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A REVIEW ON PHARMACOVIGILANCE STUDY OF VACCINES

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Abstract:
Pharmacovigilance systems are needed to safeguard the public health. The pharmacovigilance study of vaccines means science and activities related to detection, assessment, understanding, prevention and communication of adverse events of vaccines. It is an important part of clinical trials. The vaccines are the immunized preparations containing antigens which are useful against the infectious diseases which act by providing active immunity. There are severe and rare adverse events associated with vaccines. The main aim of vaccine pharmacovigilance is to detect the rare and unexpected side effects of vaccines. The vaccine vigilance is important and needed because the vaccines are administered to the healthy person and children who are sensitive to adverse events occurring after vaccination are less acceptable. The vaccine pharmacovigilance includes different methods of study like ADR reporting, drug event monitoring, cohort studies, case controlled studies and randomized controlled studies. The pharmacovigilance program in India was started with the main aim of improvement of patient safety and welfare in Indian population by effective monitoring of vaccine safety. It also provides training and consultancy support to the pharmacovigilance program. The future aspect of pharmacovigilance in India includes building and maintaining a robust system in India. Also includes education and training to health workers like doctors, nurses, pharmacists regarding the vaccine pharmacovigilance.
Key words: pharmacovigilance, India, adverse events, ADR reporting, clinical trials.

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1. INTRODUCTION:[1-2]

The data obtained from clinical trials should be able to potentially reflect the safety and effectiveness of active principle of drug for the successful launching of product in the market. Generally the clinical trials are carried out in limited number or a controlled population so that we can only able to detect the common adverse effects of drug with the help of clinical trials. But, the adverse reaction which develops in a specific person or the reactions which develops after longer period of time are remains undetected. This may occurs due to the genotype which may varies from person to person and also physiological conditions of individual person are considered. Any medicine is said to be safe only when its benefits are greater than associated risk. So to determine the complete safety profile of a drug or medicine; a constant and continuous monitoring in a large population is necessary which is possible in case of pharmacovigilance study. The pharmacovigilance deals with the complete study of drug related adverse effects and other problems. "Pharmakon" means "Drug" and "Vigilance" means "to keep watch or alert". Broadly speaking, all chemicals other than the food that can alter biological systems are called as drugs. A chemical which shows beneficial therapeutic effect on the body is called as a medicine. However, if it produces harmful or toxic effects then it is regarded as a poison. Thus we can say that every drug is poison depending on the dose and use. The noxious and unintended reactions occurring at normal therapeutic dose are called as adverse drug reactions. While, the unwanted events occurred during drug therapy having no relation with its use are called "adverse events".

In case of vaccines, the significance of vaccine safety must be understood by all practitioners. Vaccination is one of the major successful public heath interventions, worldwide, protecting global populations from most of the dangerous infections. Small-pox disease was totally eradicated globally and it is possible because of the efficacy of vaccine. Now the WHO has started many programs for total eradication of the polio virus globally. In India, market authorization of vaccines has tremendously increased from 10 in year 2005 to 137 in the year 2009. But as like other medications, vaccines also can cause various forms of adverse effects. In a study they found that among the 24292 adverse drug reactions reported nearly 42 % of adverse effects were due to vaccines.

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 Adverse Events Following Immunization (AEFI). The vaccine pharmacovigilance is of extreme importance today, as most of the pediatric population is being immunized globally. In this era of vaccines there are 13 new vaccines were introduced in this century. 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 were manufactured, new challenges emerge and require adverse event detection, analysis and management.

The vaccine vigilance is very important and needed, because the children are very sensitive group which receives nearly 37 vaccines from birth to age of 6 – 7 years. The most common local adverse events followed by immunization include injection site reactions, pain, redness and swelling at the injection site. The systemic reactions such as fever, crying, irritability and rash were also reported.

Hence, the need for this study was to analyze the pattern of Adverse Events Followed Immunization (AEFI) in population and to detect any new and rare adverse effects.

