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An overview of travel-associated central nervous system infectious diseases: risk assessment, general considerations and future directions

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PEER REVIEW

Peer reviewer

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Comments

This is a valuable review work in which authors highlighted some important aspects of travel-related illnesses from a neurological point of view. These aspects mainly includes risk assessment, general considerations and future directions. Recommendations with regard to knowledge gaps, and state-of-the-art research are made. Given an increasing number of international travelers, novel dynamic ways are available for physicians to monitor the spread of CNS infections.
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ABSTRACT

Nervous system infections are among the most important diseases in travellers. Healthy travellers might be exposed to infectious agents of central nervous system, which may require in-patient care. Progressive course is not uncommon in this family of disorders and requires swift diagnosis. An overview of the available evidence in the field is, therefore, urgent to pave the way to increase the awareness of travel-medicine practitioners and highlights dark areas for future research. In November 2013, data were collected from PubMed, Scopus, and Web of Knowledge (1980 to 2013) including books, reviews, and peer-reviewed literature. Works pertained to pre-travel care, interventions, vaccinations related neurological infections were retrieved. Here we provide information on pre-travel care, vaccination, chronic nervous system disorders, and post-travel complications. Recommendations with regard to knowledge gaps, and state-of-the-art research are made. Given an increasing number of international travellers, novel dynamic ways are available for physicians to monitor spread of central nervous system infections. Newer research has made great progresses in developing newer medications, detecting the spread of infections and the public awareness. Despite an ongoing scientific discussion in the field of travel medicine, further research is required for vaccine development, state-of-the-art laboratory tests, and genetic engineering of vectors.

KEYWORDS

Travel medicine, Infectious diseases, Nervous system disorders

1. Introduction

An estimate of 938 million people had international travels in 2010 with an increase of 3% in 2013[1]. Travellers are inevitably exposed different illnesses[2]. Therefore there is an increasing number of travelers that need risk assessment prior to their travel in order to perform suitable precautions and avoid complications during overseas travels. Such illnesses, albeit self-limiting to a large extent, affect up to a three-quarter of young travelers[3]. Moreover,

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individuals traveling to resource-limited destinations should be encouraged to seek pre-travel advice and risk assessment; mainly because the risk for illness is increased in such regions with limited advanced medical care[4,5] and more than a half of them do not seek pre-travel advices[2]. Thus, primary care physicians should be equipped with appropriate knowledge of destination-specific diseases, routine vaccines, chemoprophylaxis regimens, and self-treatment regimens for infectious and non-infectious illnesses[5,6]. In complex travelers, practitioners should advise on seeking specialized travel-medicine care, as travellers might not be aware of them.

More importantly, central nervous system (CNS) may be affected by various travel-associated pathogens[7]. CNS disorders may also need a comprehensive risk assessment, which involves detailed data gathering strategies[8,9]. Equally important are people affected with chronic CNS disorders (*e.g.* multiple sclerosis, epilepsy, brain tumors, post-surgical complications and *etc.*) that may require more comprehensive pre-travel care. All of these conditions need state-of-the-art travel health prevention and intervention strategies. However, data on travel-associated health problems in general, and neurological disorders in particular, are scarce and further work is urgently needed to organize the current evidence and shed light on the areas that require further research. Complicating factors such as increasing number of travellers, drug resistant organisms and newly emergent infections poses a major challenge with respect to travel-medicine interventions[10].

Therefore, an review need to be set out to the state-of-the-art evidence in the field, to present comprehensive overview on important CNS diseases in travel and finally to provide invaluable insights regarding research areas under-represented in the current literature of the travel medicine.

2. Pre-travel risk assessment

Risk assessment is the process of gathering detailed information on host factors, travel characteristics and environmental factors. Travellers' underlying conditions (*e.g.* chronic conditions), season of travel, destination (including region, types of available accommodation, and season of travel), purpose of travel and duration, social history, risk-taking behaviors and previous travel experience that all should be assessed and properly addressed[2]. All the required information should be collected at least 6-8 weeks from the scheduled travel. It starts even before face-to-face consultation by filling a relevant questionnaire[11]. Previous health record obtained in general practice may also be helpful. Risk assessment largely determines the nature of advice needed for the travellers and whether intervention would be necessary.

