Original Article

Incidence of Adverse Events Following Immunization With SA14-14-2 Japanese Encephalitis Vaccine Among Children of 6 to 10 Years in Kolar, India.

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ABSTRACT

The Government of India introduced the SA 14-14-2 vaccine in 2006 and nearly 50 million children, 1 to 15 years of age have been reached through vaccination campaigns and routine immunization. There is limited data on the short-term adverse events following immunization with the live attenuated SA 14-14-2 Japanese encephalitis (JE) vaccine on Indian children.

Objectives: *To find the short term adverse events following the administration of SA 14-14-2 vaccine in children aged 6 to 10 years.*

Methods: *This longitudinal study was conducted in July-August 2007 in Kolar, Karnataka and 988 children were followed for 4 weeks following the JE vaccination campaign.*

Results: *The incidence of minor adverse events was 5.36% (95% CI, 3.96 to 6.76%) for fever lasting more than 3 days, 14.37% (12.18 to 16.56%) for pain at the injection site, 5.56% (4.13 to 6.99%) for swelling and redness at the injection site, 0.2% (-0.08 to 0.48%) for cough and 0.4% (0.01 to 0.79%) for nausea or vomiting. Severe adverse events were not observed.*

Conclusions: *Mild adverse events following immunization (AEFI) is common following administration of SA14-14-2 vaccine against JE in children of 6 to 10 years. The health personnel involved in the JE control campaign should be aware of these adverse events, for counselling the recipients*

Keywords: *Japanese encephalitis, adverse events, immunization, SA 14-14-2 vaccine*

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INTRODUCTION

Over 50,000 cases of Japanese Encephalitis (JE) are reported annually across Asia mostly in children less than 10 years with 10,000 fatalities and 15,000 cases of long term neuropsychiatric sequel.[1] The epidemic of JE in the year 2005 accounted for 6,584 cases in India, with 1,765

deaths reported from 11 states. Majority of them were reported from Uttar Pradesh state with a case fatality rate of 23.3%.[2, 3] The Government of India decided to use the live-attenuated SA14-14-2 vaccine against JE in the year 2006, which is produced and widely used in China since 1988 (1,4). A single dose of this vaccine has a protective effect of 98.5% (95% CI, 90% to 99.2%) at 12 to 15 months after vaccination in children.[5] A Large randomized trial has established the short-term safety of the vaccine among Chinese children .[6]

In the year 2006, around 9.3 million children of 1 to 15 years in eleven high-risk districts for JE were vaccinated with a single dose of SA 14-14-2 vaccine. In the year 2007, around 20 million children were vaccinated in 22 districts. The strategy is a five-year plan to cover all the 101 of the country's high-risk districts for JE in the vaccine campaigns and to incorporate the vaccine into the routine immunization programme in these districts.[3,4] Around 50 million children of 1 to 15 years have received the vaccine until 2009 through the vaccination campaign and routine immunization programme.[7]

There is limited data on the adverse events following immunization with SA 14-14-2 vaccine in Indian children. Hence, a study was undertaken to observe the incidence of minor adverse events occurring up to four weeks following immunization with SA 14-14-2 vaccine in children of 1 to 15 years in Kolar district in Karnataka state. This paper reports the incidence of minor adverse events among children of 6 to 10 years in Kolar district.

MATERIAL AND METHODS

Study design: This longitudinal study followed up children in the schools for adverse events following immunization (AEFI) following the JE vaccination campaign with SA 14-14-2 vaccine over a period of 4 weeks.

Setting: The study was undertaken in the primary health centre (PHC) area of Sugatur in Kolar district in Karnataka state. Around 22,743 people in 37 villages receive primary health care services provided by this PHC. 5,452 children of 1 to 15 years received the SA 14-14-2 vaccine for the first time in the 2007 campaign. Vaccination was carried out in the schools, the anganawadi centres, the sub centres and in the PHC by the health workers.

Study population: All the lower primary schools in the study PHC area were selected. Children of 6-10 years in these schools who had received the vaccine in the JE campaign from 20th to 27th 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 Sri Devaraj Urs Medical College, Kolar, 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, Korea.[8] The age of the children was obtained

from the school records.

