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Review

Prevention of travel-related infections in solid organ and hematopoietic cell transplant recipients

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***Abstract*:** The growing population of transplant survivors receiving a solid organ transplantation (SOT) or a hematopoietic cell transplantation (HCT) and the emergence of cellular therapies are contributing to an increase in high-risk travelers to different regions of the world. Timely pretravel evaluations are essential for risk stratification and a segway to planning proper immunization, personalized antimicrobial prophylaxis, and preventative counseling based on individual medical conditions, immune status, and potential drug-drug interactions. In addition, clinicians can provide emergency and specialized medical center contacts as available. We herein review the available strategies for the prevention and management of travel-related infections in adult recipients of HCT and SOT.

Keywords: hematopoietic cell transplant, prevention, solid organ transplant, travel-related infections

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Introduction

Significant advances in hematopoietic cell transplantation (HCT) and solid organ transplantation (SOT) are contributing to an increase in the number of transplants performed with improved outcomes, leading to a growing number of survivors.[1] Progressive globalization, rise in medical tourism, and increased travel by transplant recipients to different regions of the world, which may be endemic for different pathogens, are changing the needs of travel medicine.[2,3] Evidence of the impact of travel-related illnesses in SOT and HCT recipients has been increasing in recent years. Surveys from various transplant centers indicate a high rate of illness among traveling transplant recipients, often exacerbated by insufficient pretravel counseling.[2–4] The intent of this review is to explore strategies for the prevention and management of travel-related infections in adult recipients of HCT and SOT, through the lens of a United States (US)-based traveler.

Epidemiology

The rate of international travel among HCT recipients in the initial 2 years posttransplant ranges from 8% to 32% in cohorts from the United States and Switzerland.[3,4] Nonetheless, only 35%–56% sought pretravel medical advice, and less than 10% experienced illness requiring medical attention during their travels.[3,4]

A survey of patients attending a Canadian SOT clinic revealed that 36% of 267 participants had traveled internationally beyond the US; 66% of those sought pretravel advice. However, the majority did not follow preventative measures. For example, 63% of travelers visited areas where hepatitis A (HAV) is endemic, but only 5% were vaccinated. In addition, 50% traveled to regions at risk for dengue and malaria, yet only 25% took precautions against mosquitoes, and 10% engaged in behaviors that exposed them to blood or body fluids.[5] Similarly, a transplant center in the US reported that 27% of their 1130 SOT

Figure 1. Pretravel initial visit and follow-up visit as needed.

patients traveled internationally beyond Canada, but only 4% sought pretravel advice.[6] Illnesses requiring medical attention affected 8% of these travelers.[6] A Dutch study involving 290 kidney transplant recipients found that 34% had traveled beyond Western Europe and North America.[7] Among those travelers, 29% experienced illness, and 25% required hospitalization.[7] These findings underscore the need for improved pretravel assessments by a physician familiar with both transplant medicine and travel medicine.

General principles of vaccines and travel advice

Solid organ transplantation

Pretravel evaluation. Transplant recipients should consult a travel medicine specialist familiar with their medical history and immunosuppressive therapies prior to traveling.[2] Due to the increased infection risk during heightened immunosuppression, often seen in the first year posttransplant, patients should avoid traveling to high-risk areas during this time, including areas with active disease outbreaks or limited healthcare access.[8] Pretravel consultations should include vaccinations and risk mitigation for non-vaccine-preventable illnesses (Figure 1).

Travel immunizations. Due to the potential risk of decreased immunogenicity, vaccination timelines must be adhered to, often starting months in advance to ensure efficacy. Serologic testing is suggested to document the response to vaccination. Passive immunization with immune globulin may be necessary for urgent travel.[2] As live vaccines are not recommended after transplant, evaluating the necessity of these vaccinations before the procedure is essential.[2]

The particularities of the travel-related vaccinations in the SOT population are summarized in Table 1.

Hematopoietic cell transplantation

The HCT population is unique in that, despite being significantly immunocompromised during the immediate posttransplant period, there is an anticipated restoration of immune function at approximately 12–24 months after engraftment,[9–11] except if graft-versus-host disease (GVHD) develops requiring further immunosuppressive treatment.[9,10]

Recipients of autologous HCT typically achieve a more rapid immune reconstitution compared to those undergoing allogeneic transplants, and they

Table 1. Travel vaccine indications and considerations for the SOT and HCT recipients.