Familiarity, visibility and controllability of a hazard determines its risk that should be weighed against the cost of intervention in travel medicine[11]. Risk-assessment includes both the assessment of risk of the destination (Table 1) and the risk of the individual traveller (Table 2). This should be addressed from prevention to education and a final management[11]. High-risk travellers with regard to important CNS infections can be found in Table 2. Figure 1 shows the crosstalk between hazards, exposures, susceptibility of the individual traveller that necessitates risk assessment, risk management and appropriate travel medicine intervention. Environmental factors are dynamic processes and travellers should seek new information through available real-time resources (See Table 2 for further details). Notwithstanding in a survey of 2 000 travellers, 70% had not sought pre-travel advice[12] and most of those who seek advice do so with usual practitioners who are not travel-medicine experts[13]. Even when travellers seek pre-travel advice, their adherence to travel medicine recommendations remain=s suboptimal[14]. Future research should address refined strategies to increase pre-travel care awareness. Moreover, more accessible and affordable pre-travel care (*e.g.* through social media) could eventually reduce travel associated morbidity and mortality[15].

Table 1

Environmental risk factors (with respect to neurological infections).

Risk	Example
Altitude	Mountain sickness
Heat and humidity	Nervous system tropical infections
Foodborne and waterborne health risks	Clostridium botulinum, shellfish poisoning[54]
Travellers' diarrhoea	*E. coli*, *Clostridium jejuni* and other agents[55]
Recreational waters	Cryptosporidium
Animals and insects	Arboviral infections
Intestinal parasites	Neurocysticercosis

Source: http://www.who.int/ith/other_health_risks/environmental_risks/en/index.html

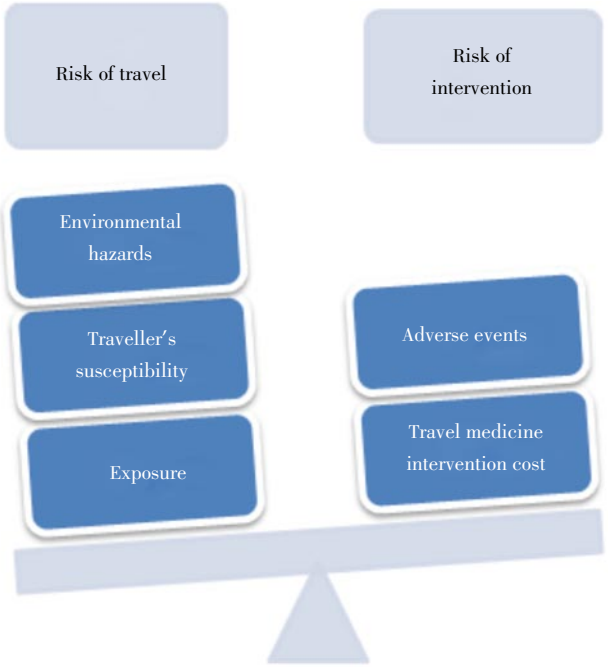

Figure 1. Risks of travel should be weighed against risk of intervention.

Risks associated with mode of travel play an important role in the risk assessment. Pre-existing neurological conditions, recent neurosurgical interventions and mental impairment

Table 2

Notable travel-associated CNS infectious diseases.

