Common-wealth of Independent States, transmitted by Ixodes ticks in endemic areas from April through August or ingestion of unpasteurized dairy products from infected cows, goats, or sheep.			Available in Canada and Europe Vaccination is currently not available in the United States Vaccines are interchangeable Because vaccine is not available in the United States, travelers will need to rely on personal protective measures against insect exposure, including protective clothing, DEET on all exposed areas of skin, and treating outdoor clothing with permethrin-containing insecticide. All travelers to these areas are advised not to eat unpasteurized dairy products.		
Tick borne encephalitis (FSME; Immuno, Vienna,	Chick embryo cell cultures	SC, 3 doses	First booster dose at 15 mo after the first vaccine dose, second booster at	Tick borne encephalitis is caused by infection with either CEEV in Europe or			Vaccination is currently not available in the United States Vaccines are interchangeable		

Austria), rapid schedule			36 mo after the first booster	RSSEV in the Commonwealth of Independent States, transmitted by Ixodes ticks in endemic areas from April through August or ingestion of unpasteurized dairy products from infected cows, goats, or sheep.		Because vaccine is not available in the United States, travelers will need to rely on personal protective measures against insect exposure, including protective clothing, DEET on all exposed areas of skin, and treating outdoor clothing with permethrin-containing insecticide. All travelers to these areas are advised not to eat unpasteurized dairy products.		
Typhoid (Typhim Vi; Sanofi Pasteur, Swiftwater, PA, USA)	Highly purified Vi capsular polysaccharide	IM, 1 dose	Boost after 2 y for continued risk of exposure	The incidence of typhoid in American travelers is relatively low (50–170 cases/1 million travelers), but among reported cases in the United States, 62% were acquired during international travel. Particularly, high risk is experienced in travel to Mexico, Peru, India, Pakistan, and Chile. Southeast Asia	Children older than 2 y Discard vaccine dose if discolored or particulate material is present	Elicits immunity 10 d after receipt of a single primary dose The protection against typhoid fever from immunization can be overwhelmed by ingestion of highly contaminated food.		Generally well tolerated. The following adverse effects were reported: common and generally mild, constipation, abdominal cramps, diarrhea, nausea, vomiting, anorexia, fever, headache, and urticarial rash. Very rarely dermatitis, pruritis and urticaria, anaphylaxis, paresthesias, and arthralgias and myalgias.

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Vaccine	Type	Administration	Booster Interval	Indications	Efficacy	Contraindications	Precautions	Comments	Side Effects
				and sub-Saharan Africa are also considered areas of increased risk. Travelers to high-risk areas who will be staying for more than 1 mo.					
Typhoid (Vivotif; Berna BioTech, Bern, Switzerland)	Live attenuated strain of Salmonella typhi bacteria (Ty21A)	Oral, 4 doses	1 capsule orally on empty stomach every 2 d. Booster at 5 y with another 4-capsule regimen A liquid suspension form is available in Europe		43%–96% in field trials in residents of endemic areas	Children older than 6 y Safety in immune-compromised individuals has not yet been demonstrated, and this vaccine should not be administered to them. The vaccine is not recommended for pregnant women	The protection against typhoid fever from immunization can be overwhelmed by ingestion of highly contaminated food.	Any condition that interferes with virus strain multiplication in the bowel may result in an insufficient antigen stimulus to induce an adequate protective response. It should not be administered during an acute gastrointestinal illness or if the individual is receiving antibiotics active against salmonella. Proguanil, one component of Malarone used for malaria prevention and treatment,	The following adverse effects were reported: common and generally mild, constipation, abdominal cramps, diarrhea, nausea, vomiting, anorexia, fever, headache, and urticarial rash. Very rarely dermatitis, pruritis and urticaria, anaphylaxis, paresthesias, and arthralgias and myalgias.

