Adverse events following immunisation with SA 14-14-2 Japanese encephalitis vaccine in children of Kolar in Karnataka

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Around 30 million children of 1 to 15 years have received the live attenuated SA 14-14-2 Japanese encephalitis (JE) vaccine in the campaign against JE in India from 2006 to 2007. This study aims to assess the short-term adverse events following JE vaccination as there is limited data on it in Indian children. A longitudinal study of children vaccinated in the campaign against JE in Kolar, in 2007 was undertaken. In July to August 2007, following the JE vaccination campaign in Kolar, 1640 children of 10 to 15 years were followed for four weeks. Events such as fever, pain at the injection site, cough, headache and nausea or vomiting were recorded. Surveillance was maintained on the referral hospitals for hospitalisation due to encephalitis and anaphylaxis following vaccination. The incidence of adverse events is summarised as frequencies and percentages with 95% confidence interval (CI). The analysis was performed using statistical package for social sciences (SPSS) 15.0 for windows. The incidence of minor adverse events was 11.3% (95% CI 9.8 -12.9%) for fever, 17% (15.2-18.8%) for pain at the injection site, 12.6% (11-14.2%) for cough, 2.6% (1.8-3.3%) for headache and 1.1% (0.6-1.6%) for nausea and/or vomiting. Severe adverse events were not observed. Mild adverse events following immunisation are common with SA14-14-2 JE vaccine. Hence the health personnel involved in JE control campaign should be aware of these adverse events. [*J Indian Med Assoc* 2012; 110: 10-2]

Key words: **Japanese encephalitis, adverse events, vaccination, SA 14-14-2 vaccine.**

Over 50,000 cases of Japanese encephalitis (JE) and 10,000 deaths are reported annually across Asia[1]. Following the massive JE outbreak in northern India in 2005, the Government of India launched a large scale vaccination campaign in the highest-risk districts[2-4]. Thirty million 1 to 15 years old children were immunised in 2006 and 2007 with SA 14-14-2 live attenuated JE vaccine[3,4]. The short term safety of this vaccine has been studied in China, but there is limited information on it in Indian children[3,5].This study observed the incidence of minor adverse events following immunisation with this vaccine in 10 to 15 years old children of Kolar.

Material and Method

This longitudinal study followed up children in the schools over a period of four weeks for adverse events following the JE vaccination campaign. The study design was reviewed and approved by the ethical committee on research studies of Sri Devaraj Urs Medical College, Kolar. The study was undertaken in the Vemgal primary health centre (PHC) area, in Kolar district of Karnataka state. Around 32,450 people in 52 villages receive primary healthcare services provided by the PHC. All the children from 1 to 15 years were vaccinated with SA 14-14-2 JE vaccine for the first time. Vaccination was carried out in the schools and the anganawadi centre of each village by the health workers of the PHC, under the direction and supervision of the district health administration. All the higher primary schools and the high schools in the PHC area were selected. Children of 10 to 15 years in these schools, who had received the vaccine in the JE campaign from 20 to 27 of July 2007, were included in the study. The children vaccinated were documented in the JE vaccination cards maintained by the health workers. Two medical faculty and four medical interns of the department of community medicine of the institute were trained in administering a structured questionnaire to the children and the school teachers and to record the minor adverse events. A surveillance-form was used to record data on acute encephalitis syndrome based on the one developed by the international vaccine institute in Korea[6]. The age of the children was obtained from the school records.

The health workers of the PHC enumerated the children and administered the vaccines. The vaccine was administered subcutaneously to the left arm with an autodisable syringe, after reconstituting the lyophilised powder in the 5-dose vial with the accompanying vaccine

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diluent. The vaccine was manufactured by the Chengdu Institute of Biological Products, Chengdu in China and imported for the Government of India by Hindustan Latex Limited[7,8]. Vaccine was not administered to children with fever, cough and cold, a history of convulsion and to those appearing sick. In the subsequent visits made by the health workers in the campaign period the children who were initially absent and whose sickness symptoms had subsided received the vaccine, but were not included in the study.

A total of five follow-up visits were made to the schools. The first visit was on day two or three considering the day of vaccination as day one. The remaining four visits were then made at weekly intervals. Presence of symptoms such as fever for >3 days, pain at the site of injection, cough, headache and nausea or vomiting was recorded. Symptoms suggestive of anaphylaxis and encephalitis were enquired. History of hospitalisation of the child after the vaccination was enquired from the child and the school teachers. In this period, surveillance was maintained on the two major referral hospitals in Kolar, to document any hospitalisations of children from the PHC area following the JE campaign. For this purpose a weekly visit was made to the hospital emergency, the paediatric wards and the medicine wards.

