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Original Research Article

Adverse events following immunization of infants – an experience at an immunization clinic of a tertiary care hospital in Odisha, India

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Abstract

Immunization especially of infants is one of the most cost effective strategies to control mortality and morbidity from infectious diseases and in India this preventive arm is being used as one of the key public health strategies. In recent years, the government has introduced Pentavalent, Rota virus vaccines in infants below 6 months of age, besides other initiatives. However in such blanket application of public health strategies, the adverse events need to be dealt with sensitively by the health provider in order to maximize gains. This study explores the vaccines offered at 6,10,14 months of age and thus offering a chance to know the variety of adverse events reported, which otherwise in most cases, go unnoticed. 96.4% infants came for their vaccination on time and the same number were being exclusively breastfed; vaccines after the 6-8 weeks dose, adverse events reporting was maximum, highest being compliant of fever (27.3%). Even after the third dose, the predominant compliant was that of fever, though reported in only 8% of the subjects. It was found that mode of delivery had a significant association (P <0.001) with the presence of Adverse Events Following Immunization (AEFI), which given the small sample size, can purely be by chance. Complaints were more commonly reported by mothers who were exclusively breast feeding but it could be an over sensitive reporting bias. This study indicates that immunization of infants is a very well received community strategy and can be made stronger by more interpersonal counselling of the guardians regarding potential side effects of the vaccines and their management.

Key words: Infant immunization, Pentavalent vaccines, Rota vaccine, adverse events, fever

INTRODUCTION

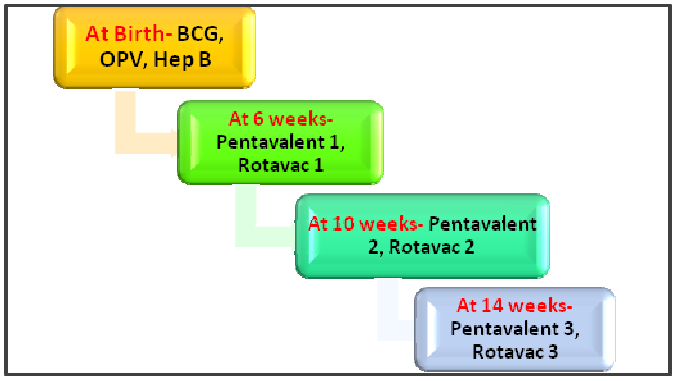
Immunization is one of the most well-known and effective methods of preventing childhood diseases. With the implementation of the Universal Immunization Programme (UIP) by the Government of India(GOI), significant achievements have been made in preventing and controlling vaccine-preventable diseases (VPDs) (Ministry of Health and Family Welfare MOHFW-India, 2012) but effective immunization requires population coverage levels of 90 to 95% depending upon the burden of vaccine-preventable disease (Sharma B et al., 2013).

The first few months of infancy plays a vital role in a child's life, therefore compliance and completion of immunization are equally important as are nutrition, growth and development of the child. Worldwide,

infectious diseases cause death of > 2 million newborns and infants less than 6 months of age. Significant reduction of this burden will require development of early life vaccination, including vaccines effective when given at birth, the most reliable point of global healthcare contact (Demirjian et al., 2009).

Currently according to National Immunization schedule (NIS) of India, Pentavalent vaccine has replaced Diphtheria Pertussis Tetanus (DPT) Toxoid, Hepatitis B (Hep B) and Haemophilus Influenza type b (Hib) conjugate vaccine at 6, 10 and 14 weeks. Rotavirus vaccine has also been introduced at 6, 10 and 14 weeks in selected states of India, including Odisha. Pentavalent vaccine provides protection to a child from 5 life-threatening diseases – Diphtheria, Pertussis, Tetanus, Hepatitis B and Hib. DPT (Diptheria+Pertussis+Tetanus) and Hep B were already part of routine immunization in India; Hib vaccine is a new addition. Together, the combination is called Pentavalent. In UIP, Pentavalent vaccine comes in a liquid form in a vial which contains 10 doses. Each dose is 0.5 ml to be given by intra muscular injection in anterolateral aspect of the mid-thigh using auto disable syringes. Thus, this timing of 6,10 and 14 weeks holds a vital clue to assessment of vaccination programs in the country and also to check for the adverse reactions to the combination vaccines, as the same cohort comes back twice for the same combination vaccines. In our country, immunization is vested with the frontline workers and its success heavily depends on the understanding and compliance of mothers to come for the successive doses.

