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Infections of the Central Nervous System in Returning Travelers and Immigrants

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Abstract
Purpose of Review This review highlights current knowledge in travel-related neuroinfectious diseases, providing insight on approaches to prevention, diagnosis, and treatment of infections of the central nervous system (CNS) in travelers and immigrants.
Recent Findings Updates on travel vaccine recommendations including vaccine-specific interactions with immunosuppressive agents, advances in Zika virus and dengue virus vaccine development, new diagnostic criteria for neurocysticercosis, updates on treatment approaches for tuberculosis meningitis.
Summary Increasing rates of travel are leading to the spread of known infectious diseases and the emergence of new diseases in travel medicine. Among these infections, neuroinfectious diseases carry significant morbidity and mortality. To reduce the effect of travel-related illness, appropriate pre-travel measures and up-to-date diagnostic and treatment strategies are essential for optimal outcomes. This review highlights important travel information relevant to neuroinfectious diseases for several populations including immunocompetent, immunocompromised, pregnant, and infant/children travelers. It also outlines the travel risk, clinical presentation, diagnosis, and management of a select list of neuroinfectious diseases by region, including neurocysticercosis, Zika virus, tuberculosis meningitis, rabies, and tick-borne encephalitis.

Keywords Infections in travelers and immigrants · Vaccinations · Parasitic infections · Encephalitis · Meningitis

This article is part of the Topical Collection on *Central Nervous System Infections*

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Introduction

Increasing rates of travel are a major driver to the spread of infectious diseases internationally. Expanding globalization has led to the emergence of infectious diseases in travel medicine, including the recent global outbreak of Zika virus. International tourist arrivals rose to 1.2 billion in 2015, and annual rates are expected to increase by over 3% each year, reaching 1.8 billion by 2030, particularly in tropical regions [1]. Neuroinfectious diseases carry the most significant risk of morbidity and mortality among infections. In order to reduce the risk, accurately diagnose, and optimize treatment, it is imperative for healthcare providers to be well-versed in risk factors, clinical presentations, and management strategies of neuroinfectious diseases acquired internationally.

Pre-travel Assessment

Travelers should receive an individualized risk assessment that is followed by appropriate prevention strategies. Special conditions, including individuals that are pregnant, immunocompromised, or traveling with infants/children, require additional considerations that are highlighted

in the following sections. Appropriate vaccination and prophylactic medications should be a primary consideration when assessing travel plans. According to the World Health Organization (WHO), vaccination prevents up to six million deaths annually [2]. Travelers should be up-to-date on their routine immunizations and receive any recommended vaccinations 4–6 weeks prior to travel. Table 2 outlines information on international travel vaccinations relevant to some neuroinfectious diseases. Travel-related risk factors (e.g., mosquito bites, poor hygiene, contaminated foods, animal contact), preventative education, emergency resources, self-treatment options, and other considerations should be discussed prior to travel (Table 1). For some diseases that require post-exposure prophylaxis, such as rabies, travelers should also prepare an emergency response plan [4].

Table 1 Aspects of the pre-travel consultation for clinicians

Assessment of individual risk	
Health Background	- Past medical history - Special conditions (e.g., pregnancy, children, immunocompromised) - Immunization history - Previous travel knowledge and experience
Trip details	- Itinerary (e.g., countries of travel, urban or rural) - Duration of travel - Season of travel (i.e., during high-transmission seasons) - Reason for travel - Travel style (e.g., backpacking, hostels, visiting family) - Special activities (e.g., camping, diving, altitude)
Prevention and Planning	
Disease prevention and education	- Immunizations - Malaria chemoprophylaxis - Other vector-borne disease prevention (i.e., use of insect repellants) - Respiratory illness risk (e.g., tuberculosis, influenza) - Sexual health and blood-borne pathogens - Other environmental hazards (e.g., occupational, sanitation) - Disease-specific counseling for pre-existing conditions - Resources for emergencies
Self-treatment recommendations	- Traveler's diarrhea - Altitude illness - Jet lag - Motion sickness - Respiratory infections - Skin conditions (e.g., allergens, irritants, fungal infections) - Urinary tract infections, vaginal yeast infections - Occupational exposure to HIV - Malaria self-treatment

Source: [3]

Immunocompromised Travelers

Moderately and severely immunocompromised travelers carry a higher risk of serious infection during and after travel [5]. Careful considerations must be taken for immunocompromised travelers, including assessment of the level of immunosuppressed state, vaccination contraindications depending on disease or condition, vaccination interactions with current medications, and healthcare options while traveling in the event of emergency [6•]. In general, inactive vaccinations are considered safe, but may not elicit an adequate protective response. Follow-up serological testing is suggested to determine conferred immunity and whether boosters are necessary [7]. Live vaccination, such as the yellow fever vaccine, is contraindicated in severely immunocompromised individuals regardless of circumstance due to the risk of life-threatening adverse reactions [6•]. Mild to moderately immunocompromised individuals should only receive live vaccinations when unavoidable travel-related risks outweigh the vaccination risk [6•, 8].

