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Adverse events following pediatric immunization in an Indian city

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Purpose: Adverse effects are noticeable immediately after vaccination, especially when vaccinated to healthy people at the time of vaccination. The vaccine may cause adverse events which are very rare but adverse event following immunization surveillance becomes correspondingly more important in a less studied population like India. Hence, there is a need for carrying out a study pertaining to vaccine safety in the pediatric population of age 0–12 years and assessing the events occurring post-vaccination.

Materials and Methods: A prospective observational study was conducted in three primary healthcare centers and two tertiary care hospitals for 6 months from April 2016 to September 2016 with a total of 826 children enrolled. Detected adverse events for suspected vaccines were analyzed for causality by the World Health Organization causality assessment instrument. Sex-specific differences in incidences of adverse events were assessed.

Results: The cumulative adverse events were found highest in pentavalent vaccines (510 incidences, 62.04%) followed by the bacillus Calmette-Guérin vaccine (189 incidences, 22.99%). The study didn't reveal any significant association in incidences of adverse events following immunization and sex of the children.

Conclusion: Vaccine safety surveillance studies are need of the hour in developing countries to maintain public trust in vaccines, the ultimate objective being to have vaccines with the most favorable benefit-risk profile. The present study discussed the various adverse events following immunization and suggested the absence of any sex-specific difference in incidences of adverse events in children.

Keywords: Injection site adverse event, Vaccine, Immunization, Pharmacovigilance, Vaccination, Causality

Introduction

The immunization of children as a preventive medical intervention had a great impact on global health [1]. Extensive immunization programs have eradicated smallpox completely and eliminated polio in almost all countries baring few. Now vaccines are considered as one of the most cost-effective public health interventions since it provides direct and effective protection against many diseases such as cervical cancer, diphtheria, hepatitis B, measles, mumps, pertussis (whooping cough), pneumonia, polio, rotavirus diarrhea, rubella, and tetanus, and so forth [2-4]. The government of India, under the Universal Immunisation Programme, is providing vaccination free of cost against vaccine-preventable diseases including diphtheria-tetanus-pertussis

(DTP), polio, measles, tuberculosis, hepatitis B, meningitis and pneumonia (*Hemophilus influenzae* type B infections), Japanese encephalitis (JE) in JE endemic districts and newer vaccines such as rotavirus vaccine, inactivated polio vaccine, adult JE vaccine, pneumococcal conjugate vaccine, and measles-mumps-rubella (MMR) vaccine. The World Health Organization (WHO) confirms global child immunization programs as highly successful in terms of controlling and even eradicating certain diseases. Both WHO and the World Bank rank immunization among the most cost-effective health care interventions available.

Though the benefits of immunization are indisputable, it is important to critically examine this intervention that is recommended for all infants. Routine immunization is supposed to provide reasonable protection against potentially serious diseases, while the risk of serious adverse events (AEs) must be low. On 4 May 2013, the Ministry of Health of Vietnam suspended the use of a pentavalent vaccine Quinvaxem (Janssen, Leiden, Netherlands) after it had caused 12 deaths [5]. The same pentavalent vaccine was introduced in Sri Lanka on January 1, 2008 and subsequently withdrawn by the government on 29 April that year following five deaths [6,7].

A major public health concern regarding vaccines relates to their safety and the risks of AEs occurring at or after vaccination [8,9]. Since vaccines are mainly administered to healthy and young people, even non-serious AEs are often deemed unacceptable by vaccinees or their parents/relatives. Hence, the adverse events following immunization (AEFIs) must be evaluated carefully and very seriously [10]. Individuals' hesitancy to get themselves or their close family vaccinated may have a negative effect on vaccine uptake. This may subsequently lead to outbreaks of vaccine-preventable diseases and more generally to major public health concerns. Experience shows that immunization coverage tends to decline if there is widespread concern about AEs. Therefore, a solid body of knowledge is needed to ensure public acceptance of vaccine usages.

Presently in India, several vaccines are commercially available which include bacillus Calmette-Guérin (BCG), DTP, MMR, rotavirus vaccine, Chickenpox vaccine, hepatitis-A vaccine, hepatitis-B vaccine, polio vaccine, and so forth. The benefits of immunization are often not visible, particularly if the target disease incidence is low. In contrast, AEs that follow immunization are promptly noticeable, especially when the vaccine was apparently healthy at the time of immunization.

So, the vaccine safety is important and is rising in global concern [3,11-13]. The effects of post-vaccination events are very minimally known and the assessment, documentation of that AEs are minimum in the Indian population. Very few systematic studies have been conducted to assess vaccine safety. Vaccines may cause AEs which are very rare but AEFI surveillance becomes correspondingly more important in a less studied population like India. Hence there is a need for carrying out a study pertaining to vaccine safety in the pediatric population of age 0–12 years and assessing the events occurring post-vaccination.