The immunisation schedule approved by GOI is as below:



The tertiary care hospital immunization clinic (place of study) had the opportunity to run two successive trials on a DPT vaccine and subsequently the newly introduced Rota Vaccines, wherein subjects were to be enrolled at 6,10,14 weeks. Thus this study was conceived to follow up the 6-8 weeks infants visiting the immunization clinic till the 14 weeks, with the aim to determine the adverse events following vaccination, their compliance and associated sociodemographic factors that might be determinants of the compliance.

Objectives

1. To determine the adverse events following each dose of Pentavalent or DPT in combination along with Oral Polio and Rota vaccines
2. To assess the dropout rates (exclusively in this study) and reasons for the same.

METHODOLOGY

Place of Study

Immunization clinic, Kalinga Institute of Medical Sciences, Bhubaneswar.

Study design

Longitudinal study with the study population being infants visiting the immunization clinic of the hospital for administration of vaccines scheduled within 6-8 weeks and whose parents/caregivers were willing and gave consent to participate in the study.

Study period

November 2015 to March 2017

Sample Size

A convenient sample size of 110 was drawn up during the study period as the sample was primarily drawn from 2 trials that ran successively in the clinic, first being- A prospective randomized two arm, single blind, parallel, active controlled, multi-centric, non-inferiority, phase II/III clinical study to evaluate the immunogenicity and safety of Diphtheria, Tetanus and Pertussis (whole cell) vaccine(adsorbed) of M/s Cadila Health Care limited compared to Diphtheria, Tetanus and Pertussis(whole cell) vaccine (adsorbed) of M/s Serum Institute of India Limited in healthy adults and second being-

A seamless sequential Phase III, randomized, multicentric single blind study to evaluate immunogenicity, safety, reactogenicity of liquid ROTAVAC 5C formulation of the live attenuated rotavirus vaccine as a 3 dose series when compared with ROTAVAC in infants (Protocol No. BBIL/ROTA5 C/III2014, Version 1.1 dated 26/7/2014)

These trials started in the tertiary care in late 2015, the first one followed by the second one in March 2016. (Figure 1 and 2)

The reason for taking the subjects from the trial was that these subjects would be definitely coming back for the subsequent doses and hence the assessment of the subjects for adverse reactions during 10 and 14 weeks would be possible. Else the subjects usually, in spite of