Group	Syndrome		Incubation period	Destination(s)	Manifestations		Preventive care	High-risk travellers	Future direction in travel-medicine
Encephalitis	Arboviral	Western equine encephalitis	2-10 d	Western USA	Meningitis and encephalitis symptoms, and myelitis as the general manifestation	Milder than EEE	Mosquito control	The very young and the elderly	Development of next-generation vaccines, prevention mechanisms in biowarfare
		Eastern equine encephalitis (EEE)	4-10 d	Eastern USA		Similar to WEE	Mosquito control	The very young and the elderly	Development of next-generation vaccines
		Japanese encephalitis	~2 weeks	East, Southeast and South Asia		Biphasic course	Vaccination	>50 years of age	Development of bioengineered and chimeric vaccines
		Yellow fever	3-6 d	South America, Africa		Fever, headache, bleeding,	Mosquito control-Vaccination (if recommended)	All travellers to endemic areas	Genetic modification of insect populations
		Dengue fever	4-7 d	Tropical areas (*e.g.* southeast Asia)		Biphasic course	*Aedes* mosquitos-vaccinations will soon become available	Old age	Entomologic and pathogenic factors influencing transmission
		Tick-borne encephalitis	8 d	Central and Eastern Europe, Russia		Biphasic course	Vaccination	Military personnel	Miniature RT-PCR chip technology for differential diagnosis[56]
	Rabies		Variable	Worldwide	Acute and progressive encephalitis following exposure to a rabid animal		Vaccination	Children	Single-dose vaccines[57] - eradication from wildlife[58]
	Mediterranean spotted fever		5-7 d	Mediterranean regions (North Africa)	Meningoencephalitis symptoms and multi-organ failure		Environmental hygiene (preventing tick bites), personal protective measures	Old age, G6PD deficiency, and alcoholism	More widespread PCR-based research for differentiating among rickettsial agents[59]
	Malaria		<2 weeks	Africa, South Asia, Eastern Europe, Central and South America	Fever, encephalopathy		Chemoprophylaxis	Traveling to Oceania and West Africa	Prognostic markers in travellers
	Neurobrucellosis		1-2 months	Arabian peninsula and Mediterranean regions	Uncommon presentation of brucellosis: headache, fever		Avoidance of dairy foods, vaccination of animals	Travelling from non-endemic areas	Wildlife disease prevention with oral vaccination[60]
	Typhoid fever		10-20 d	Africa, South Asia, Peru	Fever, Low-grade septicemia		Vaccination	Traveling to Southern Asia	Increase knowledge in Pathogenesis to develop novel immunogens
Encephalopathy	Neuroschistosomiasis		Variable	Tropical areas (*e.g.* central Africa)	Strong inflammatory response symptoms		Swimming in safe water, drinking safe water	Travelling to Africa	Developing vaccines (*e.g.* helminth custein peptidase)[61]
	Epidemic typhus		6-14 d	Under-served areas	Difficult to diagnose: headache, fever. Diagnosis with serology and PCR		Minimize exposure to arthropods	Travelling to areas with refugees	Stimulating $CD8_+$ cells to recognize intracellular antigens
	African trypanosomiasis		Weeks to months	Sub-Saharan Africa	Sleep-cycle disruption		Insect repellant and appropriate clothing	Travellers to Africa	Drug development with greater oral bioavailability[62]
	Trichinosis		1st phase=1-2 d 2nd phase=2-8 weeks	Global distribution	Headache		Avoiding raw or under-cooked meat	All travellers exposed to under-cooked meat	Detecting early diagnostic antigens
	Tuberculosis		Variable	Asia, Africa, South America	Non specific headache, more sever than other forms of meningitis		Vaccination (incomplete protection)	Travelers from non-endemic areas, immunocompromised individuals	Discovering novel intracellular stains for rapid detection[63]
Meningitis	Meningococcal meningitis		2-10 d	Hajj pilgrimage	Fever, headache, stiff neck, vomiting, light sensitivity		Vaccination	Infants less than 1 year of age, adolescent from 16-21 years of age	New prevention clinical trials (see main text)
	Strongyloidiasis		14-30 d	West Africa, the Caribbean and southeast Asia	Headache, nausea, vomiting and coma		Footwear and protective clothing	Travelling to Brazil and Thailand	New diagnostic test to monitor disease progression and helminth control
	Polio		3-35 d	Afghanistan, Nigeria, Pakistan	Flaccid paralysis		Vaccination	Substance abuse and immunosuppression	Progress toward eradication in the remaining 3 countris
Other	HIV		Variable	Worldwide	Meningitis, encephalitis and unexplained CNS involvement		Safe sexual contact	Health education	Development of antiretroviral and post-exposure therapies
	Neurocysticercosis		Variable-up to years	All low-income countries	Seizure (common), Headache, Stroke, Neuropsychiatric dysfunction		Educational campaign for travellers	Food-handlers	Finding reasons for prolonged incubation period