Materials and Methods

A prospective observational study was conducted for 6 months from April–September 2016 in two pediatric hospitals and three vaccinations centers of Warangal district, India. The study included healthy children receiving vaccines in the study sites, children undergoing vaccinations like polio, DTP, Hepatitis B, MMR, BCG, *Hemophilus influenzae* type B, rotavirus, JE, influenza, typhoid, and pentavalent measles, etc., subjects who are ready to provide contact details, informed consent and who are among the age group of 0–12 years. Children with fever, cough, and cold, who appear sick or having a history of recent convulsions, children aged ≥12 years, and subjects not willing to participate in the research were excluded from the study.

All the data required was collected from the patient's case sheets, diagnostic reports, previous prescriptions, children vaccination charts, and by a discussion with children, parents, and concerned healthcare professionals. The study was approved by the Institutional Human Ethical Committee of Talla Padmavathi College of Pharmacy, Warangal. In this study, the data were presented collectively in order to safeguard the integrity and anonymity of all those involved (patients and health care agents). The results were used only for the purpose of the statistical study and not as evidence for or against a specified vaccine. AEs here wad used to mean "any moderate or severe and/or unexpected adverse sign or symptom occurring after vaccination".

The study included a properly designed patient data collection form and an AE assessment form. The present and past vaccination details of the children were obtained by a suitable approach and all the data collected was segregated and subjected for appropriate statistical tests. Before the start of the study, the parents of all the participants were informed of the study's purpose and the procedure. Since the study is a

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non-invasive type, only verbal consent prior to administering the questionnaires was obtained. The suspected AEs were assessed for casualty, by applying the WHO-Casualty assessment form.

Descriptive statistics were used to summarize the demographic and clinical characteristics of study participants. The percentages of suspected vaccines and AEs were calculated. Odds ratio and 95% confidence interval were estimated to explore the influence of variables on dependent responses. All statistical analyses were conducted at a significance level of 0.05 using SigmaStat software ver. 3.5 (Systat Software Inc., San Jose, CA, USA).

Results

A total of 826 vaccinated children were enrolled in the study from various hospitals in the Warangal region. The mean ages of individuals were 9.368 months (who were less than 12 years of age) out of which 472 participants were males and 354 participants were females.

The study revealed that the oral polio vaccine was the most frequently (650 doses) administered vaccine among the study population accounting for 34.53% of all vaccine doses followed by pentavalent (494 doses) and BCG (151 doses) vaccine (Table 1, Fig. 1). The cumulative AEs were found highest in pentavalent vaccines (510 incidences) followed by BCG vaccine (189 incidences) accounting for 62.04% and 22.99% of all AEs encountered in the study.

The incidence of the AEs following pentavalent vaccines administration included 303 incidences (59.41%) of mild fever, 66 incidences (12.94%) of pain at the site of injection, 70 incidences (13.72%) of swelling at the site of injection, 57 incidences (11.17%) of sterile abscess at the site of injection, one incidence (0.19%) of generalized rash, seven incidences (1.37%) of localized rashes, and six incidences (1.17%) of persistent crying (Table 2, Fig. 2). There was no evidence for the occurrence of convulsion and encephalopathy among children who received pentavalent vaccines in our study.

The incidence of AEs of BCG vaccination observed in this study was found to be 189 (22.99%) events in 151 (8.02%) doses which includes 51 (26.98%) mild fever reactions, 37 (19.57%) injection site abscess with purulent discharge, 82 (43.38%) sterile abscesses at the site of injection, 15 (7.93%) swelling at the site of injection, 3 (1.58%) pain at the site of injection, and 1 (0.52%) localized rash (Fig. 3). The incidence of AEs of rotavirus vaccine (1 [0.12%]), Japanese encephalitis (46 [5.59%]), measles (3 [0.36%]) was found to be less in this study.

Table 1. Types of vaccines administered and related adverse events reported in children

Type of vaccines	Frequency of administration	Frequency of adverse events
Pentavalent	494 (26.24)	510 (62.04)
Bacillus Calmette-Guérin	151 (8.02)	189 (22.99)
Japanese encephalitis	132 (7.01)	46 (5.59)
Diphtheria-tetanus-pertussis	71 (3.77)	23 (2.79)
Inactivated polio vaccine	117 (6.21)	3 (0.36)
Measles	84 (4.46)	3 (0.36)
Measles-mumps-rubella	21 (1.11)	3 (0.36)
Oral polio vaccine	650 (34.53)	0
Hepatitis B	126 (6.69)	3 (0.36)
Rotavirus vaccine	3 (0.15)	1 (0.12)
Tetanus	4 (0.21)	0
Typhoid	4 (0.21)	1 (0.12)
Hepatitis A	5 (0.26)	0
Influenza	5 (0.26)	0
Varicella	8 (0.42)	0
Pneumonia	3 (0.15)	0
Hemophilus influenzae B	4 (0.21)	2 (0.24)

Values are presented as number (%).