The objectives of these studies are:

- To study the known adverse events for all types of vaccinations.
- To study new, unusual, and rare vaccine related adverse events in the population.

1.1 PHARMACOVIGILANCE:

As per WHO guidelines the pharmacovigilance is defined as the science and activities related to detection, assessment, understanding and prevention of adverse effects or any other drug related problems. The goal of pharmacovigilance are to increase patient care and patient safety in relation to use of vaccines and to support public health programs by providing reliable, balanced information for the effective assessment of the risk benefit profile of vaccines.

The pharmacovigilance plays an important key role in the health care system through assessment, monitoring and discovery of interactions amongst drugs and their effects in human. The variation in the human genome is a cause of variable responses to drugs and susceptibility to disease are determined, which is important for early drug discovery to pharmacovigilance. Moreover, the pharmacovigilance has traditionally involved in mining spontaneous reports submitted to national surveillance system. The adverse events reported by pharmacovigilance system potentially beneficial to the community due to their proximity to both

population and public health practitioners, in terms of language and knowledge enables easy contact with reporters by electronically. Hence, pharmacovigilance helps to the patients to get well and to manage optimally or ideally, avoid illness is a collective responsibility of industry, drug regulators, clinicians and other health care professionals to enhance their contribution to public health.

1.2 VACCINE PHARMACOVIGILANCE:

A vaccine is a biological preparation that improves immunity against a particular disease. So the vaccine is important for prevention of disease. A large number of adverse drug reaction are normally occur with vaccines during vaccination and after a long time of vaccination such as life threatening illness and medical events which may cause death of infants.

According to WHO and FDA vaccine pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and communication of adverse event following immunization and other vaccine or immunization related issues, and to the prevention of unwanted effects of the vaccine or immunization. The majority of vaccines are administered to the children and to the healthy persons so the adverse events occurring after vaccination are very less accepted as compared to other medicines, hence a safety supervision of vaccine is much needed. The vaccines are considered as medicines with anti-infective activity that work by immunological action and the vaccines are administered for the prophylaxis. The term ‘’enhanced capacity’’ for vaccine pharmacovigilance is used in the blueprint in contrast to minimal pharmacovigilance capacity. Enhanced vaccine pharmacovigilance at a minimal level, includes improved data collection, verification, analysis and communication by building capacity for stimulated and active surveillance. It also includes the ability to perform population based studies and appropriate epidemiological studies testing hypothesis by assessing relative and absolute risk ratios, when appropriate.

2. NEED OF STUDY OF VACCINE PHARMACOVIGILANCE: [3]

Under this point we study the importance of vaccine pharmacovigilance and the adverse events associated with the different vaccines are also considered.

Main objectives:

1. To monitor all Adverse Events Following Immunization (AEFI), especially those which are serious, exceptional and which occurs frequently.
2. To prepare data on incidents of (AEFI) whether already established or newly detected.
3. To monitor all the factors contributing towards or causing occurrence of adverse events.
4. To propose policy changes related to vaccine safety.
5. To promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public.
6. To improve public health and safety in relation to the use of medicines.

2.1 IMPORTANCE OF VACCINE PHARMACOVIGILANCE:

The pharmacovigilance is a concept which deals with chemical, botanical and biological medicines. The pharmacovigilance deals with the adverse effects of drug, poly-pharmacy, paradoxical reactions, and severe adverse events. It also covers vaccination failure, irrational uses, and lack of efficacy, drug interactions, poisoning, overdose, abuse, medication errors, and misuse of drug.

The goal of vaccine pharmacovigilance is the early detection of and appropriate and timely response to adverse events following immunization in order to minimize negative effects to the health of individuals and lessen the potential negative impact on immunization of the population. Continuous risk-benefit assessment and risk management are integral to the vaccine pharmacovigilance process.

