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## AN OVERVIEW OF RETROSPECTIVE STUDY OF VACCINE RELATED ADVERSE DRUG REACTIONS IN A TERTIARY CARE HOSPITAL

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### Abstract:

Pharmacovigilance is a structured activity in the professional health care field, with an important commercial and social implications aimed at monitoring the risk or benefit ratio of drugs in order to improve the patient safety and the quality of life. It plays an important role in monitoring, assessing and preventing the various adverse drug reactions. Adverse drug reactions (ADR) is defined as any noxious, unintended and undesired effect of a drug which occurs at a dose normally used in man for prophylaxis, diagnosis, or the modification of physiological functions. During the development of a new drug both the beneficial and unwanted effects are known by through clinical trials. The frequency of ADRs and the other drug related problems in the society are not known. Thus the detection and reporting of such ADR in by through clinical practice is considered as the backbone of post market surveillance. Immunization is a very important and effective public health measure in order to preventing serious and life threatening diseases. Vaccine safety is a major concern of modern world. Although, vaccines provides a good defence against some infectious diseases, but their administration may also be related to the development of adverse vaccine events. Therefore their use is continuously monitored to detect both expected and unexpected adverse effects by AEFI in a medical incident. Causality assessment is a method by which the extend of relationship between a drug and it's reaction that is suspected and causality is assessed by WHO and Naranjo's scale. In India; it runs the largest immunization programme that is [UIP] universal immunization programme in the world for the prevention of various vaccine preventable diseases. The AEFI is initiated by the government of India in the year of 1986. The aim is detection of AEFI, approval action to prevent such ADR in the future. Most of the countries are monitoring AEFI by an effective national AEFI surveillance system.

### Key words:

Pharmacovigilance, Adverse drug reactions, Vaccine, Immunization, Causality assessment, AEFI.

### INTRODUCTION

*Pharmacovigilance is a structured activity in the professional health care field, with an important commercial and social implications aimed at monitoring the risk or benefit ratio of drugs in order to improve the patient safety and the quality of life [22]. The Pharmacovigilance comes in picture after the sulphanilamide elixir tragedy in 1937, and in early 1960s more than 10000 children around 46 countries were born with a condition phocomelia caused by thalidomide which has opened the eyes of drug regulators towards drug safety. It is also a branch of pharmacoepidemiology but it is restricted to the study on epidemiological scale of adverse reactions or drug events [23]. As per WHO, Pharmacovigilance is defined as The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems [15]. Or it is the study of the safety of marketed drugs under practical conditions of clinical use in large communities. Pharmacovigilance is derived from the words "Pharmakon" (Greek) which means "medicinal substances" and "vigilia" (Latin) "to keep watch". The process of Pharmacovigilance includes detecting and reporting of ADRs. The reporting of ADR is of two types*

❖ Spontaneous reporting

❖ *Mandatory reporting*

**Spontaneous reporting:**

- *Most common form of ADR reporting*
- *Healthcare Professionals identify and report the suspected adverse drug reactions to Pharmacovigilance centres or to the corresponding drug manufactures.*

**Mandatory reporting:**

- *Manufactures are required to submit the reports that they received from healthcare providers to the National authority, in the form of a PSUR (Periodic Safety Update Report).*
- *Marketing Authorization Holders prepare a regulatory document and submitted to the respective agency.*
- *It includes all the information's belong to ADR*

