

Yellow fever vaccination for Indians travelers: an analysis

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Yellow fever is prevalent in East Africa and South America. Every year thousands of travelers from India travel to these regions. Travelers (except infant below 6 months) from yellow fever endemic regions to India need to produce a yellow fever vaccine certificate according to International Health regulations. In the absence of such certification, they are quarantined for a period of 6 days. The travelers are advised to get themselves vaccinated for their own benefit.

No case of yellow fever has been reported in Indian travelers. The Yellow fever vaccine offers life-long immunity according to World Health Organisation (WHO). Healthy travelers above 9 months of age can be safely vaccinated with currently available yellow fever vaccine. Yellow fever vaccine supply-demand ratio remains skewed most of the times in India. The only manufacturer of the yellow fever vaccine (Government approved) in India is the Central Research Institute (CRI) in Kasauli, Himachal Pradesh. Yellow fever vaccine is safe and tolerable in healthy Indians. Safety of yellow fever vaccine in immunocompromised individuals needs to be studied. Yellow fever vaccine from private manufacturers is five times costlier than the government approved vaccine. Most of the travelers vaccinated with yellow fever vaccination are unaware about the yellow fever infection. ADR reporting for yellow fever vaccine can help in building the evidence regarding the rarely occurring ADRs.

Introduction

According to World Health Organization, Yellow fever was responsible for over 200,000 cases of infection and 30,000 death annually.¹ Many of the cases and deaths remain unrecognized because of underreporting from the remote places.² Recently, the number of such cases increased in men working in forested area of South America.³ The number of yellow fever cases varies from 1 to 5000 in African Subcontinent. This may be due to variation in natural occurrence of disease, reporting and recognition of cases.⁴ Till today, there has been no case of yellow fever infection reported in India.

Yellow fever is caused and transmitted by the bite of infected mosquito. The mosquito is endemic to sub-Saharan Africa and tropical South America. Most of the infections in humans are asymptomatic. Clinically, infection's severity varies from febrile illness and headache to hemorrhagic manifestations, jaundice and multi-organ failure. The symptoms are observed in infected cases after an incubation period from 3-6 days.⁵ As there is no specific treatment available, only a symptomatic treatment can be given to the patient. Because of this risk, it is important to prevent yellow fever.⁶ The yellow fever vaccine

has been found to be safe and tolerable in healthy Indian travelers.⁷ Bhatia and coworkers, using a sample of 300, have shown that higher education, working occupation and history of previous vaccination were significantly associated with awareness of travel vaccinations.⁸

Travelers from yellow fever endemic regions need to produce a vaccination certificate for entry in India. International health regulations allow any country to deny entry on the failure to produce yellow fever vaccination certificate. Most of the travelers from India are unaware about the yellow fever; they only get vaccinated because of certificate requirement. This review analyses various dimensions of yellow fever vaccination in the Indian perspective.

Risk of yellow fever for Indian travelers

There is no single risk factor for acquiring yellow fever among travellers. The risk of yellow fever is determined by multiple factors, including location of travel, season, duration of exposure, activities while traveling, local rate of virus transmission at the time of travel and most important is vaccination status of the travellers.⁹ Monath et al. estimated the risk

of acquiring yellow fever for a stay of two week period, according to these estimates risk for travelers to West Africa and South America is 50 and 5 cases per 100,000 population, respectively.¹⁰

Limited number of yellow fever imported cases in travellers from non-endemic countries. There is no report of imported cases of yellow fever in India till now. This is due to the routine use of vaccination. In order to ensure that yellow fever will not spread in non-endemic countries, International health regulations (IHR) are in place. These regulations allow India and many other countries to have yellow fever vaccination as a mandatory requirement for entry into India from yellow fever endemic countries. The decision regarding the vaccination of travelers must take into account the overall risk for travel-associated yellow fever, high mortality, vaccine requirements as per IHR, contraindications or precautions, and risk for serious adverse events following vaccination.¹¹

Need of yellow fever vaccine for Indian travelers

Yellow fever vaccine requirements are established to prevent the importation and transmission of yellow fever vaccine. Yellow fever vaccine is recommended under IHR.¹¹ According to the list provided by WHO, all the member countries have been divided into three categories namely countries with risk of yellow fever transmission, countries requiring yellow fever vaccination for travellers arriving from countries with risk of yellow fever transmission, countries requiring yellow fever vaccination for travellers from all countries. India falls into group of countries which require yellow fever vaccination for travellers arriving from countries with risk of yellow fever transmission. Yellow fever vaccine certificate is required for any person, foreigner or Indian, (excluding infants below six months) arriving in India. Those who are arriving by air or sea without the yellow fever vaccination certificate will be kept in quarantine for a period up to 6 days if anybody arrives in India within 6 days of departure/transit from a yellow fever endemic area. Travelers exempted from the yellow fever vaccination include infants below 6 months, persons suffering from chronic illness and if the health officer is satisfied that during the transit of the passenger from yellow fever endemic area they will remain in airport premises during the period of stay (Table 1).