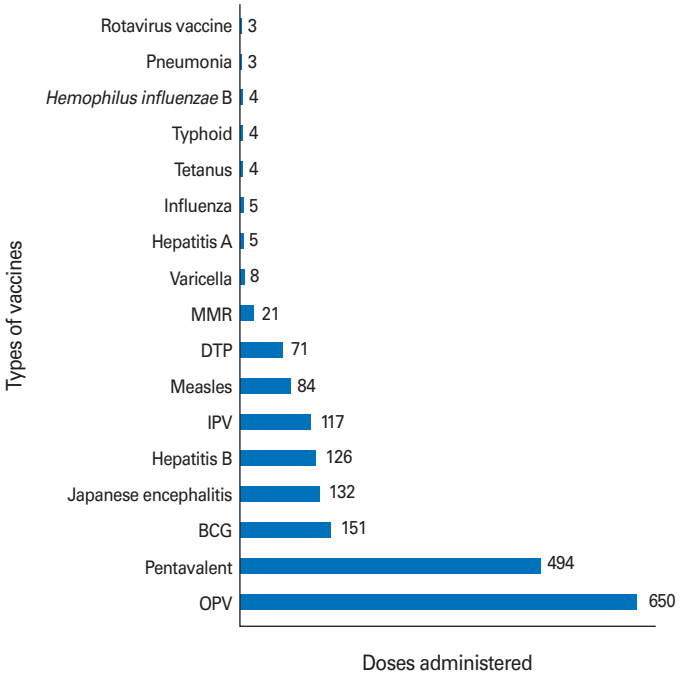

Fig. 1. Doses of vaccines administered in the study population. MMR, measles-mumps-rubella; DTP, Diphtheria-tetanus-pertussis; IPV, inactivated polio vaccine; BCG, bacillus Calmette-Guérin; OPV, oral polio vaccine.

Table 2. Adverse events associated with BCG and pentavalent vaccine administration

Type of adverse event	Frequency of adverse events	
	BCG vaccine	Pentavalent vaccine
Mild fever	51 (26.98)	303 (59.41)
Injection abscess with purulent discharge	37 (19.57)	-
Sterile abscess at site of injection	82 (43.38)	57 (11.17)
Swelling at site of injection	15 (7.93)	70 (13.72)
Pain at site of injection	3 (1.58)	66 (12.94)
Localized rashes	1 (0.52)	7 (1.37)
Generalized rashes	-	1 (0.19)
Persistent crying	-	6 (1.17)

Values are presented as number (%).
BCG, bacillus Calmette-Guérin.

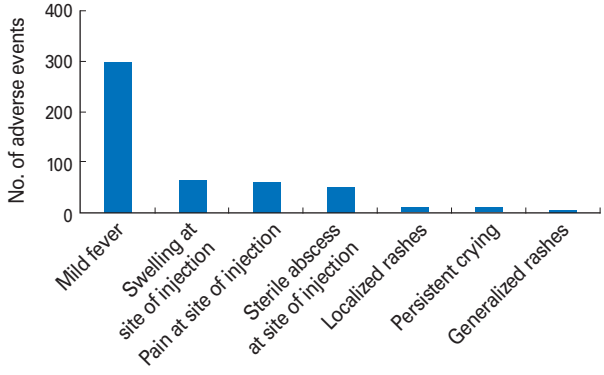

Fig. 2. Adverse events following pentavalent vaccination.

In the present study, an attempt was made to assess such variation in AEFIs based on the sex of the children. However, the study didn't reveal any significant association in incidences of AEFIs and sex of the children (Table 3). The odds ratio and 95% confidence intervals were estimated to establish any association between sex and incidences of AEFIs. Since the 95% confidence intervals for all the odds ratios span 1.0, the values of odds of various types of AEs among male or female children do not reach statistical significance.

