

Travel Medicine Research Review

Making Education Easy

Issue 1 – 2009

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Welcome to the first edition of **Travel Medicine Research Review**, a unique New Zealand publication bringing you some of the most important research on travel medicine from around the world.

The Review is a summary of what we think are some of the most significant new papers, in addition to a local commentary on why they are important and how they can potentially affect practice. The Review also provides website links to the abstract or fully published papers so you can make your own judgements.

The creation of this publication would not have been possible without support from our sponsor, and to them we give our thanks. If you have colleagues or friends within New Zealand who would like to receive our publication, send us their contact email and we will include them next issue. We hope you find this first edition stimulating reading, and we welcome any comments or feedback.

Kind regards,

Dr Joan Ingram

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Seasonality, annual trends, and characteristics of dengue among ill returned travelers, 1997–2006

Authors: Schwartz E et al

Summary: The seasonality and annual trends of dengue cases reported to the international GeoSentinel Surveillance Network were investigated in 522 returned travellers in this paper. The authors found region-specific peaks in the number of cases reported for the Caribbean (August, October), South America (March), South Central Asia (October) and Southeast Asia (June, September). Annual oscillations in the number of cases were evident. Several epidemics also occurred during the study period, with an associated increase in the annual proportionate morbidity from 50 to 159 cases per 1000 ill patients in Southeast Asia. The authors commented that pretravel advice could include the relative risks of dengue according to season, and that epidemic activity may be predicted by cases at atypical times among sentinel travellers.

Comment: Dengue is a more frequent diagnosis than malaria in ill travellers who have returned from all tropical regions other than Africa. Two percent of ill travellers seen at GeoSentinel sites have dengue. This study has sufficient numbers to reveal seasonality of dengue in travellers. For example, there is a major peak each October in South Central Asia. In the study, 24% of the dengue patients were hospitalised. Importantly for our travellers, the dengue proportionate morbidity (number of patients with dengue as a proportion of the total number of ill returned travellers from a region) for travellers returning from Oceania was second only to Southeast Asia.

Reference: *Emerg Infect Dis* 2008; 14(7): 1081-8

<http://www.cdc.gov/eid/content/14/7/pdfs/1081.pdf>

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Validity of malaria diagnosis in nonimmune travelers in endemic areas

Authors: Miranda IB et al

Summary: In this study, which investigated the validity of malaria diagnoses in endemic areas, retrospective presence of serum antibodies against *Plasmodium falciparum* and *P. vivax* in 105 nonimmune travellers who had been diagnosed with the disease in a malaria-endemic country were compared with sera from a control group of 176 nonimmune patients with microscopically confirmed malaria. Plasmodia antibodies were present within 180 days of diagnosis in 16 (15.2%) travellers, compared with 151 (71.6%) of the control group, with a similar discrepancy 8–60 days after diagnosis (17.9 vs. 92.4%). The investigators commented that malaria diagnosis in endemic areas is “frequently incorrect”.

Comment: This is not the first study to show that most travellers diagnosed with malaria during travel have not in fact had malaria at all. It is reassuring that most of those who had malaria had not been using chemoprophylaxis and the remainder had been using nonrecommended prophylaxis. I do tell travellers going to Africa about the overdiagnosis of malaria there. I do so not to make them lose faith in healthcare there, but to stop them losing confidence in their antimalarial prophylaxis. If they or their travel companions are diagnosed with malaria they will assume their prophylaxis is not working and stop taking it (and they may THEN get malaria). This study and others show that in fact it is far likelier that their prophylaxis was working and that they didn't actually have malaria. The overdiagnosis of malaria also exposes people unnecessarily to antimalarial treatment courses (sometimes by risky injections) and means that the true cause of their fever remains untreated.

Reference: *J Travel Med* 2008; 15(6): 426-31
<http://www3.interscience.wiley.com/journal/121535801/abstract>

Evaluation of mood profiles during malaria chemoprophylaxis: a randomized, double-blind, four-arm study

Authors: Schlagenhauf P et al

Summary: Mood profiles were assessed using the Profile of Mood States (POMS) questionnaire in 547 travellers to Africa before and during malaria chemoprophylaxis with atovaquone/proguanil, chloroquine/proguanil, doxycycline or mefloquine in this randomised study. The 65-question POMS questionnaire covered six categories (anger, confusion, depression, fatigue, tension and vigour), and was administered at baseline, 13–11 days before departure, 6–4 days before departure and 7–14 days after return. Overall, mood profiles did not differ significantly among the groups. Additional analyses by age, gender, medication group and time points revealed that women who received mefloquine were more fatigued and confused, and that travellers aged <34 years were more fatigued and tense than older travellers (irrespective of chemoprophylaxis agent).

