

Preventing diseases in round-the-world travelers: a contemporary challenge for travel medicine advice

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Abstract

Providing advice for travelers embarking on long-term trips poses a challenge in travel medicine. A long duration of risk exposure is associated with underuse of protective measures and poor adherence to chemoprophylaxis, increasing the chances of acquiring infections. Recently, in our clinic, we observed an increase in the number of travelers undertaking round-the-world trips. These individuals are typically aged around 32 years and quit their jobs to embark on one-to-two-year journeys. Their destinations include countries in two or more continents, invariably Southeast Asia and Indonesia, and mostly involve land travel and visiting rural areas. Such trips involve flexible plans, increasing the challenge, especially with regard to malaria prophylaxis. Advising round-the-world travelers is time-consuming because of the amount of information that must be provided to the traveler. Advisors must develop strategies to commit the traveler to his/her own health, and verify their learnings on disease-prevention measures. Contacting the advisor after the appointment or during the trip can be helpful to clarify unclear instructions or diagnosis made and prescriptions given abroad. Infectious diseases are among the most frequent problems affecting travelers, many of which are preventable by vaccines, medicines, and precautionary measures. The dissemination of counterfeit medicines, particularly antibiotics and antimalarial medicines, emphasizes the need for travelers to carry medicines that they may possibly need on their trip. Additional advice on altitude, scuba diving, and other possible risks may also be given. Considering the difficulties in advising this group, we present a review of the main recommendations on advising these travelers.

Keywords: Round-the-world travelers. Long-term travelers. Infectious diseases. Malaria prophylaxis. Vaccines.

INTRODUCTION

In recent years, we have observed a marked increase in the number of travelers embarking on long-term journeys around the world. These travelers are quite different from the young, adventurous backpackers. Among 36 such travelers who attended a travel clinic in Rio de Janeiro, Brazil, the mean age was 32 years, and the length of stay abroad was approximately 1.1 y. These young adults quit their jobs to spend long time abroad, with their destinations invariably including Southeast Asia and Indonesia. **Table 1** presents a list of places visited by the 36 travelers who attended our clinic.

These travelers do not fit into the most-studied categories of long-term travelers, such as peace corps volunteers¹, expatriates^{2,3}, or those visiting friends and relatives^{4,5}. Nonetheless, they are at risk for a long period, with increased chances of underuse of personal protective measures and poor adherence to continuous chemoprophylaxis, increasing the chances of contracting diseases^{6,7}. The particular challenge they pose on advising is the

flexibility of travel plans; they just know the approximate period to spend in each country or continent, and crucial details for travel advice will possibly change along the trip. This uncertainty is particularly important concerning malaria chemoprophylaxis, as drug therapy must start from one day to two weeks before departure³.

Considering the difficulties in advising this group, we review and summarize the main recommendations for advising round-the-world travelers (RWT).

TIME SPENT DURING APPOINTMENT

Travelers must understand the importance of following protective measures thoroughly. However, adherence to preventive strategies can be as low as 25%, tending to decrease in the long term⁸⁻¹⁰ owing to lack of motivation, health beliefs, fear of side effects, or poor communication, resulting in limited understanding and forgetting the information provided^{11,12}. Therefore, advisors' communication skills are critical. Advice should include an exhaustive discussion of the risks and protective measures, along with strategies to respond adequately to illness or injury that may occur during the trip, including sentinel symptoms suggesting serious infections, such as fever during or after visiting malaria-risk areas, profuse or bloody

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TABLE 1: Destinations visited by 36 round-the-world travelers who attended a travel clinic in Rio de Janeiro.

Destination	Travelers
	N (%)
Southeast Asia	33 (92.0)
Indonesia	27 (75.0)
Indian subcontinent	26 (72.0)
Africa	25 (69.0)
Europe	24 (67.0)
Asia (aside from India)	22 (61.0)
South America	15 (42.0)
Oceania	12 (33.0)
Middle East	11 (31.0)
North America	10 (28.0)
Central America	8 (22.0)

N: number; %: percentage.

diarrhea, or fever associated with cutaneous lesions¹². Advising RWT is time-consuming and frequently takes more than one meeting. During the first appointment, travel plans are still being built. Subsequent visits allow completing and reinforcing the advice, and verifying the extent of learning.

INFORMATION AND COMMUNICATION TECHNOLOGY

Communication between doctors and patients via telephone, internet, and video has already been accomplished decades ago. Information and communication technology (ICT) is an indispensable innovation for modern healthcare provision¹³, and such technology can certainly be beneficial to travelers and travel medicine advisors.