The incidence of adverse events is summarised as frequencies and percentages with 95% confidence interval (CI). The continuous variables are expressed as mean and standard deviation (SD). The analysis was performed using statistical package for social sciences (SPSS) 15.0 for windows[9].

Observations

The number of 10 to 15 years old children followed up in the study following the JE vaccination campaign was 1640. The mean (SD) age was 12.3 (1.47) years, and included 845 girls (51.5%) and 795 boys (48.5%). The mean (SD) duration of follow-up of the vaccinated children was 27.5 (5.3) days. The children followed-up in all the five visits were 1428 (87%). The children followed up at least once (1 to 4 times) were 205 (12.5%), and 7 (0.4%) were lost to follow-up. These 7 students were generally not regular to the school, and the teachers confirmed that they were put to work in agriculture farms and other domestic chores. No deaths were reported in the vaccinated children.

The frequency of adverse events observed is presented in Table 1. Pain at the injection site was the commonest event reported followed by cough and fever lasting for > 3 days. Events related to anaphylaxis and encephalitis was not reported by the children. The school teachers also confirmed the same. No hospitalisation occurred in the two major referral hospitals of Kolar, in the follow-up period, in the vaccinated children from the PHC area.

Table 1 — *Adverse Events during the Four-week Period following SA 14-14-2 Japanese Encephalitis Vaccination*

Event	Children reporting the event (n=1633)*	Per cent of children (95% CI)
Fever lasting >3 days	186	11.3 (9.8 - 12.9)
Pain at injection site	279	17.0 (15.2 - 18.8)
Cough	206	12.6 (10.9 - 14.2)
Headache	42	2.6 (1.8 - 3.3)
Nausea or vomiting	18	1.1 (0.6 - 1.6)

*7 children were lost to follow-up

Discussion

This study shows that minor adverse events is common following immunisation with the live attenuated SA 14-14-2 JE vaccine in 10 to 15 years children, in the 4-week follow-up period. The incidence of fever reported was 11.3%, pain at the injection site in 17% and cough in 12.6% of the vaccinated children (Table 1). A postmarketing surveillance study[3] undertaken by Government of India on 1438 children from 1 to 15 years following the 2006 JE vaccination campaign, found fever in 12% and pain at the injection site in 5 to 10% of them. Similar results have been obtained in South Korea in 2002 where 10% of the 522 vaccinated children had fever and a cough in the four-week period of active monitoring following JE vaccination[10]. The findings of the postmarketing surveillance and the Korean study are consistent with the present study. In the year 2000 in China, 266 children of 1 to 6 years were actively followed for seven days following JE vaccination. Fever and cough was observed in 4.9% (95% CI 2.7 - 8.2%) and 3.4% (1.6 - 6.1%) respectively[5]. The different rate of events observed in the Chinese and in the present study could be due to the different age groups studied and to the estimation of the events in the present study which is based on symptoms.

In the two major referral hospitals under surveillance in Kolar, no admissions were made of 10 to 15 years old children from the studied PHC area. In a large randomised prospective study[5] in China involving 26,239 children of 1 to 6 years, no cases of encephalitis were reported and no difference in hospitalisation was found between those who received the JE vaccine and the controls in the four-week follow-up period. The present study supports the observation of a negative association between JE vaccination and hospitalisation made in the Chinese study. Since hospitalisation is an important event it is unlikely that any such event following the JE vaccination was not recalled by the children and the school teachers.

Following the JE immunisation campaign in the summer of 2006, in the four Indian states of Uttar Pradesh, Assam, West Bengal and Karnataka, 65 serious adverse events (0.7 per 1 lakh immunised children) were reported and 22 of them (0.24 per 1 lakh immunised children) was

fatal. Investigation by an independent national expert committee convened by the Government of India, found no causality between the JE vaccine and the temporally associated serious adverse events. The background mortality in the same age group of 1 to 15 years was reported to be much higher in 2006 (8.6 per 1 lakh children)[3,11]. It must be noted that the sample chosen for the present study was to identify the minor adverse events and not intended to identify the rare serious adverse events.

The results must be interpreted in the light of the limitations of the study. A control group could not be included in this study because the vaccination campaign was carried out simultaneously in all the communities of Kolar. Children from the neighboring districts where the campaign was not yet held could have been compared as controls. No such attempt was made in the study because of limited logistics.

