

## Original Research Article

# Adverse events following immunization with pentavalent vaccine among infants attending the immunization clinic at a tertiary hospital in Eastern India

Shamshad Ahmad, Jayita Pal\*, Amiya Das, Sonalinandini Samanta

Department of Community Medicine, ESI-PGIMS, ESIC Medical College, Joka, West Bengal, India

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### \*Correspondence:

Dr. Jayita Pal,

E-mail: [docjayita.pal@rediffmail.com](mailto:docjayita.pal@rediffmail.com)

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## ABSTRACT

**Background:** Prevention of childhood diseases of public health importance is mainly achieved by immunization. Pentavalent vaccines provide immunity and protection quickly and safely. It also reduces the cost, occupational-environmental hazards as well as distress and inconvenience for the children and their parents. Adverse events following immunization (AEFI) are well established with DPT, Hep-B and Hib vaccine separately in numerous studies but when given in combination as pentavalent vaccine, data on AEFI with this is still lacking. Does there is any reduction in proportion of various minor and major AEFI after pentavalent vaccination in comparison to separate vaccines? To fill this gap in knowledge we carried an observational epidemiological study to find out the proportion and associated factors for various adverse events following immunization with pentavalent vaccine.

**Methods:** It was a descriptive longitudinal study carried out in immunization clinic at a tertiary care centre of Eastern India. It was done between July-September 2016. Study population constitutes all the infants who attended the immunization clinic for getting vaccines. All the infants who attended the immunization clinic and were eligible for pentavalent vaccines were selected for the study.

**Results:** A total of 230 infants participated during study period. Incidence of minor adverse events reported very high, 67 per 100 doses across all doses. Fever was most common symptom reported. Demographic character or birth history of infant had not showed an effect on occurrence of any adverse event.

**Conclusions:** Study showed that from clinical perspective pentavalent vaccine given in a single injection has increased reactogenicity in comparison when given separately.

**Keywords:** Pentavalent vaccine, AEFI

## INTRODUCTION

Universal immunization programme (UIP) in its recent move has decided to introduce pentavalent vaccine in selected states.<sup>1</sup> When given separately, it needs 9 shots [3 for DPT+3 for Hep-b +3 for Hib] to provide protection against all the above-mentioned diseases. Pentavalent vaccine reduces it to 3 shots. Besides providing immunity and protection quickly and safely, it reduces cost,

occupational-environmental hazards as well as cause less distress and inconvenience for the children and their parents. Since its introduction (2011) till now, there have been different controversies regarding the infant death across India and worldwide.<sup>2</sup>

It may be the reason itself (causal association), or, there might be some other factors (temporal association/ coincidental adverse event) for which the complications

are reported. Adverse events following immunization (AEFI) are well established with DPT, Hep-B and Hib vaccine separately in various studies but when given in combination as pentavalent vaccine, data on AEFI with this is still lacking. Does there is any reduction in proportion of various minor and major AEFI after pentavalent Vaccination in comparison to separate vaccines? It is utmost important to monitor reactogenicity of vaccine used in immunization programme. To establish and maintain the faith of community in immunization programme, identification, detection, prevention and appropriate communication is necessary.<sup>3</sup>

The term “AEFI” merely denotes a temporal relationship between vaccination and adverse events. This relationship need not to be causal from an expert point of view. But community mostly perceived it as causal. To fill this gap in knowledge we plan to carry an observational epidemiological study. Despite every care, vaccine given to infant can cause adverse events. Our study investigated the reported AEFI with pentavalent vaccine. Infants were actively followed up for this purpose. Study aimed to find out the proportion and associated factors for various adverse events following immunization with pentavalent vaccine.

## METHODS

The study was carried out in an Immunization clinic at a tertiary care centre of Eastern India, during the period of July-September 2016. It was an observational descriptive study. The study was longitudinal in nature. Study population constitutes all the infants who attended the immunization clinic for getting vaccines. It was a time bound study. All the infants who attended the immunization clinic and were eligible for pentavalent vaccines were selected for the study. Infants were excluded when, consent not given by parent, suffering from high grade fever, h/o convulsions, h/o allergy, immune-compromised, having established acute illness, suffering from malignant conditions or any type of tumours, h/o adverse/allergic effects with previous vaccines.