								decreases the immune response to typhoid vaccine, as such they should be administered 10 or more days after the final dose of vaccine.	
Yellow Fever (YF Vax; Sanofi Pasteur, Swiftwater, PA, USA)[48]	Live attenuated vaccine prepared from the 17D strain of yellow fever virus in eggs. Vaccine production is controlled by the WHO.	SC, 1 dose	Booster every 10 y, although immunity is possibly lifelong	Immunization is required for entry into some countries within the endemic zones in sub-Saharan Africa or tropical South America or may be recommended to travelers either going to rural tropical areas within the endemic zones or to both rural and urban areas during yellow fever outbreaks.	Seroconversion rates of 95% or more and a protection rate of more than 99% in immuno-competent individuals	The vaccine is not recommended for individuals with a history of anaphylaxis to eggs Immuno-suppression is a contra-indication to receiving the vaccine Most travel experts would consider administering yellow fever vaccine to HIV-positive travelers if the CD4 count is greater than 400 Not for children younger than 6 mo because of a significant but rare (1/8 million doses) risk of vaccine-associated neurotropic		A list of countries requiring yellow fever vaccination for entry can be found on either the CDC or WHO Websites. If a person for whom the vaccine is contraindicated must travel to one of these countries, a signed statement by a licensed vaccination center, on letterhead stationary, that states that yellow fever vaccine could not be administered to the traveler because medical contra-indications will be accepted	Between 1996 and 2002, 13 cases of yellow fever vaccine–associated viscerotropic disease (YEL-AVD) were reported by the CDC and WHO. It occurred 2–5 d after receiving vaccine and was a febrile illness, which led to multiple organ failure. YEL-AVD is likely related to transient viremia that occurs after vaccine receipt, and the risk is considered to be rare in first-time vaccine recipients. Risk increases with age (3.5/100,000

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Vaccine	Type	Administration	Booster Interval	Indications	Efficacy	Contraindications	Precautions	Comments	Side Effects
						disease (YEL-AND) Children 6–9 mo of age should not be vaccinated unless traveling to an area with an outbreak Generally not recommended in pregnancy except when travel to a highly endemic area cannot be avoided and the risk of actual disease is thought to be greater than the theoretical risk of adverse vaccine effects		instead of the vaccination statement according to WHO regulations.	vaccine recipients aged 65–74 y and 9.1/100,000 vaccine recipients older than 75 y). However, the protection afforded by the vaccine probably outweighs risk in those senior citizens who are traveling to endemic regions.
Polio (IPV; Sanofi Pasteur, Swiftwater, PA, USA)	Inactivated	SC, 0.5 mL deltoid. Adults who are traveling to areas where WPV cases are still occurring and who are unvaccinated, incompletely vaccinated, or whose vaccination status is unknown	For adults, available data do not indicate the need for more than 1 lifetime booster dose with IPV	Because of polio eradication efforts, the number of countries where travelers are at risk for polio (WPV) has decreased dramatically over the last 30 y, and most of the global population live		The minimum age for IPV vaccination is 6 wks IPV should not be administered to individuals who have experienced a severe allergic reaction (anaphylaxis) after a previous dose of IPV or		OPV is no longer recommended for routine immunization in the United States	Minor local reactions can follow IPV. No serious reactions have been documented.

	should receive 2 doses of IPV at least 4 wk apart and a third dose should be administered 6–12 mo after the second dose. If there is inadequate time before travel and fewer than 3 doses are administered, the remaining doses to complete a 3-dose series should be administered when feasible. Adults who are traveling to areas where poliomyelitis cases are occurring and who have received a primary series with either OPV or IPV in childhood should receive another dose of IPV before departure.	in areas considered free of WPV circulation, including the Western Hemisphere; the Western Pacific region, including China; and the European region. Vaccination is recommended for all travelers to polio-endemic or -epidemic areas, including countries with recent proven WPV circulation and neighboring countries. As of September 2008, these areas include some but not all countries in Africa, South Asia, Southeast Asia, and the Middle East.	after receiving streptomycin, polymixin B, or neomycin because these are contained in trace amounts in the vaccine.