Instant messaging and e-mail allow travelers to keep in touch with clinicians, exchanging information about symptoms, healthcare facilities, and laboratory tests. Travelers often forget instructions received during consultation¹¹, and contact with the advisor during the trip can help clarify uncertainties, improve compliance, and prevent improper use of medications. They usually seek advice when some health issue occurs to make sure they will make the best decision, such as sending a message after a dog bite or a cat scratch to make sure of the need to receive a rabies vaccination, or to confirm the commencement of malaria prophylaxis before moving to an area despite having received written information on the subject. Some ask for orientation to receive vaccines abroad after changes in travel plans. During consultation, travelers do not become skilled enough to deal with such specialized information. In our experience, a quick contact with the travel medicine doctor certainly helps the traveler to take the best decision. Nevertheless, travelers and physicians should be aware that online communication has

limitations and can be disastrous if considered a substitute to face-to-face consultation¹⁴. Physicians' availability must be agreed up on previously and included in the consultation costs. However, because of the unpredictability of occurrence, it must be made clear that physicians may not be reachable timeously. Other helpful tools are smartphone applications to store medical information, such as health history, allergies, and regular medication.

INFECTIOUS DISEASES

Infectious diseases are among the most frequent problems, and many of them are preventable with vaccines, medicines, and precautionary measures¹⁵.

vector-borne diseases

Strategies to protect from vector-borne diseases must be reinforced, as compliance with use of barrier methods such as sleeping under bed-nets or using insect repellents can be as low as 19%¹⁶, tending to decrease along the journey. Foldable net tents are more convenient and can improve compliance.

Malaria

Malaria is the most frequent cause of death from infections among travelers and is preventable with appropriate precautions^{17,18}. To properly assess the actual chemoprophylaxis needed requires a significant amount of time to discuss travel plans and map malaria risk areas. Travelers must learn to adapt the prescription if routes change and program chemoprophylaxis before reaching risk areas.

When choosing appropriate malaria prophylaxis for RWT, advisors must deal with the lack of consensus between different guidelines, and the differences in the chemoprophylactic

regimens licensed and available in different countries. RWT usually travel by land and spend lengthy time in rural areas, increasing the risk of illness in regions with precarious health systems, justifying chemoprophylaxis in places where, according to many guidelines, for short-term trips it would not be advisable, such as the Indian subcontinent and many parts of South-East Asia and Indonesia.

Doxycycline or atovaquone-proguanil are convenient drugs, as they can be started one to two days before entering a risk area, unlike mefloquine, which must be started two weeks ahead. Additionally, mefloquine resistance is reported in areas frequently explored by land or boat, such as the borders of Thailand, Myanmar, Cambodia, China, Laos, and Vietnam¹⁹.

Additional care includes carrying extra prophylactic pills in case of unplanned visits to malaria-endemic regions and carrying one/two sets of malaria treatment pills in case malaria is suspected or confirmed. Purchasing medicines in Sub-Saharan Africa or Asian countries is not advisable because drugs may be counterfeit, as reported for more than 50% of artemisinin products in those areas^{20,21}.

Travelers are frequently concerned about using malaria prophylaxis for a long time and advisors must discuss pros and cons of each choice, based on clinical conditions, resistance patterns, travel style and budget. There is little evidence of harm in long-term use of drugs for malaria chemoprophylaxis tolerated in the short term. All regimens may be used longer when justified by malaria risk^{6,22}. The inaccuracy of the data on endemicity in different risk areas, lack of information about incidence of diseases in travelers, and the many different travel styles make it impossible to determine precisely the risk of getting infected in each place. Standby emergency treatment (SBET) is recommended in some countries (e.g., Switzerland, Germany, and Austria) for travelers visiting areas where the risk of malaria is considered lower than the risk of serious adverse drug reactions from use of chemoprophylaxis²³. SBET is the self-administration of antimalarial drugs when the disease is suspected and medical attention is unavailable within 24h of symptoms onset. It is indicated only in emergency situations, as a life-saving measure. After taking the medication, the traveler must seek medical attention at the first opportunity to exclude other serious causes of fever. Travelers should also be warned that a minimal period of 6 days should have elapsed after entering the malaria-endemic area to cogitate treatment²³. Considering the uncertainty in travel plans, SBET could be a convenient option. However, RWT generally mix high- with low-risk areas, with unreliable diagnosis available, making SBET unsuitable. This strategy must be discussed with travelers reluctant to take chemoprophylaxis, who are prone to non-adherence, and who presented serious adverse events before. However, considering both the risk of buying counterfeit drugs and the long stay in areas with precarious health systems, this strategy should be recommended for RWT not as an alternative, but in addition to chemoprophylaxis.

