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Health recommendations for international travel: a review of the evidence base of travel medicine

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Abstract

Purpose of review—International travel is increasing, including travel to countries with emerging economies. Travel may pose health risks for the individual and contribute to the global spread of infectious diseases. The specialty of travel medicine is aimed at minimizing health risks associated with international travel. The field has emerged in the past 25 years, and the evidence base supporting its clinical practice is growing. This review will describe the evidence base underlying travel medicine, highlight recently updated travel medicine guidelines, and outline future research priorities.

Recent findings—Recommendations for a number of common vaccines for travelers have been updated recently. More sophisticated detection methods are leading to the identification of a wider spectrum of pathogens associated with travelers' diarrhea, and antibiotic resistance is increasingly being identified. New treatment options for malaria are available, and a fifth *Plasmodium* species causing disease in humans has been identified.

Summary—An evidence base for the practice of travel medicine is emerging. Expert opinion and consensus guidelines continue to play an important role in supporting clinical practice.

Keywords

evidence-based medicine; international travel; travel medicine

Introduction

Over the past two decades, international travel has increased dramatically, with the number of international tourist arrivals rising from 438 million in 1990 to 919 million in 2008 (Fig. 1) [1]. In particular, travel to countries with emerging economies is becoming more common; international tourist arrivals to developing countries increased from 32% in 1990

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Conflicts of interest

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to 47% in 2009 [2]. As travelers venture beyond historically popular tourist destinations in developed nations to 'off the beaten path' locales, they may come in contact with infectious diseases such as malaria, schistosomiasis, dengue fever, and typhoid fever. Travelers may also import infectious diseases into their country of origin, as evidenced in recent years by the global spread of severe acute respiratory syndrome (SARS) [3], H1N1 influenza [4], chikungunya fever [5], and dengue fever [6].

The specialty of travel medicine has emerged in the past 25 years, in response to the increase in international travel and its attendant health considerations. Travel medicine focuses on ensuring adequate pretravel preparation, minimizing the health risks associated with international travel, and providing proper care to ill travelers during or after travel. The International Society of Travel Medicine (ISTM) was founded in 1991 to promote education, service and research activities in the field of travel medicine, including administering a Certificate of Knowledge Examination focused on pretravel care and consultation. It currently has over 2500 members from more than 75 countries. As with any young medical specialty, the evidence base underlying the practice of travel medicine is in its preliminary phases. This review will describe existing sources of evidence that support the clinical practice of travel medicine and will focus on recent developments in the areas of vaccine-preventable diseases, travelers' diarrhea and malaria. We will also outline gaps in knowledge in travel medicine and highlight future research priorities.

Current practice of travel medicine

A variety of clinicians provide travel medicine services worldwide. A 1996 survey of ISTM members found that the majority of travel medicine clinics were private and physician-run, and care was frequently provided by nurses and physician assistants [7]. More than half of travel clinic physicians had trained in infectious diseases or tropical medicine. Although the travel medicine specialty has grown, recent data suggest that many travelers receive advice from clinicians who do not specialize in the field of travel medicine. For instance, a survey of outbound travelers at Boston Logan International Airport in 2011 found that primary care providers were the most common medical source of advice for travelers to low-income destination countries [8*]. The nature of health recommendations provided to international travelers, particularly by nonspecialists, is poorly characterized and might be quite variable. A 1990 survey of yellow fever vaccine centers in the USA and Canada identified the recommendation of inadequate or inappropriate immunizations in up to 75% of scenarios and the incorrect use of malaria chemoprophylaxis in up to 60% of scenarios [9].