According to Advisory Committee on Immunization Practices (ACIP), all persons aged greater/equal to 9 years and residing in or traveling to yellow fever endemic areas requires yellow fever vaccine.⁹ As per guidelines of WHO, a single dose of yellow fever offers lifelong immunity. Previously, a booster

dose of yellow fever was needed at interval of 10 years.^{5, 12}

Cost of yellow fever vaccination for Indians

The government of India approved yellow fever vaccine available at public health centers and airport costs INR 300, and the Yellow fever vaccine (Stamril™) from Aventis Pasteur in India currently costs over INR 2200. There is a huge differential in the cost of vaccine at private and public centers. This difference in cost is best explained by the fact that the yellow fever vaccine available in private

Table 1: Contraindication and precautions to yellow fever vaccination

Precautions	Contraindications
Age 6-8 months	Allergy to vaccine component
Age ≥ 60 years	Age less than 6 months
Asymptomatic HIV infection and CD4+ T-lymphocytes 200-499/mm3	Symptomatic HIV infection
Pregnancy	Thymus disorders associated with abnormal immune function
Breast feeding	Primary immunodeficiencies Malignant neoplasm Transplantation Immunosuppressive and immunomodulatory therapies

health centers is imported from the Aventis Pasteur manufacturing unit in France. The other reason for the difference could be the packaging philosophy of the yellow fever vaccine; the vaccine available in private health centers is available as a single dose unit and the vaccine in public health centers is available in multidose container.

Public & private vaccine providers

The yellow fever vaccine is available at public health centers at a lower cost in comparison to private centers.

Dkhar et al. in 2021 have shown that the wastage of vaccine is within acceptable limits.¹³ The vaccine available at the private centers is the WHO approved Yellow fever vaccine i.e. Stamril™. This vaccine is available as single dose, so individual traveller can be vaccinated. Travellers can get vaccine on any working day within working hours.

As per information available on the website of Central International health division (accessed on August 2, 2022; ihpoe.mohfw.gov.in/yfvc.php), under

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Directorate General of Health Services, Ministry of Health & Family Welfare, India, there are 50 notified facilities distributed across the country for yellow fever vaccination. The maximum number of yellow fever vaccination centers are located in Delhi followed by Mumbai, Kolkata and other states.¹⁴

Production of vaccine in India

Center Research Institute (CRI), Kasauli is the only producer of the Indian government approved yellow fever vaccine in India. WHO approved yellow fever Vaccine from Aventis Pasteur is also available for use in India; but this vaccine is not approved by India government.¹⁵ CRI, as the sole manufacturer of vaccine in India, has attracted controversies over its manufacturing due to suspension of license or due to faulty equipment.

In 2007, the two vaccination centers namely Port Health Office and King Institute of Preventive Medicine in Chennai stopped yellow fever vaccination due to shortage of yellow fever vaccine; vaccination was resumed after 45 days.

Some of the instances are as on January 15, 2008, the union health minister had suspended the licenses of many functional research and development centers including CRI, on the grounds of non-compliance with the GMP norms of WHO. Later, on union government exercises its powers of the Drugs and Cosmetics Rules, ordered revocation of suspension of licenses of these institutes including the CRI, Kasauli. On December 4, 2012 the manufacturing unit has stopped production due to some fault in its machine. CRI, Kasauli, had annual production of approximately 60,000 vaccines which were being supplied to all 17 international airports of our country.¹⁶ Apart from India, yellow fever vaccines are being manufactured in countries like China, Europe and US.

Safety of yellow fever vaccine

According to recent study on yellow fever safety during (2007-2010) vaccination campaigns in West and Central African countries by WHO in partnership with GAVI and UNICEF. From 38 million administered doses of vaccine, AEFI were observed in 3116 vaccinated subjects (2952 not serious).¹⁷ According to one of the studies in Brazilian population, neurological adverse event (Guillain-Barré syndrome, encephalitis, and autoimmune disease) reported in 0.83 per 100,000 vaccinations. Highest rate of these events reported in children range from 5-9 years.¹⁸

Multiple yellow fever vaccine ingredients like chicken proteins, gelatin, and latex can act as allergens.

These ingredients can lead to hypersensitivity in the vaccinated subjects. According to Kelso et al., yellow fever had affected 1 in 131,000 vaccinated subjects.¹⁹ Yellow fever vaccine is contraindicated in infants aged less than 6 months, subjects with compromised immune system, older than 60 years, and breast feeding mothers were found at higher risk of developing ADR due to yellow fever vaccine.²⁰ The only study by Tiwari et al. found out that yellow fever vaccine was safe and well tolerated in healthy Indian travellers.⁷ There are some minor side effects like headache, myalgia, low grade fever, and discomfort at site of injection associated with yellow fever vaccine.²²⁻²⁷

Yellow fever vaccine surveillance in India

There is a need to make improvement in the existing PvPI programme to identify and characterize the yellow fever vaccine associated adverse events. According to the available guidelines from PvPI, adverse event following immunization were reported in MCI Approved Medical Colleges & Hospitals, Private Hospitals, Public Health Programmes, Autonomous Institutes (ICMR etc.). In case of yellow fever vaccination, the travellers tend to leave the country within 2-3 weeks of vaccination, so there is a need of system in which vaccinated travelers can be contacted after vaccination for occurrence of any adverse event following immunization. There is also a need to develop an education programme for the travelers regarding the yellow fever vaccine and its possible serious adverse events and why it is important to report these side effects.

Surveillance system helps in building evidence regarding the safety of the yellow fever vaccine in Indians till date, no report is available. Surveillance system will also be helpful in understanding the demand of yellow fever vaccine so that appropriate steps can be taken to fill the gap between supply and demand of the vaccination.

Efficacy of Yellow fever vaccine

Yellow fever vaccine was found efficacious in preventing yellow fever infection. Seven observational studies (six in yellow fever endemic and one in non-endemic regions) have reported the yellow fever vaccine seroconversion rate from 75% to 100%. However, four RCT reported the seroconversion rate from 95% to 100%.²⁸ According to recent recommendations of ACIP, only one dose of yellow fever is able to provide life-long immunity.²⁹

Conclusions

The number of travelers from India to yellow fever endemic regions is increasing rapidly. There is need

to meet the increasing demand of yellow fever vaccine and there is need to increase the awareness about the yellow fever vaccine in Indian travelers.

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