**Pharmacovigilance process in India:**

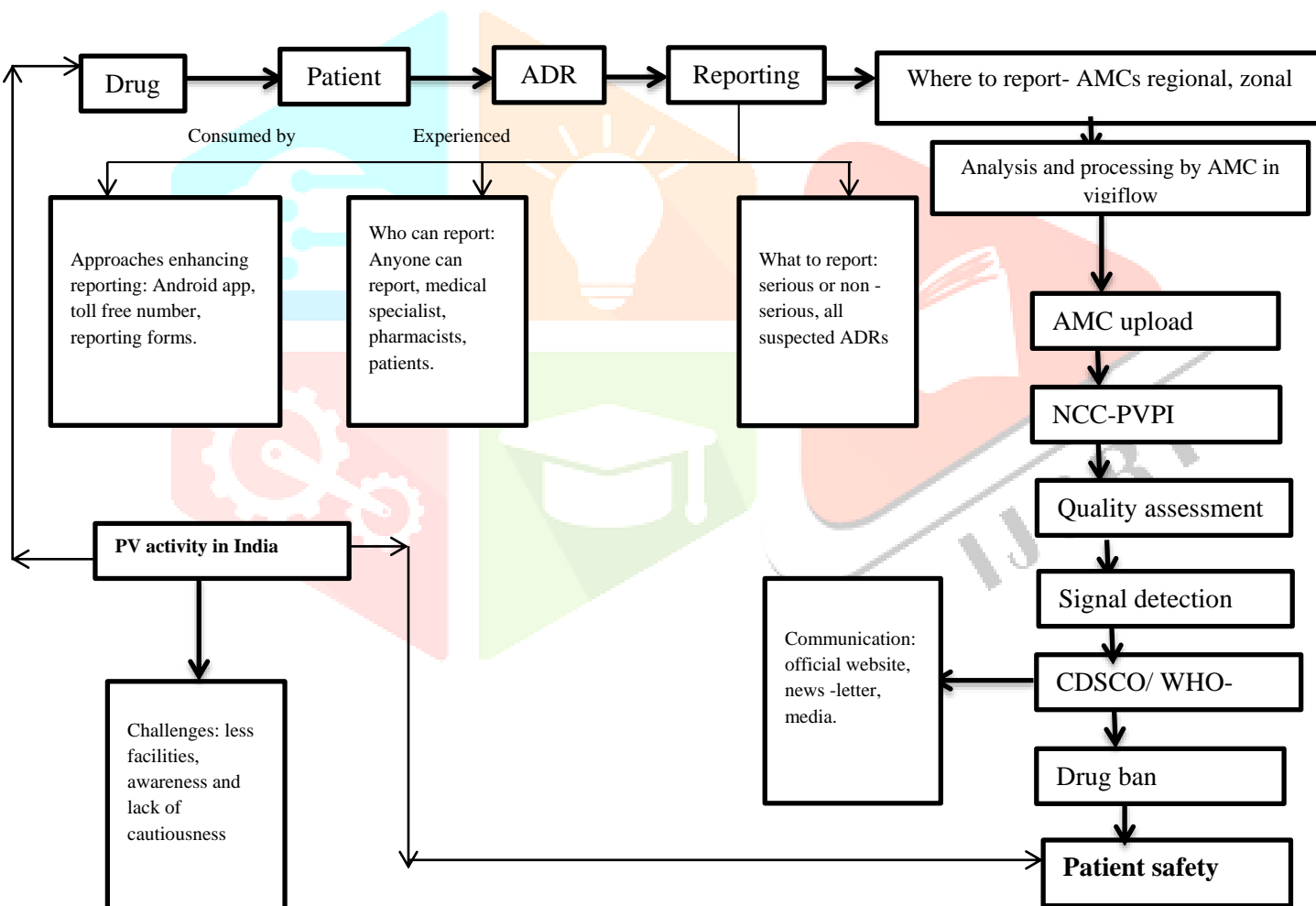


Figure1: pharmacovigilance process in India

Pharmacovigilance plays an important role in monitoring, assessing and preventing the various adverse drug reactions [11].

**Adverse drug reactions**

Adverse drug reactions (ADR) is defined as any noxious, unintended and undesired effect of a drug which occurs at a dose normally used in man for prophylaxis, diagnosis, or the modification of physiological functions[15]. Adverse drug events is any untoward medical occurrence that may present during treatment with medicine, but which may not have causal relationship

with the treatment. The various factors affecting ADR involves Patient related factors [ Age, sex, genetic influences , concurrent diseases, previous ADRs, compliance with dosing regimen , diet , smoking, environmental exposure, Total number of medications ], Drug related factors [ Dose, duration , pharmacokinetic and pharmacodynamics properties ].

#### Common cause of ADRs

- Overdosing
- Allergies towards to the chemicals in medicine
- Failure of taking correct doses
- Failure of taking drugs at correct time
- Combine alcohol with medicines
- Taking drugs that is administered to someone else.

#### Classification of Adverse drug reactions

Depending on .....