The pretravel health assessment

In optimal situations, the pretravel health assessment includes a comprehensive evaluation of the medical conditions of the traveler and the details of the planned itinerary [10**]. The clinician provides individualized health education on topics including insect avoidance, injury prevention, safe food and water, self-treatment of diarrhea, medical insurance and safer sex practices. Other topics, such as management of altitude sickness or prevention of venous thromboembolism, are also reviewed based on the risk assessment. When

indicated, malaria chemoprophylaxis is prescribed and a strategy for prevention or self-treatment of travelers' diarrhea is reviewed. Hepatitis A and typhoid vaccines are frequently administered to travelers, and destination-specific vaccines, such as Japanese encephalitis and yellow fever, are also provided. Rabies vaccine is considered for those with a risk of animal exposure or who anticipate barriers to adequate medical care after an animal bite. An underappreciated component of the pretravel health assessment is that it affords an opportunity to update routinely recommended vaccines, such as the combined tetanus, diphtheria, and pertussis (Tdap), hepatitis B and meningococcal vaccines.

Travelers' pursuit of pretravel health advice

Despite the growing field of travel medicine, many travelers, including those to higher-risk destinations, seek no health advice prior to departure. A 2004 survey at New York's John F. Kennedy International Airport found that 36% of travelers to high-risk destination countries sought no pretravel health advice [11]. Similarly, 46% of travelers departing from Boston Logan International Airport for high-risk destination countries sought no pretravel health information [8*]. Many travelers to low-income destination countries are returning to their country of origin to visit friends and relatives (VFR); these VFR travelers have been identified as being at particular risk of acquiring illness while traveling [12]. Only 3% of VFR travelers who sought pretravel health advice obtained it from a travel medicine specialist in the 2010 Boston Airport survey [8*]. In both the Boston and New York airport surveys, travelers frequently endorsed a lack of concern about health risks as the reason for not pursuing care.

Existing evidence base for travel medicine

Research studies in travel medicine are challenging for many reasons. Travelers are a heterogeneous group of individuals, with varying host factors that influence the risk of illness, such as age, medical conditions, and medication profiles. Illness risk can vary markedly by destination and by duration of travel, and data on disease-specific risk per day of travel are generally lacking [13]. Furthermore, travelers often do not seek pretravel advice, or they seek advice from primary care practitioners; these two population groups are poorly studied [14].

Nevertheless, an evidence base for the practice of travel medicine has increased in the past 20 years. In 2010, 74 articles were published in *PubMed* in association with the search term 'travel medicine', compared with fewer than 10 annually before 1996 (Fig. 2). Although studies regarding the diseases associated with international travel have been published in a variety of peer-reviewed journals, the establishment of *Journal of Travel Medicine* in 1994 and *Travel Medicine and Infectious Disease* in 2004 have particularly promoted research regarding travelers. To date, randomized controlled studies testing targeted interventions for the reduction of travelers' risk remain rare, with the exception of focused studies of the treatment and prophylaxis of travelers' diarrhea (reviewed in [15] and [16]).

Since the evidence base for travel medicine is still in its early phases, expert opinion has been used to standardize practice in the field. In 2006, the Infectious Diseases Society

of America (IDSA) published guidelines for the practice of travel medicine [17]. Another common source of recommendations for travel medicine practice is the US Centers for Disease Control and Prevention's (CDC's) biennial Health Information for International Travel (The Yellow Book), which is written by experts in travel medicine, infectious diseases and public health from within and outside the CDC [10**]. The WHO publishes International Travel and Health (The Green Book), a comprehensive summary of travel-related disease topics and vaccination requirements, as outlined by the International Health Regulations [18**]. Notably, certain recommendations related to travelers' health differ between the US and other countries, reflecting gaps in knowledge and the priorities of different stake-holders.

A number of internet resources that provide timely notification of updates in travel medicine and emerging travel-related illnesses have been developed in the past decade. Specifically, the ISTM operates an electronic discussion group of over 1350 travel medicine clinicians that serves as a forum for review of clinical cases, patient management issues and travel medicine guidelines (<http://www.istm.org/webforms/Members/MemberActivities/listserve.aspx>). The Program for Monitoring Emerging Diseases (ProMed-mail), a program of the International Society for Infectious Diseases, offers open-source reporting of outbreaks, emerging infectious diseases, and intoxications (<http://www.promedmail.org/pls/apex/f?p=2400:1000>). Health Map is a web resource that brings together a wide array of data sources to provide a map-based, real-time view of the global state of infectious diseases (<http://healthmap.org/en/>). Additionally, the systematic monitoring of internet search engines is emerging as a novel technique for identifying global outbreaks of infectious diseases [19,20].

