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Post-marketing Surveillance on Safety of Japanese Encephalitis Vaccine SA 14-14-2 in Burdwan District of West Bengal, India.

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Abstract

Background- Japanese Encephalitis with high mortality and disability is serious public health menace in South-East Asia including India. Successful JE control of other S.E.Asian countries and the largest epidemic in Uttar Pradesh, led India to initiate mass vaccination campaign, in 2006, for immunizing 1-15 years children of eleven hyperendemic districts of five states with SA-14-14-2 JE vaccine. **Methodology**- Community based Active Postmarketing Surveillance for one year was conducted, in randomly selected villages of a randomly selected block of Burdwan district, West Bengal, involving 720 target children with objective to explore the safety of SA-14-14-2 vaccine, in Indian perspective.

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Results- About 15% and ≤1% participants suffered from pain and swelling and/or redness at injection site. Fever was the most prominent general systemic reaction developed by about 10-15% subjects, < 5% children reported reactions like headache, bodyache, nausea-vomiting, listlessness, loss of appetite, pain abdomen and loose motions etc. whereas almost 5-8% vaccinees affected by cough and runny nose. No serious AEs was reported up to one year after vaccination. **Conclusion**- Being consistent with results of other studies, present findings led to conclude that short term safety of vaccine appeared satisfactory requiring long term monitoring of AEFIs to explore its remote serious AEs.
Key-words: mass vaccination campaign; active post marketing surveillance; serious adverse events; local reactions; general systemic reaction; specific systemic reactions; JE vaccine SA-14-14-2.

Introduction:

Japanese Encephalitis (JE) also called brain fever caused by JE virus, a RNA virus belonging to Flaviviridae family of Group-B arbovirus, is a mosquito (Culicine mosquitoes notably C. tritaeniorhynchus, C. vishnui) borne viral encephalitis in S.E. Asia with more than 20% case fatality and 30-60% neuropsychiatric disability among the survivors.[1,2,3,4] About 60% of the world's population live in JE endemic regions and approximately 50000 cases with 10000 deaths per annum were notified from a wide geographic range.[1] In India JE is responsible for approximately 2000-3000 clinical cases and 500-600 deaths per annum reported from all states and Union Territories of country except Arunachal Pradesh, Dadra, Daman, Diu, Gujarata, Himachal Pradesh, Jammu & Kashmir, Lakshadeep, Meghalaya, Nagar Haveli, Orissa, Punjab, Rajasthan and Sikkim. West Bengal, Bihar, Tamil Nadu, Andhra Pradesh, Uttar Pradesh, Assam, Karnataka, Manipur and Goa are hyperendemic states with highest risk at monsoon/post monsoon time among 1-15 years children living in rural areas.[2] Having very complex epidemiological features with multiple hosts and vectors JE virus becomes a part of ecosystem and is too difficult to eradicate. Vaccination remains the single most important cost-effective control measure.[2,5] Immunization with an effective, safe, cheap, simple to administer vaccine being the only way of JE control should be extended to all areas where it is a demonstrated public health problem and needs incorporation into routine immunization programme (W.H.O./SEARO/ 2006; W.H.O.J.E. position paper, 2006; Bi-regional JE meeting, 2005, WHO/PATH). Japan, China, Korea Republic, Thailand and Nepal have controlled JE to large extent using vaccine.[6,7] India uses 3 doses of killed mouse brain JE vaccine prepared at Kasauli, HP since 1988 and hasn't included in routine immunization programme as JE risk is not universal rather focal.[8,9] But in the face of expanding JE affected areas, scarcity of costly mouse brain vaccine[10,11] and above all being witnessed by massive JE outbreak in 2005 resulting in 2000 deaths and even greater disabilities in UP and Bihar;[2,3] the government of India (GOI) supported by Programme for Appropriate Technology in Health (PATH) initiated a pilot project in 2006 for immunizing children aged 1-15 years in eleven hyper-endemic districts of five states (five districts of UP, two from Bihar & Assam each, one of Karnataka & West Bengal each) by a single dose cheap[11] live attenuated SA 14-14-2 JE vaccine prepared and marketed by "Chengdu Institute of Biological products", China, and appeared to be safe and effective as per several trials held in China, South Korea, Nepal etc..[13-15] The GOI purports expansion of JE vaccination coverage in phased manner to include all high risk areas by 2010 and incorporation of it in national immunization schedule.[2,10,11] Side by side by

