Original Article

Epidemiological study of adverse events following immunization in under 5 year children

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Abstract

Background: The present study was conducted to study the socioeconomic and the demographic profile of children reporting with adverse events following immunization (AEFI) along with the determinants associated with AEFIs, based on investigation of each case and to assess the proportion of programmatic errors linked with AEFI cases. **Materials and Methods:** Record-based cross-sectional study conducted among sample of 118 cases of AEFI were reported. The case reports of all AEFI cases were procured and analyzed to identify factors associated with reported AEFI. The questionnaires related with preliminary investigation reports (PIRs) including forensic evidence of death cases were analyzed. Percentage analysis of data was done by proportions, measures of central tendencies, and Chi-square test. **Results:** Most of the cases reported were between 0 and 3 months of age constituting 39%. AEFI was seen more in male child than female. more than half of cases of AEFI were recorded following immunization with OPV/DPT/HBV together (66.94%). Most common AEFI reported were convulsion (68.64 %) and fever (58.47%) followed by local swelling at site of injection (11.86%). More than half of the cases of AEFI occurred within 12 hours of immunization (61.88%). Birth weight of most cases of AEFI were in the range between 2 and 2.4 kg (44.06%), followed by range between 2.5 and 2.9 kg (32.20%), the mean of birth weight was 2.51 kg. **Conclusion:** Convulsion was the most commonly reported AEFI, majority of AEFI occur within 12 h of immunization. Most of the AEFI were recorded following immunization with OPV/DPT/HBV together.

Keywords: AEFI, immunization

Introduction

UNICEF and WHO have been instrumental in assuring increased access of developing countries to high quality affordable vaccines. All EPI vaccines supplied by UNICEF are from WHO recommended sources. Through a process of pre-qualification, WHO advises UN procurement agencies on the quality, efficacy, and safety of vaccines available on the market.

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Although vaccines produced and regulated in keeping with WHO standards are very safe, no medicine is without risk of a potential adverse reaction. And rarely, adverse events following immunization (AEFI) occur.[1] In the 21st century, an array of microbiological and molecular allow antigens for new vaccines to be specifically identified, designed, produced, and delivered with the aim of optimizing the induction of a protective immune response against a well-defined immunogen. New knowledge about the functioning of the immune system and host--pathogen interactions has stimulated the rational design of vaccines. The design toolbox includes vaccines made from whole pathogens, protein subunits, polysaccharides, pathogen-like particles, use of viral/bacterial vectors, plus adjuvants and conjugation technology to increase and broaden the immune response. Processes such

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as recombinant DNA technology can simplify the complexity of manufacturing and facilitate consistent production of large quantities of antigen. Any new vaccine development is greatly enhanced by and requires integration of information concerning: 1. Pathogen life cycle and epidemiology. Knowledge of pathogen structure, route of entry, interaction with cellular receptors, subsequent replication sites, and disease-causing mechanisms are all important to identify antigens suitable for disease prevention. The demographics of infection, specific risk groups, and age-specific infection rates determine which population to immunize, and at what age. 2. Immune control and escape. Interactions between the host and pathogen are explored, with determination of the relative importance of antibodies, T-cells of different types and innate immunity, immune escape strategies during infection, and possible immune correlates of protection. This information guides identification and selection of antigen and the specific immune response required for protection. 3. Antigen selection and vaccine formulation. The selected antigen is formulated to remain suitably immunogenic and stable over time, induce an immune response that is likely to be protective, plus be amenable to eventual scale-up to commercial production. 4. Vaccine preclinical and clinical testing. The candidate vaccine must be tested for immunogenicity, safety, and efficacy in preclinical and appropriately designed clinical trials. This review considers these processes using examples of differing pathogenic challenges, including human papillomavirus, malaria, and Ebola.

Universal immunization program is one of the largest vaccination program in the world; there are 2.7 crore children and 3 crore pregnant women eligible for receiving the primary series of vaccines in the country. In order to reach these beneficiaries, around 8--9 lakh sessions are conducted every month across the country both in rural as well as in urban areas with over crore of doses of vaccine being administered. The 7 lakh villages in the country are mostly covered through outreach approach. Therefore, it is evident that monitoring of AEFI in the country is a challenging task nonetheless essential.

AEFI is defined as medical incident that takes place after immunization, causes concern and is believed to be caused by immunization. The majority of events thought to be related to the administration of a vaccine are actually not because of vaccine itself---many are simply coincidental events, others are because of human or program error. Some AEFI are inevitable, however its impact can be minimized by providing quality immunization services, appropriate case management and communication strategies.