##### ➤ Type of reaction :

1. Type A (Augmented): It is dose dependent and can be withdrawn by reducing the dose. Example: beta blockers – Bradycardia.
2. Type B (Bizarre): Not dose dependent and pharmacology of drug is unpredictable. Example: penicillin-anaphylaxis
3. Type C (Chemical): it occurs by through an irritant reaction and the ADR is related to drug concentration. Example: Extravasation reactions and Phlebitis.
4. Type D (Delivery): It is caused by the method of route of administration or nature of formulation and it improves if the medicine is withdrawn or the route of delivery is changed. Example: Inflammation and infection around the implanted devices.
5. Type E (exit): it is pharmacologically predictable and begins only when the medicine is stopped or the dose is reduced. It improves if the drug is reintroduced. Example: withdrawal reactions due to opioids, Benzodiazepines, clonidine
6. Type F (Familial): it occurs only in genetically predisposed individuals. Example: Haemolytic anaemia with primaquine in G6PD deficiency individuals
7. Type G (Genotoxicity): it mainly cause when there is an irreversible genetic damage. Example: teratogenicity agents like thalidomide causing genetic damage in the foetus.
8. Type H (Hypersensitivity): Activation of immunity takes place and this improves if the medicine is withdrawn. Example: Allergic skin reactions with antimicrobial agents.
9. Type U (Unclassified): Its mechanism is not known. Example: Nausea and vomiting with the use of gaseous Anaesthetics.

Medicinal drugs or substances are kindly used because of their ability to react and to produce effect biological processes in the body. But the usage such substances carries a certain risk of unwanted effects. In every occasion when a patient is exposed to a new drug is a unique situation and we can never be certain about what might happen. During the development of a new drug both the beneficial and unwanted effects are known by through clinical trials. The frequency of ADRs and the other drug related problems in the society are not known. Although the randomized clinical trials is considered as the golden standard for the evaluation of the safety and efficacy of the drug .Such design of the trials consist of small and homogenous population monitored for a short period of time making it more difficult to detect many ADR of the drugs <sup>[11]</sup>. Thus the detection and reporting of such ADR in by through clinical practice is considered as the backbone of post market surveillance <sup>[11]</sup>.

#### Detection and monitoring of ADR

- Pre - marketing studies

Clinical trials are carried out in three different phases before the submission of the marketing authorization application. The clinical trials have the ability to identify the adverse reactions of a frequency greater than 0.5 – 1.0 %. By due to the Cost reasons the clinical trials are often to have a very short duration which cannot be generate information about to the long term adverse events.

- Post marketing surveillance

A subsequent to the approval of any new products or any new drugs it should be closely monitored of their adverse reactions or their clinical safety once they are marketed. For these reasons the applicant should be submit a periodic safety update reports in order to

1. Report all the relevant information from appropriate sources
2. Indicate whether these changes should be made to the product information that is to optimize the use of product
3. Relate these Data to the patient exposure
4. Summarize the market authorization status in different countries and any significant variations related to drug safety.

A PSUR should be structured as following:

Title page

1. PSUR for the product
  - Applicant name
  - Date of approval of new drug.
  - Period Covered by the report
  - Date of reporting and marketing.
2. Introduction current worldwide market authorization status
3. Changes to reference safety information
4. Estimated patient exposure
5. Studies conducted
6. Other information
7. All but all safety information
8. Conclusion

## Vaccine

A Vaccine can be defined as a biological preparation that provides active acquired immunity for a particular infection causing pathogens. It can be made from weakened or killed forms of microorganisms. Although they are designed to protect from disease, can cause side effects, just as any other medicines. Common side effects after vaccination are mild, such as soreness, swelling, or redness at the injection site, fever, Rashes. Serious side effects are rare, but seizure or life-threatening allergic reaction is also observed. The administration of vaccines is called vaccination. The science of vaccine development and production is termed as vaccinology.

### Types of vaccines

- Live attenuated
  1. Tuberculosis (BCG)
  2. Oral polio vaccines (OPV)
  3. Measles
  4. Rotavirus
  5. Yellow fever
- Inactivated
  1. Whole cell pertussis
  2. Inactivated polio virus (IPV)
  3. Hepatitis A
- Subunit
  1. A cellular pertussis (a P)
  2. Pneumococcal (PCV-7, PCV-10, PCV – 13 )
  3. Hepatitis B
- Toxoid
  1. Tetanus toxoid (TT)
  2. Diphtheria toxoid
- Viral vector vaccine
  - Zaire Ebola Virus (RVSZ-ZEBOV)

Vaccines under the UIP, India, 2016 brief history of immunization program in India.

