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Review

Infections in immunosuppressed travellers with autoimmune inflammatory diseases—a narrative review and advice for clinical practice

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Abstract

Abstract. The management of autoimmune, inflammatory diseases has been revolutionized by biologic therapies. A beneficial consequence of better disease control is that more patients are well enough to travel the world. There is now a class of traveller, the significantly immunosuppressed person with autoimmune disease, with specific risks and requirements. This review introduces the concept of the pre-travel risk assessment and discusses the major vaccine-preventable and non-vaccine-preventable travel-associated infections. The challenges and controversies around vaccination and immunosuppression are reviewed with advice for clinical practice.

Key words: travel medicine, travel vaccines, travel-related infections, immunosuppression, immunosuppressed travellers, travel risk assessment, visiting friends and relatives, vaccine responses, autoimmune disease, targeted therapies

REVIEW

Rheumatology key messages

- Immunosuppressed travellers need a multi-disciplinary risk assessment that includes their underlying condition and treatment.
- Immunosuppressed travellers may develop more frequent, severe or atypical infections that can mimic underlying disease.
- Evidence for vaccine response with immunosuppression is lacking but it is likely to be impaired.

Introduction

In 2018 there were an estimated 1.4 billion international tourist arrivals worldwide [1]. The COVID-19 pandemic has illustrated how travel can facilitate the spread of emerging diseases [2]. Although quarantine measures have decreased global travel, the pandemic is a reminder of the importance of travel-related infection.

The growth of international travel occurred alongside the advent of targeted therapies in autoimmune diseases. These drugs mean that those living with autoimmune conditions experience a better quality of life. Whereas before they might have been too unwell to travel, they are now able to visit a range of countries and enjoy diverse activities. Immunosuppressed travellers plan similar travel itineraries to non-immunocompromised travellers and around one-third visit low-income countries [3]. A growing population of immunosuppressed travellers now exists, and their physicians frequently receive questions regarding travel health advice.

Nationally, only a small number of dedicated travel clinics exist, and most pre-travel advice comes from primary care practitioners or autoimmune disease specialists in secondary care. The purpose of this review is to

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provide information tailored to the immunosuppressed host to aid clinicians in offering pragmatic advice. Immune modulation for autoimmune disease encompasses a large number of therapies spanning multiple diseases, and this review will not attempt to consider these individually. A common theme is that immune modulation carries a small, but significant increased risk of infection.

Pre-travel risk assessment

Risk may be defined as the likelihood that a person may be harmed or suffer an adverse health effect if exposed to a hazard [4]. The perceptions and realities of travel-associated risk will be different for each individual traveller. When evaluating risk, it is necessary to weigh the possibility of harm from a travel-related disease or event against harm from an intervention.

Suggested risk assessment framework

A simple question to start the risk assessment with is: 'Who is this person and what will they be doing in this place at this time?' These areas can then be considered in more detail as follows [5] (Fig. 1).

