



YELLOW FEVER

ONE INJECTION, 10 YEARS' PROTECTION

Introduction

Traveling to a foreign country can be exciting, even for the more experienced traveler. Add unfamiliar conditions and diseases not typically found in the United States, and a certain intimidating level of nervousness and fear is inevitable for the traveler. When it comes to business travel, this should also be taken into consideration by the sending party.

Even the most organized, responsible, and fearless persons will do their due diligence by asking a series of questions to ensure that all potential risk factors have been proactively addressed. "Do I (or does the person that I am sending to represent our company) have everything that will be needed?" may naturally be the most common, and general, of questions. This question should cover not only the obvious necessary items such as proper clothing, toiletries, and business supplies, but also the less obvious and sometimes disregarded preparations, such as travel-related vaccinations and other preventative measures to reduce disease risk.

Preventative measures, including inoculations, for diseases that are rare or unheard of in the United States tend to be foolishly discredited often due to costs, especially when they are "just recommended," versus being an official requirement by the destination country. But the far greater cost actually lies in the potential of a traveler being exposed to a deadly disease endemic to the areas to which he or she is traveling, such as yellow fever. It is important to understand this disease and its history in order to fully understand the costs of becoming infected and the return on the investment in vaccinating against yellow fever.

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What is Yellow Fever?

Yellow fever is an infectious disease that is largely unknown in the United States and North America; however, globally and historically, this disease is a notorious killer. In fact, the disease is so virulent, debilitating, and potentially deadly that many nations require proof of the vaccination before allowing foreign travelers to enter the country. Understanding the symptoms of, risk factors for, and extent of yellow fever in both a historical and current context will help travelers make crucial health decisions regarding this life-saving vaccine. With one injection, travelers can guarantee themselves 10 years of protection from yellow fever.

Yellow fever is a viral disease that is related to West Nile virus and Japanese Encephalitis. The World Health Organization¹ explains that most people infected with the virus recover after the initial period of fever, body aches, and general feelings of malaise.

These symptoms typically develop three to six days after infection. According to the Centers for Disease Control and Prevention (CDC)², up to 15 percent of those infected with yellow fever will experience initial symptoms and then have a brief break from symptoms followed by an onslaught of toxicity to the entire body.

In this toxic phase of illness, patients develop severe symptoms that can lead to liver and kidney damage and include profuse bleeding from mucous membranes and orifices, vomiting curdled blood that looks like black coffee grounds, and, finally, shock. Up to 50 percent of those with severe yellow fever disease die. Those who recover from yellow fever infection retain lifelong immunity against the disease but might deal with lifelong complications such as the above-mentioned kidney and liver problems.

Yellow Fever Transmission

The mosquitoes get the virus from biting infected primates, including people. The CDC explains that a person infected by mosquitoes carrying the virus may not see any of the aforementioned symptoms for three to six days, which means the infected person may already have returned to the United States from his or her trip to the at-risk country.

Transmission of yellow fever virus follows three different but important cycles related to the ecology and environment of the transmission area. These include the jungle (sylvatic), intermediate (savannah), and urban cycles.

In the jungle cycle, transmission of the virus occurs between primates and mosquitoes living in the forest canopy. The virus can then be transmitted to people who visit or work in the jungle.

In the intermediate cycle, transmission occurs primarily from mosquitoes to humans living in the grassy border areas around the jungle. In these areas, viral transmission can also occur between monkeys and mosquitoes, monkeys and people, as well as people and mosquitoes.

In the urban cycle, the virus is typically brought to an urban setting by a person who was infected with the virus while working or traveling through the jungle or savannah. An *Aedes aegypti* mosquito then bites an infected person and spreads the infection to the urban population³.

Yellow fever virus is transmitted to people by *Aedes* or *Haemagogus* species mosquitoes.

History of the Disease and Outbreaks

Yellow Fever is a significant health concern in many tropical and subtropical regions of the globe, and its impact has been felt throughout history.

One of the first recorded outbreaks of yellow fever can be traced back to Spanish explorer Christopher Columbus and his men in 1495 during their voyages from Spain to Haiti and the Dominican Republic, known then as the Island of Hispaniola. There has been dispute as to whether the spread of this virus originated in Africa during their travels or if it was already endemic in parts of Latin America before Columbus arrived in the late 15th century. After the Spanish conquered the natives during the Battle of Vega Real, they suffered from an epidemic of yellow fever, which extended into the next year, prompting Columbus and his men to shift headquarters to a healthier location⁴. Although the exact reason as to why would not be identified until much later in the early 1900s, throughout history ships were often linked to spreading yellow fever, earning the nickname of “yellow jack” for the flags that incoming ships would display when someone on board was ill with the disease.