Vaccine	Indications	SOT-specific modifications	HCT-specific modifications
Quadrivalent Meningococcal Conjugate Vaccine	– Travelers to endemic areas (meningitis belt, sub-Saharan Africa, December–June) – Hajj or Umra pilgrims – Proof of vaccination required for Hajj/Umra	Two doses, booster every 5 years	One dose starting 6 months post-HCT in societal recommendations.[10] Two-dose series recommended by specialty centers[22]
Serogroup B Meningococcal Vaccine	– Not usually recommended for travel unless there is a reported outbreak	– Consideration for vaccination	Two doses starting 6 months post-HCT[22]
Yellow Fever Vaccine	– Travelers to areas endemic in yellow fever – Proof of vaccination is required in some endemic countries	– Live vaccine; contraindicated for SOT recipients – Waiver letter acceptable if vaccination is not given – Consideration before transplantation	One dose starting 24 months post-HCT, no GVHD, no continued immunosuppression[30,41]
Rabies vaccine	– Long-term travelers – Animal exposure cannot be avoided – Far from medical care	– Post-exposure prophylaxis required for all potential exposures – HRIG recommended for SOT recipients	– Starting 6 months post-HCT[30] – Given only by the intramuscular route – Serology should be checked 7–14 days post-vaccination to ensure that an acceptable antibody response – Post-exposure prophylaxis for all potential exposures
Japanese Encephalitis Vaccine	– Mainly rural travel in endemic areas	– Inactivated vaccine; not studied in SOT – Avoid live virus vaccine	– Inactivated vaccine starting 6 months[30] – Live vaccine not recommended*
Cholera vaccines	– High-risk travelers in cholera-prone areas – Inactivated and live attenuated vaccines available	– Not routinely recommended; may be considered on an individual basis – Live vaccine contraindicated for SOT recipients	– Inactivated: Starting 6 months pot-HCT if indicated[30] No data on efficacy – Live vaccine Not recommended *
Hepatitis A vaccine	– Travelers to destinations with intermediate to high endemic risk – Inactivated and live attenuated vaccines available	– Inactivated: 2 doses – Live vaccine contraindicated	– Inactivated: 2 doses starting at 6 months[10] – Live vaccine not recommended*
Typhoid vaccines	– Travel to areas that have a recognized risk of exposure to *S. typhi* – Inactivated and live attenuated vaccines available	– 2 weeks or more prior to travel	– Inactivated: Starting 6 months post-HCT if indicated[30] – Live vaccine Not recommended*
Tickborne encephalitis	– Travel to tickborne encephalitis endemic areas – Inactivated vaccine	– Not well studied in SOT	Timing unknown
Poliovirus vaccines	– Travel to poliovirus endemic areas – Inactivated and live attenuated vaccines available	– Parenteral booster if it has been over 10 years since their last vaccination – Live vaccine contraindicated	Three doses starting at 6 months post-HCT[10,41]
MMR		– contraindicated in adult SOT recipients	– Two-dose series 24 months following HCT no GVHD, no continued immunosuppression, 8–11 months after last receipt of IVIG products[18]

*This is primarily due to the availability of effective inactivated alternatives and the absence of safety and immunogenicity data for these vaccines in HCT patients.[22,40]
GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; HRIG, rabies immune globulin; IVIG, intravenous immunoglobulins; MMR, measles, mumps, rubella; SOT, solid organ transplantation.

are at a lower risk of developing GVHD and subsequent opportunistic infections.[12] Immune reconstitution also varies by the immunomodulatory effects of pre-HCT therapies such as rituximab (anti-CD20 antibody) and alemtuzumab (anti-CD52 antibody), after which, it may take 6–12 months to achieve recovery.[13,14] In addition, certain conditioning agents, including fludarabine, can lead to both quantitative and functional depletion of T-cells for up to 12 months after treatment.[13]

For the purposes of this discussion, when mentioning the HCT population, it encompasses both the allogeneic and autologous transplant recipients, as a similar approach is employed for travelers in these two categories unless otherwise specified.

Following HCT, recipients experience a decline in their preexisting protective titers to vaccine-preventable diseases and necessitate primary reimmunization strategies once their cellular and humoral immunity has adequately recovered.[10,15] Consequently, the timing of travel is key for this population. The Center for Disease Control and Prevention (CDC) advises against international travel transplant recipients for a period of 24 months, as they are at a heightened risk of infectious complications during their initial trip posttransplant.[10,16]

Other consensus HCT guidelines advise against travel to developing countries for up to 6 and 12 months, among autologous and allogeneic transplant patients respectively. This timeline is mainly to facilitate routine revaccination and ensure immune recovery.[9,13]

Pretravel evaluation. Pretravel evaluation of an HCT recipient should consider the time since HCT, the existence of GVHD, and the patient's overall immunosuppressive status.[13,17] When patients seek consultation earlier than advised, healthcare providers need to carefully assess the potential risks of the travel destination versus the benefits of the trip.

During the pretravel visit, the provider should gather specific information regarding the upcoming journey, including travel dates, itinerary, and planned activities, especially those involving high-risk endeavors such as cycling, mountain climbing, diving, or rafting. Additionally, they should ensure the accuracy of their medications and dosages and the completeness of primary reimmunization.