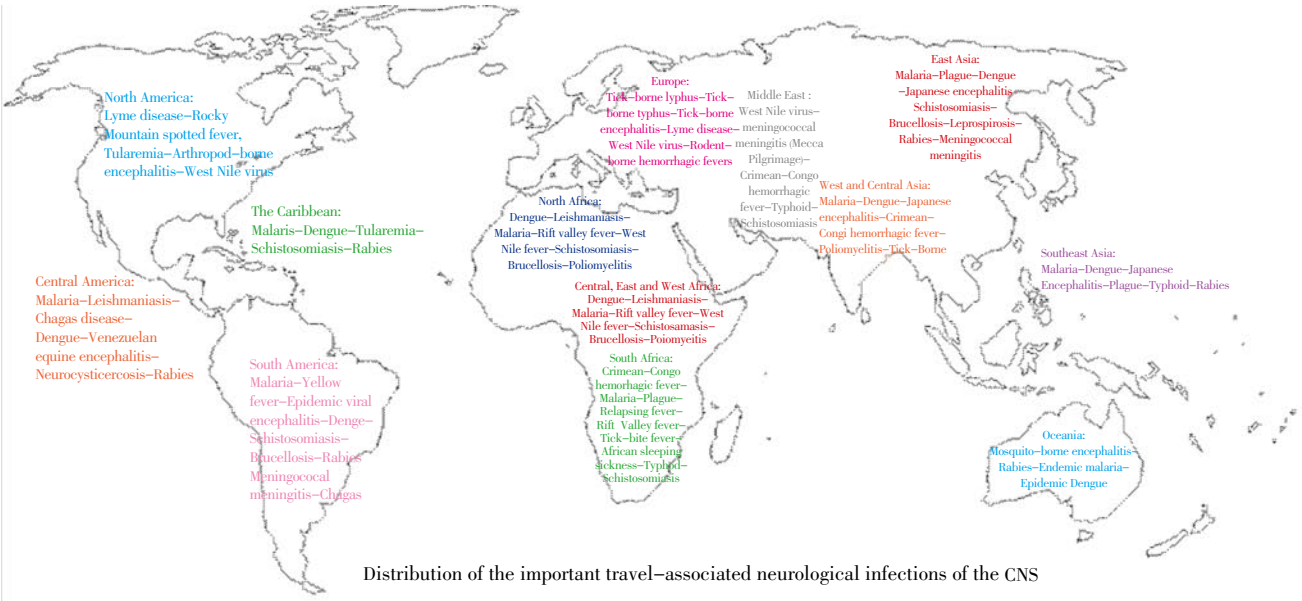

Figure 2. Common CNS infections and their geographical distribution.

all require consultation prior to fly with commercial aircrafts. Long flights can predispose travellers to barotrauma, jet lag, deep vein thrombosis, panic attacks, claustrophobia and increase the effect of alcohol on passengers[11]. Also, prolonged exposure to infectious agents plays an important role in person-to-person transmissions in longer flights.