Comment: This is a further report from a multicentre, randomised double-blind study that compared adverse events of four antimalarial regimens. This evaluation assessed subtle effects of the antimalarials on moods and feelings. Study medications were started 17 days before departure, so all but the baseline assessments were done with the travellers on their medications. There were no overall significant differences with respect to mood impact among the medication arms. Overall scores were in the normal range and no means were >1 standard deviation from the norm. When reanalysed with respect to gender, women in the mefloquine group showed more fatigue and confusion than men on mefloquine and women receiving other medications. This study is largely reassuring that none of the antimalarials had effects on traveller moods and feelings. However, it does once again show that women tolerate mefloquine less well than men.

Reference: *J Travel Med* 2009; 16(1): 42-5
<http://www3.interscience.wiley.com/journal/121637270/abstract>

Health risk among travellers: need for regular updates

Authors: Steffen R et al

Summary: This editorial points out that old data are too often used as the evidence base when health risks associated with travel are assessed, and presents an update on the monthly incidence rates, presented as a log scale, of health problems associated with visits to developing countries; the original scale was published in 1984. While the update reflects the latest available data on many of the diseases included, the author reminds readers that the scale reflects worst case scenarios, and the data on meningitis and poliomyelitis are still relatively old. A new inclusion for this update is fatal accident, which is the commonest cause of death for overseas travellers.

Comment: Robert Steffen, from Switzerland, is one of the ‘Grandfathers’ of Travel Medicine. In 1984, he first published a logarithmic scale displaying health risks for travellers. Over the years this has been revised and added to as new data have become available. This editorial displays his 2008 update and is useful for those who advise travellers. He warns us that there are shortcomings, such as the fact that the polio and meningitis data are old. It is also important to remember that travellers who visit friends and relatives have greatly increased risks of many travel-related problems such as malaria, typhoid, tuberculosis and influenza.

Reference: *J Travel Med* 2008; 15(3): 145-6
<http://www3.interscience.wiley.com/journal/120091024/abstract>

Intestinal strongyloidiasis: a diagnosis frequently missed in the tropics

Authors: Agrawal V et al

Summary: This case series highlights the importance of considering strongyloidiasis in immunocompromised patients who present with GI symptoms. The experiences of five patients with chronic liver disease, panhypo-gammaglobulinaemia and/or corticosteroid use and diagnosed with *Strongyloides stercoralis* hyperinfection while in northern India are presented. Abdominal pain, diarrhoea, GI bleeding, nausea, vomiting and bodyweight loss with evidence of malabsorption were the common symptoms experienced in these patients, and they all had normal stool examination findings and blood eosinophil counts. In all cases, strongyloidiasis was not suspected based on clinical findings, but was diagnosed on endoscopic duodenal and jejunal biopsy. The outcome was fatal Gram-negative systemic infection for three of the patients. The authors recommend testing for strongyloidiasis in all patients with a systemic Gram-negative bacterial infection without an obvious cause.

Comment: This paper provides a sobering reminder about the potentially serious syndrome of *S. stercoralis* hyperinfection. Strongyloidiasis, caused by the intestinal nematode *S. stercoralis* is often asymptomatic. Chronic infection is maintained by autoinfection, so people who have left endemic areas such as Africa, Asia, Southeast Asia and Latin America may remain infected for many years (British POWs had infection documented 40 years after World War Two). Immune suppression can lead to an increased parasite burden and widespread dissemination. This is potentially lethal as the larvae may take enteric bacteria with them leading to bacteraemia and possibly meningitis.

Before starting corticosteroids or other immune suppression, it is wise to exclude strongyloidiasis in people who have come from endemic areas no matter how long ago that was. Stool examination is very insensitive, so serology (sent to Sydney) is useful. Many patients with strongyloidiasis do not have eosinophilia. Treatment is with ivermectin. Thinking of the diagnosis is harder than treating it.

Reference: *Trans R Soc Trop Med Hyg* 2009; 103(3): 242-6
<http://tinyurl.com/TRSTMH-103-242>

Analysis of an acute Chagas disease outbreak in the Brazilian Amazon: human cases, triatomines, reservoir mammals and parasites

Authors: da Silva Valente SA et al

Summary: Details of the outbreak of Chagas disease that occurred in the Brazilian Amazon region in 1996 are presented. Symptoms of acute Chagas disease were present in 17/26 inhabitants, and all 17 had ≥1 positive parasitological test, including 11 who were positive for IgM or IgG anti-*Trypanosoma cruzi*. Parasitological tests for all nine asymptomatic inhabitants were negative and one was IgG anti-*T. cruzi* positive. All patients received treatment, 16 experienced a decrease in parasitaemia, and all became serologically negative within 7 years. There was genotypic overlap within the same ecotope, suggesting possible oral transmission.

