

Evaluation of Safety Profile of Yellow Fever Vaccine in Healthy Indian Travellers: A Prospective Observational Study

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Abstract

Introduction: Every year thousands of Indian travellers visit the yellow fever endemic regions; and, yellow fever vaccination is required for travel to these regions. Like other vaccines, yellow fever vaccine is also known to produce adverse event following immunization (AEFI). To the best of our knowledge, there is no published evidence in the open domain on the safety of this vaccine for healthy Indian travellers.

Objective: To evaluate safety and tolerability of yellow fever vaccine in healthy Indian travellers.

Methods: Healthy Indian travellers vaccinated with yellow fever vaccine at an accredited private clinic were telephonically contacted on day 7 and 14 after vaccination for the occurrence of any AEFI. The patients were sub divided into three age groups i.e. 1day-15yr, 15-65yr and >65yr.

Results: Out of 305 vaccinated travellers recruited, 297 travellers were successfully followed up. Complete follow up was possible for 248 vaccinated travellers. The average age of the vaccinated travellers was found to be 36.2 ± 0.06 years.

AEFI were observed in 16 travelers (Out of total 305 travelers). Fever was reported in only 5 travellers followed by headache in 4 travellers. The occurrence of AEFI was found to be statistically different in three age groups.

Conclusion: On the basis of findings of the present study, on a limited number of subjects though, it is fair to conclude that Yellow fever vaccine is safe and well tolerated in healthy Indian travelers.

Keywords: Yellow fever; Vaccine; Safety; Travel medicine; India

Introduction

Yellow fever (YF) is a re-emerging mosquito-borne *flavivirus* infection present in 44 countries in tropical areas of Africa and South America [1]. Despite the presence of yellow fever vaccine (YFV), the number of deaths in African and south American countries is very high [2]. In 2013, 85 of the 230 people who suffered from yellow fever virus died because of the infection [3]. The actual number of cases and deaths are not recognized because of inadequate surveillance and reporting [4].

There is a constant threat of yellow fever outbreaks in non-immunized population; and, YFV remains the only protective measure against the spread of disease in population and travellers to endemic areas [5]. According to the recommendations of WHO, a single dose of YFV can provide lifelong immunity from yellow fever [6].

Like other interventions, YFV also have certain AEFI. The severity of these adverse events varies with population and vaccine. Most of side effects are mild in nature, which include headache, myalgia, low grade fever and discomfort at the time of injection. None of these had required any intervention or treatment [7-11]. There are reports of the neurotropic adverse event cases after YFV; however, these cases have good prognosis, which should not contraindicate the use of YFV in risk of yellow fever virus infection [12-17].

Every year a large number of Indian travellers move to endemic regions and get vaccinated for yellow fever. We had noted that there are no published evidence on safety and tolerability of yellow fever vaccine in Indian travellers. This study was carried out to evaluate the safety and tolerability of yellow fever vaccine in healthy Indian travellers.

Methods

A prospective observational study was carried out at a yellow fever vaccination center for a period of one year. 97% of the recruited vaccinated travelers were successfully followed up for the occurrence of any AEFI.

Ethics statement

This study was conducted in full compliance with the principles of the Declaration of Helsinki III and in accordance with the International Ethical Guidelines for Biomedical Research Involving Human Subjects. The study was approved by the Human Ethics Committee of National Institute of Pharmaceutical Education and Research (NIPER), Mohali. Written informed consent was taken from the participants prior to participation, after complete explanation of objective, methods, benefits and potential hazards of study. Patient information sheet-cum-Informed consent form was offered in three languages i.e. Hindi, English & Punjabi. The travelers were probed on the ease of language and only one of these languages was used in the communication.

Subjects

All the healthy travelers attending the clinic for yellow fever

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vaccination were recruited in the study. Pregnant, breastfeeding women, and infants less than 9 months were not included. Travelers with a known history of sensitivity to any vaccine components or those who had received an immunoglobulin treatment earlier were excluded. Travellers were excluded further, if they had a known immunodeficiency or were on immunosuppressive drugs.