There is a very high level of safety required for vaccines. Elements to consider when conducting vaccine pharmacovigilance include the following:

- Vaccines are usually administered to healthy people, including infants.
- Vaccines may be administered to the vast majority of the population or of a birth cohort or to groups at high risk for disease complications.
- Subpopulations may be more susceptible to experience certain adverse events following immunization.
- The age at the time of immunization may coincide with the emergence of certain age related diseases for example neurodevelopment disorders.
- The benefits of the immunization may not be immediately visible, particularly if the target disease incidence is slow.
- Due to low acceptance of risks, intensive investigation of serious adverse events following immunization is necessary.
- Non-serious adverse events following immunization also should be carefully monitored because they may signal a potentially larger problem with the vaccine or immunization, or have an impact on the acceptability of immunization in general.

- Appropriate methods are needed to detect and assess any potential causal association of serious, rare, and/or delayed adverse events, or of adverse events in subgroups, with immunization.
- The administration of live vaccines can lead to disease caused by the attenuated organisms in vaccines or their contacts; this should be differentiated from coinciding natural infection.
- Vaccines are complex biological products, which may include multiple antigens, live organisms, adjuvant and preservatives. Each component may have unique safety implications. Variability and even small changes in the manufacturing process may have impact on quality, protective effect and safety.
- Consideration of de-challenge and re-challenge differs from vaccines compared with other medicinal products. Vaccines are frequently administered only once or with long intervals, and serious adverse events following immunization often prevent further vaccine administration. De-challenge may not be applicable to vaccines, given their long term immunological effects, the re-challenge information is rarely available.
- Vaccines are often administered concomitantly with other vaccines, making causal attribution to a specific vaccine difficult.
- Effective communication regarding the safety of vaccines and immunization is challenging. Despite strong evidence that a serious adverse events is not related to immunization, perceptions of harm may persist and may potentially have a negative impact on immunization of the population.

2.2 VACCINE REACTIONS AND SIDE EFFECTS:

Immunization is a corner stone of the nation's efforts to protect people from a host of infectious disease. Though generally there are very rare or minor side effects or "adverse effects" associated with some vaccines. Importantly, some adverse event following a vaccine are may be due to some coincidence and are not caused by the vaccines.

The vaccines undergo rigorous safety testing prior to being approved by the FDA and are continually monitored foe safety. All vaccines ingredients are tested to be safe. The vaccines are also studied to be administered together, to work in conjugation to increase the immunity for building protection.

According to the Centers for Disease Control and Prevention (CDC) in most of the cases the vaccine side effects are minor and go away within a few days. The side effects may vary according to the vaccine type, but the generally mild side effects may include the following;

- Pain, itching, redness, or swelling at the site of injection
- Nausea and vomiting
- Mild rash
- Dizziness or fainting (most common in adolescents)
- Headache
- Mild fever
- Muscle twitching and joint pain

A vaccine reaction is an individual's response to the inherent properties of the vaccines, even when the vaccines are prepared, handled, and administered correctly. The vaccine reactions may be classified into 2 groups as:

- Minor reactions
- Severe reactions

The characteristics of the minor reactions and severe reactions are given below:

Table 1: A review on minor and severe vaccine reactions

Minor reactions	Severe reactions
▪ Usually occurs within a few hours of injection.	▪ Usually do not result in long term problems.
▪ Resolve after short period of time and pose little danger.	▪ They can produce disability.
▪ Local reactions includes (pain, swelling or redness at the site of injection)	▪ They are rarely life threatening.
▪ Systemic reactions includes (fever, muscle pain, headache or loss of appetite)	▪ Includes seizures and allergic reactions caused by the body's reaction to a particular component in the vaccine.

Severe vaccine reactions:

The severe vaccine reactions include the conditions such as seizures, thrombocytopenia, hypotonic hyporesponsive episodes (HHE), and also prolonged crying in small children which all needed to be reported. Most severe vaccine reactions do not lead to long term problems. The anaphylaxis reactions can be life threatening but can be curable with appropriate treatment without leaving any long term effects. The health workers who give vaccination should know the signs of allergic reactions and can be prepared to take immediate action in case of emergency.

