VACCINES FOR INTERNATIONAL TRAVEL

Vaccination against these four specific diseases is recommended prior to travel to endemic areas.

By Bob Geng, MD

INTERNATIONAL TRAVEL has made the world a far more interconnected place. But, it is crucial to keep in mind that much of the world is still in process of economic development, meaning that adequate standards of public health and sanitation are also in development. Furthermore, many regions of the world have conditions and climates that are conducive for the growth and spread of certain endemic bacteria, parasites and viruses not often found in North America.

Following are some of the important vaccines often discussed in travel medicine. It is not an exhaustive list of vaccines for all potential communicable diseases that could be encountered during international travel. Further, it does not address vaccinations that are routinely recommended for maintenance of health. It is always important to be up-to-date with routine recommended vaccinations while traveling abroad.

Typhoid

Typhoid fever is caused by a bacterium called Salmonella typhi, and affects around 21.5 million people in the world per year, according to the Centers for Disease Control and Prevention. It is acquired via the oral-fecal route, meaning that it is transmitted by food or beverage handled by infected individuals or contaminated with fecal material from infected individuals. Some infected individuals even following recovery can still continue to shed the bacteria as well. In the developing world where hand sanitation in food handling is not strictly enforced, the potential for infection increases.

Symptoms of typhoid fever include high fever, lethargy, abdominal pain, nausea, headache and, occasionally, a flat rash. The way to detect typhoid infection is by analyzing the stool or blood for presence of bacteria. Typhoid is endemic to many developing countries in Asia, Africa and Latin America.
Recommendations to prevent typhoid infection are to avoid eating food and drinking beverages from high-risk unsanitary places in developing countries. Instead, only foods that are thoroughly cooked and thoroughly cleaned should be consumed, and water should be boiled before drinking.

While typhoid infections can be treated with certain antibiotics, there is a rise in multidrug-resistant strains of the bacteria, so it is far better to practice good avoidance measures, as well as vaccination for prevention. There are currently two types of typhoid vaccines available in this country. Ty21a is a live oral vaccine, and Vi capsular polysaccharide vaccine (ViCPS) is a nonlive polysaccharide vaccine.

Ty21a is given by mouth to individuals 6 years and older. It requires four doses on days one, three, five and seven. It must be given at least one week prior to potential exposure (travel to endemic area). Another booster needs to be given five years following initial vaccination. Since it is a live vaccine, it should not be given to individuals who have compromised or weakened immune systems. In addition, because it is a live vaccine and requires the body’s natural immune response to take effect, it cannot be given within 72 hours of any antibiotic therapy. Lastly, since it is a live vaccine, individuals who actively have a fever or gastrointestinal illness should not receive the vaccine.

ViCPS is a nonlive polysaccharide vaccine given as a single intramuscular injection. It has to be given at least two weeks prior to potential exposure or travel, which is a week longer than the live vaccine. The age limit minimum is 2 years, which is far lower than the limit for the live vaccine. However, it does require a booster every two years as compared to five years for the live vaccine.

Once a person is infected, the treatment of typhoid fever is antibiotics. Fluoroquinolone antibiotics have traditionally been the backbone of therapy, but due to drug-resistant strains, other antibiotics may need to be used; therefore, susceptibility testing is often necessary to decide on the best treatment regimen.

**Hepatitis A**

Hepatitis A is a virus that causes acute liver disease in infected individuals. The incidence is around three to 11 per 100,000 in areas of the world with intermediate to high risk. Like typhoid, it is not common in industrialized developed countries, but highly prevalent in underdeveloped or developing countries. It is found in higher incidence in Latin America, Africa, Eastern Europe and parts of Asia.

Unlike hepatitis B or C, hepatitis A is transmitted via the fecal-oral route, meaning that infection occurs when individuals consume substances that are contaminated by fecal materials from infected individuals. Therefore, good hygiene practices are crucial in reducing hepatitis A transmission. The presentation of hepatitis A can vary, and the length of acute illness can vary between a few weeks to several months. Unlike hepatitis B or C, hepatitis A does not lead to chronic liver disease. However, unlike typhoid, hepatitis A is a virus and not a bacterium, which means that antibiotics are not effective in its treatment. The vast majority of people completely recover from hepatitis A without treatment, but the course of disease can be severe. Rarely, hepatitis A can lead to severe liver failure and, potentially, death, mostly in patients who have concurrent chronic liver disease.

Patients who are infected with hepatitis A may experience fever, nausea/vomiting, fatigue, abdominal pain, jaundice, light-colored stools and dark urine. However, some patients may have only a few of those symptoms. Diagnostic tests include blood testing to determine whether there are antibodies made against hepatitis A.