### *Data collection procedure*

Step 1: Infants attending immunization clinic for pentavalent vaccination were screened.

Step 2: Informed consent was taken by the mother/father/natural guardians. Pre-vaccination counselling was done

Step 3: General profile, birth history and medical history were recorded followed by measurement of weight, MUAC, heart rate, respiratory rate etc.

Step 4: Infant sent to immunization room.

Step 5: Post Vaccination counselling was done related to adverse events (minor and major) and their management.

A contact number provided to the mother/father/natural guardians to report any adverse event noted.

Step 6: A telephonic contact was done within 24 hours (preferably within 8 hours), after 48 hours and between 5-7 days to know any adverse events (minor & major), if occurred.

Step 7: In a case of any serious event, the patient would be followed as per the AEFI guidelines of government of India.

### *Confidentiality*

All the information gathered during the study period would be kept confidential.

### *Statistical analysis*

Data entered in Microsoft excel 2016 student's edition. Frequency with percentage calculated. Chi-square test used to compare categorical variable. Binary logistic regression applied to obtained odds ratio. Bar diagram and Box plot used for graphical representation of data.

### *Ethical considerations*

Ethical clearance was taken from institutional ethical committee before starting the actual research work.

## RESULTS

A total of 232 infants participated in the study. Two lost to follow up. Finally, 230 infants followed up for AEFI with pentavalent vaccination.

Mothers' education of infant was compared across their gender. Among female infants 78.8% have their mother educated up to high school or above. It was 68% among male infant. The difference was non-significant. 64.8% of males and 63.9% of females were of 1<sup>st</sup> birth order. Delivery by caesarean section was high. It was 68.9% in male infant and 78.7% in female infant. More than half of infants were born preterm. Approximately 10% of infants in both sexes were born low birth weight (Table 1).

Clinical history and examination of infant was done before giving vaccine. 33.4% infants at 1<sup>st</sup> dose, 35.2% at 2<sup>nd</sup> dose and 18.2% at 3<sup>rd</sup> dose was suffering from ill health. Acute upper respiratory illness reported most commonly at each dose. 7.1%, 3.3% and 3.0% infants were febrile at the time of 1<sup>st</sup>, 2<sup>nd</sup> & 3<sup>rd</sup> dose. Similarly, in 9.1%, 4.4% & 4.0% infants fast breathing was observed at the time of 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> dose (Table 2).

A total of 194 AEFI reported in 177 infants. Incidence of all AEFI per 100 doses of pentavalent vaccine administered, calculated. It was 93 per 100 doses after 1<sup>st</sup> dose, 67 per 100 doses after 2<sup>nd</sup> dose and 41 per 100 doses after 3<sup>rd</sup> dose. Overall incidence was 67 per 100

doses (Table 3). A bivariate logistic regression was performed to ascertain the effect of gender, birth order, mothers' education, mode of delivery, maturity, and birth weight on the likelihood that infant have AEFI after administration of pentavalent vaccine. Odds ratio of occurrence of AEFI in male was 1.08 (95% CI: 0.572-2.06) and among low birth weight infants 2.36 (95% CI: 0.625-9.07). None of the variables had odds ratio found

significantly affecting the occurrence of AEFI after vaccination (Table 4). Frequency of AEFI reported within 24 hours of administration of pentavalent vaccine in relation to clinical history/examination status before immunization was analysed. A cross tabulation of adverse effect after each dose across various clinical profile was made. None of the variables were found to be significantly associated with the occurrence of AEFI.