Some adverse effects associated with different vaccines:

Table 2: adverse effects associated with different vaccines

Vaccines	Adverse effects
Hepatitis B vaccine:	Pain at the site of injection (3% - 29%), temperature greater than 37.7 C(1% - 6%), encephalitis and encephalopathy, seizures, transverse myelitis, multiple sclerosis in adults and children, chronic inflammatory polyneuropathy, anaphylaxis
Measles, mumps and rubella vaccine:	Febrile seizure, afebrile seizures, meningitis, ataxia, chronic arthritis in women, anaphylaxis, hearing loss, type 1 diabetes, chronic fatigue syndrome, autism, short term joint pain (arthralgia) in children and women
Varicella virus vaccine:	Encephalopathy, seizures, cerebral ataxia, anaphylaxis, stroke, thrombocytopenia, small fiber neuropathy
Influenza vaccine:	Encephalopathy, seizures, anaphylaxis, Bell 's palsy, chronic inflammatory polyneuropathy, myocardial infarction, stroke, oculorespiratory syndrome, transverse myelitis, encephalitis, guillian barre syndrome
Chicken pox:	Vaccine strain Varicella zoster infection and subsequent infection resulting in pneumonia, encephalitis, meningitis
Diphtheria toxoid, tetanus toxoid and acellular pertusis containing vaccine:	Encephalitis and encephalopathy, infantile spasm, seizures, sudden infant death syndrome, ataxia, autism, fibromyalgia, serum sickness, chronic urticaria, anaphylaxis, myocarditis

Other finding reveled-

- Six types of vaccines which are as given here MMR, Varicella zoster (chicken pox), influenza, hepatitis B, meningococcal, and tetanus containing vaccines are linked to the anaphylaxis.
- The injection of any vaccine can lead to sudden fainting i.e. syncope and symptoms of deltoid bursitis, or shoulder inflammation.
- Two Canadian vaccines were linked to oculo respiratory syndrome characterized by conjunctivitis, facial swelling, and mild respiratory symptoms.
- Many people who are vaccinated are suffer from acute and chronic health problems after vaccination due to biodiversity

(genetic variation) within population, age at the time of the vaccination, immune deficiencies, coinciding infections, and other environmental exposures.

3. STRATERGIES OF PHARMACOVIGILANCE STUDY: [4]

It includes the overview on methods which are used for pharmacovigilance study of vaccine. We discussed here the methods like ADR reporting, cohort studies in detail. The steps involved in the pharmacovigilance study of vaccines are also included here.

3.1 PHARMACOVIGILANCE METHODS FOR STUDY OF VACCINES:

In the pharmacovigilance study of vaccines following methods are to be used.

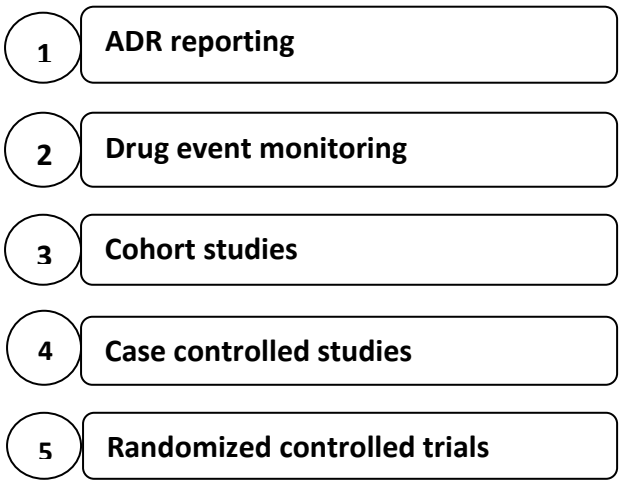

Fig. No- 1 Methods of pharmacovigilance study.

A]. ADR reporting:

According to bulletin of WHO [World Health Organization] the development of vaccines include several unexpected incidents and out of them some are very dangerous to human health.