Travelers with Human Immunodeficiency Virus

Asymptomatic HIV-infected adults with CD4 cell counts $\geq 500/mm^3$ can be vaccinated per standard recommendations [6•]. Asymptomatic HIV-infected adults with CD4 cell counts of $200–499/mm^3$ are considered to have limited immune suppression and should follow vaccination recommendations as outlined in Table 2. Symptomatic HIV-infected adults or those with CD4 cell counts of $< 200/mm^3$, as well as patients with a history of AIDS-defining illness without immune reconstitution, are considered to be severely immunocompromised. These individuals should not receive live viral or bacterial vaccination due to risk of disseminated infection (Table 2). In addition, inactive vaccinations are considered inadequate in eliciting a protective response, and therefore, revaccination should be administered after immune reconstitution with antiretroviral therapy [6•]. For maximal vaccine response with minimal risk, it is advised to administer vaccinations at least 3 months after immune reconstitution [6•].

Specific Considerations in Patients with Neurological Conditions

Multiple Sclerosis

Though inactive vaccines including hepatitis B, influenza, pneumococcal disease, and tetanus vaccines are not associated with an increase in short-term risk of relapse, it is recommended that vaccination be delayed during multiple sclerosis (MS) relapses until the patient's condition has stabilized or

Table 2 Vaccinations available for select neuroinfectious diseases

Infectious disease	Vaccination type	Endemic areas	Recommendations for deployment	Contraindications	Other relevant information
Japanese encephalitis virus	Inactivated and live forms available	Asia, some parts of northern Australia, and the Pacific [9]	Recommended for (1) travelers > 2 months of age spending > 1 month in endemic areas; (2) short-term travelers with increased rural exposure or travel during the transmission season; (3) travelers to an area with an ongoing JE outbreak [10]. Not recommended for short-term travelers restricted to urban areas or times outside transmission season [10].	Contraindicated in patients with severe allergic reaction to JE vaccination [10]. Currently, there is insufficient data on recommendations for inactivated forms in immunocompromised patients and pregnant patients [6•, 11].	Antibodies maintained for 2 years [12]. Vaccine strands based on GIII JEV genotype can induce cross-protective immunity against all major JEV genotypes [13•, 14].
Tick-borne encephalitis virus	Inactivated forms available in Europe	Eastern Europe and northern Asia [15]	Recommended only for (1) high-risk travelers with increased exposure to forested areas or (2) living in TBE-endemic countries for an extended period of time [16]. Not recommended for short-term travelers restricted to urban environments; avoiding tick bites is more practical than vaccination [16].	Contraindicated in (1) patients with hypersensitivity to the vaccine preservative thiomersal or (2) those with previous adverse reaction to previous dose [16, 17]. Insufficient data on vaccination in immunocompromised patients and pregnant patients [6•, 11].	No vaccine available in the USA. Booster requirement varies depending on specific vaccination. TBE vaccines are available in adult and pediatric formulations: FSME-IMMUN (Austria) and Encepur (Germany), TBE-Moscow and EnceVir (Russia).
Polio virus	Inactivated vaccination	Afghanistan, Pakistan [18]	Recommended for (1) all children as part of routine immunization at ages 2, 4, and 6 to 18 months and 4 to 6 years; (2) unvaccinated adults traveling to endemic areas; (3) laboratory workers handling polio virus; (4) healthcare workers treating patients that may have polio [19]; (5) immunocompromised individuals and pregnant women may be vaccinated as normal [6•, 11].	Contraindicated in individuals with severe allergic reaction to polio vaccination [20]. Vaccination should be postponed in individuals with moderate to severe illness until recovered. [19]	Oral vaccination also exists. No polio cases have been detected in India for > 3 years (previously endemic region) [18].
Rabies virus	Inactive vaccination	Asia, Africa, South America, eastern Europe [21]	Pre-exposure vaccination recommended to high-risk travelers including (1) long-term travelers to endemic areas; (2) all children visiting or living in endemic areas; (3) travelers with extensive outdoor exposure in rural areas; (4) those with increased exposure to wild animals; (5) individuals traveling to isolated areas with limited access to immediate medical care [21]; (6) pregnant women if risk of exposure is high unless otherwise indicated [11]; (7) patients at high risk that are HIV-infected with CD4 cells > 200/mm^3 or with other minor immunosuppression [6•]. Post-exposure prophylaxis is recommended to anyone with exposure to rabies virus. [21]	Contraindicated in (1) patients who are severely immunocompromised with or without HIV are suggested to postpone pre-exposure vaccinations and avoid activities where rabies prophylaxis is indicated [6•]; (2) patients with history of hypersensitivity to rabies virus vaccination. [21]	In the event of post-exposure prophylaxis, previously immunized children should receive two more shots following CDC recommendations [22]. Without pre-exposure immunization, children must receive a weight-based dose of rabies immunoglobulin (Ig) and a series of four rabies injections for post-exposure prophylaxis [22]. Neurologic complications of rabies can be preventable with prompt post-exposure prophylaxis vaccination. Consider medical evacuation insurance for travel to areas without post-exposure resources.