Hepatitis A vaccine is an inactive hepatitis A virus. It is given as two injections six months apart. The first injection can be given anytime prior to travel to an endemic region. The vaccine is licensed for anyone 1 year and older. It can often be given together with the hepatitis B vaccine in the Twinrix combination formulation. For healthy patients younger than 40 years old, one dose is sufficient prior to travel. However, for older patients and patients who have weakened immune systems, intramuscular immune globulin (IG) injection should be given concomitantly to provide additional protection.

IG therapy is a collection of antibodies derived from pooled human plasma to provide protection against infections. It can be used for prevention of hepatitis A or for post-exposure prophylaxis within two weeks following exposure before signs of infection occur. It is given intramuscularly at 0.02 mL/kg, and provides up to three months of protection. For travel that lasts longer than three months, additional doses can be given. IG therapy can be given also to patients who choose not to receive hepatitis A vaccine, as well as individuals who cannot receive the vaccine such as patients with known serious allergic reactions to hepatitis A vaccine or those who are younger than 1 year of age.

**Japanese Encephalitis**

Japanese encephalitis (JE) is a viral infection endemic to Asia and the Western Pacific regions, particularly in rural agricultural areas. It is a mosquito-borne illness that can lead to significant inflammation in the brain, leading to neurologic dysfunction. Symptoms generally develop five to 15 days following transmission from mosquito bite. There is a large variation in clinical presentation. Some patients develop very mild symptoms of fever, headache, nausea/vomiting or fatigue. Others can develop significant inflammation of the central nervous system, leading to seizures, paralysis
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Please see BIVIGAM Important Safety Information and Prescribing Information on next page, including black box safety warnings, contraindications, and dosing.

*MG is also known as IGIV, Immune Globulin Intravenous (Human).


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TABLE: Table 1. Monitoring Laboratory Values: Periodic monitoring of renal function is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of BIVIGAM and at appropriate intervals thereafter. Because of the uncommon increased risk of renal dysfunction associated with the use of BIVIGAM, perform baseline assessment of blood viscosity in patients at risk for hyperviscosity and reassess at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients undergoing hemodialysis.

Indication and Usage: BIVIGAM is an Immune Globulin Intravenous (Human), 10% Liquid, indicated for the treatment of primary humoral immunodeficiency (PI).

Contraindications: BIVIGAM is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin. BIVIGAM is contraindicated in IgA deficiency patients with antibodies to IgA and a history of hypersensitivity.

Warnings and Precautions: Thrombosis: Thrombosis may occur following treatment with BIVIGAM. Risk factors include: advanced age, prolonged immobilization, hypercoagulable conditions, a history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hypersensitivity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors. Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triglycerides (triglycerides), or monoclonal gammopathies. For patients at risk of thrombosis, administer BIVIGAM at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity. Hypersensitivity: Severe hypersensitivity reactions may occur with IGG products, including BIVIGAM. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hypersensitivity and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors. Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triglycerides (triglycerides), or monoclonal gammopathies. For patients at risk of thrombosis, administer BIVIGAM at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity. Acute Renal Dysfunction and Acute Renal Failure: Acute renal dysfunction/failure, osmotic nephrosis, and death may occur upon use of human IgG products. Ensure that patients are not volume depleted before administering BIVIGAM. Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of BIVIGAM and at appropriate intervals thereafter. If renal function deteriorates, consider discontinuing BIVIGAM. In patients who are at risk of developing renal dysfunction, because of pre-existing renal insufficiency or predisposition to acute renal failure (such as diabetes mellitus, hypovolemia, overuse, weight of concomitant non-IGG medicinal products or age of >65 years), administer BIVIGAM at the minimum infusion rate practicable. Hyperproteinemia, Increased Serum Viscosity, and Hyponatremia: Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IGIG therapy, including BIVIGAM. It is critical to distinguish a hyperproteinemia from a pseudohyponatremia that is associated with hyperproteinemia with concomitant decreased calculated serum osmolality or elevated osmolar gap, because treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity, and a possible predisposition to thrombotic events. Aseptic Meningitis Syndrome (AMS): AMS may occur infrequently with IGG treatments including BIVIGAM. AMS usually begins within several hours to 2 days following IGIG treatment. Discontinuation of IGIG treatment has resulted in remission of AMS within several days without sequelae. AMS is characterized by the following signs and symptoms: severe headache, malaise, rigidity, drowsiness, fever, photophobia, painful eye movements, nausea, and vomiting. Cerebrospinal fluid (CSF) studies frequently reveal pleocytosis up to several thousand cells per cubic millimeter, predominantly from the granulocytic series, and elevated protein levels up to several grams per liter, but negative culture results. A thorough, bacteriologic examination on patients exhibiting such signs and symptoms, including CSF studies, to rule out other causes of meningitis. AMS may occur more frequently in association with high doses (2 g/kg) of IGG products. IGG in the form of BIVIGAM may contain blood group antibodies that can act as hemolysins and induce in vivo coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis. Delayed hemolytic anemia can develop subsequent to a positive direct antiglobulin reaction and hemolysis. Patients with delayed hemolysis with intravascular hemolysis should be considered with intravascular hemolysis, has been reported. Monitor patients for clinical signs and symptoms of hemolysis. If these present after BIVIGAM infusion, perform appropriate confirmatory laboratory testing. If transfusion is indicated for patients who develop hemolytic anemia, consider cross-matching of BIVIGAM with the patient after receiving adequate cross-matching to avoid exacerbating on-going hemolysis. Transfusion-Related Acute Lung Injury (TRALI): Noncardiogenic pulmonary edema may occur in patients following IGIG treatment including BIVIGAM. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, hypotension, and left ventricular dysfunction or congestive heart failure. Symptoms typically appear within 1 to 6 hours following treatment. Monitor patients for pulmonary adverse reactions. If TRALI is suspected, perform appropriate tests for the presence of anti-neutrophil antibodies in both the product and the patient’s serum. TRALI may be managed using oxygen therapy with adequate ventilation and support. Transfusion-Dec. 2013, [10760-90-IGG-032013_R01]
and loss of consciousness. Diagnosis is made by both signs and symptoms, as well as confirmatory testing in the blood or spinal fluid for antibodies made to fight off the virus.