Surveillance databases are important tools for generating descriptive data regarding travelers presenting to specialized travel medicine clinics. The GeoSentinel network (<http://www.istm.org/geosentinel/main.html>) is a worldwide surveillance network of more than 50 travel medicine clinics, founded by the ISTM and CDC, which monitors travel-related illnesses seen at participating sites. A number of important observations have arisen from the network, including an analysis of infections that are associated with fever in international travelers [21] and evaluations of specific disease patterns among travelers, including malaria [22], diarrhea [23], respiratory infections [24] and dengue fever [25], among others. Although the GeoSentinel network has been a key source of data regarding illness acquired during travel, there are important limitations. GeoSentinel sites are located primarily in academic centers, and consequently there may be selection or reporting biases in the types of patients or illnesses seen at these clinics. Diagnoses are made at individual sites and hence there may be variability between sites in diagnostic criteria and recording. Most importantly, data are only collected on travelers who seek medical care, so short-lived illnesses or those that do not necessitate medical care may be under-represented.

A comprehensive surveillance system that could link pretravel care to intra and post-travel illness would be a useful tool for improving the evidence base for travel medicine. Such a system would facilitate the systematic evaluation of the efficacy of pretravel healthcare and would allow a more accurate determination of destination-specific risks than is possible with current approaches. As a first step in this direction, the Global TravEpiNet consortium

(www.globaltravepinet.org) was founded by Massachusetts General Hospital and CDC in 2009 to better characterize pretravel healthcare in the USA. This consortium of 19 travel clinics collects extensive data on the pretravel encounter for all individuals seen at participating sites. A priority for the Global TravEpiNet consortium is to develop techniques for linking pretravel healthcare to subsequent health outcomes.

Recent findings and updated guidelines in travel medicine

Here, we review recent evidence and revised guidelines related to the field of travel medicine.

Travel-related immunizations

There are a number of recent updates related to vaccines for travelers, including changes in rabies postexposure prophylaxis and in destinations where yellow fever vaccine is recommended.

Although the exact number of travelers who require postexposure prophylaxis for rabies is not known, there have been many reports of rabies exposure in travelers [26-28]. In 2010, the Advisory Committee on Immunization Practices (ACIP) recommended a reduced schedule of four doses of rabies vaccine for postexposure prophylaxis [29,30*]. The evidence supporting this reduction in doses included knowledge of rabies virus pathogenesis, experimental animal models, human clinical studies, epidemiologic surveillance, and health economics [29]. Although the cost of the rabies vaccine series is not expected to decrease, the dose reduction benefits the travel medicine clinician and the patient by eliminating the need for a fifth clinic visit.

To update yellow fever vaccination recommendations for international travelers, CDC, WHO, and other travel medicine experts undertook a systematic review of countries with risk of yellow fever virus transmission. The revised recommendations and maps describing yellow fever virus transmission have been recently published [10**,18**]. Notable changes include the revision of maps to depict yellow fever vaccination recommendations, rather than yellow fever risk; also, yellow fever vaccine is now generally not recommended for travel to areas in Tanzania, Somalia, Eritrea, São Tomé and Príncipe, and Zambia. The decision whether to vaccinate a traveler still must take into account the traveler's risk of exposure to yellow fever virus, country entry requirements, and individual risk factors for serious adverse events after vaccination, such as age and immune status.

Routine immunizations

The pretravel health encounter is frequently an opportunity to update routine immunizations, particularly in adults. ACIP has made revised recommendations for a number of vaccines in recent years. A single booster dose of Tdap is currently recommended for all adults aged 19–64 years [31]. In October 2010, the ACIP additionally recommended the use of Tdap in adults aged 65 years or older who have not previously received Tdap [32*]. This recommendation is particularly targeted at adults who anticipate contact with children 12 months of age or below. Tdap administration was also recommended regardless of interval since the last tetanus or diphtheria-containing vaccine. The recommended use of

the quadrivalent meningococcal conjugate vaccine has also expanded in recent years, with recommendation for a booster dose in adolescents at age 16 years and a two-dose primary series for persons aged 2–54 years with complement component deficiency [33*].

