RESEARCH ARTICLE

PATTERN OF ADVERSE EVENTS FOLLOWING IMMUNIZATION IN AN INDIAN TEACHING HOSPITAL

Nisarg D Joshi, Hiren K Prajapati, Krunal C Solanki, Anupama Sukhlecha, Hiren R Trivedi, Maganlal V Gajera, Bhadresh R Vyas
M P Shah Medical College, Jamnagar, Gujarat, India

Correspondence to: Nisarg D Joshi (nisargjoshi16@gmail.com)

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ABSTRACT

Background: Vaccination is an essential component of the public health programs and among most cost effective medical intervention. Vaccines like other pharmaceutical product are not entirely risk free; while most known side effects are mild and non-serious. But some vaccines have been associated with very rare but serious side effect. So, there is a need of a surveillance program to monitor and record such events.

Aims & Objective: To detect adverse events following immunizations (AEFI) in children and find vaccine responsible for them.

Material and Methods: A one year, prospective, vaccine safety study was undertaken in 2011 covering a pediatric population who were administered vaccines. A two-phase telephone survey of all patients was conducted, comprising of an initial call at 1 week and a follow-up call at 30 days after the vaccine administration date. All AEFI were recorded in Vaccine Adverse Event Reporting System (VAERS) form.

Results: Of a total sample of 4320 children, ranging in age from 0 to 14 years, 10110 vaccine doses were given. Each child received 2.34 vaccines on an average. Out of 4320 children, 899 children (20.8%) suffered 1003 AEFI. The most frequent types of adverse reactions to vaccines were fever (34.33 per 1000 doses), excessive crying (30.95 per 1000 doses) and injection site swelling (18.57 per 1000 doses). AEFI rate per 1000 doses was 99.2%.

Conclusion: Most of the adverse events reported were mild and non-serious. Establishment of national AEFI database can be a worthy long term goal in Indian context.

KEY-WORDS: Pharmacovigilance; Vaccines; Immunization; Adverse Events; India

Introduction

Immunization constitutes one of the most effective modern public health measures for preventing serious diseases. Unlike drugs that are given therapeutically to the diseased patients, vaccines are given prophylactically to healthy individuals, often young children. So, expectation to the vaccine safety is much higher than the drugs.

It has been estimated that under Universal Immunization Programme (UIP), 2.7 crore children are eligible for receiving vaccines in our country.[1] Immunizations currently save 3 million lives per year throughout the world and are one of the most cost effective health interventions that exist. Indeed, the majority of the population consider immunization to be an extremely important measure that parents can take to keep their children well, and one that is of great benefit to the community.[2]

Safety regarding vaccines had been questioned because of cases reported at many places.[3] As a result, certain misconceptions about the safety of the vaccines have arisen in many communities. Vaccine unacceptance by publics may hamper success of an immunization programme.[4,5] A constant flow of comprehensive information on vaccine efficacy and safety is thus called for.

AEFI is a medical incident that takes place after an immunization that causes concern and is believed to be caused by immunization.[1,6] The aim of AEFI surveillance is to monitor vaccine and immunization program safety and to detect population-specific, rare, late-onset or unexpected adverse events that may not be detected in pre-licensure vaccine trials.

The Vaccine Adverse Event Reporting System (VAERS) is a national vaccine safety surveillance program co-sponsored by the Centers for Disease Control and Prevention (CDC) and the Food and

Drug Administration (FDA). VAERS collects and analyzes information from reports of adverse events (possible side effects) following vaccination. Since 1990, VAERS has received more than 200,000 reports, most of which describe mild side effects such as fever. Very rarely, people experience serious adverse events. By monitoring these events, VAERS helps identify new safety concerns, and helps make sure the benefits of vaccines continue to be far greater than the risks. VAERS data are monitored to, (1) Detect new, unusual, or rare vaccine adverse events (2) Monitor increases in known adverse events (3) Identify potential patient risk factors for particular types of adverse events (4) Identify vaccine lots with increased numbers or types of reported adverse events (5) Assess the safety of newly licensed vaccines.[7]

Vaccine Adverse Event Reporting System (VAERS) is followed in many countries e.g. USA. It is a passive surveillance based on reports given by doctors or paramedical staff. Strengths of VAERS are that it is national in scope and timely with limited terms. There are a number of well-described limitations of such (VAERS) reporting systems. These include, for example, variability in report quality, biased reporting, under-reporting and the inability to determine whether a vaccine caused the adverse event in any individual report. Incidence rates and relative risks of specific adverse events cannot be calculated.[8]

Pharmacovigilance on vaccines in India is still in cradle stage. There is a need of pharmacovigilance of vaccines on a large scale in India.[9,10] As only a few Indian studies on adverse reactions of vaccines could be traced, we wished to collect data on AEFI in pediatric population of India through the present study.