The treatment for JE is currently only supportive, and there is no specific antiviral therapy for the condition. Therefore, prevention by vaccination is very important. The vaccine that is currently available in the U.S. is JE-IXIARO, which is an inactivated vaccine derived from cell cultures. The previously used JE-MB vaccine that was derived from inactivated mouse brain is no longer available in the U.S. JE-IXIARO vaccine is administered in two doses spaced 28 days apart. For patients 3 years and older, the dose is 0.5 mL, and for those younger than 3 years, the dose is 0.25 mL. For individuals who have ongoing risk for developing JE, another booster can be given a year following the second dose.

Patients who have had severe hypersensitivity reactions to JE vaccines should avoid getting repeated doses.

Yellow Fever

The yellow fever virus is related to the West Nile, St. Louis and Japanese encephalitis viruses. It is endemic to the tropical regions of South America and Sub-Saharan Africa, and is transmitted by infected mosquitoes. The clinical presentation of infection varies among individuals. Some patients may exhibit little or no symptoms, whereas others may develop fever, body aches, nausea/vomiting, weakness and severe headaches. The time from infection to illness varies between three and six days. In the most severe cases, patients can develop bleeding, jaundice and multi-organ system failure. The mortality rate among patients who develop these severe symptoms is between 20 percent and 50 percent.

Since there is no specific treatment following infection, and management is supportive and symptom-driven, it is important to receive vaccination prior to potential exposure in endemic regions. Some countries even have yellow fever vaccination requirements prior to entry if the traveler is coming from an endemic region. The yellow fever vaccine is a live attenuated virus. A single dose of the vaccine is considered sufficient for lifelong protection, and is indicated for people older than 9 months of age traveling to endemic regions of yellow fever. However, some countries require booster vaccines every 10 years.

Since the yellow fever vaccine is a live virus vaccine, patients with weakened or compromised immune systems should not receive it. Administration of the vaccine needs to be at least 30 days apart from administration of any other live attenuated vaccines, but can be given concomitantly with other inactivated vaccines. Patients younger than 6 months of age should also not receive the vaccine, and it must be given with caution to those between 6 months and 9 months. Individuals older than age 60 should also receive the vaccine with caution, given potentially weakened baseline health and weakened immune systems with age.

Japanese encephalitis is a viral infection endemic to Asia and the Western Pacific regions, particularly in rural agricultural areas.

Adverse effects following yellow fever vaccination can be divided into several categories. First, like all vaccines, there are individuals who may develop immediate hypersensitivity or allergic reaction to the vaccine. This is a rare phenomenon. Second, patients may develop neurologic disease that is either secondary to direct viral infection of the central nervous system or the induction of an autoimmune reaction targeting against the nervous system. The incidence of neurologic adverse events rises with older age (older than 60 years). Lastly, in rare cases, vaccination may actually lead to disseminated viral infection similar to the severe type of naturally acquired yellow fever disease. Again, individuals with weakened immune systems and older age tend to be risk factors.

Avoiding the Potential Spread of Communicable Diseases

As global travel becomes ever more prevalent, the potential spread of communicable diseases rises. Highlighted here are some of the important specific international travel-related vaccines that are available for administration in the U.S. However, in addition to these specific vaccines, individuals should be up-to-date with all their routine recommended vaccinations as well in order to be as best protected as possible whether at home or abroad. Lastly, prior to international travel, it is always important to check both the Centers for Disease Control and Prevention and the World Health Organization websites for precautions, as well as consult with a physician for additional more detailed recommendations.

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