Depending on the destination, necessary preventive actions may include vaccinations or medications for malaria prevention and/or options for self-treatment of travelers' diarrhea and counseling on safe practices (Figure 1).

Travel immunizations. Post-HCT immunization protocols advise against receiving live attenuated vaccines until at least 2 years post-HCT have elapsed, provided there is no evidence of systemic GVHD, and they have ceased all immunosuppressive medications.[9,16]

Most non-live vaccines can be re-initiated 6 months after transplantation, that is, to allow time for partial adaptive immune reconstitution to increase the likelihood of vaccine efficacy.[9,16] Seasonal viral vaccines can be administered earlier at 4 months as they will have a high benefit-to-risk ratio.[18] Many of these guidelines recognize the lack of clinical research data to accurately define practices, including the assessment of immune parameters prior to vaccination.[9,16,18]

Before traveling, HCT recipients should ensure they have completed their primary posttransplant immunization series. These include pneumococcal, tetanus, diphtheria, pertussis-containing vaccines (DTaP or Tdap), *Haemophilus influenzae* (Hib), (HAV) (in endemic areas), hepatitis B (HBV), inactivated polio, inactivated influenza, meningococcal, measles, mumps, rubella (MMR), and human papillomavirus (HPV) vaccines.[19,20]

The selection of travel-related vaccines depends on the specific epidemiological risks associated with the destination and indications can be found in the latest guidelines and advisories from the CDC.[21]

The particularities of the travel-related vaccinations in the HCT population are described in detail in Table 1.

The effectiveness of routine and pretravel vaccinations depends on the timing of administration and the level of immunosuppression present at that time. Factors such as the type of transplant, the presence of GVHD, or ongoing immunosuppressive treatment may require postponement of vaccine administration, thereby affecting the timeline for safe elective travel. The simultaneous or closely timed administration of intravenous immunoglobulins (IVIG) and live

vaccines may lead to a neutralizing effect, thereby diminishing the serological response of the vaccine. Consequently, IVIG should not be given for a period of 8–11 months prior to, and for 2 weeks following immunizations with live vaccines.[18] It does not, however, affect the antibody response to inactivated vaccines.[18]

Ideally, travel assessment for immunizations and serologic evaluation should start 6 weeks before travel. This allows sufficient time to assess the response and provide alternative treatments.[22] The dates of administration and serologic response, if measured, should be detailed in a document for the patient to have.[22]

Cellular therapy recipients

Recipients of chimeric antigen receptor T cell therapy (CAR-T) therapy are at risk of developing prolonged cytopenias and B-cell aplasia, compromising their immunity against vaccine-preventable infections and their ability to mount a response to new vaccines.[23] This differs between the two available types of therapies. CD19-directed CAR-T treatment is known to deplete memory-B and CD19-positive plasma cells while sparing the CD19-negative plasma cell population.[20] This is hypothesized to allow retention of antibody production against pathogens that were previously encountered or vaccinated against.[20,24] B-cell maturation antigen (BCMA) CAR-T therapy on the other hand depletes all BCMA-expressing plasma cells so recipients will additionally have lower seroprotection to prior vaccines after treatment.[20,24] The clinical course following the infusion also depends on the occurrence of immunotoxicities and their related immunosuppressive treatments which can further affect the timeline of their immune recovery.

At present, seroprevalence studies in these patients regarding travel vaccinations are scarce. Thus, vaccination schedules are resultant from expert opinion and echo the autologous HCT guidelines mostly restarting at 3–6 months after CAR-T for non-live vaccines and at least a year for live vaccines provided the patient demonstrates immune recovery and are not continually receiving immunosuppressive treatments.[20] A proposed objective criterion for evaluation of immune recovery includes CD4+ $>0.2\times10^9$/L, CD19 or CD20+ B cells $>0.2\times10^9$/L.[20,24,25]

Due to the unpredictable response post-CAR-T, it is also advisable to provide known needed immunizations prior to the CAR-T infection by at least 2 weeks if travel is anticipated.[20,26]

Prevention of specific infections

Measles

Measles remains prevalent in parts of Africa and Asia. Various outbreaks have occurred in European countries over the past years. The measles vaccine is part of a combined live attenuated vaccine to mumps, and rubella as well and is referred to as MMR.[2] As it contains live attenuated pathogens, it is contraindicated in SOT recipients due to the risk of severe complications, including encephalitis.[27] The vaccine is typically provided to HCT recipients 24 months posttransplant provided they are off immunosuppressants, not receiving IVIG, and without evidence of GVHD. Before traveling to endemic areas, clinicians should evaluate measles serology.[8] HCT recipients should have documentation of completion of their primary reimmunization series. For others, clinicians may consider checking serology (measles IgG).[8] HCT recipients can receive the vaccine earlier if needed per risk of exposure and if the following criteria are met: At least 1 year has elapsed since transplantation, on a single-agent for GVHD prophylaxis with proper levels, on $\leqslant$5 mg prednisone equivalent, no active systemic GVHD requiring immunosuppression beyond topical agents, a total lymphocyte count of $\geqslant1\times10^3$ µL, or CD4 cells >200/µL and CD19 cells >20/µL, and unsupported IgG >400 mg/dL and measurable IgA >6 mg/dL and not receiving active chemotherapy.[28] Early vaccination can also be considered starting 6 months post CAR-T with similar conditional factors.[28] For non-immune SOT and HCT recipients at high risk of exposure, immune globulins may be administered to provide timely protection for short-term travels.