Materials and Methods

The study was undertaken for a period of one year (from January to December 2011). The study was approved by Institutional Ethics Committee and verbal informed consent was taken from parents of children. A prospective, observational epidemiological vaccine safety study was designed, targeting a pediatric population subject to administration of vaccines according to the National Immunization Schedule (UIP).[11] This population comprised children aged 0 to14 years attending vaccination center (Well Baby clinic), at department of Pediatrics, G G Hospital, Jamnagar. The children were accompanied by parent or guardian who, after giving his/her informed oral consent, agreed to take part in the study.

The numbers of adverse event reports were calculated in five age groups: 0-1 month (neonates), 1–12 months (infants), 1–3 years (toddler), 3–6 years (pre-school) and 6-14 years (school going). Each child's detail record book was maintained which contained, name, age, sex, birth weight, contact number, address, name and batch number of vaccine(s) and history of previous vaccination. The parents/guardians of children were also given telephone number of doctors so that they could contact them in case of any problem following vaccine administration.

A two-phase telephone survey of parents or guardians was conducted, consisting of an initial call at one week and a second call at 30 days after the vaccine administration date. The parents of children were questioned about the appearance of any type of reaction that had followed administration of the vaccine. Before questioning subjects, the person responsible for the telephone calls had to ensure that the person answering was the same as the one who had originally given informed consent. Children with the complain of AEFI were called back to our hospital and were examined for AEFI by the consulting paediatrician. AEFI were diagnosed and given appropriate treatment by the paediatricians.

This list of most frequent expected adverse reactions was drawn up from the classifications used by the Vaccine Adverse Event Reporting System (VAERS).[8] The VAERS form was used to record the AEFI.[12] Data was evaluated according to patient demography, nature of the reaction, vaccine suspected for AEFI. Causality and seriousness of AEFI were assessed using World Health Organization AEFI guidelines.[6]

Method of Recording AEFI and Analysis

The causality ratings of 'certain', 'probable' and 'possible' assigned to individual AEFI records

describe the likelihood that a suspected vaccine or vaccines was/were associated with the reported reaction at the level of the individual.

Factors that are considered in assigning causality ratings include the timing (minutes, hours etc) and the spatial correlation (for injection site reactions) of symptoms and signs in relation to vaccination, and whether one or more vaccines was administered.

Because children in particular receive several different vaccines at the same time, all vaccines tend to be listed as 'suspected' of involvement of a systemic adverse event, as it is usually not possible to ascribe the AEFI to a single vaccine in many cases.

The data was recorded on Microsoft excel sheet and calculations were done.

Results

A total of 4320 children were screened. Amongst them 2234 were male (51.7%) and 2086 (48.3%) were female. These children received 10110 vaccine doses (out of which 6461 were injectable vaccines). Out of 4320 children, 2146 children were given 3 vaccines, 1498 children were given 2 vaccines and 676 children were given one vaccine. A total 1003 AEFI were reported out of a total of 10110 vaccine doses given. The rate of AEFI per thousand doses was 99.2. Out of 4320 children, there were 899 children who were suspected of having at least one AEFI. Hence, the incidence of AEFI was 20.8%.

In case of generalized systemic reactions where both vaccines could be implicated for the reaction, it was difficult to specify single vaccine responsible, so, both vaccines were considered responsible for the reaction.

As mention in Table 1, AEFI rate per 1000 doses of vaccine was most common in DPT vaccine (224.6) followed by BCG vaccine (192.4) and Hepatitis-B vaccine (191.8).

As mention in Table 2, most common AEFI per 1000 doses of all vaccination was fever (34.33) followed by excessive crying (30.95) and swelling at injection site (18.57).