Table 2 (continued)

Infectious disease	Vaccination type	Endemic areas	Recommendations for deployment	Contraindications	Other relevant information
Yellow fever virus	Live attenuated vaccination	Sub-Saharan Africa (except South Africa), Central and South America [23]	Recommended for travelers ≥ 9 months of age in endemic areas [23]. Not recommended in areas where there is low potential for yellow fever virus exposure [23]. Asymptomatic HIV patients (CD4 cells > 200/mm^3) should be vaccinated with precaution [6•].	Contraindicated in travelers that are (1) pregnant unless benefits outweigh potential adverse effects of vaccination [11]; (2) severely immunocompromised or with symptomatic HIV (or CD4 cells < 200/mm^3) unless benefits outweigh potential adverse effects of vaccination [6•]; (3) infants aged < 6 months [23].	Some countries require proof of vaccination for entry. True yellow fever viral encephalitis is very rare. [23]
Dengue virus	Live attenuated vaccination	Caribbean, Central and South America, western Pacific Islands, Australia, Southeast Asia, and Africa [24]	Recommended only for individuals aged 9–60 years living in dengue-endemic area with a high burden of the disease [25].	Contraindicated in (1) patients with severe allergic reaction to dengue vaccine; (2) immunocompromised patients or those with HIV [6•]; (3) pregnant or breastfeeding women [11]. Vaccination should be postponed in those with moderate to severe febrile or acute disease [25].	Dengue vaccination is not available in the USA. One dengue vaccine has been registered in several countries (CYD-TDV or Dengvaxia®) [25]. Several other dengue vaccine candidates are in clinical development.
Measle virus	Live attenuated vaccination (monovalent or multi-valent)	Europe, Middle East, Asia, the Pacific, and Africa [26]	Recommended for (1) children and adults (12 months or older) that have not had the vaccination and are traveling internationally (two doses, > 28 days apart); (2) infants (6–11 months) traveling internationally (one dose of measle vaccine) [26]; (3) indicated as normal for patients with asplenia, renal failure, chronic liver disease, diabetes [6•]; (4) recommended for asymptomatic HIV patients with limited immunocompromise (CD4 cells > 200/mm^3) [6•]	Contraindicated in (1) severely immunocompromised patients or those with symptomatic HIV (or CD4 cells < 200/mm3) [6•]; (2) pregnant travelers [11]	Two doses of MMR vaccine is nearly 100% effective at preventing measles. [26]
Malaria	Chemoprophylaxis	Africa, Central and South America, Asia, eastern Europe, and South Pacific [27]	Recommended for (1) adults and children traveling to malaria-endemic regions for any period of time [27]; (2) highly indicated in patients at high risk for severe malaria, including immunocompromised or pregnant patients [6•, 11]; (3) pregnant travelers are advised to use chloroquine prophylaxis [27].	Contraindicated in patients with severe renal failure (creatinine clearance < 30 mL/min) [27]. Special precautions for immunocompromised patients should be taken to ensure no conflicting drug interactions. [6•]	Risk of *Plasmodium vivax*-only primaquine chemoprophylaxis for individuals without G6DP deficiency; risk of *Plasmodium falciparum* atovaquone–proguanil or doxycycline or mefloquine chemoprophylaxis [27]. Where *P. falciparum* and *P. vivax* both occur, prevention of falciparum malaria takes priority [27].
Tuberculosis	Live vaccination	Sub-Saharan Africa and Southeast Asia, although can be found worldwide [28]	Recommended only for (1) children with a negative tuberculin skin test that are continually exposed and cannot be separated from adults that are untreated or ineffectively treated for TB or have TB resistance to isoniazid or rifampicin; (2) healthcare workers with high exposure to	Contraindicated in (1) immunocompromised or those with HIV [6•]; (2) pregnant travelers [11].	BCG vaccination should only be considered for patients that meet specific criteria and consult with a TB expert. Efficacy of BCG vaccine for immunocompetent travelers remains controversial. [28]. Risks and benefits for BCG vaccination should be considered in all cases.

Table 2 (continued)

Infectious disease	Vaccination type	Endemic areas	Recommendations for deployment	Contraindications	Other relevant information
			patients with drug-resistant TB [29]; (3) indicated as normal for those with renal failure, chronic liver disease, diabetes, or asplenia. [6•]		
Meningococcal disease	Inactivated vaccination	Sporadic cases are found worldwide, large outbreaks in sub-Saharan Africa [30]	Recommended (MenACWY) for (1) all travelers > 2 months of age from low-endemic regions who are planning to visit highly endemic regions; (2) infants 2–7 months of age; MenACWY-CRM should be administered as a four-dose series; (3) children 7–23 months of age; MenACWY-CRM or MenACWY-D should be administered as a two-dose series [30]; (4) immunosuppressed people and those with HIV [6•]; (5) pregnant travelers unless otherwise indicated [11]; (6) patients prior to receiving eculizumab treatment (both MenACWY and MenB) [31].	Contraindicated in people with severe allergic reaction to any component of the vaccine [30]	Meningococcal vaccination is a requirement to enter Saudi Arabia when traveling to Mecca during the annual Hajj [30]. Recent data suggests eculizumab interference with conferred resistance of men vaccines. Antimicrobial prophylaxis with penicillin is now recommended for long-term meningococcal disease prevention [31].