3. Vaccination

Pre-travel evaluation of travellers often addresses vaccination that depends on the risk of travellers' health, itinerary and destination. Vaccine-preventable sicknesses are shown in Table 2. Guidelines are available for required vaccines based on specific destinations[16] as well as season of the planned travel. Decision of taking vaccines might depend on various factors: duration of the stay, availability of post-exposure care (*e.g.*, rabies immunoglobulin), age, and the purpose of travelling. All travellers should be up to date with regard to routine vaccinations. A recent study showed that approximately a third of travellers need pre-travel consultation for completing routine vaccination (Yellow fever is the most frequently administered vaccine, followed by hepatitis A, typhoid fever, and meningococcal vaccine)[17]. Meningoccal meningitis is the most common CNS-vaccine preventable disease seen in unvaccinated travellers (0.04-200 per 100 000 unvaccinated persons)[18]. Individuals travelling to 'meningitis belt' in Africa in dry season are strong candidates for receiving the vaccine[19]. High-risk individuals for invasive meningitis should receive conjugate tetravalent vaccine (or pentavalent vaccine if available)[19]. Conjugate vaccines are preferable to polysaccharide vaccines as they provide a longer immunization and decreases the rate of nasopharyngeal shedding of the bacteria[20].

Dengue is the most common arthropod-borne virus in the world[21]. Dengue fever is common in returning individuals from Southeast Asia, a GeoSentinel survey showed that the possibility of infection with dengue fever in this group was more than that with malaria[22]. Several vaccines are under-development and until such time preventive measures play the most important role[21]. Live attenuated viral vaccines that need to address all four subtypes of this virus introduce new challenges that have previously hampered the efforts of researchers. Vaccines that passed the latest stages of clinical trials have successfully addressed the challenge of minimal pathogenicity and maximal immunogenicity among all serotypes[21]. Chimera Vax is a promising vaccine that introduces 4 recombinant viruses on yellow-fever virus backbone[23]. This vaccine can induce ample immunogenicity with administration at 0, 6 and 12 months to dengue 1 to 4 with a good safety profile[21,24].

Typhoid fever, tick-borne encephalitis, rabies and Japanese encephalitis may also be seen in unvaccinated travellers[18]. Between 1973 and 2008 only 55 cases were reported in non-endemic countries with an estimated risk of less than 1 in 1 million travellers[25]. Despite its rare prevalence in returning travellers, its serious consequences have increase the researchers' interest in vaccination. Vaccination against Japanese encephalitis should be recommended to all long-term and repeat travellers and to expatriates going to areas of Asia where the disease is endemic[26] although the proportion of high-risk travellers that receive Japanese encephalitis vaccine remains low[27].

The GeoSentinle survey on 320 cases from 1988 to 2005 showed that animal bites are not uncommon in returning travellers with short travel duration, especially when traveling to Asia[28]. Pre-exposure vaccinations remain controversial and depend on endemicity in the destination and availability of medical care in the destination country[29]. Intra-dermal route of pre-exposure vaccination may be beneficial for travellers[29].

Influenza remains the most common vaccine preventable disease in travellers[30]. Influenza and pneumococcal vaccines should also be considered among older travellers[31]. Yellow fever vaccination for travellers to non-endemic areas is not generally recommended. However, travellers with increased risk of mosquito bites and prolonged travellers necessitates vaccination in a small group of travellers[30]. Although yellow fever vaccine provides important protection for travellers to endemic or epidemic areas, in older adults, the risks and benefits associated with the vaccination should be weighed against each other (age associated thymus involution)[32].

4. Special considerations for people affected with long-term CNS conditions

The number of travellers with chronic underlying neurological conditions or older age is on the rise. Approximately 20% of travellers are high-risk individuals that suffer from other comorbidities[33] with more than two-times as frequent travel-related illnesses as seen in healthy individuals[33]. Most of high-risk travellers travelled to destinations with higher risk for malaria and typhoid fever, and among different neurological disorders, multiple sclerosis and other demyelinating diseases, myasthenia gravis merits special consideration.