**Table 1: Demographic profile and birth history according to gender of infants (N =230).**

Variable	Category	Male (N =122) n (%)	Female (N =108) n (%)	Test of significance
<b>Mothers' education</b>	Illiterate	11 (09)	8 (7.4)	$\chi^2 = 3.31$ p=0.507
	Primary + Middle	28 (23)	16 (14.8)	
	High school and above	88 (68)	84 (77.8)	
<b>Birth order</b>	1 <sup>st</sup>	79 (64.8)	69 (63.9)	$\chi^2 = 0.169$ p=0.919
	2 <sup>nd</sup>	35 (28.7)	33 (30.6)	
	Above 2 <sup>nd</sup>	08 (6.6)	06 (5.6)	
<b>Mode of delivery</b>	Normal vaginal	38 (31.1)	23 (21.3)	$\chi^2 = 3.25$ p=0.196
	LSCS + Assisted	84 (68.9)	85 (78.7)	
<b>Maturity</b>	Full term	56 (45.9)	43 (39.8)	$\chi^2 = 3.07$ p=0.216
	Preterm	64 (52.5)	59 (54.6)	
	Post dated	02 (1.6)	06 (5.6)	
<b>Birth weight (WHO class)</b>	Below -2 SD	12 (9.8)	10 (9.3)	$\chi^2 = 0.022$ p=0.532
	Between -2 SD to +2 SD	110 (90.2)	98 (90.7)	

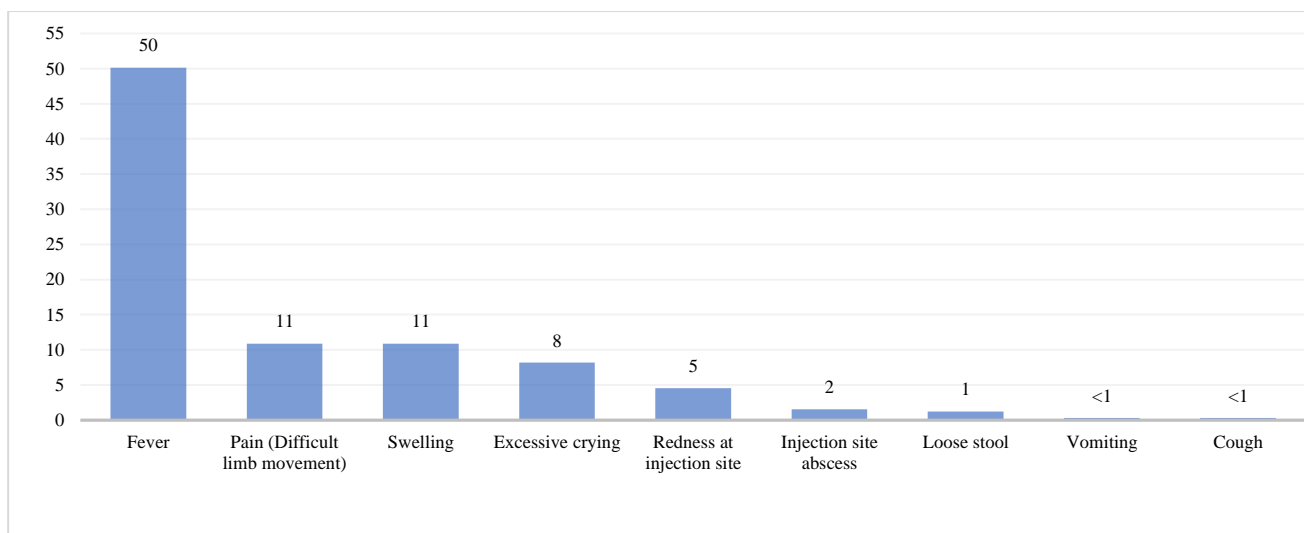
**Table 2: Status of clinical history and examination of infant before the scheduled dose of pentavalent vaccine.**

		1 <sup>st</sup> dose (N =99) n (%)	2 <sup>nd</sup> dose (N =91) n (%)	3 <sup>rd</sup> dose (N =99) n (%)
<b>Any illness before the scheduled dose</b>	Yes	33 (33.4)	32 (35.2)	18 (18.2)
	No	66 (66.6)	59 (64.8)	81 (81.8)
<b>Type of illness*</b>	Fever	09 (9.1)	--	01 (1.0)
	AURI	24 (24.2)	22 (24.2)	13 (13.1)
	Rashes	07 (7.1)	04 (4.4)	--
	Loose stool	02 (2.0)	01 (1.1)	04 (4.0)
	Vomiting	--	03 (3.3)	01 (1.0)
	Others	--	06 (6.6)	01 (1.0)
	<b>Temperature</b>	Febrile	07 (7.1)	03 (3.3)
	Afebrile	92 (92.9)	88 (96.7)	96 (97)
<b>Respiratory rate</b>	Normal/slow	90 (90.9)	87 (95.6)	95 (96)
	Fast	09 (9.1)	04 (4.4)	04 (04)
<b>Weight according to WHO classification</b>	Below -2 SD	09 (9.1)	06 (6.6)	08 (8.1)
	Between -2 SD to +2 SD	90 (90.9)	85 (93.4)	91 (91.9)

\* Figures are mutually exclusive.

