

## The immunosuppressed traveller to less developed countries: considerations for preparation

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### Key words

Travel medicine, immunosuppression, infectious diseases, vaccination

### Abstract

The immunosuppressed traveller presents several unique concerns when preparing to travel to less developed countries. Some vaccinations may be contraindicated, whilst others may provide less than adequate protection. Immunosuppressed individuals may be more susceptible to infectious diseases prevalent in the tropics and be visiting areas with limited medical care should they require it. Immunosuppressed travellers include those with HIV infection; those on immunosuppressive medications or with underlying immunosuppressive illnesses; those with specific immunodeficiencies such as asplenia; and pregnant women. Each group has specific concerns. As a general rule, live virus vaccines are contraindicated in these individuals – these vaccines include yellow fever, measles/polio/rubella, varicella, BCG and oral typhoid, cholera and polio. Inactivated vaccines are not contraindicated, but individuals with immune suppression may have less than adequate antibody responses. Specific infectious disease risks have been identified, for example visceral leishmaniasis has been recognised as an opportunistic infection in those with HIV infection. Individuals with asplenia are particularly vulnerable to malaria. Malaria is also severe in pregnant women, and they are specifically vulnerable to serious complications should they contract hepatitis E. It is essential that individuals with immunosuppressive conditions seek medical advice well in advance of their overseas travel, ideally with a travel medicine specialist who can accurately advise them on their level of risk and recommend the most appropriate preventive programme for them.

### Introduction

The immunosuppressed traveller presents a number of unique concerns when preparing to travel to less developed countries. Certain vaccinations may be contraindicated, whilst others may provide less than adequate protection. Immunosuppressed individuals may be more susceptible to infectious diseases prevalent in the tropics and they may be visiting areas with limited medical care should they require it. However, after careful consideration of an individual's itinerary, many people with immunosuppressive conditions can safely enjoy the excitement and challenge of such travel. Preparation should commence as early as possible and should be thorough.

The first question that must be asked of the immunosuppressed traveller is whether the trip can be made adequately safe with appropriate vaccinations and other preventive measures. Whilst no trip may be made 100% safe (as indeed life itself cannot be 100% safe), a reasonable risk-benefit analysis must be made in conjunction with the individual such that they can make an informed decision as to the level of risk they are prepared to take. Once it has been decided that the trip will go ahead, one must address appropriate vaccinations, and preventive measures for other potential health risks relevant to their destination.

There are three essential questions that must be asked before advising vaccinations to any of these travellers:

- is the vaccine necessary?
- is the vaccine safe?
- will the vaccine work?

For convenience, the immunosuppressed traveller will be considered in four categories:

- immunosuppressed, not HIV infected, travellers;
- HIV infected travellers;
- travellers with conditions causing limited immune deficits, eg. asplenia;
- pregnant travellers.

Each category presents unique issues for consideration.

### The immunosuppressed, not HIV infected, traveller

Immunosuppression may result from a number of conditions including congenital immunodeficiency and malignancies, or as a result of medications such as high-dose corticosteroids, alkylating agents or anti-metabolites.<sup>1</sup> Treatments and conditions not considered to cause immune deficiency include:

- short-term (< two weeks), low dose (< 20 mg prednisolone or 1 mg dexamethasone daily) steroids;
- maintenance or replacement steroid treatment at physiological doses;
- inhaled, intra-articular or topical steroids;
- malignancy that is in remission and if the patient has not received chemotherapy for at least three months.

Travellers who are considered to be immunosuppressed must be assessed on an individual basis to decide the degree of immunosuppression before decisions are made regarding vaccine administration and other preventive measures.

### VACCINATION

There are no additional risks involved with administering killed or inactivated vaccines to immunocompromised

individuals.<sup>1</sup> In some cases, however, immune response to the vaccines may be suboptimal, and extra doses or more frequent boosters may be required.

In general, live vaccines are contraindicated for immunosuppressed individuals. These include oral polio, oral typhoid capsules, oral cholera, yellow fever, BCG, MMR and varicella.<sup>1</sup> There is a risk that virus replication may be enhanced in immunosuppressed individuals after the administration of attenuated live virus vaccines.<sup>2</sup> Oral polio vaccine given to children with congenital immune deficiency has resulted in severe, progressive neurologic involvement.<sup>1</sup> Oral polio vaccine should also be avoided in household contacts or medical personnel in close contact with immunosuppressed individuals, as the vaccine virus can be excreted in the recipient's stool and urine for four to six weeks after vaccination.