- ❖ On May 1974 : expanded Programme on immunization and included immunization against 6 vaccine preventable diseases as Diphtheria, Pertussis, Tetanus, TB, Measles , Polio
- ❖ On Jan 1978: EPI (expanded programme on immunization) launched in India.
- ❖ In Nov 1985 : EPI replaced by UIP
- ❖ In 1992: UIP became a part of CSSM (Child Survival and Safe Motherhood) programme.
- ❖ On 1995: NID`s started for polio eradication.
- ❖ On 1997 : UIP become the part of RCH (Reproductive and Child Health Programme)
- ❖ On 2005: UIP became a part of NRHM umbrella programme.
- ❖ On 2010 : National Technical Advisory Group On Immunization was reconstituted
- ❖ In 2011: National Vaccination Policy released.
- ❖ On 25<sup>th</sup> December 2014: Mission Indradhanush launched.

**National immunization schedule**

- In case of pregnant women:

Vaccine	Due age	Manage	Dose	Diluent	Route	Site
TT-1	Early in pregnancy	Give as early as possible in pregnancy	0.5 ml	No	Intra muscular	Upper arm
TT-2	4 weeks after TT-1		0.5 ml	No	Intra muscular	Upper arm
TT-Booster	If received 2 TT doses in a pregnancy with in the last 3 years.		0.5 ml	No	Intra muscular	Upper arm

Table 1: National immunization schedule in case of pregnant women

- In case of infants and children (recently):

Vaccine	Due age	Manage	Dose	Diluent	Route	Site
BCG	At birth	Till 1 year of age	(0.05 ml until 1 month) 0.1 ml Beyond age 1 month	YES Manufacturer supplied diluent (sodium chloride)	Intra dermal	Upper arm-LEFT
Hepatitis B- Birth dose	At birth	Within 24 hours	0.5 ml	No	Intra muscular	Antero-lateral side of mid – thigh-LEFT
OPV-0	At birth	Within the first 15 days	2 drops	–	Oral	Oral
OPV-1,2&3	At 6 weeks, 10 weeks & 14 weeks	Till 5 years of age	2 drops	–	Oral	Oral
Pentavalent 1,2 &3 (Diphtheria + pertussis+ TT + Hepatitis B + Hib	At 6 weeks, 10 weeks & 14 weeks	1 year of age	0.5 ml	No	Intra muscular	Antero-lateral side of mid-thigh-LEFT
Fractional IPV ( Inactivated polio virus)	At 6 and 14 weeks	1 year of age	0.1 ml	No	Intra dermal	Upper arm-RIGHT
Rotavirus(where applicable)	At 6 weeks, 10 weeks & 14 weeks	1 year of age	5 drops	No	Oral	Oral
Pneumococcal conjugate vaccine (PCV) (where applicable)	At 6 weeks & 14 weeks At 9 completed months-Booster	1 year of age	0.5 ml	No	Intra muscular	Antero-lateral side of mid-thigh-RIGHT
Measles / Rubella 1 <sup>st</sup> dose	At 9 completed months- 12 months	5 years of age	0.5 ml	YES Manufacturer supplied diluent ( Sterile water)	Subcutaneous	Upper arm-RIGHT
Japanese Encephalitis – (where applicable)	At 9 months- 12 months	15 years of age	0.5 ml	YES Manufacturer supplied diluent ( phosphate buffer solution)	subcutaneous	Upper arm-LEFT
Vitamin A ( 1 <sup>st</sup> dose)	At 9 months	5 years of age	1 ml	–	Oral	oral

Table 2: National immunization schedule in case of infants and children

New vaccines which is to be introduced as per the National Technical Advisory Group on Immunization [NTAGI]