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Vaccine	Type	Administration	Booster Interval	Indications	Efficacy	Contraindications	Precautions	Comments	Side Effects
Smallpox	Vaccinia virus					No longer available commercially. It is available on a case-by-case basis from the CDC based on individual review. The requirement for smallpox vaccination for international travel was removed from the WHO regulations in 1982. The last case of smallpox acquired via natural transmission was reported in 1977.			

Required vaccination before travel

Yellow fever is the only vaccine currently required by international health regulations for travel to and from certain countries in tropical South America and sub-Saharan Africa. Updated lists of *Yellow Fever Vaccination Certification Requirements by Country* and *Authorized U.S. Yellow Fever Vaccination Clinics* are found on the CDC Traveler's Health Web site (www.cdc.gov/travel/content/vaccinations.aspx).

Over the last several years, quadrivalent (A/C/Y/W-135) meningococcal vaccination, which must have been issued not more than 3 years and not less than 10 days before arrival, has been required by the Saudi Arabian government for all infants, children, and adult pilgrims for annual travel during the Hajj. The immunization status is checked before issuance of a visa, which is not issued unless documented compliance is provided. A travel health provider letter may be issued to those individuals who are unable to receive vaccine; however, this does not guarantee issuance of a visa for Hajj travel.

MALARIA AND DENGUE PREVENTION AND THE CURRENT STATUS OF VACCINE DEVELOPMENT

Malaria in humans is caused by 5 species of the protozoan genus *Plasmodium*: *P falciparum*, *P vivax*, *P ovale* (recently split into 2 subspecies), *P malariae*, and most recently and much less frequently *P knowlesi*. Malaria is primarily transmitted by the bite of infected female *Anopheles* mosquitoes, although transmission is also documented via blood transfusion, organ transplantation, and needle sharing. *Anopheles* spp are evening feeders; therefore, transmission occurs primarily from dusk to dawn. Annually, malaria causes 350 to 500 million infections and 1 million deaths globally, largely affecting children in areas of Central and South America, parts of the Caribbean, Eastern Europe, Asia, Africa, and Oceania (see **Fig. 1** for a map of at-risk areas for malaria transmission. Regularly updated maps are available on the WHO and CDC Websites [www.cdc.gov/malaria/map/index.html]). Thirty thousand travelers from Europe and North America contract malaria each year, with 10,745 cases reported in US residents to the CDC from 1997 to 2006. Of the reported cases in the United States, 59.3% were acquired in sub-Saharan Africa, 13.9% in Asia, 13.3% in the Caribbean and Central and South America, and 0.03% in Oceania. However, when considered in the context of volume of travel to these locations, the regions of highest estimated relative risk are West Africa and Oceania; other parts of Africa, South Asia, and South America are felt to have moderate risk, whereas,

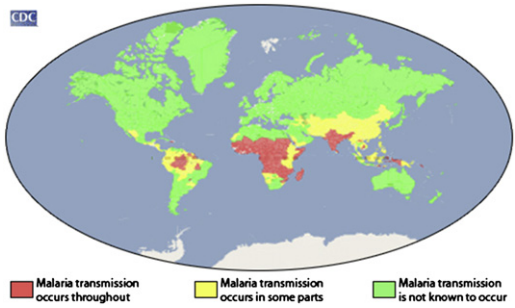

Fig. 1. Malaria transmission zones. (*Courtesy of* the US Centers for Disease Control and Prevention. A regularly updated map can be found at http://www.cdc.gov/malaria/about/distribution.html.)

portions of Central America and other parts of Asia are of relatively lower risk. Individual traveler risk varies substantially by region, including areas of differing altitude, urban versus rural travel, by season, and between travelers.[24] The level of risk presented by a particular itinerary decides whether it may be appropriate to recommend mosquito avoidance methods only, mosquito avoidance methods and chemoprophylaxis, or no specific interventions. Even short exposure, such as that experienced by cruise ship passengers, may pose risk in an area of intense transmission.