Table 3: frequency of known adverse events with selected vaccines

Vaccine	Adverse events		
	Death	Anaphylaxis	Others
Measles-mumps-rubella	Case report	1-20 per 100000	2-5% rash approximately 13-15% arthritis (adult), thrombocytopenia excess, mortality with high titer formulation.
Diphtheria-pertusis-tetanus	None	2 per 100000	0-10.5 per 100000 encephalopathy, 3.5-291 per 10000 unusual shock, sickness with to frequent repeated dose
Hepatitis B vaccine	No	Yes	No
Haemophyllus Influenza	No	No	No
Influenza A	No	No	Guillain-barre syndrome
Pneumococcus	No	No	Serum sickness with too repeated doses
Polio virus	Yes	No	Transmission of back Muted vaccine strain Virus to contact
Varicella	Yes	Yes	Transmission of vaccine Virus to Immuno compromised contact

So, reporting adverse event is important parameter for vaccines. In most of the country for reporting the event several programs are started. Out of them vaccine adverse event reporting program is most popular.

Vaccine adverse event reporting program:

The Vaccine Adverse Event Reporting System (VAERS) is a national vaccine safety surveillance program co-sponsored by the Centre for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). The Vaccine Adverse Event Reporting System is a post-marketing safety surveillance program that collects information about adverse events or possible side effects that occurred after the administration of vaccines.

Need of vaccine adverse event reporting system:

1. To detect new, unusual, or rare vaccine adverse event.
2. To assess the safety of newly licensed vaccine.
3. To identify vaccine lots with increased numbers or types of reported adverse events.
4. To identify potential risk factors in vaccines for particular type of adverse event.
5. Rapidly respond to vaccine safety concerns or public health emergencies.

The vaccine adverse event reporting system is one component for the vaccine safety monitoring. The reports are monitored carefully by the Centers for Disease Control and Prevention (CDC) and the Food Drug Administration (FDA). Report of adverse events does not mean that the problem is caused by vaccine. The reports are the signals that provide basic information about the causes and effect relationship that need to be investigated. Anyone can submit a report to Vaccine Adverse Event Reporting System (VAERS) including health care professionals, a vaccine recipient, vaccine manufacturer and a family member of people who have received a vaccine.