Hepatitis B

For SOT recipients who were not vaccinated pretransplant and HCT recipients who have not completed their post-HCT reimmunization series, immunization is indicated. This is particularly important in travelers who are likely to receive transfusions or medical procedures and to those anticipating new sexual contacts.[29] A

high-dose vaccination series has been shown to achieve better response and is recommended in this population.[30,31] Anti-HBs titers >10 IU/mL are considered to be protective.[32] The HBV vaccination series typically takes 6 months, but travel may require an accelerated schedule, which can vary in effectiveness. This highlights the necessity for early pretravel evaluation.[8]

Hepatitis A

HAV is one of the most preventable infections among travelers.[33] Travelers to endemic destinations should be vaccinated against HAV.[33] Vaccine efficacy is suboptimal in SOT recipients.[34] In a small cohort of liver transplant recipients, only 26% developed protective serologies.[34] SOT recipients are also at risk of losing seroprotection at a higher rate than the general population.[35] When evaluated 2 years after completing their vaccination, only 59% of liver transplant recipients and 26% of renal transplant recipients who seroconverted had detectable protective titers.[35] It remains unknown if higher doses or additional doses of the HAV vaccine would improve the response[2]; the response to the combination HAV and HBV vaccine (Twinrix) is often poor in this population as well.[36]

The inactivated HAV vaccine is recommended starting 6 months post-HCT. The efficacy of the HAV vaccines has not been well defined in HCT recipients. A prospective study, including 46 allogeneic HCT recipients, found poor serological response to the inactivated HAV vaccine, with only 33% of susceptible patients responding.[11] Patients should undergo antibody titer measurements.[22]

Seroconversion in autologous transplant recipients who had received rituximab 12 months before HAV vaccinations has been reported to be at 47% after the first dose in one cohort[37] and 61% after the second dose in another.[38] Time of vaccine from last rituximab dose in both cohorts was >12 months. The effect of higher vaccine dosage is not established.[22]

SOT and HCT recipients who are seronegative and do not have enough time to complete the vaccination series prior to travel should receive pooled immune globulin.[8,22] Patients receiving routine IVIG do not require additional measures for passive protection against HAV.[2]

Other viral hepatitis

Hepatitis E is transmitted through the fecal-oral route, particularly in areas with poor sanitation. It can be prevented by practicing proper food hygiene.[39] To prevent hepatitis C, patients should be advised to avoid unprotected sexual activity and to refrain from using nonsterile needles, particularly during cosmetic and tattoo procedures.[29,40]

Salmonella enterica serovar Typhi

Transplant travelers should receive vaccination with TyphimVi®, Marcy L'Etoile, Rhône-Alpes, France, an injectable polysaccharide vaccine, 2 weeks or more before traveling to endemic areas. There is a lack of data regarding the safety, immunogenicity, and efficacy of vaccines for inactivated typhoid in HCT recipients. The vaccine is hence labeled as optional or not recommended by most HCT societal recommendations.[18,41] The live oral typhoid vaccine is not recommended in both populations.[18] Prevention also necessitates practicing proper food and water precautions.[2]

Polio

Wild-type poliovirus remains endemic in Afghanistan and Pakistan while vaccine-derived polioviruses are circulating in some countries in Africa and Asia.[42] SOT recipients traveling to these areas should have completed their primary series of polio vaccines during childhood and would require a booster dose if it has been over 10 years since their last vaccination.[8] Furthermore, a booster dose might be required when traveling for a month or longer to countries where wild or vaccine-derived polio is circulating.

Revaccination with inactivated poliovirus vaccine in HCT recipients is usually effective with retentions of serological titers long-term in approximately 90%–98% for different subtypes with evidence of response in patients who receive a booster dose.[43] The oral polio vaccine on the other hand, is contraindicated in both populations mainly due to the risk of transmission.