Comment: This study is relevant for those of us who give pretravel advice or see returned travellers as it highlights the possibility of oral transmission of Chagas disease. Classically Chagas is transmitted to humans by reduviid or kissing bugs when the infective stage of Chagas from reduviid faeces enters a bite or mucosal membrane. Vector control has led to a decline in acute Chagas disease; however, recent outbreaks have been attributed to oral transmission. In this paper there were no reduviid bugs in the homes of the patients but they were found in the communal kitchen above equipment used for acai juice extraction. Recently, an outbreak in southern Brazil was traced to sugar cane juice or ‘garapa’ thought to have been contaminated by reduviid when the cane was crushed.

Reference: *Trans R Soc Trop Med Hyg* 2009; 103(3): 291-7
<http://tinyurl.com/TRSTMH-103-291>



Efficacy of soap and water and alcohol-based hand-rub preparations against live H1N1 influenza virus on the hands of human volunteers

Authors: Grayson ML et al

Summary: This study investigated the effectiveness of four hand hygiene protocols against human influenza A virus (H1N1) in 20 vaccinated, antibody-positive healthcare workers who had their hands contaminated with 1mL of tissue culture infectious dose 50/0.1mL live H1N1. Initial brief cutaneous air drying resulted in immediate reductions in PCR- and culture-detectable H1N1. All four protocols (soap and water, 61.5% ethanol gel rub, 70% ethanol plus 0.5% chlorhexidine solution, and 70% isopropanol plus 0.5% chlorhexidine solution) resulted in marked antiviral activity. Soap and water resulted in significantly greater antiviral activity ($p < 0.001$) than the alcohol-based protocols, but the actual difference was only 1–100 virus copies/mL, and the investigators concluded that all the hand hygiene protocols investigated were 'highly effective'.

Comment: Influenza is increasingly recognised as a risk to travellers because they often have close contact with large numbers of other people and may cross hemispheres and be exposed to different influenza strains. Circulation of influenza occurs year round in the tropics. Although person-to-person transmission of influenza is due mainly to aerosol spread, transmission from hand contact is also important. This study showed that although virus levels rapidly dropped with initial drying, there was then little change in the subsequent 60 minutes. It is reassuring that soap and water and the three alcohol-based hand rubs all performed well, with soap and water being a little better. Use of alcohol-based rubs is very sensible for travellers when soap, water and towels are often not readily available. It also reduces the risk of many other infections.

Reference: *Clin Infect Dis* 2009; 48(3): 285-91
<http://www.journals.uchicago.edu/doi/abs/10.1086/595845>

Prevalence and time course of acute mountain sickness in older children and adolescents after rapid ascent to 3450 meters

Authors: Bloch J et al

Summary: This paper investigated acute mountain sickness (AMS) in 48 healthy, nonacclimatised children (mean age 13.7 years) who ascended to an altitude of 3450m over a 2.5-hour period. The overall prevalence of AMS over the first 3 days at altitude was 37.5%, with a progressively decreasing rate from 25% at 6 hours after arrival to 8% at 42 hours. Five children required symptomatic treatment, and none required evacuation to a lower altitude.

Comment: AMS is a possibility for the many travellers who visit high altitude destinations, particularly if they ascend rapidly. Little data are available for children who go to altitude. This study provides reassuring data because, although 37% of the children developed AMS after ascending to 3450m over 2.5 hours, their symptoms were mild. A single dose of paracetamol (acetaminophen) was taken by 5 of the 48 children and no children needed any other intervention. The children in this study were aged between 10 and 17 years, so this information should not be assumed to apply to younger children or infants. Caution should still be advised for younger children.

Reference: *Pediatrics* 2009; 123(1): 1-5

<http://pediatrics.aappublications.org/cgi/content/abstract/123/1/1>

A new approach to very-high-altitude land travel: the train to Lhasa, Tibet

Authors: West JB

Summary: This paper details the oxygenation of an entire passenger train, which travels for >14 hours at an altitude of 4500m (peaking at 5072m [16,600 feet]) between China and Tibet, thereby exposing passengers to potentially severe sustained hypoxia. In this engineering challenge, oxygen generators in each passenger car were successfully used to increase the oxygen level from 21% to 24–25% (equivalent altitude 1200m).

Comment: Hypoxia at altitude can be mitigated by either increasing the barometric pressure or the oxygen concentration. In aircraft, cabin pressure is increased so the effective cabin altitude does not exceed 2440m. This interesting paper describes the other approach to overcoming the effects of altitude. The train from Beijing to Lhasa typically has 16 passenger cars for the 48-hour journey. The section from Golmud in Qinghai Province to Lhasa is 1142m at an average altitude of 4500m. Eighty-five percent of the track is above 4000m and the highest altitude reached is 5072m. This part of the trip takes 14 hours but there is a very rapid initial ascent from 2808m to 4768m in only 1.5 hours. At the highest point of the track, travellers would have arterial oxygen saturation near 75% without intervention. The solution has been oxygen enrichment of the air throughout the train. Each passenger car has an oxygen generator that produces 40–50% oxygen, which is added to the ventilation air of each car to achieve 24–25% oxygen concentration. This effectively reduces the train's highest altitude of 5000m to 3800m – something sedentary passengers can cope with. In addition, numerous oxygen outlets throughout the train allow passengers to use nasal cannulae if necessary.