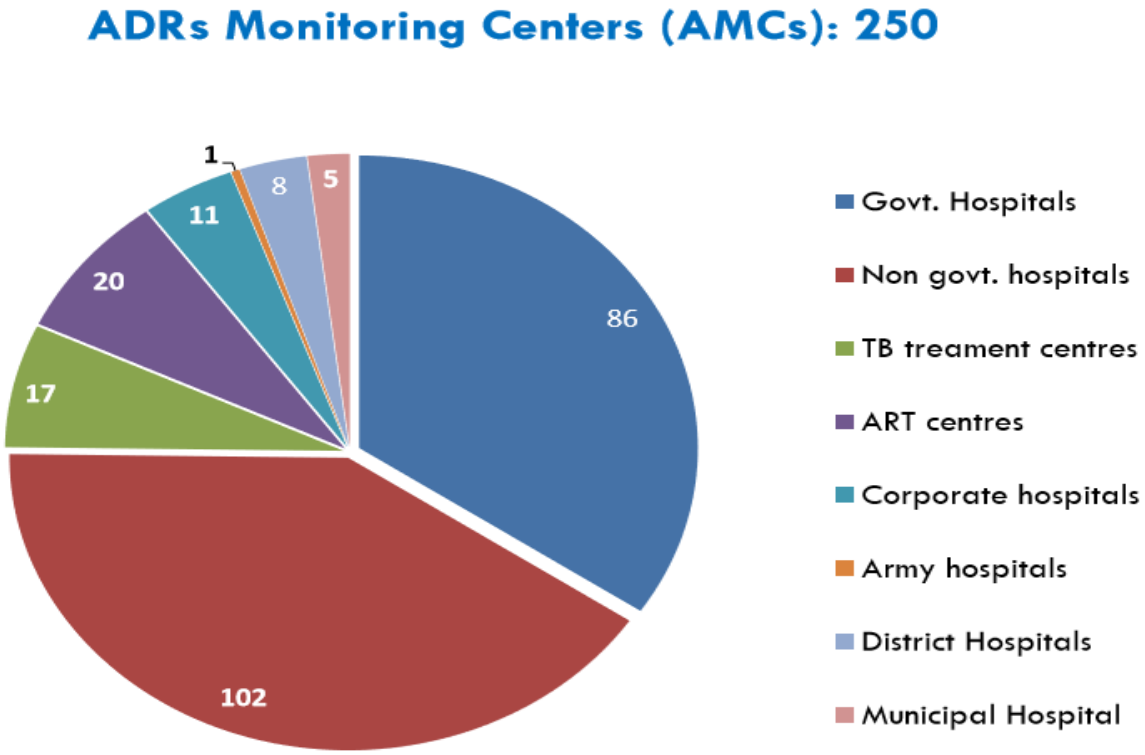

Fig 2: Adverse drug reactions monitoring centers in India

The Vaccine Adverse Event Reporting System (VAERS) forms request should have following information -

- The type of vaccine received
- The timing of the vaccination
- The onset of the adverse event
- Current illness or medication
- Past history of adverse event following vaccination
- Demographic information about the recipient.

The Vaccine Adverse Event Reporting System (VAERS) forms can be filled online or submitted by a fax. A contractor under the supervision of CDC and FDA entre the information from VAERS to database, those who reporting an adverse event receives a confirmation letter and a VAERS identification number and the additional information send to assigned identification number.

According to the bulletin of World Health Organization the development of vaccines include several un-excepted incidents and out of them some are very dangerous to human health.