Interventions: The primary health care workers enumerated the children and administered the vaccines. The vaccine was administered subcutaneously to the left arm with an auto-disable syringe after reconstituting the lyophilized powder in the 5 dose vial with the accompanying vaccine diluent. The vaccine is manufactured by the Chengdu institute of biological products, China, and imported for the Government of India, by Hindustan latex limited.[9,10] Vaccine was not administered to children with fever, cough and cold, 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 this study.

Outcome measures: 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 more than 3 days, pain at the site of injection, swelling and redness at the site of injection, cough, headache and nausea and/or vomiting was recorded. Symptoms suggestive of anaphylaxis and encephalitis were enquired. History of hospitalization of the child after the vaccination was enquired both from the child and the school teachers. In this period, surveillance was maintained on the two major referral hospitals in Kolar to document any hospitalizations 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.

Statistical analysis: The incidence of adverse events is summarized as frequencies and percentages with 95% CI. The continuous variables are expressed as mean and standard deviation (SD). The analysis was performed using SPSS 15.0 for windows (11).

RESULTS

1510 children aged 6 to 10 years received the vaccine in the JE vaccination campaign in the schools of the studied primary health centre area. Out of the 37 schools, 21 primary schools were selected for the study. All the 1004 children who received the vaccine in these 21 schools were included in this study. 988 children were followed up and 16(1.57%) children were lost for follow up. The mean (SD) age of the children followed was 7.8 (2.4) years and included 542 (54.9%) girls and 446 (45.1%) boys. The mean (SD) duration of follow-up of the vaccinated children was 26.7 (4.5) days in the four week period. The children followed-up in all the five visits were 791 (80.1%). No deaths were reported in the vaccinated children during the study period.

The frequency of adverse events observed is presented in table 1. Pain at the injection site was the commonest event reported by 14.37% (95% CI, 12.18 to 16.56%) of the children. Fever lasting for more than 3 days was reported by 5.36% (CI, 3.96 to 6.76%) of the

children. Events related to anaphylaxis and encephalitis was not reported by the children which were confirmed by the school teachers.

No hospitalization occurred in the follow-up period among the vaccinated children from the study PHC area in the two major referral hospitals of Kolar.

Table 1: Adverse events reported by 6 to 10 year old children in the four week period following JE vaccination at Kolar, 2007.

Event	Children reporting the event (n=988)	% of children (95% CI)
Fever lasting >3 days	53	5.36 (3.96-6.76)
Pain at injection-site	142	14.37 (12.18-16.56)
Swelling and redness	55	5.56 (4.13-6.9)
Cough	2	0.2 (-0.08-0.48)
Nausea or vomiting	4	0.4 (0.01-0.79)

DISCUSSION

This study shows that minor adverse events is common following immunization with the live attenuated SA 14-14-2 vaccine in 6 to 10 year old children in the four week follow-up period. The incidence of fever lasting more than 3 days was 5.36% (CI, 3.96 to 6.76 %), pain at the injection site 14.37% (12.18 to 16.56%) and swelling and redness at the injection site in 5.56% (4.13 to 6.99%) of the children. In the post-marketing surveillance study undertaken on children aged 1 to 15 years following the 2006 JE vaccination campaign with SA-14-14-2 vaccine, fever was observed in 12% and pain at injection site in 5-10% of them.[3] In South Korea, 10% of the 522 vaccinated children had fever and cough in the four week follow up period following JE vaccination with SA 14-14-2 vaccine in the year 2002.[12] In the year 2000, around 266 children Aged 1 to 6 years were actively followed for 7 days following JE vaccination in China. Fever and cough was observed in 4.9% (CI 2.7 to 8.2%) and 3.4% (1.6 to 6.1%) respectively.[6] The different rate of events observed in the present study when compared to Korean, Chinese and the Indian studies could be due to the different age groups in these studies. The estimation of the adverse events in the present study is based on symptoms in 6-10 year old children.