Table-1: Distribution of AEFI According to Vaccine Type and Rate per 1000 Doses

Vaccine	Frequency of AEFI	Doses of Vaccine Administered	AEFI Rate per 1000 Doses
BCG	288	1497	192.4
OPV	156	3649	42.8
DPT	81*+404**	2159	224.6
Hepatitis-B	10*+404**	2159	191.8
Measles	44	341	129
TT	20	305	65.6

AEFI: Adverse Event Following Immunization; *Local reactions; **Generalized systemic reactions. Here, Both DPT and Hepatitis-B vaccines could be implicated for the reaction and it was difficult to specify single vaccine responsible, so, both vaccines were considered responsible for the reaction.

Table-2: Analysis of Types of AEFI Registered (n=1003)

Type of Adverse Event	Number of AEFI Reported (%)	Rate per 1000 Doses of All Vaccinations#
Fever	347 (34.59)	34.33
Excessive Crying	313 (31.25)	30.95
Swelling at Injection site	120 (11.96)	18.57
Diarrhoea	133 (13.25)	11.17
Abscess at Injection site	38 (3.78)	5.88
Rash	22 (2.19)	2.27
Vomiting	23 (2.29)	2.17
Convulsions	7 (0.69)	0.69

AEFI: Adverse Event Following Immunization; #Total doses of vaccine administered (n=10110) is the denominator for all except for 'swelling at injection site' and 'abscess at injection site' for which only the number of vaccines which were administered by injection (n=6461) is taken as denominator

As mention in Table 3, With BCG vaccination out of 288 AEFI, fever was the most common (117 AEFI) followed by excessive crying (107 AEFI). In case of DPT + Hepatitis-B vaccination out of 404 AEFI, fever was most common (202 AEFI) followed by excessive crying (182 AEFI). In case of DPT vaccination out of 81 AEFI, most common was swelling at the injection site (61 AEFI) followed by abscess at injection site (20 AEFI). In case of Hepatitis –B vaccination out of 10 AEFI, most common AEFI was swelling at injection site (8 AEFI). In case in Measles vaccination out of 44 AEFI most common was fever (20 AEFI). In case of OPV vaccination out of 156 AEFI, most common was diarrhoea (133 AEFI) followed by vomiting (23 AEFI). In case of TT vaccination out of 20 AEFI, fever was most common (8 AEFI).

Table-3: Distribution of Types of AEFI and Vaccines Implicated for them (n =1003)

Type of AEFI	BCG	(DPT+ Hepatitis-B)$	DPT	Hepatitis - B	Measles	OPV	TT
Fever	117	202$	-	-	20	0	8
Excessive Crying	107	182$	-	-	18	0	6
Swelling at injection Site	44	-	61	8	4	0	3
Diarrhoea	0	-	0	0	0	133	0
Abscess at Injection Site	14	-	20	2	2	0	0
Rash	6	13$	0	0	0	0	3
Vomiting	0	-	0	0	0	23	0
Convulsions	0	7$	0	0	0	0	0
Total AEFI	**288**	**404$**	**81**	**10**	**44**	**156**	**20**

AEFI: Adverse Event Following Immunization; $In case of generalized systemic reactions where both vaccines could be implicated for the reaction, it was difficult to specify single vaccine responsible, so, both vaccines were considered responsible for the reaction.

Table-4: Classification of AEFI according to System Organ Class (SOC) and Preferred Terms (PT) Falling Under the Respective SOC using Med DRA version 14.1 English, (n=1003)

System Organ Classification (SOC)	Number of AEFI Reported (%)	Preferred Term (PT)	Number of Individual AEFI (%)
Injury, poisoning and procedural complication	471 (46.95)	Crying Inj. Site swelling Adm. site abscess	313 (66.45) 120 (25.48) 38 (8.06)
General disorder and administrative site condition	347 (34.59)	Pyrexia	347(100)
Gastrointestinal disorder	156 (15.55)	Diarrhea Vomiting	133 (85.25) 23 (14.74)
Skin and subcutaneous tissue disorder	22 (2.19)	Rash	22 (100)
Nervous system disorder	7 (0.69)	Febrile convulsion	7 (100)

AEFI: Adverse Event Following Immunization

Table-5: Distribution of AEFI Observed at a Time (n=1003, Observed in 899 Children)