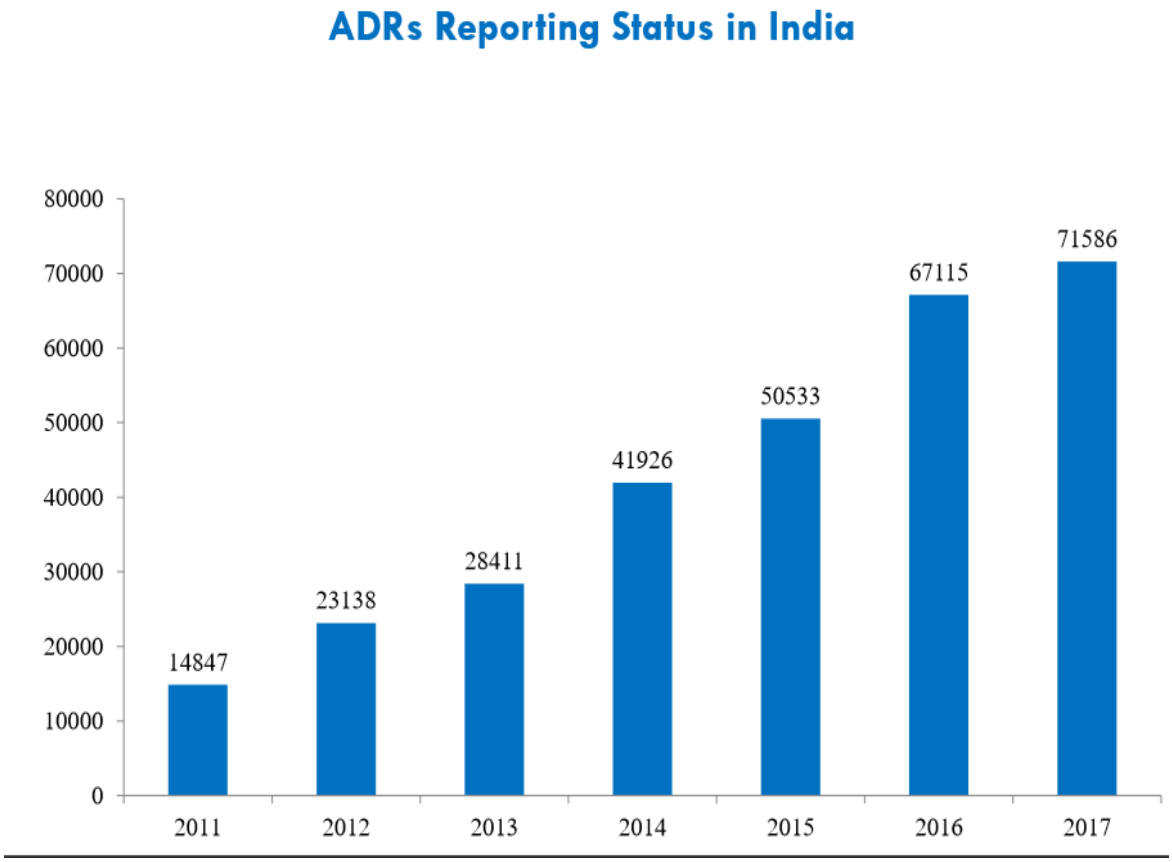

Fig 3: ADR reporting status in India

B]. Drug event monitoring:

In this all the events that occur after the vaccination are recorded and all these events can be monitored by vaccine adverse event following immunization.

Adverse Event Following Immunization:

The World Health Organization defines an Adverse Event Following Immunization as a medical incident that takes place after an immunization, causes concern, and believed to be caused by immunization.

Objectives of the Adverse Event Following Immunization -

- To find out the adverse drug reactions related to vaccines.
- To find out the anaphylactic reactions of vaccines with an appropriate treatment.
- To provide an outline for the reporting of adverse reactions.

Adverse Event Following Immunization (AEFI) is a critical component of immunization program. The serious adverse events like death, disability, cluster and hospitalization are need to be reported immediately and investigated in detail as per the procedures. Programmatic error, vaccine reaction, injection reactions, coincidental and unknown are the five board categories of AEFI.

The adverse immunization reactions may be further classified as-

Adverse vaccine reaction: Here the vaccine is casually related to the reaction example given: VAPP (vaccine associated paralytic polio) due to Oral Polio Vaccine, anaphylaxis. The VAPP is caused by a strain of polio virus that has genetically changed in the intestine from the original attenuated vaccine strain which is present on Oral Polio Vaccine.

Trigged reaction: Here the reaction is trigged by the vaccine. For example given- febrile seizure the febrile seizures are the convulsions that can occur in young children between the ages of about 6 months and 5 year olds and are trigged by fever.

Programmatic errors: These are most common causes for serious adverse events and death following vaccination. Death following measles vaccination due to toxic shock syndrome resulting from improper reconstitution and storage of measles vaccine is the most recent example of this phenomenon.

Injection reaction: Examples include syncope i.e. loss of consciousness due to pain of vaccination, injection site abscesses, nerve damage due to gluteal injection and transmission of blood borne pathogens such as HIV.

C]. Cohort studies:

In a cohort study, a population at risk for the disease is monitored for a period of time to record the occurrence of the disease. Information on exposure to disease status is available during the follow-up period for each patient. A patient might be exposed to a vaccine at one time during follow-up, but not exposed at another time. Meanwhile the population exposure during follow-up is acknowledged, incidence rates can be calculated. In many cohort studies, the vaccine exposure and evaluation of cohorts of interest are selected on the basis of vaccine used and monitored over time. Cohort studies are useful when there is a need to know the incidence rates of adverse events in addition to the relative risks. Multiple adverse events can also be examined carefully by using the similar data source in a cohort study. On the other hand, it can produce problems to arrange enough numbers of patients who are exposed to the vaccine of interest or to study very rare outcomes. Similar to case-control studies, patients in cohort studies can be recognized from large automated databases or from data collected precisely for the study at hand.