Meningococcus

Transplant recipients traveling to the meningitis belt in Sub-Saharan Africa from December to June, and those visiting Saudi Arabia for Muslim pilgrimages should receive the meningococcal

conjugate vaccine at least 10 days before arrival, with a certificate valid for 5 years after receipt of a conjugate vaccine.[2,44] The polysaccharide vaccine is no longer available in the US. SOT recipients may require periodic revaccination.[2] They should receive two doses of the quadrivalent meningococcal vaccine, with a booster every 5 years. Inactivated meningococcal serogroup B vaccines (MenBV) can be considered for those at increased risk as well.[29] The immune response of SOT recipients to both vaccines is not well established, but their administration appears to be safe and potentially effective.[8]

HCT recipients can receive the conjugate meningococcal vaccine starting 6 months post-HCT.[10] Serological efficacy has been demonstrated in allogeneic HCT recipients given the polysaccharide vaccine.[45] Response to two-dose series of MCV4 vaccine was better than one dose in a small group of allogeneic HCT recipients.[46]

Yellow fever

Due to the nature of the live virus vaccine, it is contraindicated in SOT recipients.[8,40] Individuals anticipating travel to endemic areas should be vaccinated before their transplant.[2] A study of 53 patients showed that 98% had detectable protective antibodies for 3 years posttransplant, with neutralizing antibodies still present after a median of 13 years.[2]

The yellow fever vaccine can be administered starting 24 months post-HCT provided no GVHD has occurred, and the patient is not receiving immunosuppressive medications.[20,22] Individuals who have received the yellow fever vaccine before undergoing HCT should be revaccinated after the procedure. Data from a small cohort of 21 patients who received the vaccine demonstrated retained immunogenicity and safety.[47]

Areas subject to endemic and epidemic yellow fever may require proof of vaccination. If immunization is not feasible or cannot be safely administered at that time, a waiver letter, stating the contraindication to the vaccine, is generally accepted by most official entities, provided it bears the stamp of an official, certified yellow fever vaccination center. Transplant recipients should ideally refrain from going to endemic regions especially during high seasons (January to March in Brazil and July to October in rural West Africa).[40] Family members of transplant recipients may receive the yellow fever vaccine.[40]

Rabies

According to the World Health Organization, rabies causes approximately 59,000 deaths globally each year, primarily in Africa and Asia.[29] Preexposure vaccination against rabies should be considered for long-term travels and those expecting significant animal exposure.[21] SOT recipients anticipating potential exposure should complete a rabies vaccination series of two doses on days 0, 7 followed by measurement of titer 2–4 weeks after vaccine administration. If the antibody titer is below 0.5 IU/mL, an additional dose should be administered and titers repeated. If antibody titers remain below 0.5 IU/mL after two doses, guidance from public health officials should be considered.[47,48] In the event of potential rabies exposure, all SOT recipients should receive post-exposure prophylaxis.[2] Unvaccinated individuals receive rabies immune globulin (HRIG) (20 units/kg) injected at the wound site, followed by a 5 dose-series at 0, 3, 7, 14 and 28 days regardless of the bite severity or animal status.[48,49] Those who were previously vaccinated should receive two additional doses on days 0 and 3, without HRIG.[2] Due to concerns of poor vaccination response (titers <0.5 IU/mL), some authorities recommend administering HRIG after any at-risk exposures.[2]

The Canadian and American Society of Bone Marrow Transplant (ASBMT) immunization guidelines recommend that HCT recipients receive pre-exposure rabies vaccination (non-live) at least 3 weeks before travel, starting 6 to 12 months (Canadian)[30] or 12–24 months (ASBMT)[10] posttransplant, preferably when the patient is no longer considered immunocompromised. The post-exposure vaccination regimen will depend on the individual's previous vaccinations and responses. ASBMT recommends the administration of rabies immunoglobulin (RabIg) regardless.[10] For post-exposure prophylaxis (PEP) in patients with adequate titer response to PrEP, two doses of the PEP series can be administered at 0 and 3 days, along with one dose of RabIg on day 0. If no PrEP was administered or no evidence of proper response to PrEP, a 5-dose series should be used along with one dose of RabIg on day 0.[10]

Japanese encephalitis

Immunization against the mosquito-borne Japanese encephalitis (JE) virus should be considered for individuals engaged in extensive rural travel in areas where JE is endemic, particularly during heightened transmission periods.[50,51] While efficacy data in SOT and HCT recipients are limited, its use is advised when travel plans necessitate it.[18,29,41] The inactivated JE vaccine (Ixiaro®, Vienna, Austria) is two-dose series 28 days apart. Adults aged 18–65 years can receive the second dose 7–28 days after the first dose.[51,52] A booster dose should be considered if the primary series was received more than a year before travel or continued potential exposure risk.[52] Travelers should note live JE vaccines are available in Asia and should be avoided in both populations.[2]

Tickborne encephalitis

Tickborne encephalitis is endemic to western and northern Europe through to northern and eastern Asia with peaks in early and late summer when ticks are most active.[52] Data on its efficacy are scarce in immunocompromised patients.[52]

Four vaccine doses starting at 9 months were deemed safe in a cohort of 104 HCT recipients with a 77% seropositive response.[53] A small cohort of heart transplant recipients demonstrated a poor response at 35% when compared with controls at 100%.[54]