Malaria chemoprophylaxis is a dynamic topic, because the risk of transmission is influenced by an individual travelers' behavior, may not be uniformly distributed in individual countries, and is affected by changes in resistance patterns and the availability and usefulness of newer and older drugs. The highest-risk travelers are those first- or second-generation immigrants currently living in nonendemic countries who return to their countries of origin to VFRs.[23–25] These individuals often consider themselves not at risk because they grew up in an endemic area and believe themselves immune. Unfortunately, acquired immunity is lost very quickly on leaving an endemic area. Several options for malaria chemoprophylaxis are currently available, and no single regimen is ideal for all travelers. A thorough discussion of vector avoidance, malaria chemoprophylaxis, and treatment may be found elsewhere.

Malaria vaccination development has faced numerous challenges since the initial cloning of malaria antigens in the early 1980s. At present, several questions remain regarding vaccine mode of action in this parasite's complex and incompletely understood infection biology, efficacy, dosage schedules, and potential duration of effect. Resources for research funding are relatively scarce. Goals of vaccine development have been to either prevent blood-stage infection completely via destruction of sporozoites before they enter the liver or kill the infected hepatocytes (preerythrocytic vaccine) or to limit parasite growth and density in the blood compartment via destruction of the infected erythrocytes (blood-stage vaccine), with the goal of providing a durable immune response similar in efficacy to that induced by natural infection. Significant antigenic diversity has been a barrier to the development of immunity in both the preerythrocytic and blood stages of parasite development. Although immunity to severe life-threatening disease is evidently acquired early in childhood in areas of intense malaria transmission, clearly demonstrating clinical immunity, vaccine trials have been limited by the lack of an immunologic correlate of effectiveness in vaccinated individuals.[26,27] An ideal vaccine should be directed against several novel antigens, perhaps T-cell targets, expressed in several stages of parasite development, that are likely to be highly conserved in sequence and robustly recognized by vaccine-induced immune response.[28,29]

Several stage-specific vaccine candidates are currently in trials to prevent *P falciparum* infection. One preerythrocytic vaccine targeting *P falciparum* circumsporozoite protein, GlaxoSmithKline RTS, $S/AS02_D$, is currently in phase 3 trial (NCT00866619) in 11 African centers with results expected at the end of 2011. Phase 1/2b trial of this vaccine administered to 214 Mozambican infants at 10, 14, and 18 weeks of age, staggered with routine vaccines, reported a good safety profile (32.7% vs 31.8% serious adverse events in the control group) and remained somewhat efficacious at 14 months (geometric mean titers of anticircumsporozoite antibodies declined from 199.9 to 7.3 EU/mL at 12 months, remaining 15-fold higher than that of the control group, vaccine efficacy was 33% [95% confidence interval: −4.3 to 56.9, $P = .076$]).[30] The immunogenicity data were similar to those previously reported in older children and adults.[30,31] No relation between anticircumsporozoite antibody titer and protection was demonstrated in Mozambican children aged 1 to 4 years.[31]

To successfully affect global malaria elimination, it is also crucial to attack other major malarial species that affect humans. Vaccine progress against *P vivax*, a cause of significant morbidity and mortality in Central and South America, the eastern Mediterranean, and Asia, with an estimated 70 million to 391 million cases annually, is not nearly as advanced.[32]

Dengue, currently the most prevalent arthropod-borne viral illness in humans, is caused by 4 serotypes of the dengue virus (DENV). Dengue is a member of the Flaviviridae family, as are yellow fever and Japanese encephalitis. DENVs are transmitted to humans via the bite of peridomestic day-biting *Aedes* mosquitoes, most prominently *Aedes aegypti*. Infection with DENV causes a spectrum of clinical illness, ranging from a usually mild, acute self-limited febrile illness, dengue fever, to life-threatening hemorrhagic and capillary leak syndromes of dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS). DENV causes an estimated 25 million to 100 million cases of dengue fever and 250,000 cases of DHF yearly worldwide. 2.5 billion people are estimated to be at risk for infection (**Fig. 2**, a world map indicating regions with known risk of dengue is available at http://www.cdc.gov/ncidod/dvbid/dengue). The United States has witnessed the return of autochthonous transmission since 1980, initially described in Texas, but now reported in Hawaii, Florida, and Puerto Rico. Geosentinel data, collected on 6 continents, showed dengue fever to be the second most common cause of systemic febrile illness, excluding diarrheal diseases, in returning travelers and the most common cause in travelers returning from the Caribbean, South America, Southeast Asia, and South Central Asia.[15]