Even more notable than the Hispaniola Yellow Fever Epidemic of 1495, Cuba was severely impacted in 1649 when one-third of residents in Havana died from the disease. This would later be seen magnified from 1856 to 1879 when the disease struck nearly every month, with foreign occupiers being more susceptible to the disease⁵.

Between 1895 and 1898, and estimated 16,000 Spanish soldiers died from yellow fever, and at the onset of the Spanish American war, only 55,000 out of 230,000 Spanish soldiers were healthy enough

to fight. Army Major Walter Reed, who would later head the U.S. Army Yellow Fever Board in Cuba, once wrote that a “plug of cotton in nostrils would be advisable” when he hypothesized that the yellow fever “germ” was airborne. During this war, more U.S. soldiers died as a result of yellow fever than due to the war itself.

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During the 1700s to 1800s, yellow fever was a feared contagion throughout the western hemisphere as well as the coastal areas of Africa. Although the medical community at the time did not know exactly what caused yellow fever, it did know that it occurred both as an endemic and epidemic illness; it was associated with ports of trade; new outbreaks could occur shortly after the arrival of a ship; a “germ” was suspected of causing the disease; and that, once infected, a person retained lifelong immunity. As bacteriology and scientific techniques and instruments improved, efforts at vaccine development progressed, but, at the turn of the century, there had been little significant progress in yellow fever prevention, and significant outbreaks had already begun to occur and were recorded in the United States⁶.

History of the Disease and Outbreaks (CONT.)

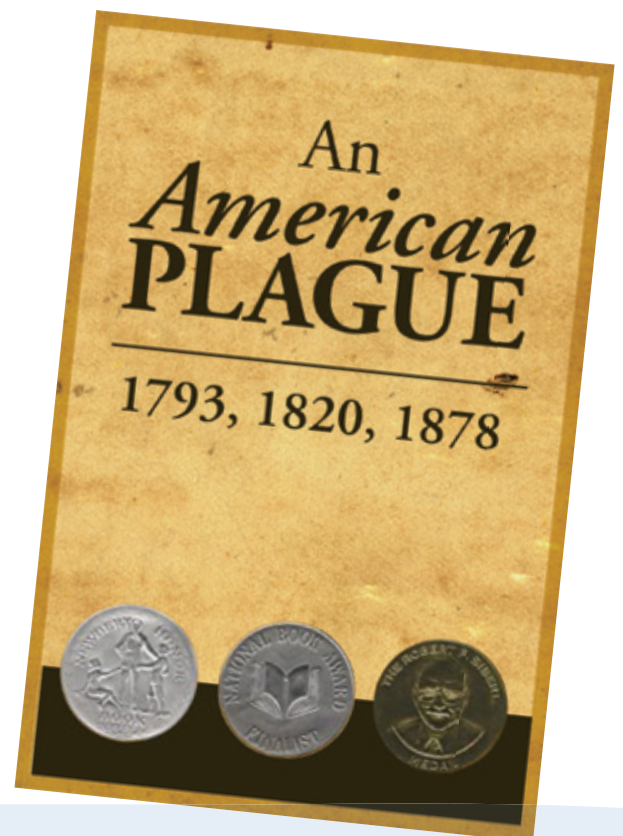
In Philadelphia in 1793, and estimated 10% out of the 50,000 citizens died from yellow fever. In what was then our nation's capital, 20,000 of those residents, including Thomas Jefferson, George Washington, and many other members of the federal government would escape the disease only by fleeing the city.

Yellow fever outbreaks continued in the United States, and by 1878, the disease had begun to spread to New Orleans to where thousands of Cuban refugees had fled. The arrival of foreigners, the impending tie to the shipping industry, and the return of soldiers would result in a new law, the Quarantine Act of 1878, empowering the Marine Hospital Service to stop disease from being spread via sailors on ships. Violations of this law would later enable this disease to spread through the Mississippi Valley, including Memphis, TN. As many as 25,000 to 27,000 Memphis residents out of 47,000 total residents would flee to more rural areas as far away as Indiana, Illinois, Ohio and Kentucky. Some areas welcomed them, and others turned them away with "shotgun barricades." During approximately the last two decades of the nineteenth century, the Mississippi Valley alone experienced 120,000 cases of yellow fever, which resulted in approximately 20,000 deaths, and bankrupted entire communities.