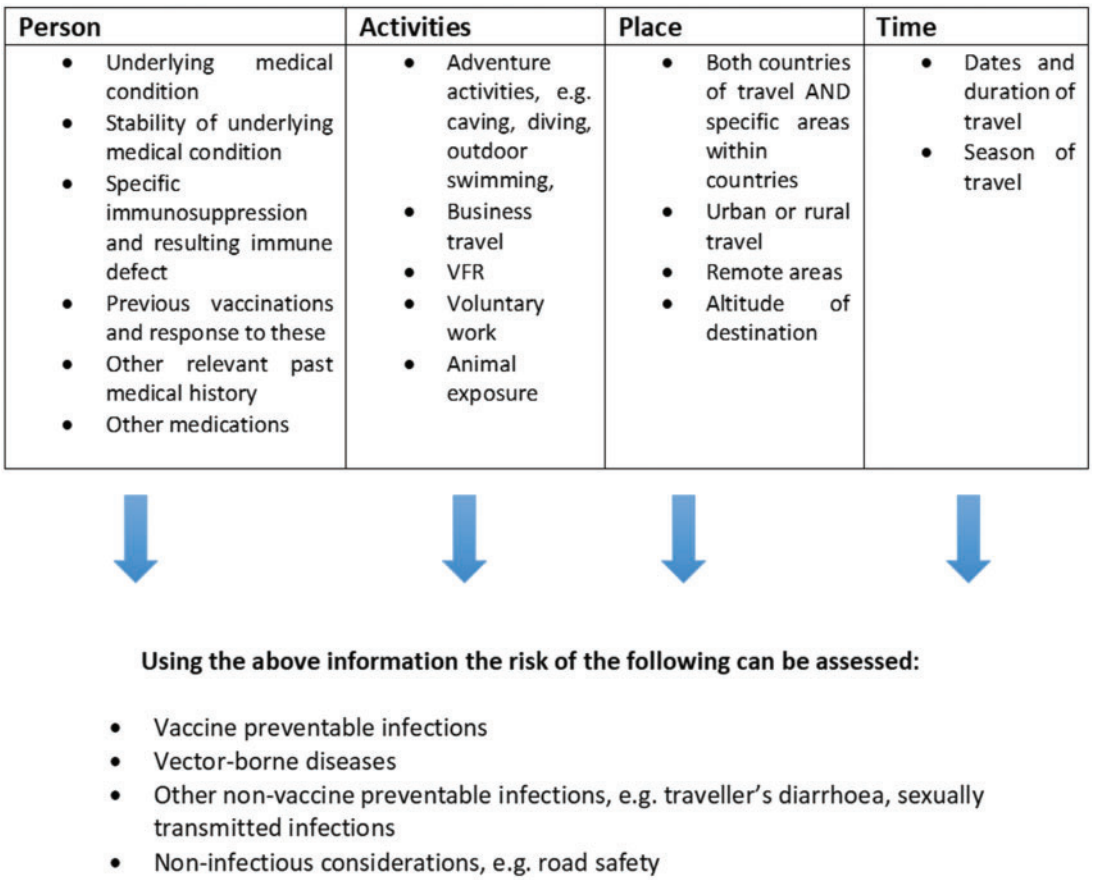
Travellers visiting friends and relatives

Travellers visiting friends and relatives (VFR) are an important group to consider since they may have a different perception of travel-related risk as they are travelling to visit familiar places and people. They may have important personal reasons for travel at a particular time and may travel with significant co-morbidities. Lack of pre-travel healthcare may be more common due to incomplete childhood vaccinations or language barriers [6].

Malaria is an example of how an infectious disease may carry different risks in the VFR group. A VFR traveller who has grown up in a malaria-endemic area may have developed semi-immunity to malaria through repeated childhood exposures, meaning malaria may only cause a mild febrile illness in this group. A British study showed that although most imported malaria cases were seen in VFR travellers of African heritage, the greatest mortality was seen in the elderly, tourists and those seen in areas with few malaria cases [7].

VFR travellers are at higher risk of typhoid. Another British study showed that most imported typhoid cases were seen in VFR travellers and those visiting South Asia. This may be due to a difference in perception of

Fig. 1 Pre-travel risk assessment



VFR: visiting friends and relatives.

risk and different behaviours around food and water hygiene [8].

Therapies for rheumatological conditions, immunosuppression and infection risk

The exact immune defect and resulting risk of infection depends on the immunosuppression used and the underlying autoimmune disease. Immunosuppressive therapies can be broadly divided into those causing non-significant and significant immunosuppression. Guidelines explaining these categories can be easily found online [9]. An overview of biologic therapies used in autoimmune diseases and their mechanisms of action is available [10].

Vaccinations in immunosuppressed travellers—general considerations

Significant immunosuppression is a contraindication to the use of live vaccinations. This is due to the risk of developing severe or fatal infection from the vaccine inoculum. In contrast, inactivated vaccinations are considered safe to use but the immune response may be impaired. Research has investigated temporary discontinuation of methotrexate around the time of influenza vaccination, demonstrating improved immunological response when methotrexate is withheld for 2 weeks following vaccination. Where vaccine response is particularly important, this strategy might be considered, although extrapolation to non-influenza vaccines is outside the evidence base [11].

All travellers should be up to date with their local routine vaccination schedule as well as any specific travel vaccinations. Infections such as measles remain common in parts of Asia and Africa [12].

Vaccine-preventable infections

A brief description of some of the most important infections and the vaccinations against them is given below. Immunosuppressed travellers should plan their trips well in advance to allow time for necessary vaccinations to be given.