The use of rapid diagnostic tests for malaria for self-diagnosis by travelers is considered inaccurate, as sick individuals have difficulty with following procedures and interpreting results^{24,25}.

Yellow fever

RWT may visit yellow fever risk areas, or invariably places without risk but with a vaccine requirement, such as Asia and Indonesia. Since June 2016, the World Health Organization (WHO) removed the 10-year booster recommendation from the International Health Regulations²⁶. Occurrence of epidemics, such as those in Angola and Brazil recently, can change requirements. Therefore, the status of each country in the travel-plan should be reviewed, as even transit may fall under requirement. In this case, a vaccine may be offered upon entry, or travelers may be detained for up to six days to ensure that they are not infected²⁷.

Japanese encephalitis

Japanese encephalitis (JE) is caused by a *Flavivirus* and is transmitted to humans through bites from infected mosquitoes of the *Culex* species. It is the most common vaccine-preventable cause of encephalitis in Asia, with only 1% developing clinical disease. The estimated risk for travelers is considered very low (< 1 per million people traveling from non-endemic countries to Asia). Cases among travelers are correlated with long stay (≥ 1 month), rural area visits, and spending time under very basic conditions; thus, immunization for JE is generally recommended²⁸⁻³⁰. There are four vaccines available for JE. The inactivated Vero-cell derived vaccines require multiple doses. The vaccine derived from the Beijing-1 strain, available in Japan, requires 28 days for complete immunization with three doses. Ixiaro[®], available in US and Europe, requires 2 doses, with an interval of 28 days, which can be decreased to 7 days. The two live vaccines, SA 14-14-2 strain, available in China, and the chimeric, with yellow fever 17D as backbone, available in Australia and Thailand, require just one dose. JE vaccine is unavailable in many countries; therefore, when recommended, a traveler should select a route through a place where the vaccine is available before entering the risk area^{28,31}. RWT visiting countries in Europe, Oceania, or the United States, Thailand, Singapore and China can receive the vaccine there. Travelers must be encouraged to visit a travel clinic and receive vaccination before their journey to the risk-prone area. Travel advisors must provide a letter prescribing the vaccine and justifying its recommendation.

Other arbovirus: dengue, chikungunya and Zika

Dengue, Zika and chikungunya are arboviruses transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes, which are common in tropical and subtropical areas but present in all continents.

Dengue is the most common arboviral disease in the world. Four dengue virus (DENV) are known to cause human infection: DENV-1, DENV-2, DENV-3, and DENV-4. Reports of travel-associated dengue infection have been increasing. However, the actual rate of seroconversion is difficult to estimate due to cross reactivity among other arboviruses, including yellow fever, JE and Zika³². Zika virus infection, since its first description in humans in Nigeria in 1954³³, had been considered a mild febrile illness characterized by maculo-papular rash, arthralgia,

and conjunctivitis. However, in 2015, during the spread of the disease in Brazil, Zika infection was found to be associated with neurological complications. In pregnant women, the disease can cause fetal brain damage and microcephaly, whereas in adults it causes Guillain-Barré syndrome. Zika virus was also found in semen, and sexual transmission has been reported³⁴. The attack rate is estimated at 14.6/1,000 inhabitants during epidemics; however, the exact risk for travelers remains unknown³⁵.

Chikungunya virus originated in Africa, and was possibly introduced into Asia, Europe and the Americas by air travelers³⁶. Chikungunya virus causes an acute febrile illness characterized by intense asthenia, myalgia, headache, rash, and typically accompanied by intense arthralgia. Chikungunya is rarely fatal³⁶; however, it is associated with chronic arthralgia, leading to persistent incapacitation, requiring long-term treatment³⁷. Risk to travelers is high in areas with epidemics³⁶.

Currently, the singular protective measure available against these diseases is to avoid mosquito bites. Travelers to endemic risk areas should be encouraged to adhere to barrier methods (bed nets) and use reliable repellents (those containing N,N-diethyl-meta-toluamida (DEET) 20-50%, picaridin 20% or para-Menthane-3,8-diol (PMD) 30%)³⁸. The licensed dengue vaccine is unsuitable for travelers owing to limited efficacy and a prolonged schedule³⁹. Visitors to areas with active Zika transmission should be warned about mosquito-borne and sexual transmission routes and Zika congenital syndrome. People must be advised to adopt safe-sex practices, and women to postpone pregnancy for up to six months after return⁴⁰.

FOOD AND WATER-BORNE DISEASES

RWT routes often include remote locations in low-income countries with poor sanitary conditions, increasing the risk of food and water-borne diseases.