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Although mosquitoes were finally pinpointed as the transmission source in 1900, the last yellow fever epidemic in the United States would be recorded five years later, again in New Orleans. This outbreak would result in 100 yellow fever cases with 20 lives lost, and it was attributed to a smuggler's ship and its banana crop, which bypassed the established quarantine, fumigation, and sanitation procedures.

In summary, yellow fever has been a devastating force throughout world and US history. **The historical toll of yellow fever outbreaks is not to be overlooked, as this seemingly "rare" disease has killed more US citizens than some wars.**



Identifying the Transmission Source of Yellow Fever, and the Vaccine

After the end of the Spanish-American War, concerns developed about endemic yellow fever in Cuba, which was an important trade and cultural center for America and other countries. According to an article in the *Yale Journal of Biology and Medicine*, U.S. Surgeon General Walter Reed found that sanitation measures in Havana had not stopped the scourge, and he was also able to determine that mosquitoes were to blame for the spread and transmission of the disease⁶. After filtering samples of infected material through filters with holes that could capture bacteria, Reed and his team of investigators were also able to determine that the causative agent was not a bacterium. Havana physician Dr. John Guiteras attempted an immunization campaign but found that many of the study subjects became ill. The attempts to find a vaccine were halted.

Yellow fever was especially known for the waxing and waning of infections¹. All the virus had to do was wait for the right conditions to emerge, such as a new human settlement or expedition into the jungle; an exceptionally rainy season; or an explosion of never-infected individuals in the population. Early in the 1900s, scientists and physicians deduced that the *Aedes aegypti* mosquito was a major vector in the transmission of the disease. This opened up an opportunity to reduce the number of infections by reducing the population size of mosquitoes.

In 1937, a vaccine for yellow fever was developed. The vaccine, known as the 17D strain, was safe, highly effective and inexpensive, making it ideal for mass vaccination campaigns. In Africa, North America, Central America, and South America, medical field workers and physicians initiated mass vaccination campaigns beginning in 1940. These campaigns were highly successful. As a result, the outbreaks disappeared, and people largely forgot about yellow fever. However, the disease was still hidden in isolated pockets among smaller populations of people and

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Identifying the Transmission Source of Yellow Fever, and the Vaccine *(CONT.)*

The vaccines in use today are still derived from those original 17D strains developed more than 70 years ago. Today, there are several vaccination campaigns against yellow fever. One is headed by the GAVI Alliance, and it aims to eradicate yellow fever in 12 countries in west and central Africa. The vaccine is provided by UNICEF, and logistics are coordinated by the World Health Organization. The focus of this vaccination campaign are the shanty-towns located in and around many of Africa's largest cities, in the nations of Benin, Burkina Faso, Cameroon, Cote d'Ivoire, Ghana, Liberia, Mali, Senegal, Sierra Leone, Togo and Nigeria. According to data collected by the GAVI Alliance, by the end of 2012, more than 70 million people had been immunized against yellow fever⁷. In 2013, an emergency mass vaccination campaign headed by the GAVI Alliance began in Ethiopia.

The current yellow fever vaccine is made with live, attenuated (weakened) virus. The CDC explains that the vaccine is given in just one shot and offers protection for up to 10 years⁸. After that, at-risk people should get a booster shot every 10 years to stay protected against the disease. People who get the vaccine will be given a yellow card, or "International Certificate of Vaccination or Prophylaxis." This card is required for travel to certain countries. Travelers who do not bring their cards may have to receive a vaccination upon entry to these countries, or they may be detained for up to six days to prove they are not infected with yellow fever. People aged 9 months to 59 years old who are traveling to a country that requires vaccination; visitors to countries where yellow fever is endemic; and laboratory and medical personnel who could be exposed to the virus should all be vaccinated. After receiving the vaccination, recipients are asked to defer blood donation for 14 days as the virus contained within the vaccine can be present within the blood and transmitted to anyone receiving the blood donation.