Patients receiving immunosuppressive or immunomodulatory treatments could be affected with skin infections more often than others[34] and they require special advice on using live attenuated virus vaccines with regard to the serious side-effects[35]. Severe immuno-compromised patients should not receive live vaccines. Patients with multiple sclerosis can receive immunization in the presence of strong indication following risk-benefit analysis, although this should be 4-6 weeks after the beginning of a relapse[8]. High-risk individuals should be referred to specialized travel-medicine clinics for further evaluation on whether they should receive vaccination[33]. Patients with epilepsy should take ample sleep and avoid fluorquinolone antibiotics[36].

Patients on special treatments (*e.g.*, warfarin following sinus venous thrombosis or stroke) require drug interaction analysis to make sure that concomitant travel-related medications (*e.g.*, malaria chemoprophylaxis) are safe. Warfarin might have interaction with malarial chemoprophylaxis and patients taking warfarin should start receiving chemoprophylaxis at least 1 week in advance of their scheduled travel[37]. Flights can cause headache and further research is needed to determine the relationship between flight-associated headaches and migraine[38]. Travel-medicine practitioners should ask about the history of thymus disorders (myasthenia gravis and thymectomy). A history of thymus disorder is a contraindication to yellow fever vaccination and affected individuals should seek other ways of prevention such as insect repellents[32]. Travel-medicine practitioners must take extra caution when advising on breast-feeding women for yellow fever vaccination, because it can be transmitted via breastfeeding[30].

4.1. Elderly population

Elderly population is an ever increasing agegroup in most nations. Increasing age is associated with certain neurological conditions such as dementia, Parkinson's disease, stroke and Alzheimeir's disease. In 2004, approximately 3 million American adults with 65 years of age or older traveled abroad[39]. This age-group are referred to travel-medicine clinics more frequently[39]. Flight diversions due to neurological emergencies constitute 20% of all emergencies seen during the flight (rank only second to cardiac emergencies)[40,41]. Cognitively impaired individuals are more susceptible to delirium in longer flights and should avoid dehydration (*e.g.* consuming coffee or alcohol) as well as hypnotic medications. Pre-travel risk assessment plays an important role in these cases to determine whether the elderly patients need an accomplice for the duration of travel or not[31].

4.2. Pediatric population

Children are less likely to receive pre-travel medical advice but are more likely to seek medical care after travel and require hospitalization[42]. They should be approached based on the specific age group with respect to destination-specific illnesses. Neurological complications are very unlikely in children, although post-vaccination side effects, such as acute disseminated encephalomyelitis might be more common[42].

5. Malarial risk of CNS involvement

Malaria can manifest as cerebral variant that is known as "black-water fever". High-risk areas for travellers include: Central and South America, Africa and Southeast Asia. This condition is most commonly caused by *Plasmodium falciparum*. High-risk populations are travellers without chemoprophylaxis, pregnant women and children. It usually presents with headache, chills, nausea, vomiting and myalgia. Severe cases can present with stupor and coma[10]. Residents of malaria-endemic areas show high prevalence of asymptomatic *Plasmodium falciparum* parasitemia, therefore positive blood film in comatose patients does not prove that coma is due to malaria[43]. Although newer markers such as malaria retinopathy and HRP2 sound promising, future researches should focus on developing more specific biomarkers useful for differential diagnosis[43,44]. Additionally, certain travellers (*e.g.* Canadian born travellers to endemic areas) are exposed to more severe symptoms and higher parasite density; this warrants further investigations into identification of prognostic markers (*e.g.* IL-20)[45]. The results of such efforts can help travel medicine to perform a better risk-

assessment in travellers.