Cholera and enterotoxigenic Escherichia coli

Cholera, caused primarily by *Vibrio cholerae* (serogroups O1 and O139), is typically linked to poor sanitation. Three formulations of inactivated oral vaccines are available.[2] Dukoral®, Lyon, France is an oral travelers' diarrhea and cholera vaccine. It has been shown to protect against *Vibrio cholera* serogroup O1, but there is no verified consistent protection against travelers' diarrhea caused by enterotoxigenic *Escherichia coli* (*E. coli.*)[55] The oral vaccine consists of 2 doses given 1 week apart. A booster is needed every 2 years if the risk of exposure continues.[56] The inactivated oral cholera vaccine available outside the U.S. has not been specifically studied in SOT and HCT recipients, though it has been well tolerated in healthy populations and may confer protection. It is hence labeled as optional in some HCT societal recommendations.[18,22,41] The oral cholera vaccine (Vaxchora®) is the only one approved for use in the US but is live, making it unsuitable for SOT travelers.[8,56] Is it also not recommended in HCT recipients due to the availability of effective inactivated alternatives and the absence of safety and immunogenicity data.[22,41] The other inactivated vaccines are not available in the US. Clinicians may consider recommending it once abroad for those at high risk.

Traveler's diarrhea

Traveler's diarrhea is prevalent among travelers.[57] While many cases are mild and self-limiting, travelers' diarrhea can pose a life-threatening risk to transplant recipients, as decreased intestinal absorption and dehydration, impairing renal function, can impact the metabolism of immunosuppressive medications, especially for those on tacrolimus. Enterotoxigenic *E. coli* is a significant concern, responsible for most cases, alongside *Campylobacter jejuni*, *Shigella* spp., and *Salmonella* spp. as well as other parasitic infections like cryptosporidium.[57]

Before traveling internationally, patients ought to be educated on appropriate food and drink safety measures.[40] They should only consume boiled or bottled water and avoid beverages made with tap water or ice.[57] Canned beverages and hot drinks such as coffee and tea are generally considered safe.[57] In addition, unpasteurized dairy foods and raw or undercooked products (including meat and fish) should be avoided.[57] Fruits and vegetables that can be peeled are safe to consume.[2]

Antibiotics for diarrhea prophylaxis are generally not recommended for travelers.[16] Bismuth subsalicylate (BSS) has demonstrated some effectiveness in treating mild diarrhea and in providing prophylaxis for short-term travel.[58]

Taking BSS can be challenging though, due to the need for frequent daily dosing and its wide range of side effects including tongue discoloration, constipation, nausea, and tinnitus. In addition, BSS is unsuitable for those with gout, renal insufficiency (especially in SOT recipients), or who take anticoagulants, methotrexate, or probenecid. Concurrent use of aspirin or other salicylates increases the risk of salicylate toxicity.[29,57]

Systemic antibiotics should be reserved for self-treatment of traveler's diarrhea lasting more than 2 days. All travelers should carry suitable antibiot-

ics depending on local destination resistance patterns for Enterobacteriaceae species for self-treatment.[57] The drug of choice has changed over time due to evolving resistance patterns. Fluoroquinolones' effectiveness is now limited by growing resistance among Campylobacter and Shigella species globally. Azithromycin is an alternative to fluoroquinolones and is currently the preferred agent for treating moderate-to-severe diarrhea.[57,59]

Azithromycin is generally well tolerated when used in combination with calcineurin inhibitors and mTOR inhibitors. However, in rare cases, it may increase the QT interval. Reports have shown decreased susceptibility to macrolides in Thailand and Ireland.[59]

Rifaximin and rifamycin SV are nonabsorbable antimicrobials effective against noninvasive enteric bacterial pathogens, making them suitable for treating noninvasive E. coli strains in adults; however, travelers should carry a separate antibiotic for potential invasive infections.[57]

Antimotility agents are not recommended in transplant recipients with infectious diarrhea. These drugs can delay toxin clearance and have harmful consequences.[17,57] If the patient experiences concomitant fever or hematochezia, they should seek medical care promptly.[10]

Travelers should be informed about the importance of fluid replacement, ideally with clean water and oral rehydration solutions available at pharmacies worldwide, if they develop diarrhea.