Immunization is a very important and effective public health measure in order to preventing serious and life threatening diseases. Vaccines are administered to large population of every healthy individual, particularly millions of infants per year through National Immunization Programme <sup>[1]</sup>. Adults too are receiving a number of vaccines in each year. Vaccines are subjected to premarket safety testing before their final approval, but as drawback certain adverse reactions are not identified in both preclinical and clinical phase. By the Immunization Division under Ministry of Health and Family Welfare, Government of India through Adverse Event Following Immunization [AEFI] division and Pharmacovigilance Programme of India [PvPI]

and the regulatory interventions on vaccines taken by Central Drugs Standard Control Organization (CDSCO), a national regulatory authority for monitoring the safety of vaccines in India.<sup>[2]</sup>

In India, Pharmacovigilance of vaccines is still at its nascent stage. There is adequate need of large scale monitoring and reporting in India as only a few Indian studies on ADR related to immunization are available. In 1986, India launched the Adverse Events Following Immunization (AEFI) surveillance program for monitoring suspected adverse events following immunization and then, the AEFI surveillance guideline has been updated periodically, with the last update in 2015. For the successful AEFI surveillance program in India required the concerted effort of all stakeholders such as National AEFI secretariat, National Technical Collaborating Centre, CDSCO, health care and marketing authorization Professionals<sup>[11]</sup>.

Vaccine safety is a major concern of modern world. Although, vaccines provides a good defence against some infectious diseases, but their administration may also be related to the development of adverse vaccine events. Therefore their use is continuously monitored to detect both expected and unexpected adverse effects by AEFI in a medical incident.

There are different type of studies have been carried out in the several parts of the world on the prevalence of hospital admissions that leads from adverse reactions and also the other drug related problems. In the recent analysis on the 25 different studies of admissions to internal medicine department 4.2 – 6.0 Percentage of admissions were due to the serious adverse reactions with a median of 5.8%. An overview in 13 Australian studies that assessing the drug related hospital admissions in between the ears of 1988- 1996 and 2.423 point six percentage of hospital admissions were likely to be drug related.

### Predisposing factors

There are several many factors that can predispose to the occurrence of adverse drug reactions in a patient.

- **Poly pharmacy:** A patient with multiple drug therapy is relatively more prone to develop an ADR due to alteration of the drug effects by through the induction mechanism or by synergistic effect.
- **Multiple and inter current diseases :** A patient with the empire hepatica this is are also at a high risk of developing an ADR to the drugs which are eliminated by the organs, so a patient with the multiple disease are have an increased risk of developing area due to the multiple drug use for their multiple diseases.
- **Age:** The pediatric and elderly patients are more vulnerable to develop the ADR. In case of elderly patient they are most acceptable due to their physiological changes and which a company by through the ageing. And in the case of neonates they differ in their drug handling capacity as compared to the adults.
- **Drug characteristics:** 13 drugs are toxic in nature and those patients who treated with these toxic drugs are at an increased risk of ADR.
- **Race and genetics:** the ADR are more common in genetically predisposed individuals. For an example : patients who are genetically predisposed of glucose 6 phosphate dehydrogenase and them are at a higher risk of developing ADR due to the use of Primaquine.
- **Gender:** Women are more susceptible to develop ADR than men.

### Causality assessment

Causality assessment is a method by which the extend of relationship between a drug and it`s reaction that is suspected. In order to understand or eliciting the causality relationship, a possible association is sufficient for an ADR report to be made. Data should be collected on about the drugs ADR and the collected data should be used to correlate and categorized between the drug and ADR. These can be done by through one or more causality assessment scales. In the causality assessment any following approach is necessary.

- Opinion of individual experts
- Opinion of panel of experts
- Formal algorithms

*In opinion of individual experts:* An individual who is an expert in area of ADRs would evaluate the case.

*Opinion of panel of experts:* They adopt a similar procedure to arrive at collective option.

*Formal algorithms:* Collected data are subjected and critically assessed by using one or more standard algorithms such as Naranjo`s scale, WHO scale, Kramer, Bayesian, Karch and Lasagna`s Etc..<sup>[24]</sup>

### WHO Causality assessment scales

*Certain*

- *Event of laboratory test abnormality with plausible time relationship to drug.*
- *Cannot be explained by disease or other drugs.*
- *Response to withdrawal plausible.*
- *Event definitive pharmacologically*
- *Re challenge.*

*Unassessible / Unfeasible*

- *A report suggesting an adverse reaction.*
- *Cannot be judged because of insufficient or contradictory information.*
- *Report cannot be supplemented or verified.*