AEFI surveillance program was started in India in 1988 and the AEFI Surveillance Guidelines were first published in 2005. Establishment of an AEFI secretariat with clear roles and responsibilities was proposed in 2008 to strengthen the current National AEFI Surveillance Program and support the Immunization Division, MOHFW as well as the National AEFI Committee on the various activities related to AEFI data management, monitoring, documentation of serious cases for causality assessments, operational research, and trainings. Correct immunization practices reduce the negative impact of the event on health and contribute to the quality of immunization activities.[2]

It is extremely important that these AEFI are reported, investigated, and treated at the earliest. They will not only build public confidence but will also prevent additional clustering of cases if because of programmatic error. Quick response in case of AEFI is extremely important. Government of India has been making efforts to strengthen the AEFI surveillance system in the country through the constitution of the AEFI committee at national, state, and district level.

Irrespective of the cause, when AEFI occurs, confusion is created among people to extent that they may refuse further immunizations for their children leaving them susceptible to vaccine preventable diseases which are more disabling and life threatening. Therefore, surveillance of AEFI provides information to help plan on regaining public confidence on immunization. Timely response to public concerns about safety of vaccines as well as prompt communication will protect the public and preserve the integrity of the immunization program as well.[3]

Hence, the present study was conducted to study the socioeconomic and the demographic profile of children reporting with AEFI, to assess the determinants associated with AEFIs based on investigation of each case, to classify types of AEFI as per WHO guidelines.

Material and Methods

The present study was a record-based cross–sectional study, conducted during period of 1 year [July 2012 to July 2013] among sample of 118 cases of AEFI reported. The metropolitan city under Municipal Corporation is divided into 24 wards. F south ward office is the head office for all the 24 wards. Therefore, all the AEFI cases of city were collected from F south wards. The case reports of all AEFI cases were procured and analyzed to identify factors associated with reported AEFI. The questionnaires related with preliminary investigation reports (PIRs) including forensic evidence of death cases were analyzed. Technical discussion for further clarification was held with the concerned stakeholders and committee members of the designated AEFI committee of public health department. New AEFI cases reported during the study period were investigated using standard reporting format as per guidelines of Ministry of health and family welfare, government of India. Ethical permission was taken from institutional ethical committee. Visits to the sites of immunization (health post/health center) was made to assess program management recourses and for interaction with the health care providers. All AEFI notified to Public health department containing complete information were included in study and AEFI notified with incomplete information were rejected. Data of AEFI cases occurring during the study period were collected using PIR record forms and face-to-face

interview of parents. Data was analyzed measures of central tendencies, proportion and Chi-square test using SPSS version 17 software.

Results

Taking sociocultural factors into account, it is observed that 54.2% (64) children were Hindu by religion, followed by Muslim 36 (30.6%), Christian (4.2%), and 11% belonged to other minorities. A total of 77% children with AEFI belonged to unreserved category and 14%(17) were belonging to SC/ST while 8.5%(10) were OBC.

It is observed that parents of most children have been educated up to middle school. Only 1.69% of mothers had graduated. Paternal occupation status revealed that about 40% were semiskilled workers followed by skilled workers, unskilled workers, and clerical. Only 0.8% were professionals. Most families constituted of about 4--6 members. The number of joint families was relatively small.

Most of the cases reported were between 0 and 3 months of age constituting 39% (46/118) of all reported cases. This was followed by children between 12 and 24 months, that is, 23%(27/118). Maximum number of cases occurred within the first year, that is, 71% (84/118). The mean age of all reported cases was 10.56 month and standard deviation was 13.58. Almost in all age group AEFI were more among males than females except in 6-12 months of age group [Table 1].

Majority of them (99.15%) hospitalized after AEFI had occurred. None of them had a past history of similar illness. Very few of them showed the presence of congenital abnormalities (4.23%), history of birth complication (3.38%), family history of AEFI (4.23%), and presence of illness during vaccination (2.54%).

It is noteworthy that more than half of cases of AEFI were recorded following immunization with OPV/DPT/HBV together (66.94%) followed by Booster dose. More than half (51.90%) of cases occurred due to 1st dose of OPV/DPT/HBV together followed by 3rd dose [Table 2].