Hepatitis A

Hepatitis A is an infection of the liver caused by hepatitis A virus. Disease is usually mild, but severity increases with age and jaundice may occur in 70–80% of infected adults [13]. Disease may be severe in immunocompromised states [14]. Fulminant hepatitis is unusual and there is no chronic carrier state. The overall case-fatality rate is low but is higher in people with underlying hepatic disease and older adults. Transmission is via the faecal–oral route and is common in areas with poor sanitation and food hygiene. Foreign travel associated cases are most frequent with travel to the Far East and South Asia. Vaccination is recommended for those aged 1 year and above travelling to areas of moderate or high disease prevalence [13].

There are several vaccines against hepatitis A including a monovalent vaccine and polyvalent vaccines combined with hepatitis B or typhoid. All are inactivated and may be given to immunosuppressed travellers. In immunocompetent people one dose of hepatitis A vaccine provides adequate protection before travel. A second booster dose is given at 6–12 months to provide longer lasting immunity for up to 25 years or more [13].

There may be an impaired serological response to hepatitis A vaccination with immunosuppression. A small study in rheumatoid arthritis patients treated with either TNF inhibitors or methotrexate found that two doses of hepatitis A vaccine provided adequate protection for most patients, but a single dose of vaccine was unlikely to provide sufficient protection [15]. Another study found 46% of patients on TNF inhibitors were protected after one dose of vaccine and 79% were protected after a second dose [16].

Typhoid

Enteric fever or typhoid is a systemic infection caused by *Salmonella enterica*, serotype *typhi.* Symptoms range from mild fever and gastrointestinal upset to severe disseminated infection with multi-organ involvement. Severe disease occurs in around 10–15% of cases. Paratyphoid, caused by *S. paratyphi* A, B and C, has a similar clinical presentation and is often less severe. Typhoid is spread via the faecal–oral route and is mainly a disease of poor sanitation and food hygiene [17]. It is common throughout South Asia, Southeast Asia and sub-Saharan Africa with an estimated 14.3 million cases per year. The estimated global case fatality rate is 1% [18].

Antibiotic resistant typhoid is rising in prevalence globally, largely due to widespread availability of over-the-counter antibiotics in countries with limited antimicrobial stewardship. A recent outbreak of extensively drug resistant (XDR) typhoid in Sindh, Pakistan [19], highlights the importance of vaccination against typhoid.

There are two types of vaccination available in the UK, the oral-live attenuated vaccine and the polysaccharide vaccine. The oral-live attenuated vaccine should be avoided in immunosuppressed people but the polysaccharide vaccine is safe. Studies in immunocompetent individuals estimate efficacy between 55 and 75% [17]. There are no data on immune response to typhoid vaccination in immunosuppressed patients but efficacy is likely to be lower [10]. There is no effective vaccination against paratyphoid, and so irrespective of vaccination good food hygiene remains important.

Meningococcal disease

Meningococcal disease is caused by *Neisseria meningitidis*. Meningococci colonize the nasopharynx in around 10% of the population. They can be spread through

inhaling respiratory secretions or by direct contact [20]. A minority of people go on to develop invasive disease. The commonest presentations are meningitis, bacteraemia or meningitis with accompanying bacteraemia.

Meningococcal disease can occur as sporadic cases, outbreaks or epidemics. Most meningococcal infections occur in children and young adults, but all ages may be at risk during large epidemics. The serogroup of a meningococcal strain is determined by its polysaccharide capsule. Serogroups A, B, C, W-135 and Y cause most invasive infections [21].

There are different forms of meningococcal vaccine containing conjugated polysaccharides against one or more of serotypes A, W, C and Y and a multicomponent protein vaccine. The vaccines are inactivated and may be given to immunosuppressed patients. Meningococcal vaccination forms part of the routine vaccination schedule in many countries [22].

The highest incidence of meningococcal disease worldwide occurs in the 'meningitis belt' of sub-Saharan Africa where large seasonal epidemics occur [21]. The Islamic Hajj and Umrah pilgrimages in Saudi Arabia have been associated with outbreaks of meningococcal disease. Saudi Arabia has made vaccination against meningococcal ACW135Y mandatory for pilgrims [23].

Unvaccinated travellers, including those who are immunosuppressed, should be vaccinated if travelling to high prevalence regions. Immunosuppressed travellers should be warned of the risk of an incomplete serological response. There is no evidence for efficacy of meningococcal vaccines in immunocompromised adults [24].