Those experiencing diarrhea unresponsive to antibacterial treatment should undergo an expanded workup to evaluate for parasitic infections.[40]

Respiratory infections

Respiratory infections are frequently encountered among travelers. Individuals should consider postponing travel to countries experiencing active epidemics, such as Middle Eastern Respiratory Syndrome.[2] Influenza seasons are less predictable in tropical regions where the virus can circulate year-round.[60] Transplant recipients are expected to receive an annual intramuscular vaccination against influenza[10] and should be up to date on immunization before travel. The vaccine can be administered at 3 months post-HCT and CAR-T.[20,26] Same timeline applies for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) whereby initial vaccination series or boosters for the HCT and CAR-T population.[20,26] Respiratory syncytial virus (RSV) vaccines are now available however, immunocompromised patients were excluded from the clinical trials. The current HCT-related societal guidelines recommend the consideration of the RSV vaccine in HCT recipients >60 years.[61] For SOT recipients, it is currently advised to administer the vaccine prior to the SOT if feasible.[62] Post-SOT, experts advise deferring the vaccine to the second year and beyond 3–6 months of augmented immunosuppressive therapy.[62] Data are lacking on the efficacy of administering booster doses in both populations as well.

Varicella and zoster infections

Varicella-zoster virus (VZV) is endemic worldwide and immunocompromised patients are at risk of disseminated disease.[19,27] Acquisition may occur via inhalation of aerosols or direct skin or mucosal contact with the vesicular fluid. Reactivation in the form of zoster disease is more frequent and severe in the HCT, CAR-T, and SOT population.[18,20] Prevention is performed through avoiding exposure to sick individuals and household members with active lesions, prophylactic antivirals, and vaccination. The live varicella vaccine for seronegative HCT recipients is contraindicated before 24 months[18,20], at any time post-SOT except for carefully selected patients[27] and should be provided after prophylaxis is stopped. The live zoster vaccine is not recommended in both SOT and HCT recipients and is not currently marketed in the US.[20,27] The recombinant zoster vaccine (RZV)'s safety is demonstrated in autologous HCT, allogeneic HCT, and SOT recipients.[27] RZV is recommended to prevent VZV reactivation at 3–12 months post autologous HCT[19,20] with a reported efficacy of 68.2%[63] and starting 6 months post allogeneic HCT[19,20] with mixed results on the immunogenic response in observational studies.[64]

Fungal infections. Endemic fungal infections prevalent in North America include histoplasmosis, blastomycosis, and coccidioidomycosis. Paracoccidioidomycosis is endemic to South America,[40] and talaromycosis in Southeast Asia.[29] Transplant recipients face a heightened risk of

invasive fungal infections. Exposure can be avoided by refraining from activities like spelunking and excavation. Wearing masks may have a protective role against these infections.[2]

Malaria

The selection of antimalarial prophylaxis should be guided by the agent that targets the geographically prevalent Plasmodium spp. in the destination. Other considerations include tolerance and drug-drug interactions with the patient's medication list.[29] The CDC Yellow Book offers country-specific guidelines and highlights the above-mentioned considerations.[65] Other important measures include screening for G6PD deficiency if primaquine is prescribed and screening for psychiatric syndromes if mefloquine is considered.[40,65] Specific to transplantation, chloroquine decreases the bioavailability of methotrexate and can cause increased levels of calcineurin inhibitors (e.g., cyclosporin, tacrolimus),[66] Concurrent use of doxycycline or mefloquine and calcineurin inhibitors or mTOR inhibitors (e.g., sirolimus) can cause increased levels of these immunosuppressant drugs.[66] Atovaquone-proguanil is noted to have no known interactions with these medications.[66] Increased risk of photosensitivity associated with doxycycline in patients more susceptible to skin cancers should also be considered.

To prevent mosquito bites, travelers should utilize insect repellents, and wear long-sleeves or clothing treated with permethrin. They should also limit their presence outdoors from dusk to dawn and sleep in screened or, ideally, air-conditioned rooms.[65]

Other insect-borne illnesses

Delayed engraftment has been described in an HCT recipient who acquired the Zika virus days before the transplant.[67] Patients should be counseled on minimizing insect bites using similar strategies described in the malaria prevention section.

In regions endemic to leishmaniasis, transmission to SOT and HCT recipients has been documented.[40,68] When visiting areas where leishmaniasis is endemic, transplant recipients should be aware of the high risk of exposure to sand flies outdoors mostly at dusk when they are most active.[68] Preventive measures also include the use of protective clothing, insect repellents, pyrethroid-treated bed nets, and residual-action insecticides in living spaces.[68] Transplant recipients traveling to Chagas endemic areas should be aware of the risks posed by contact with reduviid (kissing) bug.[40] Most dengue fever cases are self-limited in healthy immunocompetent individuals. Transplant recipients, being immunocompromised, are at higher risk of developing dengue hemorrhagic shock syndrome.[69] For patients with prior dengue infections, secondary infections heighten the risk of severe complications, particularly in immunocompromised individuals.[29] The mortality rate in a composite group of 29 renal transplant recipients with dengue was 10.8%, and new bleeding complications reached 34.8%.[70] Another cohort noted that 66.7% of the patients experienced renal graft dysfunction.[71] A case series of nine HCT recipients noted dengue-related death in two of them due to severe plasma leakage and shock.[72] Another cohort of five patients in Brazil demonstrated prolonged clinical manifestations and viremia.[73] Routinely updated, area-specific information is available on the dengue map per this link (www.healthmap.org/dengue/index.php). Transplant recipients infected with chikungunya may experience chronic polyarthritis following the acute phase and prolonged viremia and viruria.[69,74]