Vaccines for food and water-borne diseases

Hepatitis A vaccine should be offered to susceptible RWT considering its favorable safety profile, immunogenicity, and high susceptibility of exposed individuals¹⁸. Typhoid fever vaccines, despite suboptimal efficacy (60% to 70%), should be strongly considered because of the long-term exposure in high risk areas, some of which can harbor resistant strains⁴¹. Wild poliomyelitis disease is currently exported only by Pakistan and Afghanistan; nevertheless, wild virus and circulating vaccine-derived polioviruses are still present in Nigeria, Guinea, Lao People's Democratic Republic, Madagascar and Myanmar, justifying a booster dose of inactivated poliovirus vaccine if a primary polio vaccination has been administered more than 10 years before; and a complete vaccine series for unvaccinated individuals^{42,43}. A booster polio vaccine dose is advisable even if travel plans exclude those countries, but extend to neighboring places where the virus can reemerge during the long trip. Cholera vaccines are rarely prescribed for travelers, except during outbreaks, due to their short-term protection. However, the disease remains endemic in countries of Africa, Southeast Asia as well as Haiti. Outbreaks emerged unpredictably⁴⁴, as in Tanzania in 2016⁴⁵ and Haiti in 2010 after an earthquake⁴⁶.

Depending on the RWT activity plans, such as engaging in aid work, one of the following oral cholera vaccines should be considered: Dukoral® and ShanChol® (inactivated) or Vaxchora® (live)⁴⁷. Dukoral® may produce some cross protection against enterotoxigenic *Escherichia coli* diarrhea. However, additional evidence is required to support the recommendation for its use for this indication⁴⁸⁻⁵⁰.

Additionally, food and water safety precautions must be followed because of the limited efficacy of some vaccines and against other agents transmitted by the oral route, such as bacteria and viruses causing diarrhea, hepatitis E, worms, and protozoa.

Travelers diarrhea

Traveler's diarrhea (TD) is one of the most common health problems for visitors to poor sanitary areas. Advisors must consider the consequences of TD, in addition to the growing antibiotic resistance associated with TD^{51,52}, particularly in those treated with antimicrobials^{53,54}. For that reason, antimicrobials should be restricted to severe disease (incapacitating or bloody diarrhea). RWT must be instructed to recognize symptoms of severe diarrhea and to carry antimicrobials for self-administration. Azithromycin is currently the preferred antibiotic because of the widespread resistance to quinolones, particularly in Southeast and South Asia and especially related to *Campylobacter* spp. Quinolones and rifaximin are considered alternatives in some guidelines, but must be avoided in dysenteric diarrhea. Loperamide can be used as combined therapy. If symptoms do not improve in 24-36h, patients must seek medical attention⁵⁵. Those presenting with mild⁵⁵ to moderate symptoms of secretory diarrhea should be advised that those are self-limited and may improve with loperamide and/or⁵⁶ racecadotril⁵⁷.

Travelers must learn that oral rehydration and salt intake are essential, and carry rehydration packages or learn to produce an oral rehydration fluid with salt and sugar.

AIR BORNE TRANSMITTED DISEASES

Measles, chickenpox, pertussis, and mumps

The recent widespread increase in the incidence of measles, mumps, and pertussis underscores the need for RWT to be up-to-date with routine immunization to protect themselves and the people at their destination⁵⁸.

Meningococcal meningitis

Neisseria meningitidis serogroups A, B, C, Y, X and W135 cause meningococcal disease^{59,60}. Even though the risk of acquiring disease for travelers is considered low⁶¹, it is a devastating disease. The disease course is often fulminant, which makes the prognosis worse in travelers to remote areas with limited or delayed access to qualified medical care⁶². The vaccines currently available are monovalent group A or C, several tetravalent presentations for groups A, C, W135 and Y (MCV4), and two monovalent group B vaccines. The MCV4 vaccines are required for Hajj/Umrah pilgrims as a visa prerequisite. For those going to the African meningitis

belt and areas around Rift Valley and Great Lakes, MCV4 vaccine is recommended because of the increased disease prevalence^{59,63}. RWT planning to be in close contact with local populations, including activities in schools or hospitals, or living under crowded conditions, should consider vaccination^{61,64,65}. Those with underlying conditions, such as asplenia or other immune deficiencies related to immunoglobulin or complement deficiency, should also be vaccinated because of the increased risk of invasive disease⁶¹.

