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RESEARCH ARTICLE

Safety surveillance and causality assessment of adverse event following immunization in children - A vaccine vigilance study

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ABSTRACT

Background: Vaccination is one of the major successful public health interventions worldwide, protecting global populations from most of the health-impairing infections. But as like other medications, vaccines also can cause various forms of adverse effects. The need of this study was to analyze the pattern of an adverse event following immunization (AEFI) in children of Puducherry population and to detect any new and rare AEFI. **Aims and Objectives:** Objectives of this study were to find out the pattern of known adverse events and to identify any new, unusual and rare AEFI in pediatric age group and work out causality assessment for all the AEFI. **Materials and Methods:** In this observational cross-sectional study, AEFI was collected from the pediatric outpatient department of our institute, between the month of August and September 2016 and analyzed for causality assessment. **Results:** In this observational cross-sectional study conducted for a period of 2 months from August 2016 to September 2016 in MGMC and RI, Puducherry 63 nonserious suspected AEFI were reported, and it represents 19% of the vaccinated children. No rare or any serious suspected AEFI was reported during the study period. The most common AEFI was fever (44.4%) followed by fever along with swelling at the injection site (22%). The maximum AEFI was reported due to the pentavalent vaccine (46%), followed by DPT + OPV vaccine (21.5%) combination. On causality assessment, we have found that 87% of AEFI were indeterminate while 13% have a consistent causal association to immunization. **Conclusion:** The benefit of all the vaccines is undeniable; however, they need to be taken with caution and care. To overcome under-reporting, all the pediatricians should be accustomed to report any type of AEFI of different levels of severity. Even more, awareness can be created among the parents and teach them the importance of immunization. To improve effective reporting and for further analysis, all tertiary care centres should maintain a proper database of all vaccinated children and detailed reports of all AEFI.

KEY WORDS: Vaccine vigilance; Pharmacovigilance; Adverse Event Following Immunization

INTRODUCTION

Vaccine Vigilance is defined by the WHO as "the science and activities related to the detection, assessment, understanding, and communication of adverse event following immunization (AEFI), and other vaccine-related or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization." The significance of vaccine safety must be understood by all practitioners. Vaccination is one of the major successful public health interventions worldwide, protecting global populations from most of the health-impairing infections. Small-pox was totally eradicated globally because of the efficacy of vaccines and currently the WHO has involved in many programs for total eradication of the poliovirus globally.[1] In India, market authorization of vaccines has tremendously increased from 10 in the year

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2005 to 137 in the year 2009.[2] But as like other medications, vaccines also can cause various forms of adverse effects and graded severity.[1] In a study they have found that among the 24292 adverse drug reaction (ADR) reports nearly 42% of the adverse effects were due to vaccines.[3]

The Vaccine Adverse Event Reporting System (VAERS) is an immunization safety surveillance program of USFDA that collects information about adverse events and has shown its public health importance by providing health-care professionals with signals about possible AEFI. One of the significant VAERS detected signal was intussusception after the rotavirus vaccine. Many research works confirmed this increased risk of intussusception with rotavirus vaccine and that data helped for the product's removal from the US market. Vaccines pharmacovigilance is of extreme importance today, as most of the pediatric population are being immunized globally in this era of vaccines and nearly 13 new vaccines were introduced in this century.[4] Safety profiles of these vaccines tested in a small group of population in the clinical trials, would need active monitoring globally - to assess newer, serious, and rare reactions. The pharmacovigilance activity related to vaccines has to be improved in both developed and developing countries. As newer vaccines are manufactured, new challenges emerge and require adverse events detection, analysis, and management.

Vaccine Vigilance is the current need of the hour, as children are very sensitive group receiving nearly 37 shots from birth to 6 years. The most common local AEFI includes injection site reactions, pain, induration, and erythema at the injection site. The systemic reactions such as fever, crying, irritability, and rash were also reported.[5]

Hence, the need for this study was to analyze the pattern of AEFI in children of Puducherry population and to detect any new and rare AEFI.

The objectives of this study are:

- To find out the pattern of known adverse events for all childhood vaccinations**.**
- To find new, unusual, and rare vaccine-related adverse events in the pediatric age group work out causality assessment of all the AEFI.

MATERIALS AND METHODS

This observational cross-sectional study aimed to record and analyze various AEFI of children receiving vaccination in the pediatric outpatient department of our institute, between the month of August and September 2016.

Inclusion Criteria

Subjects of the pediatric age group who have received any immunization and diagnosed by the pediatrician as having AEFI were included in this study.

Exclusion Criteria

Subjects are having incomplete records about vaccination.

The study was approved by the Institutional Human Ethical Committee, and waiver of consent was obtained. Then, the subjects were enrolled in the study as per the inclusion criteria. The following parameters were noted down in a CDSCO suspected ADR reporting form. The subjects demographic details, vaccination details, type of reaction, onset of reaction, severity of the reaction, route of administration, history of allergy, and place of vaccination will be noted in the standard form. Cases of AEFI as diagnosed by the consulting pediatrician were included in the study. As per the guidelines of Vaccine Vigilance Center in India, for serious AEFI - death/disability/hospitalized, the reports were collected in the standard forms used for collecting the AEFI[6] and assessed for causality.