**Table 3: Incidence of AEFI per 100 dose of pentavalent vaccine administration.**

Schedule dose	Number (%)	No. of AEFI reported	Incidence of AEFI per 100 doses
<b>1<sup>st</sup> Dose</b>	99 (34.3)	92 (47.4)	93
<b>2<sup>nd</sup> Dose</b>	91 (31.5)	61 (31.4)	67
<b>3<sup>rd</sup> Dose</b>	99 (34.2)	41 (21.2)	41
<b>Total</b>	289 (100)	194 (100)	67

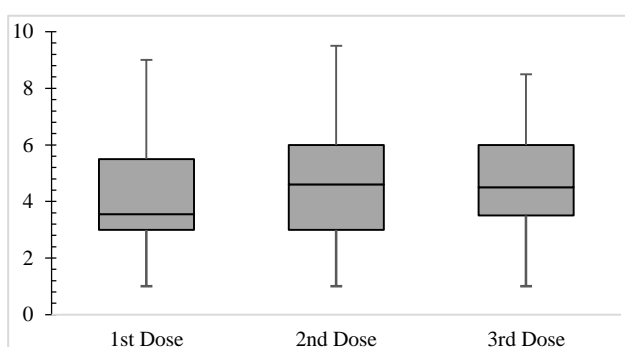


**Figure 1: Incidence of various AEFI per 100 dose of pentavalent vaccine administration.**

**Table 4: Risk factors in infants having any AEFI within 24 hours of administration of pentavalent vaccine.**

Variable		Any AEFI with all doses		
		Occurred (N =177) n (%)	Not occurred (N =53) n (%)	OR (95% CI)
<b>Gender</b>	Male	94 (77)	28 (23)	1.08 (0.572-2.06)
	Female*	83 (77)	25 (23)	
<b>Birth order</b>	1 <sup>st</sup>	111 (75)	37 (25)	0.604 (0.303-1.20)
	2 <sup>nd</sup> & Above*	66 (80.5)	16 (19.5)	
<b>Mothers' education</b>	Illiterate	12 (63.2)	07 (36.8)	0.399 (0.131-1.21) 0.621 (0.289-1.37)
	Primary + Middle	32 (72.2)	12 (27.8)	
	High school and above*	133 (79.6)	34 (20.4)	
<b>Mode of delivery</b>	Normal Vaginal	43 (70.5)	18 (29.5)	0.571 (0.275-1.17)
	LSCS+Assisted*	124 (73.4)	35 (26.6)	
<b>Maturity</b>	Full term	75 (75.8)	24 (24.2)	1.93 (0.365-10.2) 1.62 (0.306-8.59)
	Preterm	97 (78.9)	26 (21.1)	
	Postdated*	05 (62.5)	03 (37.5)	
<b>Birth weight (WHO classification)</b>	Below -2 SD	19 (86.4)	03 (13.6)	2.38 (0.625-9.07)
	Between -2 SD to +2 SD*	158 (76)	50 (24)	

\* Reference category.



**Figure 2: Box plot presentation of time duration for appearance of AEFI after administration of pentavalent vaccine.**

AEFI incidence calculated separately showed that across all doses incidence of fever was 50 per 100 doses followed by pain (difficulty in moving limb) and swelling which was 11 per 100 doses in each (Figure 1). The above Box plot depicted that median duration of occurrence of adverse events after 1<sup>st</sup>, was 3.5 hours and after 2<sup>nd</sup> and 3<sup>rd</sup> dose was 4.5 hours for both. AEFI appeared earliest by 1 hour and latest by 8.5-9.5 hours after all dose (Figure 2).

## DISCUSSION

It was a longitudinal study. Infants were followed up for occurrence of any adverse event following immunization with pentavalent vaccine.