### The HIV infected traveller

With the advent of highly-effective anti-retroviral combination therapies, there are increasing numbers of HIV infected individuals who are contemplating travel to less developed countries. Studies on the safety and efficacy of vaccines in HIV+ve individuals are limited. Once again, the questions must be asked on an individual basis – is this vaccine necessary, is it safe and will it be effective?

As a result of quantitative and qualitative defects in the CD4 lymphocytes, and B-lymphocyte dysfunction, vaccinations may be less immunogenic in the HIV infected individual.<sup>3</sup> This reduced antibody response may manifest as lower seroconversion rates, lower antibody levels, an accelerated loss of antibodies or diminished conversion of IgM to IgG.<sup>4</sup> As the degree of diminished response is generally in proportion to the degree of immunosuppression, measurement of CD4 count and the HIV viral load is an essential part of the pre-travel assessment.

In general, individuals with a CD4 count of greater than 200 will develop antibodies. As antibody responses are better in individuals in the early stages of disease and in those with higher CD4 counts, consideration should be given to enquiring of HIV+ve individuals if they have any intention of travelling in the future. If they are planning some overseas travel it seems sensible to recommend vaccination at an earlier stage of their disease, when they are more likely to mount an adequate antibody response.

### VACCINATION

Inactivated vaccines appear to be well tolerated, however some studies have shown a small, transient increase in viral load after the administration of influenza, tetanus toxoid and hepatitis B vaccines. No permanent effect on the CD4 count or apparent clinical progression was seen.<sup>3</sup> However, decreased efficacy of vaccines may occur. One small study showed a seroconversion rate of only 77% to hepatitis A

vaccine in HIV+ve individuals, as compared to 99% in those uninfected.<sup>5</sup> As expected, those with lower CD4 counts were less likely to seroconvert. Another study showed only a 64% seroconversion rate after hepatitis A vaccination in individuals with a CD4 count of less than 200.<sup>6</sup> Similarly decreased seroconversion rates and antibody levels have been demonstrated for Japanese B encephalitis vaccine<sup>7</sup> and rabies vaccine in HIV infected individuals.

In addition to any recommended inactivated travel vaccines, pneumococcal pneumonia vaccine is recommended for HIV+ve individuals,<sup>3</sup> as is an annual flu vaccination.<sup>8</sup>

Care should be taken before administering any live vaccines. BCG is definitely contraindicated.<sup>1</sup> Tuberculosis is, however, a well known opportunistic infection in HIV+ve patients, so consideration should be given to pre- and post-travel Mantoux testing for high-risk individuals.

Measles vaccination is recommended for HIV infected children and susceptible adults who are not severely immunocompromised (ie. CD4 > 200). Measles remains a risk in many travel destinations. Recent outbreaks have also occurred in many developed countries such as New Zealand, Australia, Ireland and Italy. As vaccination rates drop below critical levels in the UK, public health departments are gearing up for an epidemic. In 1999, nearly 75% of measles cases in the United States occurred either as a direct result of travel, or secondary to an imported case.

Measles is a devastating disease in the HIV infected person, with a 40% case fatality rate reported in the USA.<sup>9</sup> There is, however, a small risk associated with administration of the vaccine, and there has been one death recorded as a result of measles pneumonitis secondary to vaccination.<sup>10</sup> HIV infected adults who already have measles antibodies prior to HIV infection, whether from natural infection or vaccination, maintain good antibody levels even as their immunosuppression progresses.<sup>11</sup>

When considering measles vaccination in an HIV infected individual, one should check the disease activity in the destination, and if there is a risk, check the individual's antibody level before making a recommendation.

Yellow fever vaccination may be required for entry into yellow fever-endemic or -infected countries. A careful analysis of the individual's itinerary should be made in order to assess the absolute need for vaccination. The vaccine is contraindicated in those with symptomatic HIV disease or CD4 counts of less than 200. It is considered safe in those with a CD4 count of greater than 500 and is administered to such individuals if required.

The decision to vaccinate should be a collaborative one between the individual's infectious diseases physician, the travel medicine specialist and the traveller. Individuals should be advised against visiting an area of yellow fever

disease transmission if they are unable to be vaccinated, as the disease has a case fatality rate of 20–40%, with no specific treatment available. Beyond these concerns regarding vaccine efficacy and safety, there are several other issues of particular concern to the HIV infected traveller.

