Original Articles

REACTOGENECITY OF INDIGENOUSLY PRODUCED MEASLES VACCINE

Indra Bhargava, Bharat C. Chhaparwal, Mrudula A. Phadke, Simin F. Irani, B.K. Chakladhar and C.P. Maheshwari

From the Serum Institute of India Research Foundation, Pune 411 028; M.G.M. Medical College and Chacha Nehru Hospital for Children, Indore 452 001; G.S. Medical College and K.E.M. Hospital, Bombay 400 012; B.J. Medical College and Sassoon Hospital, Pune 411 001 and Kasturba Medical College, Manipal 576 119.

Reprint requests: Prof. Indra Bhargava, Director, Serum Institute of India Research foundation, 212/2 Hadapsar, Pune 411 028.

Received for publication: October 30,1995; Accepted August 1,1996

Objective: *To assess the safety and reactogenecity of indigenously produced measles vaccine derived from EZ strain.* ***Design:*** *A longitudinal clinical follow up after vaccination.* ***Setting:*** *Hospital based and home follow up, as required.* ***Subjects:*** *12,470 children, 9 to 15 months old, immunized with measles vaccine of EZ strain, in accordance with the National Immunization Schedule, at five centers.* ***Methods:*** *A clinical follow up of children at 1 day, 1 week, 2 weeks, 3 weeks and 6 weeks after measles vaccination. A detailed clinical neurological examination in children showing side effects.* ***Results:*** *Mild side effects were documented in 31%. Of these, 90% were seen in the first two weeks, out of which two thirds were seen during the first week. Commonest side effects were coryza (10%), fever (9.8%), cough (3.2%) and diarrhea (3.2%). Convulsions, with no later sequelae were documented in 2 cases only.* ***Conclusions:*** *Measles vaccine manufactured in India, using EZ strain is a safe vaccine. It has a level of reactogenecity including neurological aspects, lower than that reported in India with the Schwarz strain vaccine.*

Key words: *Measles vaccine, EZ strain, Reactogenecity, Safety, Side effects.*

MEASLES vaccination has been in vogue in India for almost a decade with excellent results. This vaccine is regarded as an effective and a safe vaccine. It has few side effects, generally mild in nature, which include fever lasting for a day or two, occurring between 7 to 12 days in 5 to 15% of cases(l), rash lasting for a day or two occurring between 7 to 10 days in 5% subjects and febrile seizures in some vaccinees(2-5). Encephalopathy between 7 to 14 days of vaccination, has been reported in a few cases(6-9). However, the encephalopathy does not leave any permanent sequelae(l0).

Only a few studies(ll-14), mostly on small sample sizes(ll-13) have evaluated the reactogenecity of measles vaccine in India. These reports are based on the imported vaccine prepared from the Schwarz strain, and the observed incidence of side effects has shown considerable variation.

In late eighties, indigenously manufactured measles vaccine using Edmonston Zagreb (EZ) strain was introduced in India. Since this changeover, millions of doses of this vaccine have been administered to children in India without any serious adverse side effects.

The common side effects reported are mild fever, diarrhea and coryza. In a recent study, it was reported that side effects with the EZ strain measles vaccine manufactured in India are lower than those reported with the vaccine prepared from Schwarz strain(15). However, the sample size of this study was not adequate to evaluate all the documented side effects, especially those related to neurological system. The present study was therefore, undertaken in a multicentric approach to assess the reactogenecity of indigenously produced EZ strain measles vaccine, with special attention to neurological side effects.

Subjects and Methods

A total of 12,980 children in the age group 9 to 15 months, were enrolled for this study. All these children were immunized with measles vaccine according to the National Immunization Schedule. This vaccine had been produced from the EZ strain of measles virus by Serum Institute of India Ltd., Pune. Ethical clearance for this study had been obtained from the respective institutions. One hundred and forty children in the Indore urban slum area, with age upto 24 months, who had missed immunization till 15 months age were also included in the study. Out of these 510 children could not be followed up. Thus, 12,470 children consisting of 6,175 boys and 6,295 girls were evaluated. The details regarding the numbers enrolled, drop outs and boys and girls included in the study at each center are shown in *Table I.*

Details regarding history of concurrent minor illnesses like coryza and fever, past history of measles and convulsions and contact with a measles case during the last 72 hours, as well as presence of malnutrition were recorded for each subject. The children were called for a follow up 24 hours, 48 hours, 1 week, 2 weeks, 3 weeks and 6 weeks after immunization. Home visits were made by the health workers for most of the children, especially those, who could not report for a follow up. After 6 weeks of follow up, parents of the children were asked to contact the institution concerned in the event of a side effect. Specific addressed post cards were also provided to them for this purpose. Side effects particularly recorded included local pain and swelling, high and mild fever, cough, coryza, loose motions, a transient rash, irritability, drowsiness and vomiting. High fever was defined as body temperature above 38.4"C and mild fever was defined as body temperature between 37° C to 38.4°C. Cases with side effects were examined by a pediatrician with particular attention to a complete neurological assessment.

Sample Size

The sample size was adequate to evaluate an. expected side effect of 0.03% frequency within a range of 0.01% with a power of 80%.