improved [6•, 32, 33]. In general, it is recommended that MS patients who are experiencing a serious relapse that affects their ability to carry out activities of daily living should defer vaccination until 4–6 weeks after the onset of the relapse [6•]. Inactivated vaccines are generally considered safe for people with MS, including those who are taking interferon medications, teriflunamide, glatiramir acetate, fingolamide, alemtuzamab, mitoxantrone, dimethyl fumarate, or natalizumab [33, 34]. Live, attenuated vaccines are generally not recommended for patients with MS. For patients who are prescribed ocrelizumab, all necessary vaccinations should be administered at least 6 weeks before a person starts treatment. [33, 35]. No live attenuated or live vaccines should be given during treatment or following treatment until B cells have returned to normal levels [33, 35]. For more detailed vaccine recommendations for MS patients, refer to Rutschmann, et al. [33] for the American Academy of Neurology guidelines and Mailand & Frederikson [34] for a systematic review.

Neuro-oncology Patients

Pre-travel assessment for cancer patients must take into consideration the severity of their illness, the individual's physical capabilities, the mode of travel, and the travel destination. Travel may need to be delayed if a patient is undergoing chemotherapy, anticipating chemotherapy, or within 3 months of their last treatment [36]. If a patient is capable of travel, appropriate arrangements with healthcare providers abroad should be made prior to travel, including emergency care. Medication arrangements with special considerations of controlled drugs should also be made [36]. Patients with a history of cancer with malignancy in remission who completed their last chemotherapy treatment at least 3–6 months prior are able to be immunized similar to the general population [6•, 36].

Patients on Immunosuppressive Medications

Patients taking high-dose corticosteroids (receiving a dose of > 2 mg/kg body weight or ≥ 20 mg of prednisone or equivalent per day in patients weighing > 10 kg, who are receiving therapy ≥ 14 days), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents, tumor necrosis factor blockers, and other biologic agents are considered to be severely immunosuppressed [6•]. These patients should not receive live vaccinations due to the compromised host immunity, and inactive vaccinations may not elicit a protective response (Table 3). For patients receiving eculizumab, both MenACWY and MenB vaccines are recommended prior to treatment due to increased incidence of meningococcal infection [31]. Worryingly, recent studies suggest that eculizumab interference with antimeningococcal antibodies impedes conferred resistance from the vaccination [31]. Antimicrobial prophylaxis with

Table 3 Immunosuppressive biologic agents that preclude the use of live vaccines [6•]

Generic name	Trade name	Mechanism/target of action
Abatacept	Orencia	Anti-CD28/CTLA-4
Adalimumab	Humira	TNF blocker
Alemtuzumab	Campath	Anti-CD52
Anakinra	Kineret	IL-1 antagonist
Basiliximab	Simulect	IL-2R/CD25
Belatacept	Nulojix	CTLA-4
Bevacizumab	Avastin	VEGF
Certolizumab pegol	Cimzia	TNF blocker
Cetuximab	Erbitux	EGFR
Dasatinib	Sprycel	Bcr-Abl tyrosine kinase inhibitor
Dimethyl fumarate	Tecfidera	Activates the nuclear erythroid 2-related factor 2 transcriptional pathway
Etanercept	Enbrel	TNF blocker
Fingolimod	Gilenya	Aphingosine 1-phosphate receptor modulator
Glatiramer acetate	Copaxone	Immunomodulatory; target unknown
Golimumab	Simponi	TNF blocker
Ibritumomab tiuxetan	Zevalin	CD20 with radioisotope
Ibrutinib	Imbruvica	Tyrosine kinase inhibitor
Imatinib mesylate	Gleevec, STI 571	Signal transduction inhibitor/protein-tyrosine kinase inhibitor
Infliximab	Remicade	TNF blocker
Interferon alfa	Pegasys, PegIntron	Block hepatitis C viral replication
Interferon beta-1a	Avonex, Rebif	Immunomodulatory; target unknown
Interferon beta-1b	Betaseron	Immunomodulatory; target unknown
Natalizumab	Tsabri	α4-integrin
Ofatumumab	Arzerra	CD20
Panitumumab	Vectibix	EGFR
Lenalidomide	Revlimid	Immunomodulatory
Rilonacept	Arcalyst	IL-1
Rituximab	Rituxan	CD20
Secukinumab	Cosentyx	IL-17A
Sunitinib malate	Sutent	Multikinase inhibitor
Tocilizumab	Actemra	IL-6
Tofacitinib	Xeljanz	JAK kinase inhibitor
Trastuzumab	Herceptin	Human EGFR 2 (HER2)
Ustekinumab	Stelara	IL-12, IL-23
Vedolizumab	Entyvio	Binds integrin α4β7

Table adapted from the Centers for Disease Control and Prevention. CDC Yellow Book 2018: Health Information for International Travel. New York: Oxford University Press; 2017

penicillin is now recommended for long-term disease prevention [31].