Influenza

Human influenza A and B viruses cause seasonal outbreaks of influenza or 'flu'. Influenza is a respiratory disease that is usually self-limiting. Severe disease with complications including pneumonia can occur and such cases can be life threatening or fatal. Those at increased risk of severe disease include the elderly, young children, pregnant women, people with certain chronic conditions and immunocompromised individuals. Influenza viruses are predominantly transmitted by droplet inhalation but may be transmitted via contaminated surfaces.

Influenza is one of the commonest vaccine preventable infections amongst travellers [25]. Cruise ships and attending mass gatherings such as The Hajj may increase the risk of disease [26]. Many national guidelines advise annual vaccination for those at risk of severe infection, including immunosuppressed patients. Many significantly immunosuppressed travellers will therefore have been vaccinated but influenza risk should be discussed as part of the pre-travel consultation. The live influenza vaccination should be avoided in significantly immunosuppressed patients. Inactivated influenza vaccines are safe but there may be an impaired serological response [27].

Yellow fever

Yellow fever virus is spread by the *Aedes aegypti* mosquito and is endemic in over 50 countries in sub-Saharan Africa and tropical South America. Outbreaks have occurred in recent years in Brazil, Nigeria, Angola and the Democratic Republic of Congo [28]. The incubation period is typically less than 7 days following a bite from an infected mosquito. The disease has a biphasic presentation with an initial short, febrile illness followed by a toxic phase that develops in up to 15% of patients. The toxic phase consists of fever, renal failure, hepatic failure, jaundice, haemorrhage and cardiovascular compromise. Multi-organ failure may develop and up to half of patients in the toxic phase die within 7–10 days [29].

Under the International Health Regulations (2005) a yellow fever vaccination certificate may be required as a condition of entry to a country. This aims to reduce the chance of viraemic individuals importing the virus and triggering a new outbreak. Guidance from the WHO suggests that one dose of yellow fever vaccination offers lifelong protection in most cases and a booster dose after 10 years is generally not required [30].

The risk of a traveller acquiring yellow fever is determined by their vaccination status, travel destination, season of travel, duration of exposure, activities undertaken and the rate of yellow fever transmission. The risk is estimated to be around 10 times higher in rural West Africa compared with South America [31].

Although an effective live attenuated vaccine is available, it is contraindicated in immunosuppressed patients due to the risk of vaccine-associated neurotropic and viscerotropic disease. Unvaccinated travellers should be discouraged from travelling to endemic areas. If travel is unavoidable, they should be informed of the risk of yellow fever and the importance of strict mosquito bite avoidance measures during both daytime and nighttime, as *Aedes* mosquito species chiefly feast on humans during the day, but may also bite at night in well-lit areas.

If an immunosuppressed traveller requires an International Certificate of Vaccination or Prophylaxis (ICVP) then a Medical Letter of Exemption (MLoE) may be issued instead by their treating specialist or travel clinic [32]. This should be taken into consideration by their destination but patients should be aware that it may not guarantee entry.

MLoEs are valid for one trip and should be written on headed paper from the treating clinician's hospital or clinic. A sample MLoE can be found at: https://nathnacyfzone.org.uk/factsheet/6/medical-letter-of-exemption.

Animal bites and rabies

Almost all human cases of rabies are caused by rabies virus genotype 1. Most cases are caused by bites from rabid dogs, often strays in urban areas, but any infected terrestrial mammal may act as a vector. The virus can be spread via scratches or through broken skin or mucus membranes. Other lyssaviruses, spread by bats,

may cause an indistinguishable syndrome. Rabies causes an acute viral encephalomyelitis and established disease is fatal as there is no effective treatment. Death occurs from respiratory failure [33]. Most cases are reported in Africa and Asia and there are at least 60 000 deaths worldwide per year [34].

Rabies is rare in travellers, but animal bites and scratches are common. All travellers should be advised of the risks and to avoid contact with animals. Travellers deemed to be at higher risk, for example those travelling to high-risk areas for over a month, can be vaccinated with a course of pre-exposure vaccination [35].

Travellers who sustain a bite, scratch or exposure of animal saliva to broken skin or mucus membranes should be advised to wash the wound thoroughly as soon as possible. A disinfectant should be used along with a dressing. They should have an urgent risk assessment [33].

Pre-exposure vaccination primes the immune system to produce an antibody response following rabies exposure. Post-exposure vaccination is still required so travellers should seek medical attention quickly following an exposure.