Various studies have taken place since the 1930s to determine the efficacy of the yellow fever vaccine. Between 1962 and 1997, 24 studies were conducted worldwide and used 17D vaccines. These studies involved nearly 2,600 adults and 991 children, including infants and yielded a seroconversion rates greater than 91% in all but two studies, and never lower than 81%. Out of these 24 world-wide studies, five were conducted in the United States between 1962 and 1993, administering the YF-VAX vaccine to 208 adults. This, again, yielded the lowest result of 81% in one study of 32 subjects, with the remaining four studies of 176 subjects yielding 97% to 100% immunity.

In two separate clinical trials, 100% of subjects seroconverted within 14 days of vaccination; 90% of this group seroconverted within 10 days. International Health regulations now stipulate that the vaccination certificate for the yellow fever vaccine is valid 10 days after administration of the vaccine. Vaccination is the most important step in prevention, but awareness of mosquito-borne disease and other preventative measures such as mosquito netting, repellents, etc. also play a key role.

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Where is Yellow Fever Endemic?

Yellow fever disease is mostly concentrated in South America and sub-Saharan Africa, reports the CDC⁹. South and Central American countries where yellow fever is endemic include Argentina, Bolivia, Brazil, Colombia, Ecuador, French Guiana, Guyana, Panama, Paraguay, Peru, Suriname, Trinidad, Tobago and Venezuela. Yellow fever is also endemic in the African countries of Angola, Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Congo, Republic of the Côte d'Ivoire (Ivory Coast), Democratic Republic of the Congo, Equatorial Guinea, Ethiopia, Gabon, The Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Liberia, Mali, Mauritania, Niger, Nigeria, Rwanda, Senegal, Sierra Leone, Sudan, South Sudan, Togo, and Uganda.

Many of the countries in the endemic zone require proof of vaccination in order to enter the nation. These countries include Angola, Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Congo, Republic of the Côte d'Ivoire, Democratic Republic of Congo, French Guiana, Gabon, Ghana, Guinea-Bissau, Liberia, Mali, Niger, Rwanda, São Tomé and Príncipe, Sierra Leone and Togo, reports the Passport Health website¹⁰. Each nation may require different forms of proof of vaccination, so travelers should check before departing to any of these countries to be sure they have proper documentation in place.

What is the Risk of Yellow Fever for Travelers?

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The risk to travelers visiting areas of the world where yellow fever is endemic is serious and real. An individual's particular risk level for infection, serious disease and death include factors such as his or her immunization status, the location of travel, season (rainy has a higher infection rate), duration of exposure, geographic area of the country being visited (urban, jungle or savannah), work and recreational activities while traveling, and the local rate of virus transmission at the time of the person's trip. Older travelers who are more than 60 years of age have an especially high risk of becoming ill and suffering from complications if infected. In western Africa, the risk of infection is highest July through October, while in South America, infection rates are highest in the rainy season, which is January through May. However, in urban environments, just a single case with a high amount of virus in the blood can initiate an epidemic during any time of the year.

The threat for urban outbreaks of yellow fever is real and significant in many African cities. Even one case of yellow fever within a major city can set off a widespread epidemic of illness.

- In 1960 in Ethiopia, 100,000 people were infected, and 30,000 died in an urban outbreak.
- Following this, in 1983 in Ghana and Burkina Faso, a large urban outbreak resulted in a case fatality rate of 80 percent.
- In 1992, Kenya had its first outbreak of yellow fever in 49 years.
- In 1996, the nation of Benin suffered its first outbreak in 55 years. The chain of transmission between people lasted for more than eight months.
- Cote d'Ivoire suffered its first urban outbreak in 2001, as did Senegal in 2002.

Where is Yellow Fever Endemic? *(CONT.)*

As these urban outbreaks make all too clear, yellow fever is not just a risk factor for travelers planning a safari or a trek through the jungle. The disease is also a very real concern for business travelers who will likely spend most of their time overseas in a major city.

From 1970 through 2011, nine unvaccinated travelers were infected with yellow fever. Eight of those nine people died. An unvaccinated traveler staying in an endemic region for a two-week time period will face an infection risk as follows:

- West Africa has 50 infections per 100,000 population and 10 deaths per 100,000 population.
- South America has five infections per 100,000 population and one death per 100,000 population.

Note that these statistics reflect infection prevalence in the native population; as is further explained below, travelers actual face a higher risk of infection than locals.

The actual individualized risk level for a traveler will depend on whether the traveler takes precautions such as using mosquito repellent containing DEET, wearing long pants and long-sleeved shirts that cover the skin, using mosquito netting while sleeping, staying in dwellings with window screens, limiting outdoor exposure, spending time among immune citizens of the country, avoiding exposure to infected primates and knowing one's personal immunity profile.