Then, the individual AEFI was analyzed for causality using Halsey *et al*. algorithm.[7]

This helps to classify AEFI as [Figure 1]:

a. Consistent causal association to immunization.
b. Inconsistent causal association to immunization (coincidental).
c. Indeterminate when adequate information on the AEFI is available, but it is not possible to assign it to either of the above categories.

This has been obtained from definition and application of terms for vaccine pharmacovigilance report of the CIOMS/ WHO working group on vaccine Pharmacovigilance.

Statistical Analysis

Descriptive statistical analysis was done with NCSS software. Reporting rates of AEFI per 1000 distributed doses were analyzed for each vaccine.

RESULTS

The study was done for a period of 2 months from August 2016 to September 2016. Out of 480 vaccine doses given to 331 children, 63 non-serious suspected AEFI was reported. Among them 32 (51%) were males and 31 (49%) were females. The most common AEFI was fever (44.4%) followed by fever along with swelling at the injection site (22%). Other suspected that AEFI was rashes, erythema, excessive crying, and pain at the injection site. No serious AEFI was reported during the study period.

A total of 331 children were vaccinated with a total number of 480 doses of different vaccines (individual or combination), 63 non-serious suspected that AEFI was reported representing 19% of the vaccinated children. No rare or any serious suspected that AEFI was reported during the study period.

I. Is there strong evidence for other causes?	Y N UK NA	Remarks
Does a clinical examination, or laboratory tests on the patient, confirm another cause?	□□□□	
II. Is there a known causal association with the vaccine or vaccination?		
Vaccine product(s)		
Is there evidence in the literature that this vaccine(s) may cause the reported event even if administered correctly?	□□□□	
Did a specific test demonstrate the causal role of the vaccine or any of the ingredients?	□□□□	
Immunization error		
Was there an error in prescribing or non-adherence to recommendations for use of the vaccine (e.g. use beyond the expiry date, wrong recipient etc.)?	□□□□	
Was the vaccine (or any of its ingredients) administered unsterile?	□□□□	
Was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal at the time of administration?	□□□□	
Was there an error in vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	□□□□	
Was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)?	□□□□	
Was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)?	□□□□	
Immunization anxiety		
Could the event have been caused by anxiety about the immunization (e.g. vasovagal, hyperventilation or stress-related disorder)?	□□□□	
II (time). If "yes" to any question in II, was the event within the time window of increased risk?		
Did the event occur within an appropriate time window after vaccine administration?	□□□□	
III. Is there strong evidence against a causal association?		
Is there strong evidence against a causal association?	□□□□	
IV. Other qualifying factors for classification		
Could the event occur independently of vaccination (background rate)?	□□□□	
Could the event be a manifestation of another health condition?	□□□□	
Did a comparable event occur after a previous dose of a similar vaccine?	□□□□	
Was there exposure to a potential risk factor or toxin prior to the event?	□□□□	
Was there acute illness prior to the event?	□□□□	
Did the event occur in the past independently of vaccination?	□□□□	
Was the patient taking any medication prior to vaccination?	□□□□	
Is there a biological plausibility that the vaccine could cause the event?	□□□□	

Note: Y: Yes; N: No; UK: Unknown; NA: Not applicable.

Figure 1: The causality assessment checklist

The male:female ratio was 1.1:1. The most common AEFI was fever (44.4%). The vaccine for which maximum AEFI was reported was Pentavalent (Diphtheria, Pertussis, Tetanus, Hepatitis B, and Haemophilus influenzae type B) vaccine (46%), followed by DPT + OPV vaccine (21.5%) combination. The percentage of reported AEFI to both the individual and combination of vaccines is given in Table 1. Figure 2 represents the types of suspected AEFI and number of cases reported. Nearly 94% suspected that AEFI was related to the vaccine included in the National Immunization Schedule whereas remaining 6% were due to vaccines not included in the national schedule. No AEFI were reported for typhoid and rotavirus vaccines. Reporting rates for the individual and combination vaccines are shown in Table 2.

Then, the individual AEFI was analyzed for causality assessment using Halsey *et al*. algorithm.[7] This helps to classify each AEFI as:

- Consistent causal association to immunization.
- Indeterminate.
- Inconsistent causal association to immunization (coincidental).

Of the 63 AEFI reports 87% were of category B (indeterminate) while 13% have a consistent causal association to immunization.