Travelers' diarrhea

New and more sophisticated detection methods have led to the identification of a wider spectrum of pathogens associated with travelers' diarrhea, which includes enteroaggregative *Escherichia coli* [34], norovirus, [35,36] and enterotoxigenic *Bacteroides fragilis* [37]. A recent assessment of 456 enteropathogens isolated from travelers to Mexico, India, and Guatemala suggests the presence of increasing resistance to azithromycin and the fluoroquinolones – the most commonly prescribed antibiotics for treatment of travelers' diarrhea [38*]. These results suggest the need for continued, geographically based surveillance for antibiotic resistance among pathogens associated with travelers' diarrhea.

Malaria

With a goal of standardizing the approach to malaria chemoprophylaxis, the CDC Expert Meeting on Malaria Chemoprophylaxis has released comprehensive, evidence-based reports on many of the key chemoprophylactic drugs, including primaquine [39], atovaquone–proguanil [40], and most recently doxycycline [41*]. New treatment options for malaria are also becoming available. Artemether–lumefantrine (Coartem), an artemisinin-based combination therapy, has been shown to be effective in randomized trials [42–46] and was approved by the FDA in 2009 for the treatment of acute, uncomplicated malaria. Intravenous artesunate, also in the artemisinin class, is available from CDC as an investigational new drug for the treatment of severe malaria. Of note, a fifth *Plasmodium* species causing disease in humans, *Plasmodium knowlesi*, was recently identified in humans [47].

Priorities for research and implementation in travel medicine

A number of key research questions and implementation concerns relate to travel medicine (Table 1). One particularly high priority is increasing the frequency with which travelers access pretravel consultations. More research is needed to identify the most effective means of using clinical, internet, and media resources to convey pretravel health messages, particularly to those at highest risk of travel-associated illness. Given its frequency, the quality of care provided outside specialized travel medicine settings requires further study. From a health-systems perspective, more research is also needed to ascertain the cost-effectiveness of pretravel health preparation and its various components.

The risk of illness during travel relates not only to the destination but also to an individual's behavior while traveling. Research on the behavioral components of travel-related illness is necessary to optimize pretravel counseling and to increase adherence to pretravel advice and chemoprophylaxis during travel. Given the increasing frequency of global travel, quantifying the epidemiologic role of travelers in the spread of infectious diseases is important and provides support for strategies aimed at optimizing the pretravel health encounter. The role of screening for travel-related illness is also undefined.

Specific research priorities for the field of travel medicine were outlined in a 2010 statement by the research committee of the ISTM [48]. These guidelines were developed by consensus of a writing group, with invited review from the membership of the ISTM. The ISTM research priorities range from highly specific questions, focused on such issues as the prophylactic use of antiprotozoal agents, to broader questions, such as determining the benefit of pretravel counseling. These research priorities provide a strong and specific guide for future work in the field of travel medicine.

Conclusion

An evidence base for the practice of travel medicine is emerging. Expert guidelines, particularly CDC's Yellow Book and the WHO's Green Book, continue to play an important role in standardizing practice. Travel medicine networks, such as the well established GeoSentinel surveillance network and the newer Global TravEpiNet pretravel network, are generating systematic data on proportionate morbidity in returned travelers and pretravel care in the USA. Increasingly sophisticated internet-based resources are also allowing the rapid dissemination of information about illness in travelers. Nevertheless, many research and implementation challenges remain in the field of travel medicine; chief among these are increasing access to and compliance with pretravel health advice, standardizing the quality of pretravel health advice, and quantifying destination-specific risk of illness for travelers. The establishment of a professional organization and topic-specific journals has contributed to the advancement of research in the field of travel medicine, and the evidence base for the field will likely continue to grow in coming years.

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- of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 509).