Frequency of AEFI at a Time	Number of Children with AEFI
One	812
Two	70
Three	17
Total	**899**

AEFI: Adverse Event Following Immunization

AEFI have been classified according to System Organ Class (SOC) and Preferred Terms (PT) falling under the respective SOC using Med DRA version [Table 4]. As mention in Table 4, most common SOC associated with AEFI was injury, poisoning and procedural complication (46.95%) in which crying was most common AEFI (66.45%). Second most common SOC associated with AEFI was general disorder and administrative site condition (34.59%) in which pyrexia was most common AEFI (100%). There were more than one AEFI noted at a time in many children [Table 5]. As mention in Table 5, out of 899 children with AEFI, 812 children developed one AEFI at a time followed by 70 children developed two AEFI at a time and 17 children developed three AEFI at a time.

Figure-1: Age Group-wise Distribution of AEFI Registered (n=1003)

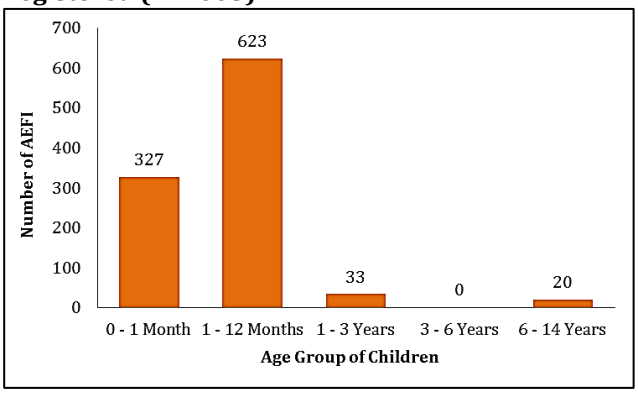
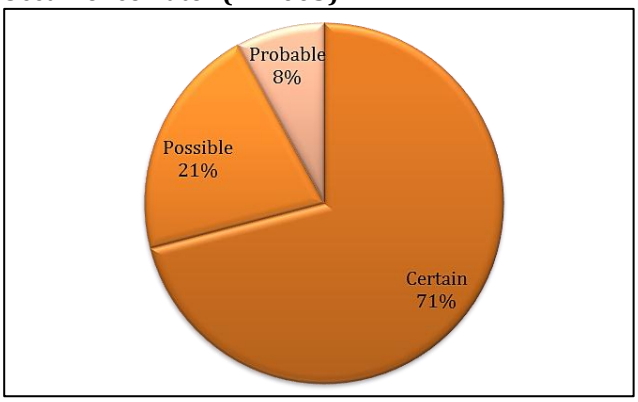


Figure-2: Causality Assessment of AEFI and Occurrence Rate* (n=1003)



* World Health Organization – Adverse Event Following Immunization Guideline

As shown in Figure 1, the AEFI were distributed in various age-groups of children unevenly. Out 1003 AEFI, 623 (62.1%) AEFI were noted in 1-12 months of age group of children followed by 327 (32.6%) AEFI were noted in 0-1 month of age group. As shown in Figure 2, Causality assessment as per WHO guidelines showed that 71% of AEFI were certain due to vaccines followed by 21% of AEFI were possible and 8% of AEFI were probable.

Discussion

Our method of reporting was an active search using telephonic survey. Our study was prospective for one year on 4320 cases. Our method was similar to a study done by Carrasco-Garrido et al in Spain but it was for 6 months on 946 cases.[13] A study by Zhou et al in USA was on more than 1.9 million cases. It was based on VAERS and was for 10 years.[8]

A study by Aagaard et al in Denmark was for 10 years and retrospective.[14] A similar study by Mansoor et al in New Zealand was for 5 years and passive.[15] Studies have been conducted in different countries as a part of national surveillance programme. A study done by Mahajan et al in Australia was for 1 year and passive.[16] A similar study was done by Lawrence et al for 1 year and 9 months in Australia.[17]

There was no significant difference between AEFI in males and females in our study (51.7% males and 48.3% females, total children=4320). These findings are similar to a study by Zhou et al in USA and Carrasco-Garrido et al in Spain.[8,13]

In our study, the most common age group of children with AEFI was 1 month to1 year (57.9%) which is comparable to a study by Mahajan et al in Australia where the most common age group was less than 1 year.[16] In study by Aagaard et al in Denmark, it was 0 to 2 years (80% cases).[14]

The AEFI reported in our study were 99.2 per 1000 doses. In a study by Carrasco-Garrido et al in Spain, the rate was 14.6 per 1000 doses.[13] Studies conducted in US, Denmark and Australia report of lower AEFI rates.[8,14,16] The lower reporting rates could be because of the method of passive surveillance followed in these countries.