The risk to travelers is much higher than natives due to herd immunity as well as local knowledge of how to avoid mosquito bites. Indeed, members of the local population may have had a case of yellow fever in the past, so they are now immune. The risk of infection for travelers to South and Central America is lower than to other areas of the world such as Africa due to less human interaction with mosquitoes that carry the virus; in other words, the mosquitoes tend to be located deeper in the jungle than they are in Africa.

The World Health Organization estimates that each year, 200,000 people become sickened by yellow fever, and 30,000 of those people die. When an epidemic occurs in an unvaccinated population, the fatality rate of the disease when it progresses to the severe level can range from 50 to 70 percent, as no treatment beyond comfort measures is available.

Why is vaccination important?

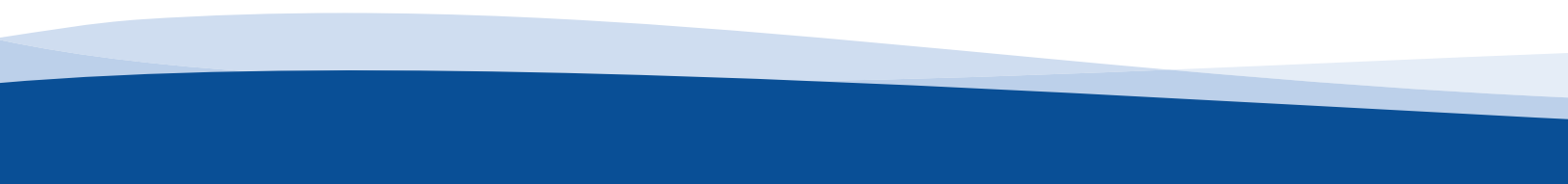
SOCIETAL BENEFITS:

The Yellow fever vaccine is not only an important safeguard for personal health; vaccination also confers a myriad of societal benefits, reports the World Health Organization¹¹. Vaccination for yellow fever virus has reduced the burden of illness, disability and mortality throughout the Americas and sub-Saharan Africa. According to the Mayo Clinic, the yellow fever vaccine is known to be safe and has few complications or side effects¹². In addition, it has a high level of effectiveness and is easy to use in mass vaccination campaigns where there are rudimentary conditions, such as no refrigeration. Vaccination is part of an overall strategy to reduce the burden of infectious disease, along with vector control, education and other prevention activities. With mass vaccination campaigns, diseases like yellow fever can be eliminated in local areas. When mass vaccination campaigns are able to take place throughout an area for a prolonged period of time, elimination of the disease in communities is even more effective. Vaccination is especially important when vector eradication is impossible. It is not possible to entirely rid the environment of mosquitoes, so vaccination is essential to the prevention of yellow fever.

Business travelers who have taken proper steps to thoroughly safeguard their health through preventative measures, including receiving a vaccination for yellow fever, will enjoy activities more freely during their personal time to de-stress and regroup

The benefits to society of vaccination against yellow fever are many. In countries in sub-Saharan Africa and in Central and South America, preventing yellow fever through vaccination can reduce the burden to the healthcare system. Keeping people healthy through vaccination also reduces social concerns such as loss of household income, children becoming orphans, and the prevention of premature death. Vaccination can also help mitigate the severity of the disease. Vaccinated individuals may be less likely to progress to the severe stage of yellow fever or die of the disease if infected. Herd immunity is also an important result of mass vaccination of yellow fever.

When the majority of a population is vaccinated against a disease, this protects individuals like babies, the elderly, immune-compromised individuals, and those who are contraindicated for the vaccine due to other reasons. Thanks to herd immunity, some diseases have been eradicated even without 100 percent vaccination coverage. When a community is vaccinated, there is less inequality due to illness and lost income. Vaccination against yellow fever can extend life expectancy, enhance the safety of travel, reduce childhood mortality and safeguard pregnant women against pregnancy complications.



Why is vaccination important? (CONT.)