Reference: *Ann Intern Med* 2008; 149(12): 898-900

<http://www.annals.org/cgi/content/abstract/149/12/898>

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Efficacy of RTS,S/AS01E vaccine against malaria in children 5 to 17 months of age

Authors: Bejon P et al

Summary: The effectiveness of malaria vaccine RTS,S with the immunogenic adjuvant system AS01E was compared with rabies vaccine (control) in this randomised trial involving 809 evaluable children aged 5–17 months. Overall, there were 38 episodes of malaria reported among the 402 RTS,S recipients, compared with 86 among the 407 control recipients; adjusted rate of efficacy against all malarial episodes 56% (95% CI 31, 72; $p < 0.001$). In an intention-to-treat analysis ($n = 894$), the unadjusted efficacy rate was 49% (95% CI 26, 65; $p < 0.001$).

Reference: *N Engl J Med* 2008; 359(24): 2521-32

<http://content.nejm.org/cgi/content/full/359/24/2521>

Safety and immunogenicity of RTS,S/AS02D malaria vaccine in infants

Authors: Abdulla S et al

Summary: In this phase 2B RCT, 340 infants were randomised to receive malaria vaccine RTS,S with the adjuvant system AS02D or hepatitis B vaccine along with WHO Expanded Program on Immunization (EPI) vaccines (diphtheria and tetanus toxoids, whole-cell pertussis vaccine, and conjugated *Haemophilus influenzae* type b vaccine) at ages 8, 12 and 16 weeks. There were ≥ 1 adverse events during a 9-month surveillance period in 18.2% and 24.7% of the malaria and hepatitis vaccine recipients, respectively. Noninferiority of the malaria vaccine was demonstrated in terms of antibody responses to the EPI antigens. Almost all the RTS,S recipients (98.6%) had positive anticircumsporozoite antibody titres 1 month after vaccination, and the 6-month efficacy of the RTS,S vaccine against first infection with *Plasmodium falciparum* following the third dose was 65.2% (95% CI 20.7, 84.7; $p = 0.01$).

Reference: *N Engl J Med* 2008; 359(24): 2533-44

<http://content.nejm.org/cgi/content/full/359/24/2533>

Comment: These two studies assessed the same vaccine with different adjuvant systems and in different paediatric age groups. In both, three doses were given each separated by a month. The vaccine was safe, did not interfere with EPI vaccines and was about 60% effective. Although it will be a number of years before this vaccine is on the market, these and other studies of it are encouraging. It cannot come soon enough, because in Africa one child in 20 dies of malaria before they reach 5 years of age. Use in travellers is a lower priority, and as yet has not been thought about.

Toxic hepatitis after consumption of traditional Kava preparation

Authors: Christi SU et al

Summary: This paper describes the case of a 42-year-old man who developed kava-induced hepatic toxicity. He presented with weakness, loss of appetite and scleral and skin jaundice 3 weeks after returning from a 20-day trip to Samoa, where he repeatedly ingested traditional kava preparations (cumulative quantity 2–3L). His liver aminotransferase levels were markedly elevated, his serum ferritin level was also elevated, and tests for a viral or genetic cause were negative. Histology findings were consistent with toxic liver injury, and he was diagnosed with kava-induced toxic hepatitis. His liver enzyme levels slowly improved, followed by an improvement in his physical status, and he had completely recovered after 36 days.

Comment: This case report from Germany describes a 42-year-old, previously well man who presented with weakness, anorexia and jaundice 3 weeks after a honeymoon in Samoa. While there he had consumed 2–3L of traditional kava. His hepatitis was diagnosed as kava-induced toxic hepatitis. Toxic hepatitis, hepatic failure and deaths have been reported after exposure to kava in western herbal medicines. Little is known about toxicity of kava consumed in the traditional way, although there are reports of hepatic injury from New Caledonia. Although the risk seems to be very small, maybe travellers should be aware of it.

Reference: *J Travel Med* 2009; 16(1): 55-6

<http://tinyurl.com/JTravelMed-16-55>



Independent commentary by Dr Joan Ingram, an Infectious Diseases Physician with a special interest in Travel Medicine. She was a foundation member of the New Zealand Society of Travel Medicine and one of the first in New Zealand to be awarded a Certificate in Travel Health by the International Society of Travel.

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