the help of PATH and Society for Applied Studies (SAS) GOI also arranged "An Open Label, Multicenter, Post Marketing Study" to evaluate the safety and immunogenecity of single dose Live attenuated SA 14-14-2 JE vaccine in Indian perspective.[10] Authors were part of the Post marketing surveillance project and paucity of information regarding the safety of live JE vaccine in Indian subcontinent indulged them for contemplating the present study with following

objectives-

- To describe the magnitude and pattern of adverse events following immunization (AEFI);
- To assess the serious AEFIs of the vaccine within 12 months of post vaccination period;
- To find out the relation between few attributes of the vaccinees and AEFIs

Methodology:

It was a community based observational follow up study from June, 2006 to August, 2007 with a vaccine cohort comprising of both sexes of 1-15 years children. Out of the eleven hyperendemic districts selected for mass vaccination campaign in 2006; Burdwan, West Bengal and Bellary, Karnatak were randomly selected for post-marketing surveillance.[10] The present study was limited in Burdwan, West Bengal where the Block Memary-1 with Gram Panchayat (GP) and villages were selected randomly from the list of Blocks of Burdwan district, list of GPs with their villages of Memary-1 block. Village Purbagantar, Gantar, Dakshingantar of Gantar GP and Kashiara, Mallikapur, Mogra, and Shankarpur of Radhakantapur GP were selected for the purpose. In next step, consecutive children of both sexes from the selected villages were included in the study with subsamples of ≥ 200 children adjusted with 20% drop out for each age group of 1-5, 6-10 and 11-15 years. Thus, 720 children were involved in the study. Thirty young graduates were deployed as Field Investigators (FIs) after thorough training by the supervisors, Principal and Co-principal Investigators (PI &CoPI) who were all doctors and trained about the project by SAS at its head office at New Delhi. Village identification and area allocation to the FIs was done by the help of Panchayat personnel. List of potentially willing beneficiaries from selected villages was prepared by FIs along with panchayat personnel conducting a door to door survey when a notice regarding the vaccination & study was read out to the families having children aged 1-15 years and were called to a destined place on scheduled date of vaccination (four vaccination posts held at Gantar G P from 24th to 27th June, 06 and four posts at Radhakantapur GP from 7th to 10th July,06. On the vaccination day FIs were to ensure that children were brought to the immunization sites. Guardians of these children were briefed about the purpose, risks-benefits and voluntary nature of the participation clearly and all their queries were answered by supervisors, PI - CoPI. After obtaining written consent and assent (if necessary), the children were screened thoroughly by the supervisors using proforma containing predesigned exclusion/inclusion criteria. Selected children were then vaccinated by the Auxilliary Nurse Midwives (ANMs) and meticulously observed for minimum 30 minutes by a supervisor. Then, he/she was offered a participant card. The weight and height for a subsample of 360, who consented for giving blood samples for immunogenecity part of the study;[10]were measured as per standard methods and documented before vaccination. The children who refused to participate in study

and/ or disqualified in screening were sent to ANMs for vaccination as other than study participants. Subsequently, daily home visits were paid to all participants from the late part of the vaccination day through 7th post vaccination day by the FIs to obtain information on any illnesses or AE after vaccination. Then, the FIs made home visits and / or contacted the enrolled child and his/her parents through telephone or visited the child's school on 14th (±2), 21st (±2) and 28th (±2) post vaccination days for collecting informations on any illnesses or AEs occurred since previous visit. Afterwards quarterly visits at home or school on 3rd (±7days), 6th (±7days), 9th (±7days) months, and 1 year (±14days) after vaccination were made to ascertain any serious AEs occurred. During each visit, the child was thoroughly examined by FIs to explore any AE of the vaccination or any illness. He/she was to record the AEs detected by him/her or stated by the care givers in predesigned formats, earmarked separately for each day's field visit, handed over to him/her after demonstration. FIs had to measure the body temperature, local swelling or redness at site of injection, if present at the time of visit, for which necessary equipments were demonstrated and supplied. They had to submit their filled up formats to the respective supervisor at the end of visits. If a family was not available on the day of visit, two repeat visits were paid on that day and daily subsequently, till the child was contacted. If the family was not available for seven consecutive days or if information was received that the family left their home, the child was censored for the study and deemed lost to follow up. The families of enrolled children were asked to consult the principal investigator and or bring their children along with the participant cards offered to them (for identification of study subjects) to the Memari rural hospital or Burdwan Medical College in case the child had any symptom or illness. All the FIs were provided with supportive supervision and close monitoring by supervisors during field work. At the end of each day's visit, all the formats were scrutinized by respective supervisors and then the PI along with CoPI checked these format for grading and relating the AE, if any, with vaccination based on the guidelines provided thereon and handed over to SAS, Delhi for data entry, if the AEs were graded as I & II; faxed to Independent Safety Monitor (ISM), Delhi when the AEs were earmarked as Grade-III and faxed filled up Serious Adverse Events (SAE) form urgently within 24 hours to ISM, SAS, ICMR in any case the AEs were grouped as grade IV (serious/life threatening/death).Thus, at the end of the study at August, 07, complete data for 712 study subjects were available and analysed by using proportion, $\chi 2$ test etc. Another extra visit was paid to all study subjects on January, 2009.