DISCUSSION

In this observational cross-sectional study conducted for a period of 2 months from August 2016 to September 2016, in Puducherry, 63 non-serious suspected that AEFI was reported, and it represents 19% of the vaccinated children (n= 331) who were administered a total number of 480 doses of different vaccines (individual or combination). No rare or any serious suspected that AEFI was reported during the study period. The most common AEFI was

Table 1: Reported AEFI to both the individual and combination of vaccines

Vaccine	Percentage of AEFI
BCG+Hepatitis B+OPV	9.5
DPT+OPV	21.5
Quadruple	11
Pentavalent	46
Measles	3
Hepatitis A	1.5
MMR	3
Pneumococcal	3
Varicella	1.5

Table 2: Reporting rates for the individual and combination vaccines

Vaccine	Number of AEFI[#]	Total number of vaccine doses	Reporting rate per 1000 vaccine doses
DPT	2	13	153
Quadruple	4	22	181
Pentavalent	29	186	155
Measles	2	29	68
MMR	2	51	39
Bivalent OPV	35	212	165
IPV	21	116	131
Varicella	1	7	142
Hepatitis A	1	13	76
Pneumococcal	2	19	105

[#]More than one vaccine may be responsible for the suspected AEFI if 2 or more vaccines are given together. AEFI: Adverse event following immunization

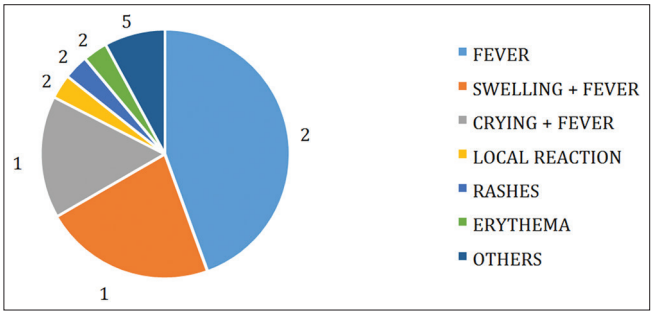

Figure 2: Types of and number suspected AEFI reported

fever (44.4%) followed by fever along with swelling at the injection site (22%). The maximum AEFI was reported due to Pentavalent (Diphtheria, Pertussis, Tetanus, Hepatitis B, and Haemophilus influenzae type B) vaccine (46%), followed by DPT + OPV vaccine (21.5%) combination. On causality assessment, we have found that 87% of AEFI were of category B (indeterminate) while 13% have a consistent causal association to immunization.

In our study, the number of AEFI reported was 19% which is similar to a study conducted by Carrasco-Garrido *et al*. in which they have done a 6-month, prospective, observational, and multicentre vaccine safety study in 2002 in vaccinated pediatric population and found 191 AEFI reports from 946 vaccinated children records.[8] The most common AEFI reported in our study was fever (44.4%) which is consistent with the study done by Hu *et al.* in which the most frequently reported AEFI was fever (46.2%), [9] but this was unsupportive by the Carrasco-Garrido *et al*. study in which they have observed injection site edema as the most frequent AEFI (12.2 per 1000 doses).[8] In another surveillance study conducted in the year 2013 by Mahajan *et al*., 5.790 events were collected from 3.161 AEFI records in which they have found that the most commonly reported adverse events were injection site reactions (13%) followed by rash (10%) and pyrexia (8%).[10] This difference might be because of the shorter duration of study which is uncomparable with other vaccine surveillances conducted usually for a lengthier period at least for a time period of 6 months.

We have noted that maximum AEFI was reported due to Pentavalent (Diphtheria, Pertussis, Tetanus, Hepatitis B, and Haemophilus influenzae type B) vaccine (46%), followed by DPT + OPV vaccine (21.5%) combination. This is inconsistent with the two different research conducted by Cunha *et al.*[11] and Hu *et al.*,[9] in which they have identified the most common vaccine causing AEFI was DTP/Hib with 57.8% and 30% of the reported AEFI, respectively. The picture is entirely different in a study conducted in Oman for a period of 10 years by Awaidy *et al*., noticed that BCG vaccine was responsible for the highest number of AEFI reports (41.3%).[12]

Strengths

Major strength of this study is that it is a prospective observational study through which we can get more reliable data than retrospective record-based study. Causality assessment was done with an appropriate algorithm designed especially for analyzing vaccine-related adverse events.

Limitations

This has limitations inherent to any passive surveillance study, and major limitation is underreporting of AEFI. We have calculated only the crude reporting rate for each vaccine which cannot be used to interpret the exact incidence of AEFI.

CONCLUSION

In this observational cross-sectional study conducted for a period of 2 months from August 2016 to September 2016, 63 nonserious suspected that AEFI was reported, and it represents 19% of the vaccinated children. No rare or any serious suspected that AEFI was reported during the study

period. The most common AEFI was fever (44.4%) followed by fever along with swelling at the injection site (22%). The maximum AEFI was reported due to Pentavalent (46%), followed by DPT + OPV vaccine (21.5%) combination. On causality assessment, we have found that 87% of AEFI were indeterminate while 13% have a consistent causal association to immunization.

The study participants who were diagnosed as having AEFI were given proper treatment and assurance was given to their parents. All the pediatricians should be aware of common and also rare AEFI. To improve effective reporting and for further analysis, all tertiary care centres should maintain a proper database of all vaccinated children and detailed reports of all AEFI. All the severe AEFI should be notified immediately. The national pharmacovigilance program of India must enhance AEFI reporting, create awareness regarding the importance of reporting and a proper database should be maintained nationally.

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