Several case-control studies have demonstrated protective efficacy rates of 98.5% and above following a single dose of the vaccine[12-14]. In a recent study[15] in Nepal, the protective efficacy was 96.2% at five years after single dose vaccination in children. The World Health Organisation's (WHO), global advisory committee on vaccine safety (GACVS) reviewed the efficacy and safety of this vaccine in the year 2005 and 2006, and concluded that the vaccine efficacy is high after a single dose and the short-term safety profile appears satisfactory[10,16]. The Government of India's introduction strategy includes a five-year plan to cover all the 101 of the country's highest-risk districts for JE in the vaccine campaigns, followed by incorporation of the vaccine into routine immunisation programme in the targeted districts[3,4]. However, concern exists for the long-term safety of this primary-hamster-kidney cell line substrate derived vaccine. Also the vaccine is not prequalified by the United Nations[16,17].

Use of this vaccine is a new experience to the health personnel involved in JE control activities in India. Given the frequency of occurrence of minor adverse effects with the SA 14-14-2 JE vaccine in children in this study, it is necessary that the health personnel, anganawadi workers, and school teachers involved in the JE campaign are aware of it. The short-term and long-term safety of the vaccine should be investigated on Indian children by controlled studies.

References

1 World Health Organisation — Japanese encephalitis vaccines: WHO position paper. *Wkly Epidemiol Rec* 2006; **34 & 35:** 331-2.

2 World Health Organisation — Outbreak encephalitis 2005: cases of encephalitis in India 2005. www.searo.who.int/en/section 1226/section 2073. Asp (accessed June 11, 2007).

3 World Health Organisation — Report: third biregional meeting on control of Japanese encephalitis, Vietnam, 26-27 April 2007. www.wpro.who.int (accessed September 1, 2007).

4 Biswal P, Khalakdina A, Sarkar S, Ghosh RS, Dhalaria P, Sivalenka S, *et al* — Partnering for the successful introduction of Japanese encephalitis vaccine in India. www.path.org/vaccineresources/files/partnering_successful_intro_JE_vaccine_India_PATH.pdf (accessed September 2, 2007).

5 Liu ZL, Hennessy S, Strom BL, Tsai TF, Wan CM, Tang SC, *et al* — Short-term safety of live attenuated Japanese encephalitis vaccine (SA 14-14-2): results of a randomized trial with 26,239 subjects. *J Infect Dis* 1997; **176:** 1366-9.

6 PATH — Sentinel site surveillance of Japanese encephalitis, 2006. www.path.org/files/sentinel_surveillance_guidelines_JE.pdf (accessed June 4, 2007).

7 PATH — 2006 Japanese encephalitis vaccination campaign, India. www.path.org/vaccineresources/files/India campaign_summary.pdf (accessed June 4, 2007).

8 PATH — JE vaccines at a glance. www.path.org/vaccineresources/files/JE_vaccines_at_a_glance.pdf (accessed July 9, 2007).

9 SPSS. 15.0 — www.spss.com (accessed September 4, 2007).

10 World Health Organisation — Safety of SA 14-14-2 Japanese encephalitis vaccine. *Wkly Epidemiol Rec* 2005; **28:** 242-3.

11 World Health Organisation — Safety of JE vaccination campaign in India. *Wkly Epidemiol Rec* 2007; **82:** 17-24.

12 Ohrr H, Tandan JB, Sohn YM, Shin SH, Pradhan DP, Halstead SB — Effect of single dose of SA 14-14-2 vaccine 1 year after immunization in Nepalese children with Japanese encephalitis: a case-control study. *Lancet* 2005; **366:** 1375-8.

13 Hennessy S, Zhengle L, Storm BL, Min WC, Lian LH, Xiang WT, *et al* —Effectiveness of live attenuated Japanese encephalitis vaccine (SA 14-14-2): a case-control study. *Lancet* 1996; **347:** 1583-6.

14 Bista MB, Banerjee MK, Shin SH, Tandan JB, Kim MH, Sohn YM, *et al* — Efficacy of single-dose SA 14-14-2 vaccine against Japanese encephalitis: a case-control study. *Lancet* 2001; **358:** 791-5.

15 Tanden JB, Ohrr H, Sohn YM, Yoksun S, Ji M, Nam CM, *et al* — Single dose of SA 14-14-2 vaccine provides long-term protection against Japanese encephalitis: a case-control study in Nepalese children 5 years after immunization. *Vaccine* 2007; **25:** 5041-5.

16 World Health Organisation — Japanese encephalitis vaccination. *Wkly Epidemiol Rec* 2006; **21:** 215.

17 Plesner AM — Allergic reactions to Japanese encephalitis vaccine. *Immunol Allergy Clin North Am* 2003; **23:** 665-97.