Results and Discussion:

Male participants was 51.4% and 33.8%, 33.6% and 32.6% study subjects belonged to the age group 1-5 , 6-10 and 11-15 years, respectively. No AE whatsoever was reported within 30 minutes after vaccination. Analysis of information obtained up to 96 hours after vaccination showed that among local reactions, pain affected 14.46% of vaccinees with mean duration of 1.51±0.69(m±sd) days followed by swelling and redness (2.5-5cm) at injection site troubling 1.54% and 0.56% of subjects with mean duration of 1.73 ±0.9 and 1.5±2.0 days, respectively (table-1). Among the general systemic reactions occurred within this period, fever affected 10.67% of vaccinees with mean duration of 1.83±1.08 days; followed by headache (4.77%), body-ache (3.51%), dizziness (3.08%), nausea (2.24%) , listlessness (3.67%), loss of appetite (3.23%) with mean duration of 1.38± 0.6 ,1.68± 0.84 ,1.45±0.72 ,1.68±0.84 ,1.42±0.6 , and 1.82±0.91 days, respectively (table-1).

Table-1: AEs developed amongst the vaccinees (N=712).

Adverse reactions			≤96 hrs,	5-28 days,
Local	Pain at site		103(14.96)	----
	Swelling		11(1.54)	-----
	Redness		04(0.56)	------
General	Fever*		76(10.67)	104(14.6)
	Headache		34(4.77)	14(1.96)
	Bodyache		25(3.51)	09(1.26)
	Dizziness		22(3.08)	04(0.56)
	Chill		06(0.84)	---
	Nausea		16(2.24)	10(1.4)
	Vomiting		11(1.54)	15(2.1)
	Listless		19(2.67)	07(0.98)
	Rash		04(0.56)	02(0.28)
	Loss of appetite		23(3.23)	25(3.5)
	Irritable		06(0.84)	01(0.14)
	Weakness		01(0.14)	03(0.42)
	Skin irritation		01(0.14)	01(0.14)
	Yellowish urine		01(0.14)	01(0.14)
System involved predominantly	RTI	Cough	54(7.58)	46(6.46)
		Runny	41(5.75)	35(4.91)
		Sore	---	06(0.84)
	GIT	Pain	22(3.08)	19(2.66)
		Loose	19(2.67)	12(1.68)
	CNS	Convulsio	--	01(0.14)
Miscellaneous			11(1.54)	20(2.8)

More than 1 million children have been followed in a safety study showed side effects were rare, most common being transient fever in approximately 5-10% and local reactions, rash or irritability in 1-3% of vaccinees. Neither acute encephalitis nor hypersensitivity reactions have been associated with this vaccine.[15] Similar results have been obtained from a randomized control trial with 26239 subjects[14] and from post-marketing surveillance conducted in South Korea since 2002.[15] As per report of the Bi-regional meeting on JE,WHO-2005; local reactions in the form of pain, swelling and redness at site found in less than 1%, mild systemic reactions like headache, myalgia, Gastro-Intestinal (G I) symptoms, low grade fever (<0.5%) etc. found in total 21% of subjects with no report of hypersensitivity or encephalitis. Local reactions, within seven days of post-vaccination period included redness (< 1%), swelling (1% to 5%) and pain (5% to 10%). The most common systemic symptom was fever (12%).[11].