*Probable*

- *Event or lab test abnormality with reasonable time relationship during intake.*
- *Unlikely to be attributed to disease or other drugs.*
- *Response to withdrawal clinically reasonable*
- *Re challenge not necessary.*

*Possible*

- *Event or laboratory test abnormality, with reasonable time relationship to drug intake.*
- *Could also be explained by disease or other drugs.*
- *Information on drug withdrawal lacking or unclear.*



<p><i>Unlikely</i></p> <ul style="list-style-type: none"> <li>➤ <i>Event or laboratory test abnormality with a time to drug that makes a relationship improbable.</i></li> <li>➤ <i>Diseases or other drugs provide plausible explanations.</i></li> </ul> <p><i>Conditional</i></p> <ul style="list-style-type: none"> <li>➤ <i>Event or laboratory test abnormality.</i></li> <li>➤ <i>More data for proper assessment needed or additional data under examination.</i></li> </ul>
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**Naranjo’s causality assessment scale**

QUESTIONS	YES	NO	DON'T KNOW
1. Are there is previous conclusive reports on this reaction?	+1	0	0
2. Did the adverse event appear after the suspected drug was Administered?	+2	-1	0
3. Did the adverse reaction improve when the drug was Discontinued or specific antagonist was administered?	+1	0	0
4. Did the ADR reappear when the drug is re administered?	+2	-1	0
5. Are the alternative causes that could solely have caused the reaction?	-1	+2	0

6. Did the reaction reappear when placebo was given?	-1	+1	0
7. Was the drug detected in blood in a concentration known To be toxic?	+1	0	0
8. Was the reaction more severe when the dose was increased Or less severe when the dose was decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar Drugs in any previous exposure?	+1	0	0
10. Was the adverse event confirmed by objective evidence?	+1	0	0

**Table 3: Naranjo's causality assessment scale**

#### **Modified Hartwig and Siegal Severity Assessment Scale**

<b>LEVEL</b>	<b>CRITERIA</b>
Mild(level 1)	The ADR requires no change in treatment with suspected drug
Mild (level 2)	The ADR requires that the suspected drug be withheld, discontinued or otherwise changed No antidote or other treatment is required, and there is no increase in length of stay
Moderate (level 3)	The ADR requires that the suspected drug be withheld, discontinued or otherwise changed and or an antidote or other treatment is required, with no increase in length of stay
Moderate (level 4)	Any level 3 ADR that increase length of stay by at least one day or the ADR is reason for the admission
Severe(level 5)	Any level 4 ADR that requires intensive medical care
Severe(level 6)	The ADR causing permanent harm to the patient
Severe(level 7)	The ADR either directly or indirectly leading to the death of the patient

**Table4: Severity assessment (Modified Hartwig and Siegal Scale)**

#### **Global scenario:**

Most of the countries are monitoring AEFI by an effective national AEFI surveillance system. The vaccine adverse events reporting system is implemented in order to monitor the safety of US licenced vaccines. It is established in the year of 1990 and it is co-sponsored by US food and drug agency along with the Centre of disease control and prevention.

In Canada; they follow the immunization surveillance system. It is implemented by collaborative effort of public health authorities of Canada.

In UK; they follow the MHRA that is the Medicine and health care products regulating agency. The reporting of the ADR of vaccine is done by through yellow card scheme. In case of India; it runs the largest immunization programme that is [UIP] universal immunization programme in the world for the prevention of various vaccine– preventable diseases. The AEFI is initiated by the government of India in the year of 1986. The aim is to detection of AEFI, approval action to prevent such ADR in the future. AEFI first operational guideline is published in 2005 with the technical support of WHO and this guideline was revised and updated in 2010<sup>[16]</sup>.

## CONCLUSION

The studies that we made clearly justify the need of reporting of adverse drug reactions along with the name of the drug product (vaccine name), brand name, batch number, lot number, efficacy, manufactures details, which will help for the proper monitoring and detection on the safety of vaccines there by, the patient safety. So the reports that made annually through AEFI reporting systems will indirectly provide awareness to the public on the safety of immunization. Thus such post marketing surveillance open up a way to detect the rare ADRs on the vaccine. By through the proper monitoring of such ADRs of post-vaccination will contribute the public confidence in immunization programmes.

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