

# Adverse events following Live JE Vaccination – An Observational Study

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## ABSTRACT

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**Objectives:** To study the safety profile of live JE vaccine. To analyse the possible risk factors for development of adverse events.

**Methods:** 1500 children aged 1 year to 15 years, vaccinated with live JE vaccine during a mass vaccination campaign, were followed up for a period of 6 months from the time of vaccination. Outcome measures were major and minor adverse events during the first two weeks and any neurological events thereafter.

**Results:** No serious adverse reactions were noted in the 1st two weeks following vaccination. 22.3% reported minor events like fever, headache, upper respiratory symptoms, vomiting, rashes and local reactions. Those with a personal or family history of atopy showed an increased risk of adverse events. No significant correlation between age, sex, or nutritional status and risk for development of adverse events were noted. None of the vaccine recipients experienced any major neurological events within next 6 M.

**Conclusion:** Live attenuated JE vaccine is safe in children below 15 years. Those with a history of atopy have a higher risk of developing minor adverse events following the vaccine.

**Keywords:** Japanese Encephalitis, Live JE vaccine, Adverse events, Risk factors

\*See End Note for complete author details

## INTRODUCTION

Japanese encephalitis is the leading viral cause for acute encephalitic syndrome in Asia, primarily affecting children below 15 years. 70% of the affected either die or suffer from severe long term neurological disability.<sup>1</sup> Though vector control seems to be the best method for disease control, huge resources needed for that is a limiting factor in the resource limited settings of the affected countries. Therefore the most promising tool appears to be vaccination against the disease. The live attenuated JE vaccine from China is widely used and is found to be safe and effective. WHO recommends this vaccine for routine immunization in endemic areas and for travelers to these areas.<sup>2,3</sup> The CDC of America opts for the killed vero cell culture vaccine that requires multiple doses and is more expensive. Similar are the vaccination protocols against JE for the developed countries of the west.<sup>5,6</sup> This probably is due to lack of faith in the safety of the live vaccine.

Government of India started campaign mode vaccination with live JE vaccine from 2006 onwards in

endemic areas.<sup>4</sup> When such a campaign was proposed to be conducted in Alappuzha district of Kerala, a lot of concern was raised from various corners regarding its safety.

It appeared that, in spite of various studies that testify the safety of the live JE vaccine, there still exists a doubt in this issue. It was in this scenario that we took up the present study.

## METHODS

The study was conducted in selected Anganwadis and schools within the town of Alappuzha, a Southern district of Kerala, South India. It was done over a period of 6 months starting from 14<sup>th</sup> September 2008, when the JE vaccination campaign started in Alappuzha.

Study population: Children aged 1 to 15 years from 2 schools each from lower primary, upper primary and high school section and 18 Anganwadis located in Alappuzha town.

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**Inclusion criteria**

1. Children aged 1 to 15 years who received single dose of live attenuated JE vaccine in the campaign.
2. A valid consent from parents of all participants and also the assent of the participants for those >7 years of age.

**Exclusion criteria**

1. Those who received any other vaccine in past 4 weeks.
2. Presence of a serious systemic illness-acute or chronic during the vaccination period.
3. History of seizures, including febrile seizure in the past.

A total of 1500 children who fulfilled the inclusion criteria were enrolled in the study. All of them received a single dose of 0.5ml of JE vaccine subcutaneously, containing 5.41 PFU of live JE virus (strain SA-14-14-2). The vaccine was produced by Chengdu institution of biological products (CDIBP), China. The hamster kidney cell vaccine had gelatin added for stabilisation. The lyophilized vaccine was diluted with sterile water for injection. Vaccination was done by trained junior public health nurses under the direct supervision of a pediatrician. Each child was observed for at least 30 minutes for any immediate reactions.

Performa was given to all enrolled in the study. They were to be taken home to be filled by the parents and to be collected by the class teacher. Subjects were also given contact number of the investigators. All were instructed to check temperature from local health care facility in case of fever. Temperature >37.4 C was considered as fever. Subjective symptoms like headache, malaria, myalgia, dizziness, abdominal pain etc were considered significant if they were severe enough to seek medical attention and/or interfering with daily activities.