So far as the specific systemic reactions revealed by the present study, the vaccine seemed to affect the Respiratory Tract (RT) mostly e.g. 7.58% and 5.75% study subjects suffered from cough and runny nose with mean duration of 2.7 ±1.75 and 3.0±1.84 days. However, 3.1% and 2.8% participants also suffered from pain abdomen and loose motion with mean duration of 1.5±1.83 and 1.8±1.16 days (table-1). Most of these symptoms were mild necessitating medication for 12.2% of affected participants with a mean duration of 2.2±1.55 days but no hospital admission and restricted activity of daily living (ADL) was reported so far. Two participants having high fever for 7 and 8 days (positive Widal test), with some interference of ADL (moderate = grade-II) were excluded from analysis because fever inherent to inoculation didn't persist so long and these two cases were considered coincidental illness.[2] On the whole 14.5% participants were affected by local reactions amongst which 93.3% took place on the day of vaccination. On the other hand 40.7% and

28.2% of the general systemic reactions occurred on the day of vaccination and 1st post vaccination day. Out of the specific systemic symptoms, 43.4% and 31.6% were reported on the day of vaccination and 1st day after vaccination.

During 5-28 days of post vaccination period, mentionable general systemic symptoms were fever, headache, bodyache, nausea, vomiting, loss of appetite etc. affecting 14.6%,1.96%, 1.26%, 1.4%,2.1% and 3.5% of vaccinees, respectively (table-1). During this period, one fellow developed one spell of seizure and another developed jaundice with some interference of ADL but were not hospitalized. Apart from these two moderate (grade-II) AEs, all symptoms were mild in nature where 45.4% of the affected participants (163) had to use medicine but without hospitalisation or restriction of ADL. In a study in West China, no serious AEs have been reported within 30 days follow up in 13266 children. Rate of AEFIs was 4.1/10000 after 1st dose.[13] In a comparative observational study with approximately 26000 subjects in China most common reactions were fever, rash, vomiting and no serious reactions were found within 30 days follow up.[18] Information from both active and passive post-marketing surveillance in Republic of Korea where the SA-14-14-2 was first licensed in 2001 showed that of 522 vaccinated children actively monitored for AEs for 4 weeks after vaccination, approximately 10% developed fever higher than 38^0C and cough. Redness-swelling at site of injection observed in < 1%.These findings were consistent with those reported from China.[18]Scott B H et al reported that numerous large scale evaluations of vaccine safety demonstrate low rates (0.2%–6%) of short-lived local and systemic (i.e. fever) reactogenicity and essentially no neurotoxicity.[19] Saxena P observed in his study in Bareilly that this vaccine was found very safe, out of the 2279 vaccinated children only 6.6% children were suffered from swelling and 3.5% children suffered from fever.[20] There was no major AE due to this vaccine like encephalitis, meningitis, respiratory distress, anaphylaxis and death during or after campaign.[20]

It was revealed from the analysis that all immediate AEs (as considered up to 96 hrs after vaccination) e.g. local, general and systemic affected almost equal proportion of candidates in three age categories but general and systemic reactions during 5-28 days interval after vaccination involved significantly more fellows from the lowest age group (table-2).

Table-2: Distribution of vaccinees developed one or more AE(s) up to 4 weeks after vaccination

Age gr.	Follow up Interval			
	≤96 hrs, No. (%)	χ2 at df 2, p	5-28 days, No. (%)	χ2 at df 1, p; RR (95%CI)
1-5 yrs [n_1=241]	76(31.5)	0.05, 0.97306719	86(35.68)	23.37, 0.0000013; 2.19 (1.57-3.05)
6-10 yrs [n_2=239]	75(31.38%)		39(16.3)	*
11-15 yrs [n_3=232]	71(30.6%)		38(16.4)	0.00, 0.9856461;1.00 (0.67-1.51)
Total [N=712]	222 (31.2)	-------	163 (22.9)	12.39, 0.0004312;1.36 (1.15-1.62)#

Among the AEs local reactions were reported significantly less from lowest age category in comparison to their counterparts whereas the general systemic reactions found to be equal across the age groups (table-3). Again specific systemic

involvement within first 96 hours and both general and specific systemic reactions observed during 5-28 days after vaccination were reported to be declined significantly with advancing age (table-3) conforming to existing knowledge.[2]

Table-3: Distribution of vaccinees developed one or more AE(s) up to 4 weeks after vaccination