Over half of all documented cases of adverse reactions following vaccine administration during the period under investigation were convulsion (68.64%) and fever (58.47%), followed by local swelling at site of injection (11.86%) [Figure 1].

The most common adverse reaction reported was convulsion which showed highest frequency after administration of OPV/DPT/HBV together followed by Booster 1. Second most common adverse reaction reported was fever which also occurred after administration of OPV/DPT/HBV together. Fever was not reported after vaccine administered at BCG/OPV/HBV given at birth [Table 3].

Most commonly, local reaction occurred after DPT administration. [Figure 2] Few other adverse reactions such as vomiting, frothing, cyanosis occurred after immunization. Four cases of vomiting occurred after OPV vaccination while five cases of frothing were reported after OPV/DPT/HBV together. Cyanosis as adverse event reported after OPV/DPT/HBV together. Out of three cases of rash, two cases occurred with OPV/DPT/HBV together and one case with Measles. Also two cases of breathlessness and up rolling of eyeball were reported after administration ofOPV/DPT/HBV together.

A single case of bleeding occurred after vaccine administered at BCG/OPV/HBV given at birth. One case of giddiness occurred after administration of Booster 2. One cases each of decreased feeding, and lethargy and reduced intake occurred after OPV/DPT/HBV together administration. One case of loose motion occurred after administration of OPV.

Discussion

A total of 130 PIR forms was examined, among them 118 was selected as per our inclusion criteria. Maximum numbers of cases reported in the study (71%) were in the first year of life. Similar findings were reported by Cunnha *et al.* which shows children's ≤1 year old were more susceptible to AEFI.[4]

Most AEFI cases were reported in the age group of 0--3 months (39%). These findings corroborated with the findings of

Table 1: Distribution of subjects according to age and gender.

Age in months	Male (%)	Female (%)	Total (%)
0-3 month	24 (20.33)	22 (18.64)	46 (38.93)
3-6 month	14 (11.86)	4 (3.38)	18 (15.25)
6-12 month	9 (7.62)	11 (9.32)	20 (16.94)
12-24 month	15 (12.71)	12 (10.16)	27 (22.88)
>24 month	5 (4.23)	2 (1.69)	7 (5.93)
Total	67 (56.77)	51 (43.22)	118 (100)

Table 2: Frequency of AEFI reported after specific vaccination.

Vaccine		Frequency (%)
Vaccines administered	OPV during outreach camps	6 (5.08)
	BCG, OPV, HBV given at birth	3 (2.54)
	OPV/DPT/HBV together all primary doses	79 (66.94)
	Measles	4 (3.38)
	Booster 1 (16-20 month)	22 (18.64)
	Booster 2 (54-60 month)	4 (3.38)
	Total	118 (100)
OPV/DPT/HBV together	1st dose (Given at 1.5 month)	41 (51.90)
	2nd dose (Given at 2.5 month)	18 (22.79)
	3rd dose (Given at 3.5 month)	20 (25.31)
	Total	79 (100)

Table 3: Frequency of Fever and convulsion after specific vaccination

Vaccine	Only Fever (%)	Only Convulsion (%)	Fever with convulsion (%)
OPV during ORC	1 (0.84)	2 (1.69)	1 (0.84)
OPV/BCG/HBV at birth	0 (0)	0 (0)	0 (0)
OPV/DPT/HBV together all primary immunization	43 (36.44)	55 (46.61)	26 (22.03)
Measles	4 (3.38)	3 (2.54)	3 (2.54)
Booster 1	18 (15.25)	20 (16.94)	17 (14.40)
Booster 2	3 (2.54)	1 (0.84)	1 (0.84)
Total	69 (58.47)	81 (68.64)	48 (40.67)