Influenza and other respiratory infections

Influenza vaccine can be recommended; however, efficacy may be limited considering the varied viruses circulating across hemispheres. Advice includes avoiding crowded, enclosed spaces, close contact with individuals with respiratory infections, and washing hands frequently⁶⁶. Travelers going to avian flu risk areas in Asia or Southeast Asia should avoid exposure to wild birds and poultry^{67,68}. During trips to the Arabian Peninsula, travelers must avoid contact with camels and their products, such as raw milk, urine or undercooked meat because of the Middle East respiratory syndrome coronavirus⁶⁹.

DISEASES CAUSED BY ANIMAL AND ENVIRONMENTAL EXPOSURE

Rabies

RWT itineraries frequently include high-risk rabies transmission areas, such as the Indian subcontinent, South East Asia, North Africa, Indonesia⁷⁰, and Sub-Saharan Africa⁷¹. Immediate access to appropriate medical care is usually limited, and availability of rabies vaccine and rabies immunoglobulin (RIG) is uncertain or products are ineffective⁷². In some countries, such as Brazil, equine RIG (ERIG), or purified fractions of ERIG, may be available⁷³; however, they may be less effective, have a shorter half-life and carry the risk of serum sickness⁷⁴. Most injured travelers in those countries⁷⁰ will need to access a neighboring place or their home country to start or continue proper care⁷⁴. Therefore, rabies pre-exposure prophylaxis is strongly recommended.

Schistosomiasis and leptospirosis

These diseases affect people exposed to lake and river waters. RWT frequently engage in activities in close contact with nature in wild and rural areas. Therefore, advice must include the risks of bathing in fresh water, mainly in areas wherein schistosomiasis is endemic. Considering the unpredictability of risk areas in some countries, screening of possibly exposed travelers on return must be considered⁷⁵. Leptospirosis has a worldwide distribution, with a higher incidence in tropical climates, especially after flooding. Chemoprophylaxis is not generally prescribed; however, those taking doxycycline for malaria prevention will additionally be protected against leptospirosis. Awareness of leptospirosis risk factors will increase chances of early appropriate treatment for this potentially lethal disease⁷⁶.

SEXUALLY TRANSMITTED INFECTIONS

Traveling has historically been an important risk factor for acquisition and spread of sexually transmitted infections (STIs). Over the last decades, 5-50% of short-term travelers engaged in casual sex during foreign trips, with a substantial risk of developing STIs^{77,78}. RWT, even those with a partner, need advice about STIs, condom use, and hepatitis B vaccination, and to come for screening after return if they have engaged in casual sex during the trip⁷⁸.

MEDICINES TO CARRY

According to the WHO, up to 10% of drugs available worldwide may be counterfeit; 78% of those are found in developing countries and 50% are antimicrobials⁷⁹. Thus, RWT should carry medicines they may possibly needed along the trip, including antibiotics such as levofloxacin, azithromycin, and amoxicillin/clavulanic acid, for most respiratory, urinary tract, or intestinal bacterial infections. Medication should cover any preexisting medical conditions and general medications like pain and fever relievers, pre-packed rehydration salts, antacids, decongestants, antihistamines, motion sickness medication, and saline eye and nose drops⁸⁰. Narcotic or psychotropic substances are subject to international laws, and lists with the amounts of those medicines allowed by each country must be checked before traveling⁸¹. Travelers must carry medicines in the original containers with clear labels, along with copies of all medical prescriptions in the language spoken at destination or, minimally, in English⁸⁰.

NON-INFECTIOUS RISKS

RWT frequently engage in activities such as scuba diving, climbing and trekking at altitude which require alertness and fine motor coordination. Such activities can impact some infectious disease prophylactic decisions, such as prescription of mefloquine in those planning activities such as scuba diving or doxycycline for those planning heavy sun exposures¹⁸. These situations require a detailed discussion and more complex planning regarding malaria prophylaxis, sometimes requiring use of different drugs over the trip.

CONCLUSIONS

RWT are people embarking on long touristic adventures including risky places, with poorly predicted schedules at the time of consultation. Travel advice for RWT comprises an extensive range of travel medicine expertise. The challenges are: 1) to commit travelers to their own health; 2) to make individuals understand the risks and the importance of adopting preventive measures throughout the journey; 3) to decide the best options for malaria prophylaxis, preferably making notes in the travel plans about risk areas and right times to start and stop medication; 4) to discuss strategies for disease sentinel symptoms; 5) to prescribe medicines for potential illness, preexisting medical and general conditions; 6) to dedicate enough time to ensure most information is acknowledged; and, finally, 7) to deliver advice without undermining traveler's motivation for such a life experience.

Conflict of interest

The authors declare that there is no conflict of interest

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