Follow up interval	AEs	1-5 yrs[n_1=76] No. (%)	6-10 yrs[n_2=75] No. (%)	11-15 yrs[n_3=71] No. (%)	χ2, p at df 1*	RR (95% CI)*
≤96 hrs. [n_1=222]	Local	27(35.5)	44(58.6)	34(47.8)	8.11,0.0043921 1.70,0.1918762 2.31,0.1285191	0.61 (0.42-0.87) 1.23 (0.90-1.67, 0.74 (0.50-1.09)
	General	43(56.57)	42(56.0)	47(66.2)	0.01,0.9428322 1.59,0.2068184 1.43,0.2316964	1.01 (0.76-1.34) 0.85 (0.65-1.10) 0.85 (0.66-1.11)
	Systemic	46(60.5)	33(44.0)	22(30.98)	4.13,0.0420597 2.63,0.1048058 12.89, 0.0003312	1.38 (1.01-1.88) 1.42 (0.92-2.18) 1.95 (1.32-2.89)
5-28 days [n_2=163]	General	60(78.9)	27(36.0)	30(42.2)	28.51,0.0000001 0.60,0.4388386 20.82,0.0000050	2.19 (1.59-3.03) 0.85 (0.57-1.28) 1.87 (1.39-2.51)
	Systemic	45(59.2)	15(20.0)	19(26.76)	24.24,0.0000009 0.93, 0.3340514 15.72,0.0000733	2.96 (1.81-4.83) 0.75 (0.41-1.35) 2.21 (1.44-3.39)

Anthropometric data were available for 349 participants of a subsample of 360 children and their nutritional status could be determined thereon using the WHO's MGRS standard. Rate of malnutrition was 24.4% and analysis revealed that the nutritional status as well as gender failed to influence the AEFIs significantly (table-4).

Table-4: Distribution of participants as per AE developed within 28 days after vaccination & gender and nutritional status

Attribute		AEFI+ve No. (%)	AEFI-ve No. (%)	Total No. (%)	χ^2,p values at df 1
Gender [N=712]	Male	159(43.4)	207(56.6)	366(100.0)	χ^2=0.45,p>0.05
	Female	159(46.0)	187(54.0)	346(100.0)	
Nutritional Status	Normal	145(54.9)	119(45.1)	264(100.0)	χ^2=0.79,p>0.05
	Undernouris	42(49.4)	43(50.6)	85(100.0)	

Both general systemic and specific systemic reactions were reported to be signicantly more in the lowest age group and also on 3rd month's follow up and declined over time with increasing age, being minimum on 1 year's visit (figure:1 & table-5).

Fig-1: Distribution of vaccinees as per therir reported halth problem during 3 months through 1 year follow up

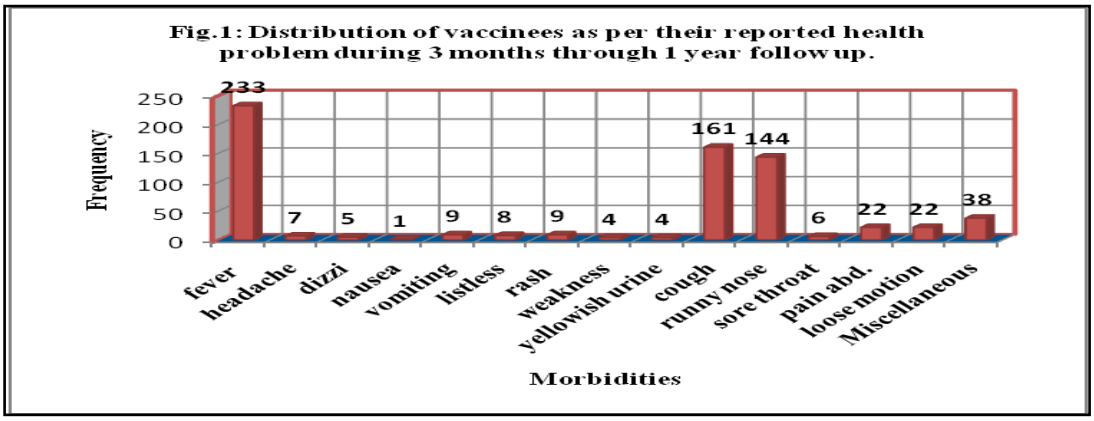

Table-5: Distribution of vaccinees reported health problems over time during 3 months through 1 year follow up