Vaccine

Yellow fever virus 17 D-204 strain (live, attenuated) not less than 1000IU produced in specified pathogen-free chick embryos were used in study.

Safety evaluation

The travelers' demographic details were collected at the time of vaccination. The vaccinated travelers were followed telephonically on day 7 and day 14 post-vaccination to assess safety and tolerability of the yellow fever vaccine. The primary safety parameters evaluated were presence of headache, fever, malaise and myalgia, nausea and vomiting, abdominal pain, diarrhea, urticaria, local reaction and any other serious reaction.

Various safety parameters were defined as following: Headache – Pain in the head region after vaccination; Fever – Body temperature higher than normal (98.6°F); Malaise - A generalized feeling of discomfort, illness, or lack of well-being; Myalgia - Pain in the muscles or within muscle tissue; Nausea and Vomiting - Nausea is an uneasy feeling in the stomach with an urge to vomit; Abdominal pain - Pain in abdominal region; Diarrhoea - loose, watery stools more than three times in one day; Urticaria - Red and itchy bumps on the skin and Local reaction - Injection site tenderness.

Any other serious event that occurred and not mentioned above was also considered.

On the basis of the severity, the adverse drug reaction was classified as 'mild' (noticeable but doesn't interfere with daily activities), 'moderate' (interferes with normal daily activities) and 'severe' (prohibiting normal daily activities; need of medical assistance and/or medication prescription). A 'serious adverse event' was defined as an event that required hospitalization (or prolonged the existing hospitalization), caused significant disability, and resulted in death. Furthermore, an event was defined as serious if it required intervention to prevent hospitalization.

Statistical methods

The data was organized using spreadsheet and analyzed by using SPSS Version 20.0. Percent and averages with standard error were used for descriptive analyses. As the expected frequency count was less than five, Fisher's exact test was used to determine the relation between the sex and occurrence of AEFI. Kruskal wall is test was used to evaluate the relation of particular age group with that of AEFI. Independent sample t test was used to assess the difference in age group between male and female travellers.

Results

In this prospective observational study, a total of 305 travellers received yellow fever vaccine. The average age of the vaccinated travellers were found to be 36.2 ± 0.6 years comprising 240 male and 57 female patients (Table 1).

Follow up of the vaccinated travellers

Vaccinated travellers were followed up twice i.e. on day 7 and 14 post vaccination. Complete follow up (i.e. on day 7 and day 14) were taken for 248 vaccinated travellers. For 49 of the travellers, only one follow up could be captured. Eight travellers were lost in the follow up.

Profile of vaccinated travellers

According to the prevailing rules at the time of vaccination, the yellow fever vaccine needs to be taken again if the last vaccination was 10 years or more. Of all the 305 travellers, only 16 travellers needed second vaccination. 3 vaccinated travellers were found to be allergic toward a medicine or food item.

Primary outcomes reported after the vaccination

Minor AEFI were observed in 16 vaccinated travellers. Fever was found to be the most common in 5 travellers followed by headache in 4 travelers (Table 2).

The average age of male travellers was found to be higher compared to the female travellers; but, this difference was statistically insignificant. However, AEFI encounters were found to be nearly equal among both the sexes (Table 3). AEFI were reported in 12 male and 4 female patients; and the difference, however, was statistically insignificant ($P = 0.520$, Fisher's exact test).

Most of the travellers belonged to the age group 15-65Y (272 travellers) followed by geriatric and paediatric group of population (14 and 11 travellers, respectively). The reports of minor AEFI were found higher in paediatric and geriatric group of population (Table 4). The occurrence of AEFI in three age groups was found to be statistically significantly different in three age groups ($P = 0.045$, Kruskal wallis test)

Discussion

Yellow fever is prevalent in tropical region of Africa and South America. In order to ensure that YF will not spread in non-endemic countries, International health regulations made certain regulation. These international regulations allow India and many other countries to have YF vaccination as mandatory requirements for entry into India from Yellow fever endemic countries [18].