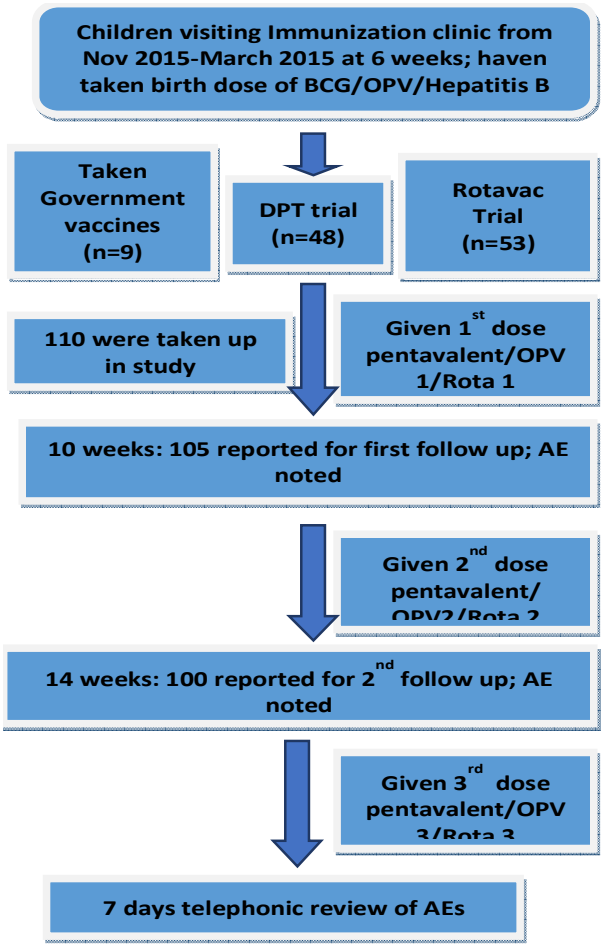


Figure 1. Flow chart of subjects taken up for the study

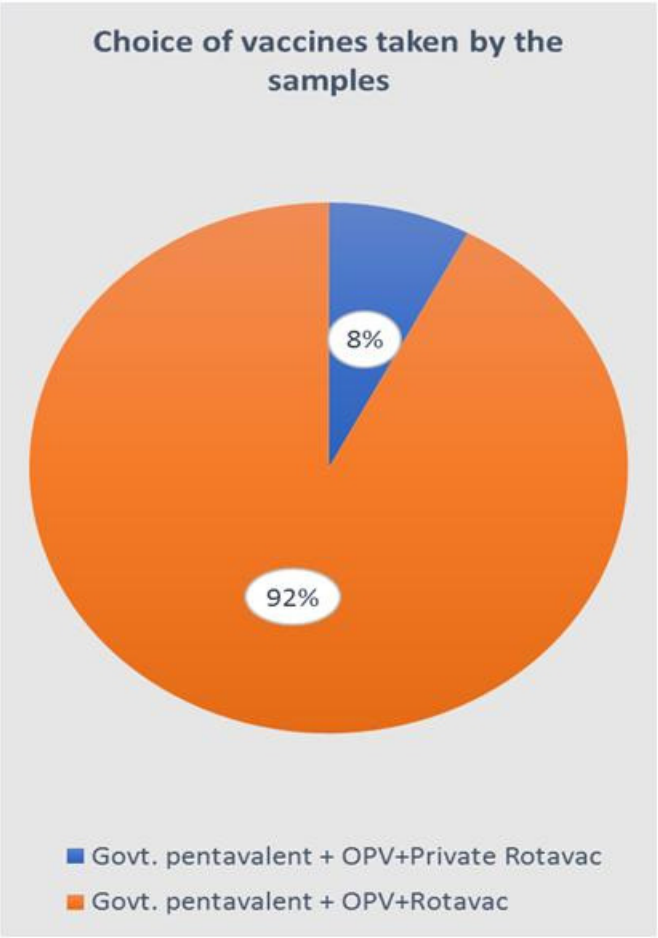


Figure 2. Choice of vaccines taken by the samples

all counselling break away to take the subsequent doses in their villages or outstations due to availability of the vaccines universally in the country.

The trial subjects complied in terms of reporting of adverse events (AE) as it was mandatory as per the trial protocol and continued the series at one clinic. Few of the non trial subjects, who were from the catchment area around clinic were also enrolled, subject to their willingness to take all 3 doses of DPT/Pentavalent, Oral Polio Vaccine (OPV) and Rota vaccines at the study clinic site

The inclusion criteria thus was fixed at 6-8 weeks of subject who would be have availed the at birth vaccines; willing to take vaccinations at 6, 10, 14 weeks at our clinic and availing DPT or Pentavalent form along with Oral Polio and Rota and ready to share the vaccination experience till 7 days after vaccination. Thus, most of the recruits were from the trials ie around 92.3% and rest took the government vaccines of Pentavalent, Oral Polio and Rota (it was taken on purchase in case of those on DPT trial and the non trial subjects before 2015 and was given free to the subjects on the Rota trial). Thus it was ensured that all subjects in the current study at least received DPT (Plain/ Pentavalent), Rota vaccine as well as OPV on all the 3 visits.

A pre- designed, pre-tested, semi structured questionnaire was used to collect data from the parents/caregivers of the infant enrolled in the study. Questions on socio-demographic characteristics, delivery type, birth weight, delivery and new-born care practices, feeding habits including practice of exclusive breastfeeding, vaccination at birth, choice of vaccination, willingness to continue vaccination at the same institution, satisfaction with the immunization services were noted. Anthropometric measurements like current weight, length, head circumference were taken after the first dose. A day after one week of vaccination, a telephonic conversation with the parents/caregiver was made and questions about any adverse effects or side effects were asked and noted. They were also asked to visit the immunization clinic if they needed any consultation or advice regarding any such adverse effect.

The same method was followed after the 10^{th} and 14^{th} week vaccination as well. The number of dropout study subjects at the 10^{th} and 14^{th} week was thus calculated, though here the disclaimer is that the dropout rate is the