6. Post-travel consultation

Despite the emphasis on pre-travel consultation and administration of suitable prophylaxis, illnesses also occur in returning travellers[46]. Approximately 8% of travellers seek medical care during or after travelling[22,47]. A detailed history plays an important role for defining the cause; it should include: travel itinerary, pretravel consultation (immunization and chemoprophylaxis), duration of travel, exposures and underlying conditions[47]. The most important diagnostic clue seems to be traveller's destination[22]. The highest risk areas that cause illnesses in travellers are Asia and sub-Saharan Africa[48]. A large survey showed that common vaccine-preventable diseases in returning travellers are: typhoid and paratyphoid fever, influenza, and viral hepatitis[49]. Fever is a common symptom among returning travellers[48] and when it is associated with CNS involvement it raises the possibility of the following diagnoses: Meningococcal meningitis, malaria, Japanese encephalitis, West-Nile encephalitis, trypanosomiasis and rabies[47]. Infections presenting with mental status changes require inpatient medical care and infectious diseases specialist consultation, other illnesses can be treated on an outpatient basis.

7. Neurobiological epidemics: bioterrorism

From a neurological perspective agents for bioterrorism might include: botulinum toxin, Venezuellan equine encephalitis, anthrax, smallpox, Q-fever, and tularemia[50,51]. Signs and symptoms constitute a broad range from headache and meningitis to encephalopathy and seizure. Interested readers have been referred to an excellent review by Ostebauer *et al.* with further details on this issue[50]. In general, travel-medicine practitioners should be able to recognize the event and differentiate it from other causes of unusual epidemics[51-53]. Disease occurrence in unusual age, rapid increase in incidence, concurrent animal deaths and high level of suspicion could help care-givers to discriminate bioterrorism and other causes of disease outbreaks[51].

8. Conclusions

In this review, the important aspects of travel-related illnesses from a neurological point of view has been highlighted. Neurological infections that affect international travellers are numerous and require skilled travel-medicine caregivers. Destination of the individuals is amongst the most important factors for addressing the interventions that might be needed for each traveller. Comprehensive assessment both before and after the intended travel could help to prevent or reduce morbidity, mortality and cost of intervention. Individuals with underlying and chronic neurological conditions should also be born in mind as they usually need extra assessment and sometime different medications before their travel. It is also underscored that future directions on a disease-by-disease basis warrants further research. State-of-the-art vaccines, genetic engineering of vectors, real-time monitoring of disease outbreaks and increasing knowledge of the public are important challenges in the future of travel medicine.

Conflict of interest statement

We declare that we have no conflict of interest.

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Comments

Background

Nervous system infections are among the most important diseases in travelers. Healthy travelers might be exposed to infectious agents of CNS, which may require in-patient care. An overview of the available evidence in the field is, therefore, urgent to pave the way to increase the awareness of travel-medicine practitioners and highlights dark areas for future research.

Research frontiers

The authors collected and reviewed related information from varieties of sources, such as PubMed, Scopus, and Web of Knowledge that including books, reviews, and peer-reviewed literature. Works pertained to pre-travel care, interventions and vaccinations that related neurological infections were retrieved. The current study could provide information on pre-travel care, vaccination, chronic nervous system disorders and post-travel complications. Recommendations with regard to knowledge gaps and state-of-the-art research are also made.

Related reports

Data were collected from PubMed, Scopus, and Web of Knowledge (1980 to 2013) that including books, reviews, and peer-reviewed literature. Works pertained to pre-travel care, interventions, vaccinations related neurological infections were retrieved.

Innovations and breakthroughs

The authors reviewed the state-of-the-art evidence in the field, present comprehensive overview on important CNS

diseases in travel, and finally to provide invaluable insights regarding research areas under-represented in the current literature of the travel medicine.

Applications

Comprehensive assessment both before and after the intended travel could help to prevent or reduce morbidity, mortality and the cost of intervention. Individuals with underlying and chronic neurological conditions should also be born in mind, as they usually need extra assessment and sometime different medications before their travel.

Peer review

This is a valuable review work in which authors highlighted some important aspects of travel-related illnesses from a neurological point of view. These aspects mainly includes risk assessment, general considerations and future directions. Recommendations with regard to knowledge gaps, and state-of-the-art research are made. Given an increasing number of international travelers, novel dynamic ways are available for physicians to monitor the spread of CNS infections.

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