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Key points

- International travel is increasing, including travel to countries with emerging economies.
- The field of travel medicine has arisen in response to the increase in international travel and its attendant health considerations.
- An evidence base for the practice of travel medicine is developing; expert opinion and consensus guidelines play an important role in supporting current clinical practice.
- Research and implementation challenges in the field of travel medicine include increasing access to and compliance with pretravel health advice, standardizing the quality of pretravel health advice, and quantifying destination-specific risk of illness for travelers.

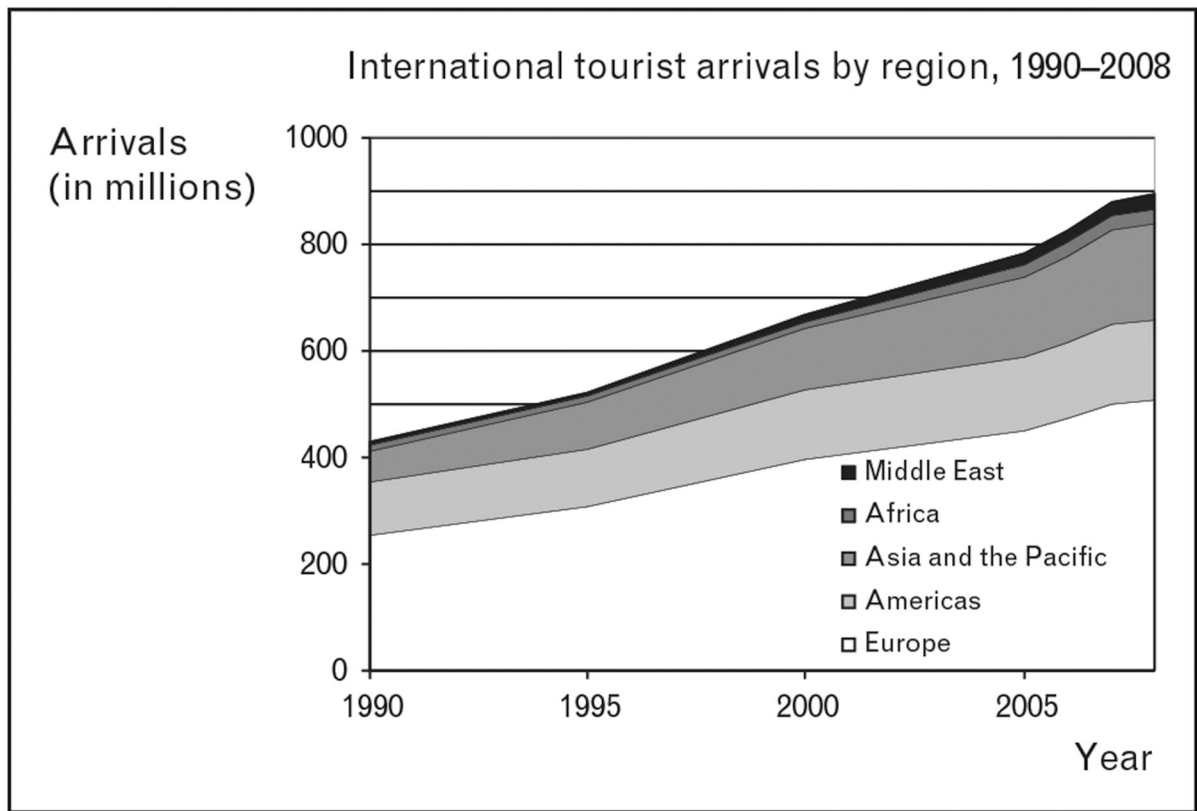


Figure 1. International Tourist Arrivals, by Region, 1990–2008
Adapted from [1].