Table 1. Socio-demographic, delivery and feeding practices of the sample

Variables		Frequency (n= 110)	Percentage (%)
Gender	Female/Male	58/52	**52.7/47.3**
Religion	Hindus	99	**90.0**
	Muslims/Christians/Sikhs	6/3/2	5.5/2.7/1.8
Residence	Rural/Urban	21/89	19.1/**80.9**
Fathers' education	Just literate/ High school and above	3/107	2.7/**97.3**
Fathers' occupation	Professionals and Semi-professionals/Others	55/55	50/50
Mothers' education	Illiterate/Just literate/ High school and above	2/6/102	1.8/5.5/**92.7**
Mothers' occupation	Housewives/Working	97/13	88.2/**11.8**
Family income/month (Rs)	8989- 13494	1	0.9
	13495-17999	13	11.8
	18000-36017	44	40.0
	>36017	52	47.3
Place of delivery	Home/Institutional delivery	7/103	6.4/**93.6**
Mode of delivery (including home deliveries)	Caesarean Section/Normal	54/56	49.1/50.9
Birth weight category	Very low birth weight (<2 kgs)	13	11.8
	Low birth weight (2 -2.5 kgs)	28	25.5
	Normal birth weight (>2.5 kgs)	69	62.8
1^{st}/ 2^{nd} /3^{rd} - visit- Exclusive breastfeeding practice*	No	4/10/11	3.6/9.1/10
	Yes	106/95/89	96.4/90.4/89

*n (at 1^{st} visit) = 110, n (at 2^{nd} visit) =105, n (at 3^{rd} visit)= 100

number who dropped out from seeking vaccination at this center/ trial. It necessarily did not equate with drop out from the vaccination process as a whole.

Data was entered into Microsoft excel and analysed using SPSS software (version 20). Chi- square test was applied and a p value of ($p<0.05$) was considered significant.

RESULTS

A total of 110 study participants were enrolled in the study for a period of 3 months and followed up till the completion of 14^{th} week vaccination. The Mean ± S.D. age of the participants at the time of enrolment in the study was found to be (6.13±0.43) weeks which hint that the guardians are very well sensitized to come for vaccination after 6 weeks of birth.

The Mean ± S.D birth and current weight (at 6-weeks vaccination visit) of the infants were 2.65 ± 0.658 kg and 4.08 ± 0.651 kg respectively.

100% of the infants had taken BCG and OPV vaccines at birth and 87.3% had taken hepatitis B vaccine at birth. The 12.7% who did not get Hep B vaccine was due to Low birth weight.

96.4% infants came for their vaccination on time, the rest 3.6% were delayed their vaccination. The main reason for delay was admission in NICU.

Maximum number of study participants (92.3%) had chosen to take Pentavalent vaccine/ DPT along with OPV and Rotavac being trial patients as specified before , the rest opted for the Government Pentavalent vaccine along with OPV and a Private Rotavirus vaccine ,as depicted in Figure 2 above.

Table 1 shows the distribution of the study subjects according to gender, current age in weeks, birth weight category, religion, place of residence, parents education, occupation income, delivery details and feeding practices.

Among the study subjects only 6.4% had home delivery, out of which all (100 %) of deliveries were performed by skilled birth attendants. 5 (4.5%) infants

Table 2. Adverse events -as reported at 1st, 2nd and 3rdvisits

Time of visit	Adverse events					
	Fever	Swelling and Redness	Pain on touch	Increased crying	Vomiting	Diarrhoea
First visit (at 6-8 weeks) (n= 110)	30 (27.3%)	7 (6.36)	2 (1.8%)	9 (8.2%)	1 (0.9%)	0
Second visit (n=105)	5 (4.8%)	5 (4.8%)	2 (1.9%)	0	2 (1.9%)	1 (0.95%)
Third visit (n=100)	8 (8%)	2 (2%)	0	2 (2%)	0	0

Table 3. Presence of AEFI and its associated factors

Variables	Presence of AEFI		P value
	Yes (n=13)	No(n=97)	
Mothers' education			
Illiterate	0	2	0.8187
Just literate	1	5	
High school and above	12	90	
Mothers' occupation			
Housewife	11	86	0.4747
Working	2	11	
Caretaker of the baby			
Both parents	3	28	0.5379
Only mother	8	64	
Other family member	1	3	
Babysitter	1	2	
Mode of delivery			
Caesarean section	11	43	0.006
Normal Delivery	2	54	
Exclusive Breastfeeding (1st Visit)			
No	0	4	0.6001
Yes	13	93	

were admitted to Neonatal Intensive Care Unit (NICU), among them 4 were due to Low birth weight and 1 was due to neonatal jaundice.

At the time of enrolment 96.4% of the study participants were being exclusively breastfed. Among the rest who were not, 1.8% took packaged formula feed and another1.8 % took homemade feed and packaged formula feed both.

From the above table 2 it is evident that the vaccines after the 6-8 weeks dose, adverse events reporting was maximum, highest being the compliant of fever(27.3%), inconsolable crying (8.2%) followed by swelling and redness at the injection site (6.36%). Even after the third dose, the predominant compliant was that of fever, though reported in only 8% of the subjects. Due to study constraints, it was not possible to know the pattern of adverse events reported on an individual basis and the table reports only cumulative percentages. The data also included multiple responses for adverse events like the same child complaining of fever, crying and swelling but for the ease of presentation, the complaints have been analysed independently.