Pregnant Travelers

Women that are pregnant should receive pre-travel consultation with an obstetrician to establish the gestational age of the pregnancy, evaluate potential high-risk conditions, and identify the mother's blood type and Rh status [11]. An individualized assessment for pregnant travelers should consider the risk versus benefits for any vaccination, special contraindications (Table 2), and important considerations regarding the recent Zika virus outbreak. Zika virus has become one of the greatest infectious risks to pregnant travelers in recent years and is associated with congenital birth defects in infants of infected mothers [37]. Pregnant women should avoid travel to high-risk areas, with the most updated travel advice and developments from the CDC (https://www.cdc.gov/zika/) [38]. Currently, there is no vaccine or medication available to prevent or treat Zika [39]. If travel is unavoidable,

pregnant travelers should otherwise strictly follow steps to prevent mosquito bites and prevent sexual transmission during and after the trip**.** If a woman is trying to become pregnant, she should wait at least 8 weeks from the last potential Zika exposure, and male partners should wait at least 6 months after the last possible exposure before trying to conceive [39]. The National Institute of Allergies and Infectious Diseases (NIAID) highlights some of the most prominent advances currently in Zika vaccination development, which is summarized in Table 4 [40].

Traveling with Infants and Children

Studies have found that children are less likely to receive pre-travel advice prior to international travel but more likely to seek care after travel and require hospitalization [41]. The highest risk for infection is seen in very young travelers and those that visited sub-Saharan Africa, followed by South America and Southeast Asia [42]. Vaccinations should follow recommended age criteria based on potential adverse effects, efficacy data, safety data, and maternal antibodies [43]. Although neurological complications from infections are very unlikely in children, they may be more susceptible to post-vaccination side effects such as acute disseminated encephalomyelitis, an inflammatory demyelinating disease of the CNS [41, 44].

Malaria, rabies, and meningitis present some of the greatest risks in pediatric travelers, and exposure risk should be considered prior to travel. Malaria is among the most serious and life-threatening diseases that can be acquired by pediatric international travelers. Children can rapidly develop heavy parasitemia and severe malaria, with an increased risk of cerebral malaria which can cause seizures, coma, and death [45]. Initial diagnosis of malaria in children can often be delayed as symptoms mimic causes of common pediatric febrile illness [45]. Malaria chemoprophylaxis is strongly recommended for pediatric patients. Medications used for children are generally the same as adults, with two exceptions. Doxycycline should not be given to children < 8 years of age because of risk of teeth staining and atovaquone-proguanil should not be used for children < 11 lb due to lack of data on safety and efficacy [45].

Rabies exists in developing countries worldwide and is more common in children than adults due to increased contact with animals [46]. For young travelers to developing countries, it is recommended for children to receive a three-shot pre-exposure immunization to simplify post-exposure prophylaxis treatment. Recommendations for post-exposure prophylaxis can be found in Table 2. Numerous studies indicate that post-exposure prophylaxis with timely administration of vaccination and rabies Ig preceded by appropriate wound cleaning is uniformly effective in preventing rabies [47].

Bacterial meningitis, particularly meningococcal meningitis, can be found worldwide and is endemic in the meningitis belt of sub-Saharan Africa. Even when treated appropriately, pediatric patients that recover from bacterial meningitis often have long-term complications, including deafness, developmental delay, learning disabilities, spastic or paralyzed muscles, and seizures [48]. In a systematic literature review of pediatric bacterial meningitis cases, up to 49% of patients were reported to have one or more long-term sequelae [48]. Young travelers (> 2 months of age) who visit countries where meningococcal disease is endemic, including the meningitis belt of sub-Saharan Africa, should receive vaccination with a quadrivalent meningococcal vaccine (MenACWY). Infants and children immunized with Hib-MenCY-TT are not protected against serogroups A and W and thus should receive a quadrivalent vaccine before travel [48].

Specific Diseases by Region

South America, Central America, and Caribbean

Neurocysticercosis

Travel Risk Neurocysticercosis (NCC) is a parasitic infection caused by the ingestion of eggs from the adult tapeworm *Taenia solium.* It is typically transmitted through fecal-oral

Table 4 Current Zika vaccinations under development

Vaccination in development	Company/institution	Trial phase
DNA-based Zika vaccine	NIAID Vaccine Research Center	Phase 2
Purified inactivated Zika vaccine (ZPIV)	Walter Reed Army Institute of Research	Phase 1
Live attenuated Zika vaccine	NIAID Laboratory of Infectious Disease	Phase 1
mRNA-based Zika vaccine	Moderna/Valera (others entering trials soon include NIAID, GlaxoSmithKline, University of Pennsylvania)	Phase 1
Genetically engineered stomatitis virus	NIAID	In development
AGS-v (multiple mosquito-borne disease vaccination)	SEEK and hVIVO	Phase 1

Source: [40]

contamination and is common in rural areas with poor sanitation where pigs have access to human feces. Endemic regions include Central and South America, sub-Saharan Africa, India, and East Asia [49, 50]. NCC is the most common parasitic infection of the brain and a leading cause of epilepsy in the world [51]. Recent systematic reviews found NCC to be present in 30–40% of patients with epilepsy in rural and endemic regions [52, 53]. NCC is rare among international travelers and is mainly seen in immigrants. The rate of clinical disease in travelers to endemic areas is estimated to be 1:250,000 per episode of travel [54]. Those at highest risk are long-term travelers, with an average length of 56.6 months of travel [49].