The rabies vaccine is inactivated and safe in immunosuppressed people. The literature demonstrates that immunocompromised people may not mount an adequate serological response to a full course of post-exposure vaccination [36]. All immunosuppressed individuals should be warned of the risk of rabies if travelling to an endemic area and offered a pre-exposure vaccination course.

Non-vaccinated travellers require a longer course of post-exposure vaccination. They will also require human rabies immunoglobulin (HRIG) following a significant exposure. This is infiltrated around the wound and neutralizes rabies virus. Due to the risk of an impaired serological response, significantly immunosuppressed travellers should be managed as if they are unvaccinated regardless of their vaccination history. They will require a full course of post-exposure vaccination, HRIG and antibody testing post-treatment to assess their serological response [33]. All suspected cases of rabies should be discussed with specialist services.

Non-vaccine-preventable infections

Travellers' diarrhoea

Travellers' diarrhoea (TD) is common in travellers from high-income countries to lower income countries, affecting 20–60%. It is defined as three or more loose stools in a 24-h period with or without other symptoms of fever, nausea or cramps [37]. TD is spread via the faecal–oral route due to poor food and water hygiene. It is caused by a variety of pathogens including bacteria (50–75% of cases), viruses (5–20%) and parasites (0–10%) [38].

The incidence of TD is not increased in patients on immunosuppressive therapies [39], but certain food or waterborne infections can be more severe or lead to chronic disease. These include salmonellosis, shigellosis, campylobacteriosis, giardiasis, listeriosis and cryptosporidiosis [9]. *Cryptosporidum* may cause chronic, intractable infection, including pancreato-biliary disease, in immunosuppressed patients. This can be very difficult to clear [40].

There is no strong evidence that dietary measures reduce the risk of TD [37], but travellers should be advised to follow good food and hygiene measures. Those with TD should maintain good hydration and use oral rehydration therapy. Short courses of antibiotics (1–3 days), taken at symptom-onset, reduce illness duration from 3 to 1.5 days [37].

Significantly immunosuppressed travellers can take an emergency pack of antibiotics for self-treatment of TD. Prophylactic antibiotics may be considered, especially for short-term travel to high-risk countries, but the risk of drug interactions and side effects should be considered. The choice of drug depends on the travel destination. For patients on biologic agents or Janus kinase inhibitors, azithromycin would be a suitable choice as it avoids the risk of antimicrobial resistance [41] and tendon rupture associated with fluoroquinolones and does not interact with commonly prescribed immunosuppressants.

Clinicians should be aware that travel has been associated with acquisition of multi-drug resistant Enterobacteriaceae (MDRE). These are increasingly common in low- and middle-income countries. Travel has been associated with MDRE acquisition rates of 21–51%. South Asia has the highest risk of MDRE acquisition with rates of up to 85%; other areas of Asia are also high risk. Antibiotic use during travel raises the risk MDRE carriage. MDRE carriage may persist for 6 months or more following a traveller's return [42].

Clinicians should consider investigating TD lasting 14 days. Investigations may be sent sooner if there are concerning features such as fever or dysentery. Useful tests include full blood count, renal and liver function tests, inflammatory markers and stool for microscopy and culture, PCR and examination for ova, cysts and parasites. The presence of eosinophilia and a relevant travel history should prompt investigation for strongyloidiasis, schistosomiasis and other helminthic infections. Imaging may be performed in the presence of local tenderness or severe colitis. Non-infectious causes of chronic diarrhoea such as malignancy or inflammatory bowel disease should be considered [37].

Malaria

Malaria is caused by the parasite *Plasmodium*. More than one hundred species have been described but only *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae* and *P. knowlesi* commonly cause human infection. The parasite is spread via the *Anopheles* mosquito. Malaria can be divided into uncomplicated and severe disease. Most severe malaria is caused by *P. falciparum*. There were an estimated 228 million cases worldwide in 2019, 93% of which were in Africa [43].

Effective chemoprophylaxis is available and should be offered to travellers to endemic areas. The choice of agent will depend on patient preference, the medical history and destination. Healthcare professionals should consult relevant local or national travel guidelines for malaria and be aware that these differ between countries [44].