Environmental exposures

Patients visiting regions endemic to *Schistosoma* species should refrain from swimming, bathing, or wading in rivers, lakes, ponds, or irrigated fields.[29,40] Travelers in areas where strongyloidiasis is common should be advised to wear footwear, especially in damp or muddy regions. Walking barefoot is discouraged, and closed-toe shoes are recommended.[16,17]

Strongyloidiasis can persist indefinitely, and transplant recipients are at risk of progressing to the hyperinfection stage.[40] Patients may require screening after travel if there are signs of itching or hypereosinophilia.

Other recommendations for safe travel

Transplant patients visiting friends and relatives might underestimate the risks and should remain vigilant against food, and waterborne illnesses (Table 2). They should be reminded to maintain routine infection prevention practices and counseled on the importance of good hand hygiene.[8]

Table 2. General travel advice for transplant recipients.

Basic precautions	– Maintain routine hand hygiene. – Carry hand sanitizer while traveling. – Avoid sick contacts. – Use procedural masks if exposure is unavoidable.
Diarrhea	– Educate on food and water safety (drink only boiled/bottled water, avoid unpasteurized dairy, street food, and raw foods). – Eat only fruits/vegetables that can be peeled. – Start oral fluid replacement promptly – Carry prescription antibiotics for self-treatment. – Seek medical attention for severe symptoms (fever and bloody stools). – Avoid trimethoprim/sulfamethoxazole and antimotility agents due to risks.
Respiratory infections	– Consider postponing travel to areas with active respiratory outbreaks. – Avoid high-risk activities (e.g., spelunking). – Use masks to prevent infections. – Maintain up-to-date vaccination status.
Malaria	– Provide prophylaxis as per CDC guidelines, considering drug interactions. – Consult specialists for mosquito exposure prevention and chemoprophylaxis. – Use insect repellents and wear protective clothing.
Arboviruses (Dengue, Chikungunya, Zika)	– Minimize insect bites using repellents, protective clothing, and bed nets. – Stay in screened or closed temperature-controlled accommodations. – Be aware of risks associated with secondary dengue infections.
Environmental exposures	– Refrain from contact with freshwater in endemic areas. – Refrain from contact with contaminated water. – Wear footwear in Strongyloidiasis-endemic regions. – Monitor for signs of schistosomiasis and seek screening if symptomatic.
Sexually transmitted infections	– Consistent use of condom during anal, vaginal, or oral sex – If anticipated high-risk exposure, obtain the HAV, HBV, and human papillomavirus if eligible – Consider HIV pre-exposure prophylaxis if eligible based on sexual behavior risk.

HAV, *Haemophilus influenzae* (Hib); HBV, hepatitis B.

They should avoid exposure to sick individuals and consider wearing surgical masks if they cannot avoid contact. Travelers involved in high-risk healthcare work in tuberculosis-endemic areas should consider wearing appropriate masks (fitted N95), while a surgical mask may suffice in lower-risk environments.[16,40]

Patients should keep a summary of their medical history and current medications, ensuring prescriptions are available in original containers.[8] It is essential to have a clear discussion about the optimal timing for medication administration to avoid potential toxicity or gaps in therapeutic effectiveness and to have extra medication supplies to account for unexpected travel. Having health insurance coverage for their travel destinations is also recommended.[16]

Patients should receive instructions on the steps to take if they fall ill, including familiarizing themselves with the healthcare facilities available at their travel destination. For a comprehensive list of global travel clinics, visit the provided link: https://www.istm.org/clinic-directory/.

Medical and transplant tourism, which can involve unregulated procedures, and suboptimal serologic testing poses a higher risk for infections such as HIV, hepatitis, malaria, and others,

leading to complications that impact graft and patient survival.[2] Therefore, healthcare providers should screen for blood-borne pathogens and optimize prophylactic measures upon these patients' return.

Conclusion

Traveling poses significant challenges for transplant recipients, requiring thorough pretravel preparation and awareness of specific pathogens and necessary prevention strategies to reduce the associated risks. Transplant programs should implement processes to enhance access to pretravel healthcare for anticipated travelers, enabling recipients to undertake safer journeys and minimize complications related to their immunocompromised conditions. In addition, immunization studies should prioritize the inclusion of these patients, as they are the most vulnerable to the consequences of inadequate protection.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Rita Wilson Dib: Conceptualization; Investigation; Methodology; Writing – original draft.

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Joseph Sassine: Conceptualization; Validation; Writing – review & editing.

Emily A. Siegrist: Validation; Writing – review & editing.

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