Follow up	1-5 yrs[n_1=241]	6-10yrs[n_2=231	11-15yrs[n_3=232]	Total [N=712]	χ^2 for trend, p
3	88(36.5)	64(26.8)	63(27.2)	215(30.2)	4.377, 0.03643
6	55(22.8)	37(25.5)	29(12.5)	121(16.9)	1.012, 0.31445
9	50(20.7)	24(10.1)	21(9.1)	95(13.3)	13.966, 0.00019
1 yr.	32(13.3)	27(11.3)	16(6.9)	75(10.5)	5.019, 0.02507

However, none of the participants developed any sort of serious AEs whatsoever or death during 3months-1 yr. period. All the reactions during this period were mild without any restriction of ADL or hospital admission. Last visit of all study subjects in the January, 2009 also provided no information about any serious AEs whatsoever.

Investigating causality of AEFIs, particularly those are most serious, is challenging.[16] In this post-marketing surveillance, association between administered vaccine and AEs was determined based on the analysis of follow up reports, consistent findings revealed by similar studies at different settings, a strong similarity of AEs to the infection the vaccine is intended to prevent and there was a non-random temporal relationship between administration and the adverse events. [16]The children were rigorously screened before entering the study paying special attention to contraindication as potential confounding factor [16] and no subject with acute illness was included to avoid confusion between the symptoms of existing illness and AEs of vaccine. Again during follow up, each symptom reported was verified by the FIs by cross-checking the statements of the mother/care giver, child (in case of older children) and sometimes other members of the family, whether that symptom was present before vaccination. AEs of this vaccine could be categorized in to a)

immediate-inherent to inoculation, reaction due to programmatic error (tried to be kept minimum by strict maintenance of cold chain, sterility, supervision and monitoring of vaccination sessions by PI-CoPI & supervisors and finally taking notes on each and every vaccination e.g. lot no. and expiry date of the vaccine vial, time of inoculation etc.) and reactions caused by hypersensitivity to the vaccine constituents. It was considered that the local reactions inherent2 to inoculation, general reactions attributable to the vaccine constituents [17] and their extension might have been prevalent in no way more than 96 post vaccination hours and definitely related with the vaccination process. (b) Intermediate events-some AEs might be attributed to the pathogenecity caused by the attenuated microorganism and thus not be distinguishable (except perhaps in severity) from the disease against which the vaccine was being administered.[16] Here, in this study, considering the incubation period of concerned disease (JE) as 5-15 days, keeping in view that acute disease state might sustain for more than a week with prolonged convalescence; the AEs noted from 5th post vaccination day upto four weeks after vaccination might be grouped into this category.

During this period all the reported symptoms akin to the original, natural JE infection were opined **probably** related with vaccine. And for (c) remote AEs due to neurological or some other involvement – all participants were observed from 1 month through 1 year for detection of remote serious AEs, if any. The significantly higher rate of symptoms (mainly fever, cough, runny nose with few cases of pain abdomen and loose motion) among the lowest age group and on the 3rd month of follow-up could partly be due to the increased incidence of ARI and viral diarrhea, specially among the lower age group, during the winter season and partly to the continuation of some AEs developed during 5-28th post vaccination days. However, all these reactions were considered **unrelated** with vaccination and rather incidental. Some of the reported reactions opined in no way related with vaccination were categorized as miscellaneous and not entertained during analysis. Possibility of any concomitant/coincidental illness up to 28th post-vaccination days follow up period could not be over ruled. However, the findings of the present study were corroborating with other study results. Global Advisory Committee on Vaccine Safety (GACVS) acknowledged the excellent safety and efficacy profile of the SA-14-14-2 vaccine.[18] In relation to serious AEs reported after mass campaigns in India during 2006, no direct causality has been established between reported illness and the vaccine.[21]

Conclusion:

Consistency of present results with those of similar other studies held in different settings is helpful to conclude that the short term safety of the vaccine appeared to be satisfactory and although the present vaccine cohort didn't produce any serious AEs within one year two months follow up period after vaccination, yet, it is thought that such cohort should have been observed for another couple of years or larger post-marketing study might be conducted to comment on the long term safety profile and many other unexplored issues about the vaccine like its safety among immuno-compromized, infants, pregnant women; its potentiality for co-administration with other vaccines etc.

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