According to World health statistics, 9% (nine) of all birth in India were by caesarean section.<sup>3</sup> Present study reported very alarming finding. 68% of all infant were born by caesarean section at our setting. No biological or medical reason can explain this finding. It may a behaviour issue for giving utmost preference to caesarean section by family. This should be explored separately.

The rate of pre-term birth ranges from 5-18% of babies born across 184 countries according to WHO (WHO report 2004).<sup>4</sup> Indian foundation for premature babies reported (2013) this rate around 21%. In present study, more than 50% of infants born preterm. This may be because most of the beneficiaries<sup>7</sup> in our setting opt for elective caesarean section. Even on mild discomfort near term they OPT it instead of waiting for child maturity. This observation needed further evaluation.

In India, nearly 20% of new-born have low birth weight (LBW). Males have less frequency of LBW than female.<sup>5</sup> Present study reported lower proportion of LBW i.e. 10% and almost equal in male and female infant.

Before immunization, clinical history and examination of all infant was done. 18-35% of infants were found to suffering from some illness at the time of immunization. Although these illnesses were minor, which included mostly acute upper respiratory tract infection (AURI) constituting 13-24% cases? Other was fever (1.0-9.0%), rashes (4.4%-7.1%), loose stool (1.1-4.0%). Researcher counselled and reassured the mother that these mild illnesses should not be reason to delay routine immunization. MoHFW 2010 operation guidelines also recommend this. Further, many good-quality studies support this recommendation. Ratnam et al, in their study showed that presence of AURI during the preceding 28 days, at the time or up to 7 days after immunization had no effect on antibody response to MMR vaccine.<sup>6</sup> Similar effect is reported by Cilla et al.<sup>7</sup>

Researcher observes that about 50% of infant came for immunization were born preterm and 10% as LBW. It is recommended that all medically stable preterm and low birth weight infants should receive full dose of vaccine at chronological age consistent with the national immunization schedule.<sup>8</sup>

Study reported high incidence of AEFI per 100 doses administered, after each scheduled dose. It ranged from 41-93 per 100 doses. This could be because we actively and continuously followed up the infant after immunization. This led to reporting of any minor or major events that appear after immunization. Several studies reported this incidence in per 100,000 doses administered which is very low in comparison to present study. Incidence of Fever was 50 per 100 doses administered. This is again a high figure. Various authors also reported incidence of fever in 12-90% of infant after immunization.<sup>3,9</sup>

Other symptoms like pain (difficult limb movement). Swelling, excessive crying and redness at injection site

reported between 5-11 episodes per 100 doses. This was supported by finding of Kimmel et al.<sup>10</sup>

All AEFI reported during first telephonic contact only i.e. within 24 hours of vaccine administration. During 2<sup>nd</sup> and 3<sup>rd</sup> telephonic contact after each dose, no fresh AEFI reported. Whatsoever AEFI reported in 2<sup>nd</sup> and 3<sup>rd</sup> contact was continuation of that reported in 1<sup>st</sup> contact. Majority of infants with AEFI were recovered within 24-48 hours of onset. 42 adverse events continued till 2<sup>nd</sup> contact and only 5 continued till 3<sup>rd</sup> contact. No major adverse events reported during study period.

Median duration of occurrence of adverse events in our study ranged from 3.5-4.5 hours across all doses. All adverse events occurred within 24 hours of immunization. Cunha, et al had got similar finding in their study.<sup>11</sup>

### **Key messages**

First 24 hours after pentavalent vaccination was very important period to observe for any AEFI. Within this, first 6 hours after immunization remained very crucial. This finding could be used as prognostic indicator for post-immunization counselling of parent at clinic.

### **CONCLUSION**

Adverse event with DTP, Hep-B and Hib vaccine has been well established separately. These antigens given in combination as pentavalent vaccine. Its reactogenicity to infant need to be explore. We carried an observation longitudinal study. Infants were followed up after immunization via calling to their parents. The entire adverse event reported by parents had been noted. A total of 230 infants participated during study period. Incidence of minor adverse events reported very high, 67 per 100 doses across all doses. Fever was most common symptom reported. Demographic character or birth history of infant had not showed an effect on occurrence of any adverse event. This study shows that from clinical perspective pentavalent vaccine given in a single injection has increased reactogenicity in comparison when given separately.

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*Ethical approval: The study was approved by the Institutional Ethics Committee*

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