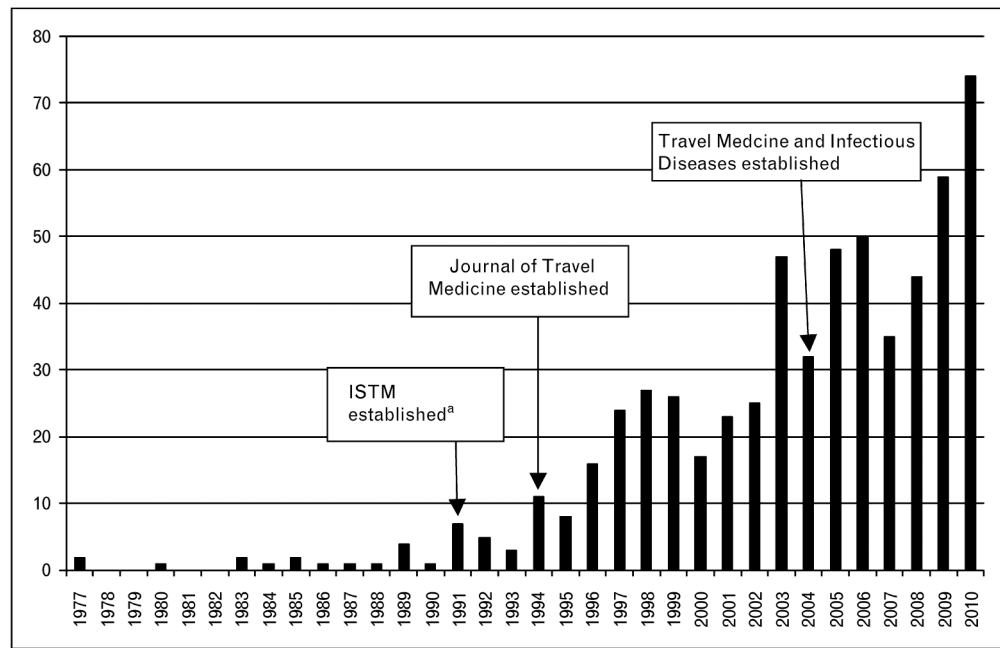


Figure 2. Number of travel medicine publications indexed in PubMed, 1977–2010
PubMed was searched on 8 March 2011, with 612 articles retrieved under a ‘travel medicine’ search term. ^aThe International Society of Travel Medicine (ISTM) was established during the second Conference of International Travel Medicine in 1991.

Table 1
Selected key research questions and implementation concerns in travel medicine

Phase of travel	Selected key research questions	Implementation concerns
Pretravel	<p>What is the quality of pretravel advice provided by clinicians with differing levels of professional training in travel medicine?</p> <p>Can effective pretravel advice be provided by using alternate sources, such as the media or the internet?</p> <p>What are the barriers for travelers in seeking pretravel consultations with clinicians?</p> <p>What approaches can be applied to encourage travelers, particularly those at higher risk of travel-associated illness, to seek pretravel advice?</p> <p>What is the cost-effectiveness of pretravel counseling, chemoprophylaxis, and vaccination?</p>	<p>Increasing the accessibility of pretravel counseling while maintaining quality</p> <p>Increasing the frequency of pretravel consultations among those at higher risk of travel-associated illness (e.g. children, the elderly, VFR travelers, those with immunosuppressive conditions, and those traveling for medical tourism)</p> <p>Making pretravel counseling, chemoprophylaxis, and vaccination affordable for travelers</p> <p>Ensuring that travelers are appropriately immunized for routine as well as travel-related diseases</p>
During travel	<p>What are specific risk behaviors during travel, as related to infectious diseases and injury?</p> <p>What are destination-specific risks of intra and post-travel illness?</p>	<p>Providing counseling specific to travel-associated risk behaviors</p> <p>Increasing adherence to pretravel advice and chemoprophylaxis during travel</p>
Post-travel	<p>What are sources of healthcare for those who become ill while traveling?</p> <p>What contribution do travelers make to the global spread of infectious diseases, particularly emerging infectious diseases?</p> <p>What is the role, if any, for asymptomatic screening of returning travelers for selected infections (e.g. schistosomiasis, intestinal parasites, tuberculosis)?</p> <p>What is the best method for identifying travel-associated illness?</p>	<p>Increasing preparedness of travelers for illness that develops while traveling</p> <p>Decreasing the spread of infectious diseases across international borders</p> <p>Improving surveillance for travel-associated illness</p>

VFR, visiting friends and relatives. Adapted from [48^{*}].