In brief, the pathogenesis of DHF/DSS reflects a complex interaction of viral virulence determinants and the host immune system. Infection with one serotype of DENV renders the individual immune to that strain for life but with only transient immunity to other strains, and individuals are at risk for DHF/DSS with secondary DENV infection with another strain. An increased risk of DHF/DSS also occurs in children within their first year of life when born to DENV-immune mothers. These observations served as the basis for the hypothesis of antibody-dependent immune enhancement (ADE) in DHF/DSS, which is supported by the findings of increased peak viremia in severe DHF/DSS, and ADE is seen in vitro in DENV-infected monocytes. A pathologic cytokine response, including increased levels of interferon γ, interleukin 10, and tumor necrosis factor γ, after $CD8^+$ cell activation is thought to contribute to the capillary leak syndrome seen with dengue hemorrhagic fever (DHF). Most protective antibodies are directed against the surface E glycoprotein of the virus. Antibodies to the M and NS1 proteins also have been shown to demonstrate some protection. At present, there is no established dengue immune correlate of infection.

Dengue vaccine development dates back to the 1920s. At present, no DENV vaccine is approved by the US Food and Drug Administration. Vaccine development

Fig. 2. Dengue transmission zones. (*Courtesy of* the US Centers for Disease Control and Prevention. A regularly updated interactive map can be found at http://www.healthmap.org/dengue/index.phpt.)

has been hampered by the absence of a validated animal model of dengue infection. Based on the current understanding of virus-immune system interactions, an effective vaccine should produce high titers of neutralizing antibodies against all 4 strains. Failure to achieve this potentially increases the individual's risk of severe DHF/DSS if challenged by a natural virus infection with a different strain. Several tetravalent live attenuated virus candidate vaccines are in development (see **Table 2** for a list of current candidate DENV vaccines). Tetravalent serologic responses have been observed in some individuals during trials; whereas each portion of the tetravalent vaccines has not been shown to elicit high titer responses, monovalent vaccines were shown to elicit higher levels of neutralizing antibodies than when they were combined in multivalent combinations, and many individuals mount insufficient levels of neutralizing antibodies despite multiple immunizations. Alternative vaccine candidates include subunit-based vaccines containing purified proteins or DNA plasmids, which have been shown to produce protective antibodies in mice at fairly low neutralizing titers; live attenuated vaccines, including dengue and dengue-yellow fever chimeras; and nonreplicating vaccines, including virus-like particles, DNA vaccines, and inactivated virus vaccines. Long-lasting protective neutralizing antibodies are elicited against a specific serotype, but they have been shown to be poorly cross-reactive against infection with another serotype. Similar problems were encountered in the development of OPV, and the imbalance in seroconversion was overcome by the administration of 3 doses of the multivalent vaccine.[33–38] A Sanofi Pasteur