**Follow up:** On day14, the subjects were revisited and performa collected. Those who experienced any adverse events or their parents were interviewed directly or telephonically and further details needed were collected. Those who were absent were traced with the help of teachers. Those who could not be traced and those who lost performa were declared to be lost to follow up.

**After 6 months:** Those children who continued in the study on day 14 of vaccination were followed up at 6 months at schools and Anganwadis. Enquiry was done on occurrence of neurological symptoms like seizures, altered sensorium etc. or any illness requiring hospitalization during the follow up period. Details were collected in such cases and medical records were checked when made available.

In this study, serious adverse event (SAE) was defined as any event that resulted in death or was potentially life threatening or requiring intensive care in hospital or resulted in permanent disability. This included seizures, encephalopathy, demyelinating illness, polyneuritis, anaphylaxis etc. The study was approved by the institutional ethics committee of our institute.

**Data analysis:** Statistical analysis was performed with SPSS (16) software. Significance tested using chi-square test. P value > 0.05 was considered insignificant.

**Observations:** Out of the 1500 children enrolled in the study 1365 remained on D- 14. The age wise and sex wise distribution of the vaccine recipients and those with adverse events are indicated in **table 1**.

**Table 1. Age & sex wise distribution of vaccine recipients & those with adverse events**

	Vaccinated n(%)	No. with adverse events in the group n(%)
Total	1365	304(22)
Male	656 (48)	132(20)
Female	709 (52)	172(24)
<5 y yrs	332 (24)	65 (21)
6 – 10 yrs	573 (42)	131 (23)
11 – 15yrs	460 (34)	108 (23)

None of the children developed any serious adverse reaction in 1<sup>st</sup> 30 minutes. 304 (22.3%) children experienced minor adverse reaction within the first 14 days post vaccination. 249 (18.2%) had it in 1<sup>st</sup> 7 days itself.

**Table 2. Distribution of adverse events in different age groups**

Event	Fever n(%in the age category)	Headache n(%in the age category)	Upper resp. symptoms n(%in the age category)	Vomiting n(%in the age category)	Malaise n(%in the age category)	Myalgia n(%in the age category)	Dizziness n(%in the age category)
1 – 5	33 (10)	8 (2)	41 (12)	6 (2)	14 (4)	3 (1)	0 (0)
6 – 10	68 (12)	43 (8)	63 (11)	19 (3)	27 (5)	24 (4)	3 (1)
11- 15	39 (8)	36 (8)	44 (10)	7 (2)	29 (6)	23 (4)	3 (1)
Total	140 (10)	87 (6)	148 (11)	32 (2)	60 (4)	50 (3)	6 (0.4)
p value	0.424	0.014	0.259	0.231	0.341	0.026	0.362

Age group	Rash n(%in the age category)	Abd. Pain n(%in the age category)	Persistent Cry n(%in the age category)	Itching n(%in the age category)	Swelling n(%in the age category)	Redness n(%in the age category)	Pain n(%in the age category)
1 - 5	0 (0)	9 (3)	6 (2)	2 (0.6)	2 (0.6)	1 (0.3)	2 (0.6)
6 - 10	2 (0.3)	22 (4)		7 (1)	9 (1.6)	2 (0.3)	7 (1)
11- 15	4 (0.8)	16 (3)		8 (2)	9 (2)	5 (1.1)	18 (4)
Total	6 (0.4)	47 (3)	6	17 (1.2)	20 (1.5)	8 (0.6)	27 (2)
P- value	0.172	0.983		0.698	0.088	0.088	0.001

### Adverse events:

5 children were hospitalized during the first 14 days post vaccination. The distribution of various adverse effects in different age groups is as indicated in **table 2 and table 3**. Two had fever with rashes, one with fever alone and two with symptoms of gastroenteritis. Out of 1365 children in the group, only 1204 remained in the study at 6 M. None experienced any neurological events during follow up period of 6 months.

## DISCUSSION

In this study we observed that there were no serious adverse reactions among the 1356 children followed up for 14 days. 22.3% experienced some form of minor adverse reaction including upper respiratory symptoms, fever, headache, malaise, myalgia vomiting, dizziness, abdominal pain, itching, rash, and local reactions. None of the patients experienced any major neurological events during 6 months post vaccination.