BENEFITS FOR TRAVELERS:

As with any other foreign land, countries where yellow fever is endemic also have many incomparable and highly enjoyable experiences to offer. Business travelers who have taken proper steps to thoroughly safeguard their health through preventative measures, including receiving a vaccination for yellow fever, will enjoy activities more freely during their personal time to de-stress and regroup. This type of freedom is especially crucial during extended stays when there is even more time at his or her disposal. He or she may choose to simply relax and take a leisurely stroll on hotel grounds, or, they might elect for a more adventurous and culturally interactive experience, such as hiking through the jungle or other local terrain, shopping at a local outdoor market, exploring local food and dance, volunteering locally, or going on a wildlife safari. However they choose to spend this valuable time, they will be more at ease and open to enjoy it due to the security and peace of mind in knowing that their health has been made a priority. It is much more likely that they will eagerly anticipate sharing stories about their trip upon return, nearly forgetting that a deadly disease was ever a potential threat on their trip. This peace of mind is priceless.

Now that the benefits of vaccination are clear, how should an individual go about obtaining a yellow fever vaccine? People considering a trip to a country where yellow fever is endemic should visit a travel health specialist at least 10 to 14 days before travel. When a non-immune person is vaccinated, the body produces antibodies against the virus. These antibodies fight off the yellow fever virus if a person is bitten by an infected mosquito. Vaccination against yellow fever is recommended for anyone 9 months to 59 years old who will be visiting an area where the illness is endemic. Just one shot confers protection against yellow fever for 10 years. A booster shot is recommended every 10 years for continued protection against infection.

In addition to vaccinating travelers against yellow fever, travel health specialists offer advice so individuals can better protect themselves against illness while traveling. They provide guidance on packing mosquito repellent, mosquito netting, first aid supplies and other personal care products to enhance a traveler's health. After getting vaccinated, travelers can enjoy immunity against yellow fever for 10 years, making future travel convenient and less risky to one's health.



Why is vaccination important? (CONT.)

ECONOMIC BENEFITS: COST SAVINGS TO THE TRAVELER AND COMPANIES

Similarly to how many U.S. cities were financially impacted up to the point of bankruptcy during the earlier outbreaks, financial and emotional impacts which far surpass the cost of having the yellow fever vaccination administered exist in the event of exposure to the disease.

From the standpoint of a business traveler, the benefits of vaccination are obvious. An hour visit with a travel health specialist is much more pleasant and preferred than falling ill while abroad. The benefits of thorough and proactive care from the employer also prevent lost work days on important assignments abroad, and also costly medical evacuation for serious illness.

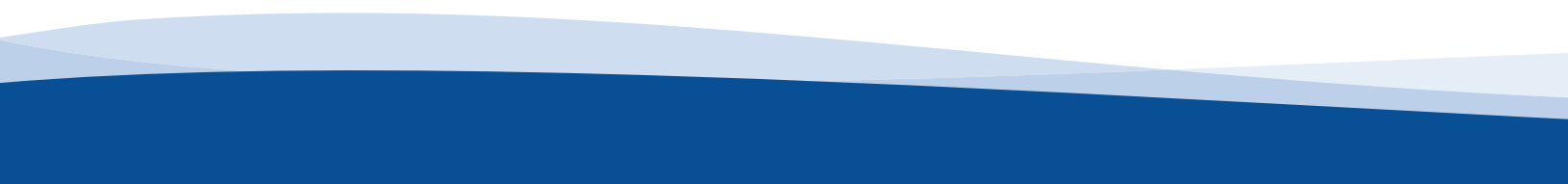
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Medical evacuation for serious illness can range from \$10,000 for a last minute commercial plane ticket to \$100,000 for a full evacuation with on-board medical assistance. Add these expenses to the regular salary and loss of contributions from the employee, and these figures can grow astronomically.

In the era of skyrocketing medical costs, avoiding unnecessary doctors' visits or even time in the hospital can result in savings of thousands of dollars or more. According to a study by the National Center for Health Statistics, the average cost of a visit to the emergency room in 2010 was calculated between \$969 and \$1062¹³. It is important to note that these figures exclude emergency room visits which developed into in-patient admission; the charges associated with in-patient admissions and continual healthcare easily amount to tens of thousands of dollars. One vaccine can prevent incurring these substantial costs.

Although recommendations and care plans based on the individual and additional itinerary-related factors, the average cost of a thorough travel consultation and vaccinations, including yellow fever, is \$400, an insignificant fraction of the potential costs of exposure, as enumerated above. At this small investment, the value and comfort that can only be found in peace of mind and protection for the traveler and their employer is included, free of charge.

Remember, with one injection, you can guarantee yourself or your travelling employee population 10 years' of protection.



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