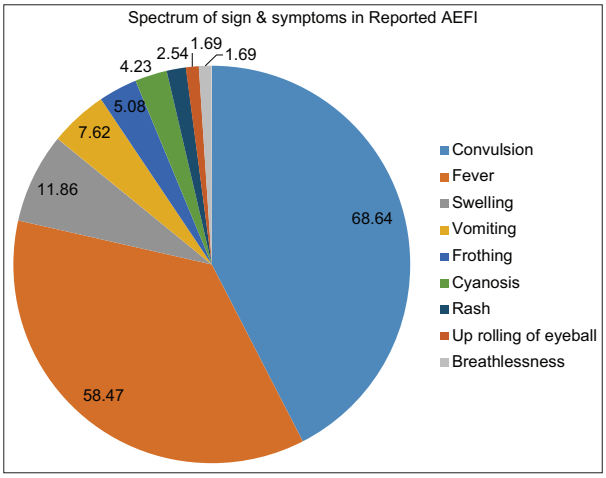

Figure 1: Distribution of presentation of AEFI cases

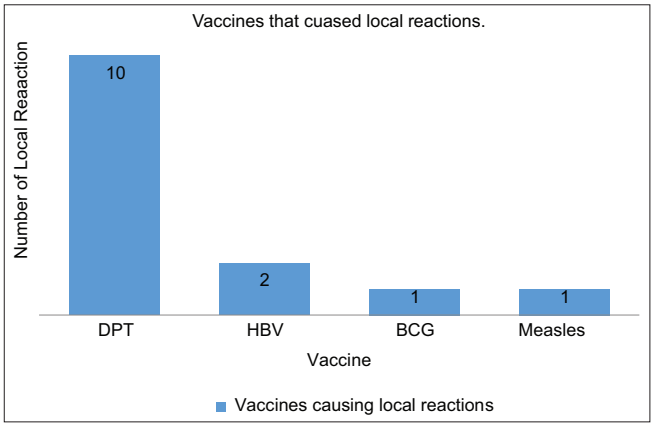

Figure 2: Vaccines associated with Local reactions

Aderbigbe *et al.* (More than half of the cases reported were between 2 and 4 months of age constituting 57.9% of all reported cases.)[5]

Proportion of male was found to be more than in female in all age groups except in age group of 6-12 months. In our study mean age was 10.56 month, while Aderibigbe *et al.* found the mean age of all reported cases to be 4.368 ± 2.794 with a modal age of 2 months. This discrepancy may be attributed to differences in the national immunization policies of different countries.[5] In a study by Hazel J Clothier, 18% (969/5455) of SAEFVIC reports received in the first 6 years of operation (2007--2013) met the definition of "serious."[6]

Our study shows that there was a male preponderance (56.77%) among the AEFI cases. Similar findings were reported by Aderbigbe *et al* (A majority of cases were males accounting for 59.6%)[5] and Michael Gold *et al* (Of those presenting with an AEFI, 55% were boys) in their studies.[6]

It is noteworthy that more than half of cases of AEFI were recorded following immunization with DPT/OPV/HBV all together primary immunization, that is, (67.79%), followed by Booster 1. Vaccination given at OPV/HBV/BCG given at birth rarely causes adverse reactions compare to others. SA Aderibigbe *et al.* reported that about half of all cases documented (49.1%) were given DPT before development of adverse reactions.[5]

Among the three doses of OPV/HBV/DPT given together, more than half cases (51.90%) were reported after first dose. Over half of all documented cases of adverse reactions following vaccine administration were convulsion (68.64%) and fever (58.47%). Both of them showed highest frequency after administration of OPV/DPT/HBV together followed by Booster 1. Fever was not reported after vaccine administered OPV/HBV/BCG given at birth. Similar findings were reported by Michael Gold *et al.* (37% cases presented with HHE, convulsions, skin rash). AEFI Surveillance and Response Guidelines MOHFW show fever in up to 50% of cases after DPT administration followed by Measles 5--15% and HBV 1--6%.[7] In contrast to present study, Miyake S. *et al.* reported convulsions in 1.7% of the cases after administration of Measles followed by DPT 1.1%.[8] SA Aderibigbe *et al.* state that over half of all documented cases of adverse reactions following vaccine administration during the period under investigation were local swelling at site of injection (50.9%) followed by cellulites (29.8%) and injection abscess (19.3%).[5] Paolo Bellavite *et al.* reported that severe hyperpyrexia, neurological symptoms and gastrointestinal diseases occurred in 38, 20, and 15 cases/1,000 enrolled, respectively. Previous epidemiological study showed much incidence of AEFI.[9]

Local reactions most commonly occurred after DPT administration (71.42%) while two cases of Local reaction occurred after HBV administration (14.28%) and one case each after measles and BCG administration (7.14% each). Similar findings were reported by AEFI Surveillance and Response Guidelines MOHFW documented Local reactions (pain, swelling, and/or redness) in up to 50% cases after DPT administration followed by measles (10%), HBV (5%). In contrast to present study, Michael Gold *et al.* showed that 63% had a history of a

local reaction, fever, irritability, screaming, vomiting, or diarrhea post-vaccination.[10]