### GASTROINTESTINAL INFECTIONS

As a result of decreased CD4 lymphocytes within the intestinal lamina propria, and diminished non-specific defence mechanisms, HIV infected individuals are theoretically more susceptible to gastrointestinal infections. Gastrointestinal infections are the most common of travel-related ailments, with up to 50% of travellers on a two-week trip developing traveller's diarrhoea.<sup>12</sup>

HIV infected individuals are considered more susceptible than most to the following pathogens – *Campylobacter jejuni*, *Salmonella spp.*, *Shigella spp.*, *Cryptosporidium*, *Cyclospora*, *Isospora belli*, *Cytomegalovirus* and *Microsporidium spp.*<sup>3</sup> In particular, they may have significant trouble clearing *Salmonella* infections, and *Cryptosporidium* is a well recognised opportunistic infection in HIV infection. There are, however, no data to suggest they have any increased risk of contracting *Giardia lamblia*, *Entamoeba histolytica*, hepatitis A, *Enterotoxigenic E coli* or viral enteropathogens.

### RESPIRATORY AND OTHER INFECTIONS

Respiratory infections are the second most common cause of illness in travellers, and HIV infected individuals are more susceptible to invasive disease with *Streptococcus pneumoniae* and *Haemophilus influenzae*.<sup>13</sup> Hence it is recommended that HIV infected travellers receive pneumococcal and influenza vaccines even if they are not travelling. The pre-travel consultation may be a good opportunity to ensure compliance with this recommendation. Of great concern are potentially serious opportunistic infections such as *Mycobacterium tuberculosis* and *Legionella*.

Certain vector-borne diseases are now recognised as opportunistic infections. In particular, visceral leishmaniasis, a sandfly-borne disease endemic in many parts of the world including the Mediterranean, rural India, parts of South America and the Middle East, has been shown to run a complicated and protracted course in HIV infected individuals.<sup>14</sup> Fortunately, other vector-borne diseases such as malaria and dengue fever don't appear to pose any increased risk to this group of travellers.

### SKIN PROBLEMS

Various skin disorders, including drug reactions are common in HIV infected individuals. One small study found that 28% of the cohort developed skin complaints, the most common of which were excessive sunburn and excessive reactions to insect bites,<sup>15</sup> compared with around 5% of

skin-related health problems in non-HIV travellers.<sup>16</sup> Clearly, it is essential for HIV infected individuals to be adequately insured, to have contact details for the most reliable medical facilities at their destination, and to carry a well stocked medical kit for use to treat common travel-related illness.

### The asplenic traveller

Asplenic individuals (functional or anatomic) are a group that show a limited immune deficiency. There are no vaccines that are contraindicated in this group of travellers. The pre-travel consultation is once again an opportunity to ensure that they are current with all recommended vaccines. In addition to the standard vaccinations suggested for their destination, asplenic individuals should be up to date with pneumococcal, *Haemophilus influenzae b*, meningococcal and influenza vaccines.

Of particular concern for asplenic patients is their dramatically-increased susceptibility to malaria. They should be aware of their risk, take the best possible anti-malarial medication available and be meticulous with personal protective measures, such as insect repellent, mosquito nets and appropriate clothing. One should consider prophylactic antibiotics for the duration of travel.<sup>17</sup>

### The pregnant traveller

Pregnancy is a state of relative immunosuppression, with cell-mediated immunity in particular being decreased. The pregnant traveller faces a number of risks that may be classified as:

- risks associated with pregnancy itself, eg. miscarriage, thrombosis;
- risks associated with the act of travel, eg. motor vehicle accident, travellers thrombosis, etc.;
- risks associated with a particular destination, eg. infectious diseases, high altitude, etc.<sup>18</sup>

The second trimester is considered the safest time for pregnant women to travel, when the woman usually feels at her best and is at least risk of miscarriage or premature labour. There are a number of relative contraindications to travel in pregnancy (see Table 1) and it is incumbent upon the advising doctor to ensure that women in these categories fully understand the potential risks they are taking, not only for themselves but also for the health of their fetus. It is advisable to take an ultrasound prior to travel to ensure there is a viable intrauterine pregnancy and to establish the expected date of delivery.