Malaria should always be suspected in a febrile traveller returning from an endemic area. Suspected cases should be discussed with local infectious diseases specialists. Treatment depends on the infecting species and disease severity. There are no specific data on malaria severity in patients on immunosuppressive therapies. The immunosuppressed traveller should be advised on measures to avoid mosquito bites and prescribed prophylaxis. Care should be taken to avoid drug–drug interactions [24].

Tuberculosis

Tuberculosis (TB) is caused by bacteria of the *Mycobacterium tuberculosis* complex (*M. tuberculosis*, *M. bovis*, *M. africanum* or *M. microti*). An estimated 10 million people developed TB in 2019 and it caused ∼1.4 million deaths. TB rates are highest in Southeast Asia and sub-Saharan Africa [45].

Approximately one-quarter of the world's population is infected with *M. tuberculosis* and their lifetime risk of developing active TB is ∼10% [45]. Most healthy people infected with *M. tuberculosis* never develop active TB. Immunosuppression raises the risk of latent disease progressing to active TB. Evidence suggests that anti-TNF-α therapies are associated with a 2- to 4-fold increased risk of active TB [46].

Most cases of active TB in people on biologic therapies will be due to reactivation of latent TB. Travellers are generally considered to be at low risk of acquiring TB and prolonged exposure to an infectious person is usually required. Travellers with extended stays in higher risk areas are at greater risk of infection with *M. tuberculosis* [47]. This includes VFR travellers, long-term travellers, healthcare workers and those with prolonged contact with an infectious individual.

The BCG vaccine forms part of the routine immunization schedule in the UK and is targeted at high-risk individuals. It is a live vaccine and is contra-indicated in significantly immunosuppressed individuals [48].

Travellers at high risk of TB infection, for example VFR travellers, should be advised to avoid prolonged contact with people with active TB. This advice is important for those who are immunosuppressed. They should also be advised to seek urgent medical advice if they become unwell with fever, cough or other constitutional symptoms.

All patients should be screened for latent TB infection before commencing a biologic although the optimal screening strategy remains uncertain. In the UK, guidelines recommend an IFN-γ release assay (IGRA) alone or in combination with a tuberculin skin test (TST) [49]. The use of serial IGRA testing whilst on a biologic is complex as IGRAs are inherently dynamic in a serial testing setting. This is demonstrated in the literature, which shows high rates of both conversions and reversions. This pattern is seen in low, intermediate and high TB incidence settings, suggesting that some of the observed variations may be due to the assay independent of exposure risk [50]. Repeat IGRA testing may be considered in travellers with a significant TB exposure and a previously negative IGRA result. This should be discussed with a local TB specialist.

Other infections

A discussion of other infections relevant to the immunosuppressed traveller can be found in the Supplementary data (available at *Rheumatology* online).

Limitations of this review

The most important limitation of this review is scope. This review is a narrative appraisal of the evidence base, and by the nature of its length, cannot cover all possible infections acquired abroad. However, we have signposted many external resources that offer further detail.

There is a recurring acknowledgement that vaccine efficacy may be lower in immunocompromised hosts, but this statement is largely based upon small studies of laboratory markers of seroconversion rather than true estimates of disease prevention. Consequently, clinicians should not interpret the statements regarding weaker vaccine responses as a reason to withhold vaccination.

Finally, it is relevant to note that whilst this review has intentionally focused on infection, one of the greatest risks to travellers remains road traffic accidents [51]. These are not specific to the immunosuppressed host, but nonetheless, every time a clinician offers travel advice, it is wise to remind people about the value of the seatbelt.

The true burden of travel-related infection amongst immunocompromised patients is not known. Future research is needed to quantify risks of travel and further evaluate the effectiveness of vaccinations.

Conclusions

Travel-related infections in the significantly immunocompromised traveller are complex and comprise vaccine-preventable and non-vaccine-preventable infections. A thorough risk assessment should be performed before travel. The risk assessment should include non-infection considerations, which are outside the scope of this review and take the patient's preferences into account. Ideally significantly immunosuppressed travellers would benefit from a multi-disciplinary review from their treating rheumatologist and a travel medicine or infection specialist prior to travel, but this may not be practical due to a lack of local resources. Rheumatologists should consider discussing immunosuppressed patients at high risk of travel-related infections with local infection specialists where appropriate, including those travelling to tropical regions, VFR travellers and those planning

extended trips abroad. The decision to travel is one that must be taken by the patient after a personalized assessment of the risks and benefits.

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Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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