Clinical Presentation When *T. solium* larvae migrate to the CNS, they can spread parenchymally or extraparenchymally. NCC has a median latent period between 2 and 5 years, and symptoms can vary depending on the number, location and stage of cysts, and the host immune response [49, 50, 54]. Cysts within the host tissue develop through several stages, from immature stages to larval cysts over several months. Clinical symptoms typically present once cysts begin to degenerate, and there is a significant host inflammatory response [55]. Parenchymal cysts occur in over 60% of patients with NCC. Clinical presentation is typically associated with seizures and headaches, although many lesions are found incidentally [56]. Epileptic seizures are the most common clinical manifestation of intraparenchymal cysts occurring in up to 70% of patients [49]. Cysts that are actively degenerating are the most epileptogenic and are typically associated with new-onset seizures [56]. These can present with edema and/or contrast enhancing lesions on imaging. Multiple active cysts with cerebral edema may clinically resemble encephalitis, which most commonly manifest in young women and children [56]. Calcified granulomas are usually associated with chronic epilepsy [57]. Extraparenchymal cysts (including subarachnoid, ventricular, and cisternal) can present with elevated intracranial pressure or hydrocephalus by blocking CSF flow through mass effect or inflammatory processes. Racemose NCC is a variant of extraparenchymal cysts, which manifest as multi-lobular basal subarachnoid cysts with significant morbidity and mortality [58].

Diagnosis Any patient with new-onset epilepsy that has spent prolonged time in an endemic region should be evaluated for NCC. The revised diagnostic criteria have been simplified into three categories which take into consideration clinico-laboratory features, neuroimaging findings, and exposure history [59•]. Definitive diagnosis can be made with any of the following absolute criteria, including histopathological evidence of parasites, identification of a scolex within a cystic lesion radiographically, or evidence of subretinal cysts [59•]. One retrospective study found a 93.2% sensitivity and 81.4% specificity when using these diagnostic criteria to evaluate NCC [60].

Treatment Prognosis depends on the number of cysts and degree of inflammation, with more favorable outcomes in those with a single enhancing lesion rather than multiple areas of involvement [61]. Brain magnetic resonance imaging (MRI) can provide information on the stage of the cyst which is important for treatment decisions. For treating active parenchymal NCC, recommendations include albendazole plus dexamethasone or prednisolone for adults and children to decrease the number of active lesions and reduce the frequency of long-term seizures [62]. Calcified cysts suggest a dead infection and thus do not require antiparasitic treatment. For chronic management of NCC with epilepsy, patients typically respond well to first-line epileptic drugs [62].

Since tuberculosis (TB) is endemic in many regions where NCC is, evaluation for latent TB should be performed in all patients with presumed NCC [63]. Strongyloides should also be tested for prior to corticosteroid therapy to avoid the risk of strongyloides dissemination [64]. Intraocular cysts must be ruled out by ophthalmic examination since antiparasitic therapy can lead to retinal detachment and blindness [65]. For patients with elevated intracranial pressure, antiparasitic therapy should not be used alone since cyst degeneration can worsen cerebral edema. In these cases, neurological management (e.g., steroids, mannitol) plus neurosurgical treatment should be used in conjunction with antihelminthic therapy [65, 66]. Surgical removal of cysts may be necessary for patients with spinal cord compression [65]. Patients with subarachnoid cysts, including racemose NCC, should receive antiparasitic treatment with immunosuppression until CSF and neuroimaging abnormalities have resolved [66].

Zika

Travel Risk Zika is an arthropod-borne RNA flavivirus transmitted primarily by *Aedes aegypti* mosquitoes or through sexual transmission [37, 67]. Other modes of transmission include blood transfusion, organ transplantation, and laboratory exposure [68]. Between 2007 and 2016, transmission was reported in South America, Central America, the Caribbean, Africa, Southeast Asia, and the western Pacific [38, 69]. Pregnant women and women that are trying to become pregnant are high-risk travelers and are advised to avoid travel to endemic areas. More information can be found in the "Pregnant Travelers" section of this paper, and further information on Zika virus infection can be found in the chapter on "Neurologic Complications of Zika Virus" [70]

Africa

Tuberculosis

Travel Risk TB is an infection caused by *Mycobacterium tuberculosis,* which can spread hematogenously from the lungs to the CNS to establish tuberculous foci in the brain, meninges, or adjacent bone [71]. TB meningitis (TBM) is the predominant form of CNS TB, resulting from abscesses in the meninges that can rupture and spread the infection throughout the subarachnoid space [28]. Other forms include intracranial tuberculoma and spinal tuberculous arachnoiditis [71]. TB predominates in developing countries, especially in sub-Saharan Africa and Southeast Asia [28]. Travelers with anticipated long-term exposure to TB, for example, in healthcare facilities, correctional facilities, or homeless shelters, or for those with extended travel duration in endemic regions are at higher risk for contracting the disease [28]. The most vulnerable populations are children and immunocompromised individuals [6•, 72].