In terms of general care, the pregnant traveller should ensure she has adequate travel insurance, and be aware of medical clinics at her destination at which she can continue to receive antenatal care, and emergency facilities should they be required. She may suffer from any of the typical problems of pregnancy and should be prepared to manage these. She should be made aware of symptoms that require immediate medical attention, such as per vaginal bleeding

**TABLE 1**  
**RELATIVE CONTRAINDICATIONS TO**  
**INTERNATIONAL TRAVEL DURING**  
**PREGNANCY**  
**(adapted from Lee<sup>26</sup>)**

**Obstetric risk factors**

- history of miscarriage
- incompetent cervix
- history of ectopic pregnancy
- history of premature labour or premature rupture of membranes
- history of or existing placental abnormalities
- threatened abortion or per vaginal bleeding (current pregnancy)
- multiple gestation
- history of toxæmia, hypertension or diabetes in pregnancy
- primigravida over 35 or under 15
- assisted reproduction

**General medical risk factors**

- history of thromboembolic disease
- severe anaemia
- chronic medical condition requiring ongoing interventions
- congenital or acquired heart disease

**Potentially hazardous destinations**

- chloroquine-resistant malaria endemic
- yellow fever endemic areas
- areas with outbreaks of any life-threatening food-, water- or vector-borne disease

or abdominal pain. Motor vehicle accidents are a significant cause of morbidity in travellers, and pregnant women are particularly susceptible.

**VACCINATION**

In terms of vaccinations, live virus vaccines should be avoided in pregnant women. Advise women against getting pregnant for three months after administration of these vaccines. Theoretically, there is a risk that live virus vaccines could cross the placenta and cause infection in the fetus. However, retrospective studies on women inadvertently vaccinated with live rubella or polio vaccines during pregnancy have failed to show any evidence of increased risk of foetal malformations.<sup>19</sup> Therefore, inadvertent vaccination of a pregnant woman with a live vaccine should not be regarded as a reason to consider a termination.<sup>20</sup>

In regards to inactivated vaccines, each should be considered on an individual basis after examining the exact itinerary and style of travel that the woman will be undertaking. Whilst

there are no theoretical risks associated with administration of inactivated vaccines during pregnancy, there is a lack of data to unequivocally guarantee their safety. Table 2 lists current recommendations regarding vaccinations in pregnancy.

Malaria is a serious disease in pregnant women and can result in significant maternal and fetal morbidity and mortality. Clinical disease with severe complications including cerebral malaria, massive haemolysis, and acute renal failure is more common in pregnancy.<sup>21</sup> Spontaneous abortions, stillbirths, pre-term deliveries, low-birth-weight infants and congenital infections are also a risk.

Chloroquine is considered safe in pregnancy, however there are few areas of the world in which chloroquine is still an effective anti-malarial (parts of the Middle East and Central America only). Proguanil (Paludrine) is also considered safe and may be taken in combination with chloroquine to offer increased protection. However, there are few areas of the world where this combination is considered to offer adequate protection. Additionally, proguanil is an anti-folate, so folate supplements must be taken in conjunction with it. Mefloquine (Lariam) is now considered safe in the second and third trimesters, but there is conflicting opinion on its safety during the first trimester.<sup>22</sup> General opinion still holds that mefloquine should be avoided in the first trimester unless the circumstances are exceptional. Doxycycline is definitely contraindicated and there is not yet enough evidence to support the safety of Malarone, hence

**TABLE 2**  
**CURRENT RECOMMENDATIONS FOR**  
**VACCINES IN PREGNANCY<sup>25</sup>**

Vaccine	Type of vaccine	Use
BCG	Live	No
Cholera oral	Live*	No
Hepatitis A	Inactivated virus	If indicated
Hepatitis B	Recombinant	If indicated
Influenza	Inactivated virus	If indicated
Japanese B	Inactivated virus	Seek advice
MMR	Live	No
Meningitis	Polysaccharide	If indicated
Pneumococcal	Polysaccharide	If indicated
Polio, inactivated	Inactivated virus	If indicated
Polio, Sabin	Live	No
Rabies	Inactivated virus	If indicated
Tetanus/diphtheria	Toxoid	If indicated
Typhoid Vi antigen	Polysaccharide	If indicated
Typhoid capsules	Live	No
Varicella	Live	No
Yellow Fever	Live	No

\*In Australia, Orochol is used and this is a live vaccine. In New Zealand, Dukoral is used and this is *not* live, however it is rarely indicated.

it cannot be recommended.<sup>23</sup>

The World Health Organisation advises pregnant women to avoid travel to areas with chloroquine-resistant malaria.<sup>24</sup> If she must travel, she should be fully aware of the risk she is taking and must ensure that she takes extra precautions to avoid being bitten by mosquitoes. This will also help to avoid other vector-borne diseases such as dengue fever.