No admissions were made among children aged 6 to 10 years from the studied PHC area of Kolar in the two major referral hospitals which were under surveillance. In a large

randomized prospective study in China involving 26,239 children of 1 to 6 years, no cases of encephalitis was reported. Also no difference in hospitalization was found between those who received the JE vaccine and the controls in the four week follow-up period in the study.[6] The present study supports the observation of a negative association between JE vaccination and hospitalization made in the Chinese study. Since hospitalization 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 immunization campaign in 2006 in the four Indian states, 65 serious adverse events (0.7 per 1 lakh immunized children) was reported and 22 of them (0.24 per 1 lakh immunized children) were fatal. Investigation by the national expert committee found no causality between the JE vaccine and the reported serious adverse events that was associated temporally. The background mortality in the same age group of 1 to 15 years was reported to be much higher (8.6 per 1 lakh children) (3,13). 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 district. Children from the neighboring districts where the campaign was not 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 (5,14 & 15). In a recent study in Nepal the protective efficacy was 96.2% at five years after single dose vaccination in children (16). The WHO's Global Advisory Committee on Vaccine safety (GACVS) reviewed the efficacy and safety of this vaccine in 2005 and 2006 and concluded that the vaccine efficacy is high after a single dose and the short-term safety profile appears satisfactory.[12,17] 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.[17,18]

Given the frequency of occurrence of minor adverse effects with the SA 14-14-2 vaccine in children, it is necessary that the health care personnel and the school teachers involved in the JE vaccination campaign are aware of it for counselling the recipients. The short-term and long-term safety of the vaccine should further be investigated on Indian children by controlled studies.

ACKNOWLEDGEMENT

The technical assistance of the medical officer and the health assistants of primary health centre in Sugatur is acknowledged gratefully. The assistance of Sarala HS, Kishore Kumar KS and Mohammed Ajmal Athani is acknowledged.

REFERENCES

1. World Health Organization. Japanese encephalitis vaccines, WHO position paper. Wkly Epidemiol Rec 2006;34/35:331-32.

2. World Health Organization. Outbreak encephalitis 2005: cases of encephalitis in India 2005. Available from http://www.searo.who.int/en/section 1226/section 2073.

3. World Health Organization. Report: third biregional meeting on control of Japanese encephalitis, Vietnam, 26-27 Apr 2007. Available from http://www.wpro.who.int.

4. Biswal P, Khalakdina A, Sarkar S, Ghosh RS, Dhalaria P, Sivalenka S, Jacobson J. Partnering for the successful introduction of Japanese encephalitis vaccine in India. Www.path.org/vaccineresources/files/partnerig_successful_intro_JE_vaccine_India_PATH.pdf.

5. 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;366:1375-78.

6. 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;176:1366-69.

7. Beasley DWC, Lewthwaite P, Solomon T. Current use and development of vaccines for Japanese encephalitis. Expert Opin Biol Ther. 2008;8:95-106. Accessed from PubMed.

8. PATH. Sentinel site surveillance of Japanese encephalitis, 2006. Http://www.path.org/files/sentinel_ surveillance_guidelines_JE.pdf.

9. PATH. 2006 Japanese encephalitis vaccination campaign, India. Http://www.path.org/vaccineresources/files/India campaign_summary.pdf

10. PATH. JE vaccines at a glance. Http://www.path.org/vaccineresources/files/JE_vaccines_at_a_glance.pdf.

11. SPSS. 15.0. Available from http://www.spss.com.

12. World Health Organization. Safety of SA 14-14-2 Japanese encephalitis vaccine. Wkly Epidemiol Rec 2005;28:242-43.

13. World Health Organization. Safety of JE vaccination campaign in India. Wkly Epidemiol Rec 2007;82:17-24.

14. 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;347:1583-86.

15. 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;358:791-95.

16. Tanden JB, Ohrr H, Sohn YM, Yoksun S, Ji M, Nam CM, Halstead SB. 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. Vaccines 2007;25:5041-45.

17. World Health Organization. Japanese encephalitis vaccination. Wkly Epidemiol Rec 2006;21:215.

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

Source of Support: Nil Conflict of Interest: Nil