Four cases of vomiting occurred after OPV vaccination while five cases of frothing were reported after OPV/DPT/HBV given together. Cyanosis as adverse event reported after OPV/DPT/HBV given together vaccination. Out of three cases of rash, two cases occurred with OPV/DPT/HBV given together and one case with Measles vaccination. Also two cases of breathlessness (apnea) and up rolling of eyeball were reported after administration of OPV/DPT/HBV given together. Tom Jefferson *et al.* documented rash in up to 5% of measles vaccine recipients.[11] AEFI Interpretation and clinical definitions guide document showed that Measles/MMR vaccine may produce a mild, non-transmissible measles like illness that can manifested by a generalized rash and fever.[12]

One case each of decreased feeding, lethargy, and reduced intake occurred after OPV/DPT/HBV given together. One case of loose motion occurred after OPV vaccination.[7] Similar findings were reported in study done by Tamie Sugawara *et al.* which showed Diarrhea cases in approximately 10% of patients who received OPV. For cases of diarrhea, the odds ratio of the OPV group to health checkup group was 1.776. This finding strongly suggests that cases of mild diarrhea were closely related to the administration of the OPV.[13]

More than half of the cases of AEFI occurred within 12 h of immunization (61.88%), among which 37.31% of cases occurred within 6 h after immunization, while 17.79% cases occurred after 24 h.[13] Similar findings were reported by Cunha MP *et al.* which showed that more than half (54.2%) of AEFIs occurred within 6 h following vaccine uptake.[4]

More than half cases of Convulsion occur within 12 h of immunization (65.42%) except those produced by measles which commonly occur after more than 24 h (2 out of 3 cases). Convulsion in case of OPV administration commonly occurs within 6 h of vaccination. Vaccination given at the time of birth rarely causes convulsion.

Most cases of local reaction occurred after more than 24 h of immunization. Almost all cases of local reaction at HBV site and BCG site occurred after more than 24 h of immunization. Similar findings were seen in document AEFI: Interpretation and clinical definitions guide which showed that local reactions tend to occur within 48 h of vaccination.[1]

Birth weight of most cases of AEFI in the range between 2 and 2.4 kg (44.06), followed by range between 2.5 and 2.9 (32.20), the mean of birth weight was 2.51. Clifford V. *et al.* showed that lower birth weight was possible risk factors for recurrence ($p = 0.04$)[14]

Most of the cases of adverse reaction were recovered (91%). Death occurred in 9%. No residual morbidity was seen in any of the cases reported.

From our study, it was seen that most of families preferred government services during illness (67.79%), that is, Health post and Government hospitals, of these the government hospitals seem to be the most preferred mode of healthcare among the families. Almost all cases of adverse reactions to vaccine administration, (91%) were seen at government places and among them more commonly at primary level of health care. This is because mass immunization is not practice in private sector hence government sector bears the risk of facing challenges of AEFI. Similar findings were reported by AEFI Surveillance and Response Guidelines MOHFW documented that main service provider for childhood immunization in India is the government sector.[3]

Healthcare professionals (HCPs) form a very significant group among the stakeholders of vaccine safety.[13,15] Vaccines go through the phases of drug development from discovery, preclinical testing, and clinical trials just like pharmacological agents do, before approval by regulatory agencies for use.[16] Post-market surveillance of vaccines after their regulatory approval is crucial, because it helps to identify rare and late-occurring adverse events that were not discovered during clinical trials. The spontaneous reporting of suspected AEFI by HCPs is vital for the monitoring of post-licensure vaccine safety.[17] Evidence shows that in most low and middle-income countries (LMICs) without robust pharmacovigilance systems, HCPs play a significant role in observing medicine related harms and documenting them; this process has often led to the improvement in the functionality of pharmacovigilance systems, or their establishment in countries without these systems. This study aims to highlight the most common adverse event occurring after specific vaccine administration and its time interval after immunization so that healthcare professionals can anticipate and be prepared for tackling health emergencies. This study also emphasize on regular and prompt reporting of AEFI to higher authority so that preventive measures can be taken and guidelines against AEFI prevention can be updated.

Conclusion

Convulsion was the most commonly reported AEFI, majority of AEFI occur within 12 h of immunization. Most of the AEFI were recorded following immunization with OPV/DPT/HBV together. Most of families preferred government services during illness (67.79%) and 90% AEFI were reported from Government facilities.

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Conflicts of interest

There are no conflicts of interest.

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