Table 3 shows the association of AEFI with certain socio demographic factors taken in the study. Among the 110 participants 97 (88.2%) participants did not present with any adverse events considering all the 3 visits and also a few who had complaints in any one visit alone, meaning thereby that the complaints would be fairly by chance and not attributable to the vaccines. Total of 13 (11.8%) study participants had complaints of AEFI in all 3/at least 2 visits, which would be more justifiable to be attributed to vaccines.

It was found that mode of delivery had a significant association ($P < 0.001$) with the presence of AEFI, which given the small sample size, can purely by chance and would need further studies.

In the table above, the complaints reported are more in case of housewives and when the caretaker is the mother. This does not go against the immunization but in favour of the exclusive care that is rendered by the

mother to her own child in care, that no lapse in health misses any mention. Same goes for the exclusively breastfed infants.

Out of the 10 who dropped out most (7) cited difficulty to come to the clinic at the scheduled time as the major reason to drop out and the other 3 denied vaccines because of the fever.

This simple study calls for strengthening of the immunization services regarding interpersonal communication to guardians regarding handling of AEFI and reminders being sent to parents regarding the vaccination dates.

DISCUSSION

This short study emphatically brings out the success of the immunization drive in the country, especially for the infants. The basket of choices offered free under the Universal Immunization Programme is becoming inclusive of more infectious diseases and by 14 weeks the infant is immunized against seven diseases.

The UIP in India has come a long way, battling misconceptions, poor vaccine coverages, non-compliance of beneficiaries in continuing with the subsequent doses and adverse events of vaccines which have thwarted most good results in the past. The most common reasons for partial or non-immunization were: inadequate knowledge about immunization or subsequent dose, belief that vaccine has side-effects, lack of faith in immunization or that oral polio vaccine is the only vaccine required as reported in some studies in North India. (Kumar D et al., 2010), (Mathew JL et al., 2002), (Nath B et al.,2007)

Over the recent years the UIP has been very dynamic and has introduced several new vaccines in the immunization basket, especially the infants i.e. Pentavalent in 2014-2105 and Rota vaccines in 2015 for the state of Odisha where the study was undertaken. The importance of the vaccines was that they offered prevention against infectious diseases and at the same time needed at least three doses for optimum protection. The 6, 10, 14 weeks thus was a crucial timing to come back for a full package of combination vaccines and our study brings out the fact strongly that the adverse reactions were not very severe in this sample. Fever was the predominant symptom along with crying which could be attributed to the whole cell Pertussis component in the DPT or Pentavalent vaccine. (Schumacher Z et al., 2010), (LIU DW et al., 2008), (WU WD et al., 2009), (Lone Z et al., 2010). For this prophylactic paracetamol drops is recommended in most settings so that it does not become a deterrent for the guardians to get the infants for the subsequent doses. The guardians have to be patiently counselled regarding the possible adverse events and explained to them what measures are to be taken in case of an adverse event too. This simple inter-personal counselling minimizes the impact the adverse reactions that may be happening after immunization. The oral Polio and Rota vaccines were very well received in the current scenario and the adverse events too were nominal. However the scientific world should be cautious regarding the immunogenicity and safety in the larger cohort and encourage community trials to reflect the same.

Low Birth Weight (LBW) of the baby did not show any significant association as the sample for this study was predominantly from the urban areas and LBW babies receive good care both from the guardians and in terms of access to quality health services. In this case it was observed that at the time of recruitment into the study ie 6 weeks, most of the LBW babies had optimally gained weight and fallen into the normal weight for age category. However more studies especially in rural areas are warranted.

The limitations in the study is an inability to report on more infants taking the combination vaccines reasons being the study was limited to the centre and for a specific period. Gratitude is expressed to Cadila and Bharat Biotech for the trials at the centre, where some of the sample during the study period was drawn and information on AEFI alone was taken. More such collaborative studies should be encouraged to get robust data and AEFI and study factors associated with it.

We are also grateful to the interns and the sister in charge Mrs. Bishnupriya who was the backbone of the immunizing sessions.

CONCLUSION

Immunization is indeed a very cost effective strategy not just in terms of service delivery but also in terms of service givers, as this is one strategy that has been handled by the frontline workers very well. However good training and Interpersonal Communication (IPC) is encouraged in order to maximize benefits and a strong surveillance system be put up for reporting of AEFIs, so that preparedness can be initiated to handle them.

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