The incidence of AEFI in our study population was 20.8% (899 children with AEFI out of 4320 children who were vaccinated) which is similar to a study by Carrasco-Garrido et al in Spain which reports AEFI to be about 19%.[13]

In our study, the most common adverse event was fever (34.6%) which was also reported by a study by Zhou et al in US (25.8%).[8] Another common adverse event was injection site inflammation A study by Carrasco-Garrido et al in Spain and by Mansoor et al in New Zealand mentions swelling at the site of injection as the most common AEFI.[13,15] In our study it was 18.57 %, while in a study by Zhou et al in US, it was 10.8%.[8]

Common systems involved in our study were injury, poisoning, procedural complications followed by general disorders, administrative site conditions and gastrointestinal disorders. While in a study by Aagaard et al in Denmark, most common system involved was general disease and administrative site conditions followed by skin and subcutaneous disorders and nervous system disorders.[14]

In our study, the most common vaccines causing AEFI were DPT + Hepatitis- B followed by BCG. In a study by Carrasco-Garrido et al conducted in Spain, it was DPT + Hib followed by MMR.[13] A study by Mansoor et al in New Zealand reports them as DPT + Hib followed by H influenza.[15] A study by Mahajan et al in Australia reports influenza, H1N1 and DPT vaccines that are commonly associated with AEFI.[16] In a study in US, analysis confirmed a higher concentration of endotoxin in whole-cell DTP vaccines compared with DTaP or DT vaccines as high concentrations of endotoxin may be correlated with a higher incidence of adverse events.[18] The vaccines implicated in provoking some of these reactions could be because of their components. In our case, the DPT vaccine would seem to be more implicated in causing febrile convulsions than Hepatitis B as reported in literature and various studies.[19]

In our study, majority of AEFI were mild in nature, only 0.7% (n=1003) were febrile convulsions which were serious. A study by Aagaard et al in Denmark reports one-third AEFIs as serious and

there were two deaths (n=.2600)[14] A study in US reports as 14.2% of AEFI as serious (study population>1.9 billion).[8] A description of the characteristics of the adverse reactions presented show that the great majority were mild in nature (fever, injection-site edema, etc.).[20]

The results of a study undertaken by Morales-Olivas et al in Spain over a 10-year period, based on yellow-card records kept by Pharmacovigilance System, attributed 11.9% (n = 291) of all adverse reactions occurring to the administration of vaccines.[21]

Limitations of This Study

AEFI were ascribed to a vaccine without establishing a relationship of causality. In case of generalized systemic reactions where both vaccines could be implicated for the reaction, it was difficult to specify single vaccine responsible, so, both vaccines were considered responsible for the reaction.

Conclusion

Most of the adverse events reported were mild and non-serious. An active search system for adverse reactions to vaccines is a good method for detecting and quantifying those reactions that, owing to their mild nature, tend not to be reported by passive surveillance systems. Studies like ours enables in obtaining the information on the incidence and pattern of AEFI in the local population. On-going surveillance of adverse events following immunisation (AEFI), and regular analysis and reporting of these data should be integral to the management of immunisation programs. Establishment of AEFI database can be a worthy long term goal in Indian context.

At present, different procedures exist for detecting and assessing adverse reactions to vaccines, ranging from passive surveillance systems to epidemiological case-control or cohort studies. However, circumstances such as under-reporting or difficulty in finding a causal association between the appearance of the adverse reaction and the administration of the vaccine tend to hinder pharmaco-vigilance. The benefits of immunisation in preventing disease continue to significantly outweigh the risks of immunisation-related adverse events. Vaccines have side-effects, but none of them are as severe as the diseases themselves. After identifying the vaccines responsible for adverse reactions and the characteristics of the reactions registered in our population, we may continue to regard vaccines as safe biological products.

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