#### TRAVELLER'S DIARRHOEA

Traveller's diarrhoea is the most common health problem afflicting travellers and presents particular problems in pregnancy. Dehydration as a result of diarrhoea could lead to inadequate placental blood flow, so pregnant women should be extra vigilant about their food and water intake. If they develop diarrhoea, they should ensure they remain adequately hydrated, and seek medical attention early in the illness if they are vomiting. Drugs routinely used in the treatment of diarrhoea such as loperamide and the fluoroquinolone antibiotics (eg Norfloxacin and Ciprofloxacin) are not recommended during pregnancy. If necessary, Azithromycin is considered relatively safe and is an effective antibiotic for many of the bacterial causes of diarrhoea (particularly *Campylobacter*).<sup>25</sup>

#### OTHER CONSIDERATIONS

Hepatitis E is a food- and water-borne virus that can have devastating consequences if contracted during pregnancy. It is a rare disease in travellers, however maternal and fetal mortality rates of up to 33% have been reported in women living in endemic countries during the third trimester.

Most commercial airlines will allow travel up to the 32nd week of pregnancy only, so travel plans should allow for this. There is no risk of fetal hypoxia in commercial flights. Pregnant women should wear compression stockings, drink plenty of non-alcoholic drinks and move their legs frequently on long-haul flights to decrease the risk of thrombosis. Finally, an individually-prepared medical kit with medications that are considered safe in pregnancy is strongly recommended to manage minor health problems.

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## Resources for travel medicine

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#### Key words

Travel medicine, World Wide Web, medical society, textbook, medical journal

#### Abstract

Travel medicine is becoming recognised as a sub-specialty of both General Practice and Infectious Diseases. There are a number of related resources for those who are interested in developing their interest in the area. Societies such as the International Society of Travel Medicine, the Wilderness Medicine Society and the International Society of Mountain Medicine all maintain peer-reviewed Medline-indexed journals for their members and run international conferences. Information is presented on useful textbooks and web sites.

#### Introduction

Travel medicine is becoming recognised as a sub-specialty of both General Practice and Infectious Diseases. There are a number of useful textbooks, courses and societies available for those with an interest in travel medicine. Additionally, the World Wide Web provides many useful sites of reference. There are also a number of computer software programs that provide accurate and up-to-date country-by-country travel health information.

([www.ismmed.org](http://www.ismmed.org)) is dedicated to high altitude medicine. The membership is a mixed group of American, European and South American physicians. An international symposium is held every two years, the next being held in Tibet in 2004. *High Altitude Medicine and Biology* is part of ISMM membership. *The Australasian College of Tropical Medicine* ([www.tropmed.org](http://www.tropmed.org)) has a Faculty of Travel Medicine. Information can be found on their website. *Clinical Infectious Diseases* often features relevant articles.

#### Societies and journals

*The International Society of Travel Medicine* ([www.istm.org](http://www.istm.org)) is the largest society dedicated to travel medicine and has 1,200 members from 53 countries. Every two years it holds a world congress – the next will take place in New York in May 2003. *Journal of Travel Medicine* is part of ISTM membership.

*The Wilderness Medical Society* ([www.wms.org](http://www.wms.org)) is an American-dominated society that focuses on all aspects of wilderness medicine, in particular high altitude medicine, diving medicine and wilderness toxicology. It runs a number of well organised courses and conferences throughout the year in the United States. *Wilderness and Environmental Medicine* is part of WEM membership.

*The International Society of Mountain Medicine*

#### Textbooks

There are a number of useful textbooks dedicated to travel medicine. Useful information can also be gathered from various infectious diseases and parasitology texts.

The most useful texts are as follows:

*Manual of Travel Medicine*. Tilman Ruff and Alan Yung. Published by the Victorian Infectious Diseases Service at the Royal Melbourne Hospital, 1999. This text is written by two well known infectious diseases physicians from Melbourne who have a special interest in travel medicine. It is logical and practical and represents the best text in the Australian context.

*The Textbook of Travel Medicine and Health*. Edited by Robert Steffen and Du Pont. Published by BC Decker,