Of 305 yellow fever vaccinated travellers, 297 were successfully followed up telephonically as per the protocol. Male to female ratio was found out to be 4:1; and, this is easy to understand because most of the travellers were travelling for an employment and/or business.

The symptoms reported after yellow fever vaccination were 'mild' in nature and treated without any specific treatment, but a causal relationship with yellow fever cannot be established. Identification of selected symptoms following yellow fever vaccination allows study personnel to gather additional information and recommend medical follow-up. In this study, there was no case of serious adverse event or neurotropic disease following immunization.

Follow up of eight vaccinated travellers were lost due to early

Demographic Parameters	Vaccinated travellers
No of vaccinated travellers	305
Number of travellers followed up	297
Average age of the travellers (years)	36.2 ± 0.6
Male: Female ratio	3.9:1

Table 1: Demographic profile.

	Headache	Fever	Headache +Fever	Malaise +Fever	Fever+Headache +Malaise	Fever+Headache +Myalgia	Total
Sex							
Male	3	3	2	1	2	1	12
Female	1	2	0	0	1	0	4
Total	4	5	2	1	3	1	16
Age							
1d-15Y	0	2	0	0	0	0	2
15-65Y	3	3	1	1	2	1	11
>65Y	1	0	1	0	1	0	3
Total	4	5	2	1	3	1	16

Table 2: Primary outcomes reported by YFV vaccinated travellers.

Sex	Number	Av. Age ± SEM	No. of AEFI	Percentage AEFI	p-value
Male	240	37.5 ± 2.0*	12	5(12/240*100)	0.520#
Female	57	34.9 ± 0.8*	4	7(4/57*100)	

#Fisher's exact test; *Independent sample t test

Table 3: Sex based profiling of the travelers and AEFI.

Age group	Number	Av. Age ± SEM	No. of AEFI	Percentage AEFI	p-value
1day-15Y	11	8.6 ± 2.5	2	18 (2/11*100)	0.045*
15-65Y	272	38.3 ± 0.6	11	4 (11/272*100)	
>65Y	14	74.1 ± 1.2	3	21 (3/14*100)	

*Kruskal wallis test

Table 4: Age wise profiling of travelers and AEFI.

departure of the vaccinated traveller to the destination country. Two follow up were completed successful for 248 vaccinated travellers. One follow up, each, could not be completed for 49 travellers due to inability to contact to the travellers.

At the time of study, there was a need of revaccination or booster dose of vaccine. But according to the latest recommendation from WHO, only one vaccination provides lifelong immunogenicity in travellers of all age groups and different medical conditions all around the world [19]. Sixteen travellers were vaccinated second time with yellow fever vaccine as it provides protection up to 10 years of period (5%).

No 'severe' side effects were observed after vaccination. Only 'mild' side effects were observed in 16 travellers. The results of this study are comparable with the results of Durbin et.al. Wherein a total of 2326 vaccine recipients were followed through a telewatch system. 'Mild' side effects were observed in 4% of the vaccinated travellers. Fever, headache and muscle pain were the most common side effects observed in 3% of the vaccinated travellers in the study of Durbin et al. [7].

Lindsey et.al. have confirmed a total of 660 minor adverse events out of 100,000 vaccine recipients (0.6%) [8]. Likewise, Fitzner et.al. reported a total of 87 minor adverse events from 2 million vaccine receivers (0.004%) [20]. Fernandez et.al. have conducted the longest study between 1999-2005. They reported a total of 55 adverse events following immunization of 499,714 persons (0.01%) [15].

On the basis of findings of the present study, on a limited number of subjects though, it is fair to conclude that Yellow fever vaccine is safe and well tolerated in healthy Indian travelers. The authors suggest continuation of the study to include larger number of travellers.

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