Table 2
Current status of dengue virus vaccine development

Vaccine Type	Developer	Collaborator	Status
Live Attenuated Virus, Tetravalent	Walter Reed Army Institute of Research, USA	GlaxoSmithKline	Phase 2
Live Attenuated Virus, Tetravalent	National Institutes of Health, USA	Biologic E. Panacea	Phase 2
Live Attenuated Virus, Tetravalent	Mahidol University, Thailand	Sanofi Pasteur	Completed phase 2, halted
Live Attenuated Virus, Tetravalent	National Institute for Allergy & Infectious Disease, USA	Vabiotech	Phase 1/2
Live Chimeric Virus, Tetravalent	CDC, USA	Inviragen	Phase 1
Live Chimeric Virus, Tetravalent	Acambis, USA (acquired by Sanofi Pasteur, 2008)	Sanofi Pasteur	Phase 3
Live Recombinant DNA and Subunit, Tetravalent	Naval Medical Research Center, USA	University of Pittsburgh	Phase 1/preclinical
Replication-defective Arbovirus (E)	University of Texas Medical Branch	Acambis	Preclinical
DNA	University of Pittsburgh		Preclinical
Live Recombinant DNA and Subunit, Tetravalent	Hawaii Biotech Inc, USA		Preclinical

Data from Refs.[35–38]

tetravalent live attenuated chimeric yellow fever-dengue vaccine has entered hase 3 trials (NCT01134263). Phase 2 trials suggest that the vaccine is safe and immunogenic.[35] Preliminary results of an ongoing phase 2b efficacy and safety trial in Thai children are expected to be available by the end of 2012.

TRAVELER'S DIARRHEA AND THE ROLE OF VACCINATION

Traveler's diarrhea is a significant concern among international travelers. It is usually self-limited, consisting of several days of watery diarrhea, sometimes accompanied by low-grade fever, headache, malaise, nausea, and abdominal cramping. Thirty to seventy percent of travelers may be affected during a 2-week trip, largely depending on the travel destination. The highest attack rates are seen in travelers to Asia, Africa, Mexico, Latin America, and the Middle East. Intermediate risk is seen with travel to the Caribbean, Eastern Europe, the former Soviet States, southern Europe, Israel, and South Africa. Travel to the developed nations in North America, Europe, Japan, New Zealand, and Australia provides the lowest attack rates.[39,40] A recent study examining the Geosentinel data found that female travelers seem to be at disproportionately increased risk for acute diarrhea, chronic diarrhea, and irritable bowel syndrome than male travelers.[41] Contrary to popular belief, traveler's diarrhea does not only occur in travelers from temperate, economically developed countries to semitropical and tropical developing countries, as evidenced by the serious recent outbreak of shiga-toxin–producing *Escherichia coli* serogroup O104:H4 (STEC) with hemolytic uremic syndrome (HUS) in northern Germany. Any traveler may experience an acute intestinal upset, as this is increasingly recognized as a disturbance of the normal ecology of an individual's gastrointestinal tract by exposures to new water, foods, and spices as well as to microorganisms. Gastrointestinal dysfunction, in the form of irritable bowel syndrome, may persist in up to 13% of individuals who develop traveler's diarrhea.[42,43] Other postinfectious sequelae include Guillain-Barre and reactive arthritis.

Many viral, bacterial, and protozoal microorganisms cause traveler's diarrhea. Symptoms may result from the ingestion of preformed toxins, such as that seen with *Bacillus cereus*, staphylococcal food poisoning, and botulism. In general, bacteria are the most commonly identified cause of acute diarrheal disease in travelers visiting tropical and developing countries (80%–90%), with risk modified by geographic region, time of year, and the presence of local outbreaks. In many cases, no causative organism may be identified. Enterotoxigenic strains of *E coli* (ETEC), which may carry both heat-labile and heat-stable plasmid-coded enterotoxins, are the most commonly identified bacterial cause. Oral cholera vaccine produces some protection against traveler's diarrhea, because it elicits antibody production against the B subunit of cholera toxin, which cross-reacts with the heat-labile toxin of ETEC. In the past decade, *Campylobacter* species, most commonly *Campylobacter jejuni*, have become increasingly common pathogenic agents of traveler's diarrhea. These seem to have seasonal and geographic variance, with the peak incidence in the United States in summer months, whereas the peak incidence in other regions, such as North Africa, occurs in winter months. Other bacteria implicated in traveler's diarrhea include enteroadherent *E coli*; *Salmonella* spp, including *S typhi*; *Shigella* spp; *Yersinia enterocolitica*; *Aeromonas*; *Vibrio* spp, including *V parahemolyticus*, *V cholera*, and *V vulnificus*; and *Plesiomonas shigelloides*. Norovirus is a common cause of traveler's diarrhea (10%–15% cases), notably in several cruise-ship outbreaks. Rotavirus and astroviruses are less common pathogens in adults (5%–14%). Hepatitis A and E also cause gastrointestinal illness in travelers. Hepatitis E is of particular concern in