Clinical Presentation About one third of the world's population has latent TB with a 10% lifetime risk of developing active infection [28, 73]. In about 1% of TB cases, CNS infection occurs [28]. TBM clinically progresses through three phases that are differentiated based upon mental status and focal neurologic signs. The prodromal phase lasts 2–3 weeks and presents with malaise, headache, mild fever, and personality changes but no focal neurologic signs. The following meningitic phase has more pronounced neurologic changes, including meningismus, vomiting, confusion, lethargy, protracted headache, and cranial nerve palsies or hemiparesis. The paralytic phase progresses rapidly into stupor, coma, and seizures. Vasculitis may develop leading to ischemic events, and blockage of CSF flow can lead to hydrocephalus [74]. If untreated, most patients die within 5–8 weeks from the onset of symptoms [28, 74, 75]. Intracranial tuberculomas may occur with or without TB meningitis and can be located in the cerebrum, cerebellum, or spinal cord or in the subarachnoid, subdural, or epidural space [74].

Diagnosis CSF culture of *M. tuberculosis* is the gold standard for diagnosis though there are major delays due to the organism being slow-growing. The CSF of patients with TBM is characterized by a mononuclear pleocytosis with lymphocytic predominance, with elevated protein and lowered glucose [76]. Atypical CSF findings in co-infected HIV patients may include normal cell counts, polymorphonuclear cell predominance, and normal glucose levels [76]. Polymerase chain reaction (PCR) amplification of *Mycobacterium* DNA is a promising TB diagnostic with results available within 2 h and a 56% sensitivity and 99% specificity [28]. The WHO recommends using Xpert MTB/RIF assay on CSF as an initial test for TBM. In one systematic review, this method was found to have an 81% sensitivity and 98% specificity [77]. Neuroimaging can also be used to identify basal meningeal enhancement, hydrocephalus, and infarctions that are most commonly seen in the basal ganglia and midbrain [76]. Tuberculomas within brain parenchyma may also be observed histopathologically or on radiographic imaging. For patients co-infected with HIV, neuroimaging findings may be atypical. [74]

Treatment Treatment should not be delayed for laboratory confirmation of TB, but should be started with any strong clinical suspicion of TB infection. The WHO recommends the same regimen for pulmonary and extrapulmonary TB, with an extension of treatment of 9–12 months for CNS TB [73]. Guidelines recommend a rifampicin, isoniazid, pyrazinamide, and ethambutol during the initial intensive phase, followed with rifampicin and isoniazid during the continuation phase of treatment [78]. Without appropriate treatment, 45% of HIV-negative people with CNS TB on average and nearly all HIV-positive people with CNS TB will die [73]. Some studies indicate that high-dose rifampicin and an oral fluoroquinolone early in the course of infection may decrease morbidity and mortality [78]. However, a randomized control trial (RCT) in Vietnam demonstrated no change in survival in TB meningitis patients with a higher dose rifampicin (15 mg/kg/day) and fluoroquinolone [79•]. Corticosteroids have been shown to reduce mortality in TBM in both adults and children and should be administered regardless of disease severity at presentation [80]. As part of the challenges to treatment, CNS penetration of first-line antituberculosis drugs can be variable, and few second-line drugs have adequate CNS penetration [81]. In addition, multi-drug resistant (MDR) TB is on the rise causing higher rates of mortality in disseminated patients [76, 78]. Further additional clinical trials are needed to define optimal treatment plans in these circumstances.

Asia

Rabies

Travel Risk Rabies is a fatal and progressive encephalomyelitis caused by a member of the *Lyssavirus* genus and is almost exclusively transmitted through the bite of a rabid animal [22]. The majority of human deaths caused by canine-mediated rabies occur in regions of Asia, especially India, as well as in Africa, although rabies can be found almost anywhere in the world [21]. The estimated rate of rabies exposure in travelers ranges from 16 to 200 per 100,000 travelers, although true rates may vary significantly due to lack of sufficient data and reporting [22]. Pre-exposure vaccination is recommended for travelers who anticipate prolonged stays in rural areas with high levels of endemic rabies, including areas where canine rabies is poorly controlled, for those who plan to have high levels of

animal contact and for those with exposure to caves (see "Traveling with Infants and Children" section) [20].

Clinical Presentation Clinical presentation typically begins after an incubation period from 1 to 3 months, although this period can vary from days to years. Clinical symptoms rapidly progress from a prodromal phase to an acute neurological phase followed by coma and death, with rare exception [22, 82]. Rabies exposure in densely innervated areas, such as the head, neck, and face, can shorten the incubation period [46]. Most deaths occur within 2 weeks after the onset of clinical symptoms, most commonly as a result of secondary complications [82]. The acute neurological phase of classic rabies presents in two forms, either an encephalitic form (about two thirds of patients) or paralytic form, while non-classic rabies may present without any distinct neurological characteristics. Hydrophobia and aerophobia are both pathognomonic for encephalitic rabies, occurring in up to 50 and 9% of rabies patients, respectively [83, 84]. Encephalitic rabies can also present with fever, altered consciousness, autonomic instability, agitation, muscle spasticity, and increased muscular tone, which progresses to delirium, seizures, rapid coma, respiratory or vascular collapse, and death [20, 22, 82]. Paralytic rabies can present similarly to the Guillain-Barré syndrome and has a late onset of cerebral involvement. Acute paralysis starts at the site of infection with a loss of deep tendon reflexes, sensory changes, and occasional pain. Paralysis eventually spreads throughout the body, leading to dense paraplegia, respiratory collapse, and death [82].