Discussion

Active vaccine safety surveillance processes that are in place to collect, analyze and communicate around AEFI can increase the confidence of healthcare providers and the public in immunization. The present research is such an initiative to assess the AEs following routine immunization in a south Indian city. The incidence of the AEs following pentavalent vaccines administration included a higher incidence (59.41%) of mild fever. However, a different pattern of AEs was reported by a research group from Iran [14] with 12.6% (10.7–14.6) for mild fever. The researchers justified the lesser incidences of mild fever in their study population with prophylactic usages of acetaminophen. Though some studies have shown that paracetamol interferes with antibody responses following immunization, a recent post hoc analysis of data from a clinical trial of a pentavalent vaccine in Indian infants confirmed no evidence that paracetamol usage either as prophylactic or for treatment impacts immunological responses to a pentavalent DTwP-HepB-Hib (diphtheria toxoid, tetanus toxoid, whole-cell pertussis, hepatitis B surface antigen, *Hemophilus influenzae* type B) combination vaccine [15]. There was no evidence for the occurrence of convulsion and encephalopathy among children who received pentavalent vaccines in our study. Moreover, in an attempt to compare AEs following pentavalent vaccines and DTP vaccines, Sadoh et al. [16] has reported a higher incidence of AEs following pentavalent vaccines (22.1%) than DTP vaccines (13.5%) which are in agreement with our findings.

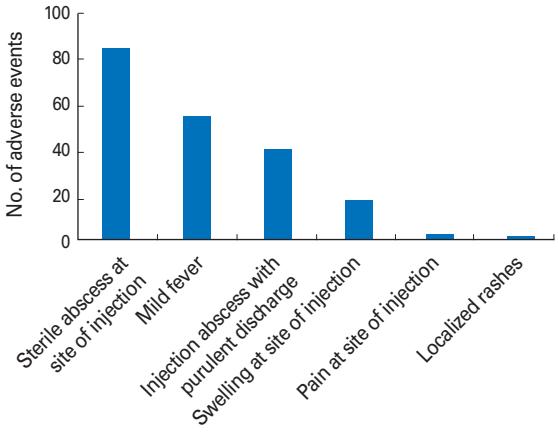

Fig. 3. Adverse events following bacillus Calmette-Guérin vaccination.

BCG vaccine is used worldwide, with high efficacy against childhood Mycobacterium tuberculosis meningitis and miliary tuberculosis. Though the BCG vaccine is considered safe, AE rates vary between differing BCG strains and age of children being vaccinated [17-20]. Researchers worldwide have reported higher incidences of AEFIs with BCG in male children compared to female children [17,18]. However, no such pattern was observed in our study. Lotte et al. [19] analyzed and classified complications associated with BCG vaccination in detail. This classification which is based on clinical, bacteriological, histological, and biological information clas-

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Table 3. Types of adverse events reported in male and female children following immunization

Type of adverse event	Frequency of incidence in each sex		OR (95% CI)[a]
	Male	Female	
Mild fever			0.99 (0.75–1.3)
Yes	244	184	
No	228	170	
Persistent crying			1.5 (0.27–8.26)
Yes	4	2	
No	468	352	
High fever			0.25 (0.03–2.4)
Yes	1	3	
No	471	351	
Injection abscess with purulent discharge			0.92 (0.48–1.78)
Yes	21	17	
No	451	337	
Pain at site of injection			0.88 (0.56–1.4)
Yes	44	37	
No	428	317	
Sterile abscess at site of injection			1.18 (0.83–1.68)
Yes	96	63	
No	376	291	
Swelling at site of injection			1.39 (0.91–2.14)
Yes	66	37	
No	406	317	
Localized rashes			0.61 (0.16–2.3)
Yes	4	5	
No	468	349	
Generalized rashes all over body			NA
Yes	1	0	
No	471	354	

OR, odds ratio; CI, confidence interval.
[a]Female sex was considered as control for estimation of OR (95% CI).

sifies complications into the following categories. Category 1 involving extensive local lesions and regional suppuration, BCG-related lymphadenitis, which is usually but not always bacteriologically and/or histologically confirmed. Categories 2 and 3 comprise more serious complications. Non-fatal cases (localized or multiple changes) are included in category 2, while fatal cases (generalized lesions usually associated with immunodeficiency) are in category 3. Category 4 includes complications that occur upon BCG administration, but are not definitely confirmed either bacteriologically or histologically. Keloid formation belongs to this category. In the present study, the complications found were of category 1.

There is growing evidence of age and/or sex-based biological differences in vaccine response [21]. Reportedly, higher immunogenicity and reactogenicity of vaccines in females has been consistent which include more frequent incidences of severe adverse reactions such as fever, injection site pain, and inflammation [22,23]. However, the present study didn't find any significant sex-specific AEs following immunization. Such surveillance studies are need of the hour in developing countries to maintain public trust in vaccines, the ultimate objective being to have vaccines with the most favorable benefit-risk profile. The present study also affirms the need for the participation of clinical pharmacists to increase the reporting rate and improving the quality of reporting AEs. The study has limitation of being a short-term study with a limited sample size. Further multi-cantered study with larger sample size is needed to evaluate the generalizability of the study.

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