pregnant women as it may lead to severe, life-threatening illness. Most parasites implicated in traveler's diarrhea are protozoa, including *Giardia lamblia*, and less commonly *Cryptosporidium* spp, *Cyclospora cayetenensis*, *Isospora belli*, *Entamoeba histolytica*, and occasionally *Dientamoeba fragilis*. Helminths are also reported to cause diarrheal disease in travelers. Ingested plant, fish, and shellfish toxin-related illness, including Ackee poisoning, Scombroid, Ciguatera, paralytic, neurotoxic, and diarrheal shellfish poisonings, may also cause gastrointestinal disease in travelers.

Pretravel vaccination and counseling regarding safe food and water practices can provide varying degrees of protection against enteric infection; however, even with the greatest of care, the risk of developing diarrhea remains high. The natural protective mechanisms of the intestinal tract, most prominently gastric acidity, and immune stimulation provided by vaccination can be overwhelmed by the ingestion of heavily contaminated water and food and moderated by traveler specifics, such as immune suppression, hypochlorhydria, gastrectomy, and concurrent medications.[44] Environments lacking appropriate sanitary conditions and clean water provide significant stool contamination highly accessible to flies. Attempts to select safe foods, such as those freshly prepared and served hot, can be counteracted by contamination introduced during preparation, storage, and handling.[45]

Although many travelers want to experience local culture and cuisine, commonsense food and water precautions may help individuals to make safer choices. These precautions are harder to maintain in those VFRs, those staying in local homes or pursuing more adventurous travel, and those staying in highly contaminated areas for prolonged periods of time. This article does not focus on a detailed discussion of food and water precautions, water treatment, and treatment and prevention of traveler's diarrhea.

At present, few vaccines are available to prevent the most common causes of traveler's diarrhea. Hepatitis A vaccine and oral and intramuscular typhoid vaccines are effective and well tolerated, although limited data address the actual level of protection afforded by oral and injectable typhoid vaccines to travelers from nonendemic areas visiting endemic areas.[46] Cholera vaccine seems moderately effective against non-O139 strains. A transcutaneous *E coli* LT vaccine is currently in phase 3 trials.

GENERAL RECOMMENDATIONS

Additional pretravel recommendations, such as jet lag mitigation, protection against sun exposure, venous thrombosis avoidance, prevention and treatment of altitude illness, baric risk, marine bites and envenomation attendant to diving and water sports, and the risks of extreme heat or cold, depend on the individual traveler's agenda. Safety regulations and practices are less prevalent in many nations than in the United States, Canada, and Europe. Most US medical insurance policies do not provide coverage for illness or accidents occurring outside the country and coverage for medical evacuation; however, many companies provide this insurance. A thoughtful discussion of these topics, and the management of the traveler returning with illness, lies outside the scope of this article.

In summary, individual travel for business and pleasure has grown tremendously in the past several decades, with an increasing number of at-risk individuals traveling and travelers visiting more remote and dangerous areas. Travelers potentially face several risks during travel. Thorough, epidemiologically and itinerary-based discussion and management of these risks before travel with a provider appropriately educated and experienced to provide this care, taking into consideration the individuals' risk tolerance, medical belief system, and finances, provide individuals the ability

to travel more safely and to maximally experience their trip. Information gleaned from illness and injury experienced by travelers and, infections developed during travel and potentially brought back to the home country, continues to improve care and inform home countries about potential risks to their citizens and to improve the global management of transmissible illness.

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