Diagnosis Rabies should be included in the differential diagnosis of undiagnosed encephalopathy in any patient returning from a country where rabies is endemic. Diagnosis can be straightforward in a patient with a compatible history and a classic clinical presentation; however, variations in clinical presentation or a lack of exposure history can complicate this [22]. The low sensitivity of certain individual tests can be improved to 100% by performing multiple diagnostic tests on various specimens (e.g., skin biopsies, serum, CSF, saliva, urine) [85]. In one prospective study, PCR of skin biopsies at the nape of the neck was found to have the highest sensitivity (98%) and specificity (98.3%) [85]. Skin biopsies may also be examined for antigen presence in the cutaneous nerves of hair follicles. Saliva samples can be tested by virus isolation or reverse transcription followed by PCR. Serological evidence of rabies virus in serum or CSF can confirm the disease in an unvaccinated patient [82]. However, antibodies in serum and CSF typically will not be detected until the disease is much later into progression. Prior to coma onset, neuroimaging using MRI can be used to identify T2 single intensity without contrast around areas of the brainstem, hypothalamus, and limbic structures [82].

Treatment There is no evidence-based treatment for rabies, with patients managed with symptomatic and palliative care. There is an experimental approach known as the Milwaukee protocol, which involves inducing a coma and treating with antiviral drugs, though it carries a high risk for neurological sequelae [22]. Rabies is still considered 100% fatal once clinical symptoms have manifested [22, 47].

Eastern Europe

Tick-Borne Encephalitis

Travel Risk Tick-borne encephalitis (TBE) is a central nervous system infection caused by a virus that belongs to the *Flaviviridae* family [15]. Transmission usually occurs through the bite of an infected tick of the *Ixodes* species, including *Ixodes ricinus* (European subtype) or *Ixodes persulcatus* (Siberian and Far Eastern subtypes). Although less common, TBE can also be acquired from ingesting unpasteurized dairy products from infected goats, sheep, or cows [15]. TBE is endemic in areas of eastern Europe and Asia, extending from eastern France to northern Japan and from northern Russia to Albania, with Russia having the largest number of reported cases. There are up to 13,000 TBE cases reported each year [15]. The overall risk of acquiring TBE for an unvaccinated traveler in an endemic area during the high season (April to November) is estimated at 1 case per 10,000 person-months of exposure, and the incidence and severity of TBE is highest in travelers over 50 years [15]. The majority of infectious tick bites are acquired in forested areas, often during outdoor activities such as camping, hiking, fishing, or military training, among others. There is minimal risk for travelers staying in an urban environment and for those that avoid unpasteurized dairy products [15].

Clinical Presentation The median incubation period for TBE is 8 days (range 4–28 days) following a tick bite [86, 87]. TBE infection is typically recognized as an acute neuroinvasive disease, although the disease course can be milder or present in a biphasic course. The first phase typically lasts several days and includes a non-specific febrile illness with headache, myalgia, and fatigue. Up to two thirds of patients will recover following this first phase without any further complications [15]. The second phase presents as a CNS infection that includes aseptic meningitis, encephalitis, or myelitis [15]. The recovery period can be long, and many patients can incur permanent neurologic symptoms as well as neuropsychiatric sequelae. Death typically occurs 5–7 days after the presentation of neurological symptoms [16]. Disease severity increases with age and is least severe in children. In addition, the clinical course and long-term outcome vary by TBE virus subtype [11]. The European subtype is typically milder with less than a 2% mortality rate and 30% of patients having

neurological sequelae. The far eastern subtype is associated with a more severe course, with up to a 40% mortality rate and a higher rate of neurological sequelae. The Siberian subtype typically presents with a chronic or progressive encephalitis, with only a 2–3% mortality rate [15].

Diagnosis Serology tests are typically used for laboratory diagnosis. IgM-capture ELISA performed on serum or CSF is highly sensitive during the neuroinvasive phase of the illness, although cross reaction from other infections or vaccinations must be considered when interpreting results [15]. Prior to the neuroinvasive phase, TBE virus or viral RNA can sometimes be detected in serum by virus isolation or RT-PCR. However, once neurological symptoms present, virus or viral RNA is usually undetectable and thus should not be used to rule out the diagnosis [15]. Other common laboratory findings during the first phase include leukopenia and thrombocytopenia, with mild elevation of liver enzymes in the serum [16].

Treatment There is no specific drug therapy for TBE [16]. A vaccine is available in some disease-endemic areas, although not currently in the USA and may present adverse vaccine reactions in children (see Table 2) [16].

Conclusion

Globalization and urbanization, coupled with environmental factors and microbial adaptation, are increasing the risk of emerging and reemerging infectious pathogens in global health. Additionally, antimicrobial resistance is occurring throughout the world, increasing the risk of disseminated disease and compromising our ability to treat infectious diseases. The primary role of healthcare personnel should be around preventative health care, including a comprehensive pre-travel risk assessment. Increased globalization requires clinician awareness to help mitigate the spread and impact of travel-related neuroinfectious diseases, recognizing clinical syndromes, and rapidly diagnosing and treating conditions.

Compliance with Ethical Standards

Conflict of Interest Haley Thompson has nothing to declare.

Dr. Thakur declares that she serves as an external consultant to the World Health organization.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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