Reports from Bellary and Burdwan on AEFI following live JE vaccination in 2006 which studied 717 and 720 vaccines respectively did not show any immediate serious reactions.<sup>7,8</sup> The 10 year long post marketing study of Kitasato Institute reported an incidence of anaphylactic reaction in 0.063 per million live JE vaccine doses.<sup>9</sup>

Among the minor adverse reactions, fever was one of the most frequent one, which occurred in 7.7 % in 1<sup>st</sup> week & 2.6 % in 2<sup>nd</sup> weeks. This is comparable to the observation of Liu ZL et.al<sup>10</sup> where 4.9 % in a population of 266 children experienced fever. 6.9 % of vaccines from Bellary and 14.7 % from Burdwan experienced fever in the first week after vaccination. Xin et al did not come across fever during the 1<sup>st</sup> 2 weeks in the 47 children aged 5 – 6 years who received the vaccine.<sup>11</sup>

The other two adverse events noted were headache (6.3%) and upper respiratory symptoms of cough

and rhinorrhea (11%). Though these symptoms are quite common in a pediatric population, a significant difference in their occurrence was noted in the 1<sup>st</sup> week as compared to the 2<sup>nd</sup> week post vaccination. i.e. out of 87 children who experienced headache 70 (80%) had it in the 1<sup>st</sup> week. So also among 148 children with upper respiratory symptoms, 101 (68%) had it during first week immediate post vaccination. This suggests a causal role of the vaccine. Similar observations were made from Bellary too. But Liu ZL et al reported upper respiratory symptoms in only 3.4 % in the first week.

Two particular events noted were generalized itching (1.1%) and skin rashes (0.4%). 5 children were hospitalized during the 1<sup>st</sup> week post vaccination – 2 with fever & rashes, another 2 with a/c gastroenteritis and one with fever alone. In all the five cases, it was the parental anxiety which led to hospitalization for observation for less than 2 days.

### Risk factors for development of adverse events:

No significant correlation with occurrence of adverse events and the age was noted, except for headache and myalgia which were observed at a higher rate in older children. But this could be due to the fact that they are less likely to be expressed by younger children. A significantly increased incidence of adverse reaction was noted in children with personal history of atopy. Among the vaccine recipients 68 gave history of atopy (**table 4**). It was noted that the incidence of adverse reaction – both systemic and local were significantly higher among them than in non-atopic children. (51.4 % vs 20.7%, p-value 0.000). A similar observation was made by Berg S W et al.<sup>13</sup> It may be postulated that a history of allergic disorders could be a risk factor for developing adverse events following immunization (AEFI) with live JE vaccine. It is possible that many of the adverse events are due to allergy to gelatin, the stabilizer used in the vaccine rather than to the vaccine itself.<sup>14,15</sup>

Those children who experienced minor AEFI in past (n=64) did not show any increased rate of AEFI

Risk factor	Atopy	h/o AEFI in past	Malnutrition
Total no. with the risk factor	68	64	276
h/o AEFI in the group(%)	35(51)	17(26.5)	60(22)
p-value	.000	0.525	0.924

this time, as compared to those who never had such reaction is past (26.5% vs 22.05% p-value = 0.525). A possible role of malnutrition in the occurrence of AEFI was looked into. No significant difference in the incidence of AEFI was noted among undernourished and well nourished vaccine recipients. (21.7% vs 22.4% p-value 0.924). This observation was comparable to that of Aason E et al.<sup>16</sup>

Follow up at 6 M: None of the 1204 children followed up at the end of 6 M developed any neurological problems. This is comparable with the results of Zhore B et al and Wang J L et al.<sup>12,17</sup>

## CONCLUSION

The live attenuated JE vaccine is a safe vaccine. Minor systemic or local adverse events can occur in around 22% of vaccine recipients. A history of atopy is a possible risk factor for developing adverse events following live JE vaccination.

## END NOTE

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**Editor's Remarks:** Adverse reactions following live vaccine administration is a sensitive issue with even political ramifications. Resistance to vaccination is often assiduously created with false news about adverse events following vaccination. This is followed by campaigns in the social media creating a scare. This original research has attempted to study the safety

profile of live JE vaccine and analyse the possible risk factors for development of adverse events. This study is recommended both from a pediatric, internal medicine point of view as well as public health point of view.

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