Results

Side effects to measles vaccine were seen in 3901 subjects (31.3%) and all of them were mild in nature. Most of these effects were seen within two weeks of vaccination *(Table II).* The side effects observed, in order of frequency were coryza (10.0%), fever (9.84%), cough (3.18%), diarrhea (3.18%), irritability (1.87%), transient rash (1.52%), local reactions (1.25%) and conjunctivitis (0.35%). Most of the febrile reactions (40.6%) were seen at Indore and Manipal centers. A majority of subjects with coryza and cough (66.1%) were seen at Bombay and Manipal centers.

Drowsiness was observed in 7 cases during the first week at Manipal center only. Only two cases of convulsions were seen, one in the first week in the Indore urban slum area, where third dose of DPT was given

TABLE I–*Centerwise Details*

Center	Enrolled	Drop outs	Studied	Males	Females
Indore Hospitals	3250	170 (5.2)	3080 (24.7)	1608	1472
Indore Urban slums	3180	91 (2.8)	3089 (24.8)	1500	1589
Bombay	2445	119 (4.9)	2326 (18.7)	1154	1172
Pune	2352	70 (3.0)	2282 (18.3)	1052	1230
Manipal	1753	60 (3.4)	1693 (!3.5)	861	832
Total	12980	510 (3.9)	12470 (100.0)	6175	6295

Figures in parentheses indicate percentages.

simultaneously but at a separate site and the other at the Manipal center during the second week. In none of the two cases convulsions were repeated and no sequelae were observed afterwards.

Only one child died. The death was a result of diarrhea 4 weeks after vaccination at Manipal.

Discussion

Side effects after vaccination with measles vaccine produced from EZ strain in children were seen in 31% of the subjects. In earlier studies in India using Schwarz vaccine, the incidence was 10% and 70% in small sample investigations(11, 12) and 44.1% and 38% in larger sample re-ports(13,14). The side effects with indigenously produced measles vaccine of EZ strain were therefore, lower than those observed in the earlier studies in India with the imported vaccine prepared from the Schwarz strain.

All the side effects observed were mild in nature, predominant ones being fever, diarrhea and coryza. The spectrum of these adverse reactions is similar to that documented in earlier observations. In the present study, convulsions were observed in only two cases. No after effects were seen in these subjects. This is in contrast to the earlier reports of 8 cases out of 5283 subjects(14) and 7 cases out of 1599 subjects(13). In both these studies, measles vaccine from Schwarz strain was used. This indicates that the measles vaccine derived from the EZ strain had a low reactogenecity with respect to neurological manifestations.

Almost 90% of the side effects were seen in the first two weeks after vaccination. Of these, two thirds were observed in the first week. This suggests that the children should be observed for one to two weeks after vaccination, for such side effects.

It is concluded that the indigenously manufactured measles vaccine from the EZ strain has a high safety and low reactogenecity in Indian children aged 9 to 15 months of age. The vaccine has a level of reactogenecity including neurological aspects which is lower than that reported in India with the Schwarz strain vaccine.

TABLE II–*Side Effects in 12,470 Immunized Subjects.*

Symptom	Time Period (days)					Total
	3-6	7-13	14-29	30-44	> 45	
Coryza	742 (59.6)	281 (22.5)	91 (7.3)	70 (5.6)	62 (5.0)	1246 (10.0)
High fever	405 (59.4)	225 (33.0)	32 (4.7)	19 (2.8)	1 (0.1)	682 (5.47)
Mild fever	372 (68.2)	101 (18.5)	36 (6.6)	17 (3.2)	19 (3.5)	545 (4.37)
Cough	268 (67.8)	128 (32.2)	0	0	0	396 (3.18)
Diarrhea	293 (74.0)	81 (20.4)	7 (1.8)	10 (2.5)	5 (1.3)	396 (3.18)
Irritability	150 (64.4)	77 (33.1)	5 (2.1)	1 (0.4)	0	233 (1.87)
Rash	108 (57.1)	78 (41.3)	2 (1.1)	1 (0.5)	0	189 (1.52)
Local pain	78 (80.4)	19 (19.6)	0	0	0	97 (0.78)
Redness, Swelling	51 (86.4)	8 (13.6)	0	0	0	59 (0.47)
Conjunctivitis	30 (69.7)	13 (31.3)	0	0	0	43 (0.35)
Others*	14 (93.3)	1 (6.7)	0	0	0	15 (0.12)
Total	2511 (64.4)	1012 (25.9)	173 (4.4)	118 (3.0)	87 (2.3)	3901 (31.3)

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NOTES AND NEWS

PRE-CONFERENCE WORKSHOP ON MEDICAL EDUCATION: TEACHING METHODOLOGY AND ASSESSMENT

A 2-day workshop will be organized by the IAP-Education Center on 3-4 January 1997 at Ahmedabad as a part of the forthcoming IAP National Conference. It will cover a variety of topics related to medical education with a focus on teaching-learning methodology, rational use of media and assessment. The aim is to enable the participants to excel as teachers and to promote education and training in pediatrics in the country that is relevant, competency-based and of assured quality. The workshop is suitable for the teachers in pediatrics and will be limited to 25-30 participants only. In case you are interested in attending, kindly write to the undersigned before 30th November 1996 along with registration fee of Rs. 200/- (through cheque/DD in favor of 'Pedicon '97', payable at Ahmedabad). Please write to Dr. S.N. Vani, Organizing Secretary, *separately* regarding your boarding/lodging.

R.N. Srivastava
President IAP and Chairman IAP-Education Center,
Department of Pediatrics,
All India Institute of Medical Sciences,
New Delhi 110 029.