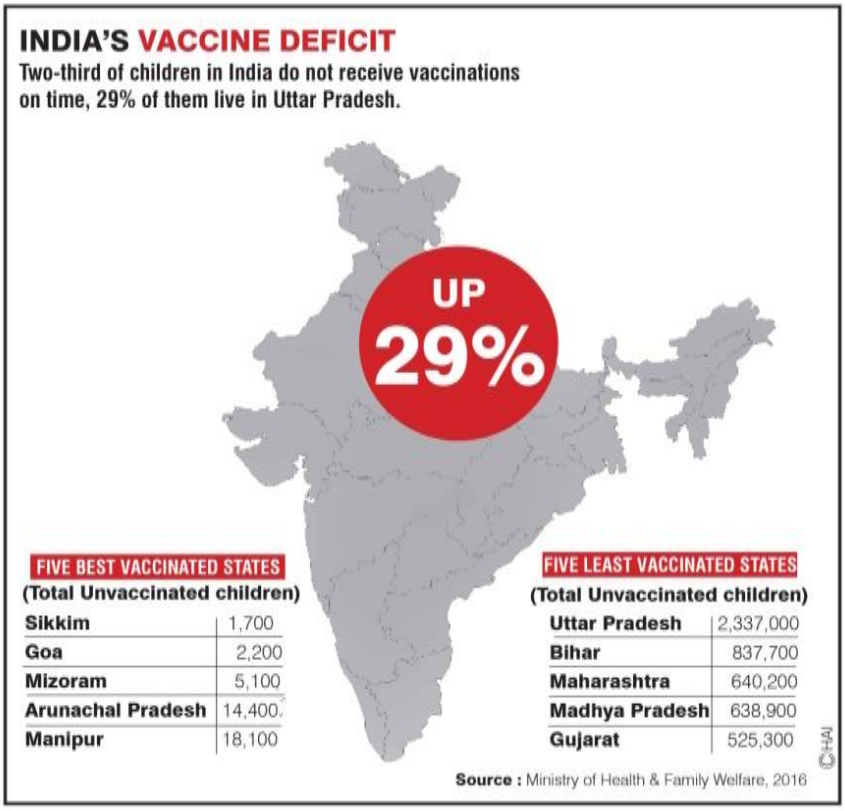

Fig 4: vaccination rate in India according to states

When vaccine coverage is high a large population is vaccinated and a large remain unvaccinated and both are differ in important aspects especially in adverse drug reaction and a direct comparison is carried out. The observation period is defined during which individuals are followed. The incidence rate of each risk factor is determined. Adjustments of age are made by subdividing each period into age groups in which the incidence is roughly constant. The cohort approach is used for both unique events (such as sudden infant death syndrome) and potentially recurrent events (such as febrile convulsions). The cohort model is based on the assumptions that events arises in an age dependant Poisson process. In its simplest form the background incidences assumed to be same for all individuals.

D]. Case controlled studies:

Evaluation of vaccine safety is an important aspect of any vaccination program. Although vaccines are tasted extensively for relatively common adverse events in clinical trials before they are licensed for use. Case-control study designs are commonly used to investigate vaccine safety. The case-controlled study is used to determine the disease and potential risk factors by taking separate samples of disease cases and of control risk of developing disease information is collected from both the case and control on genetic, social, behavioral, environmental or other determinants of disease risk. Case-controlled design used frequently to investigate the risk factor associated with sudden infant death syndrome.

In a case-controlled study, cases of disease are recognized. The controls or patient in whom the disease or event of interest has not happened, are

then carefully chosen from the source population that gave rise to the cases. The controls should be selected in such a way that the prevalence of exposure among the controls exemplifies the prevalence of exposure in the source population. The case control studies are predominantly useful when the goal is to examine whether there is a relationship between a medicine and one specific rare adverse event, as well as to identify risk factors for adverse events. The risk factors can include conditions such as renal and hepatic dysfunction, which might modify the relationship between the drug exposure and adverse event.

E]. Randomized controlled trials:

Randomized controlled trial is the most simpler but a powerful technique for research. In randomized controlled trials the peoples are allocated at random to receive the vaccine. Randomized controlled trials are used to determine the effect of intervention on particular outcomes such as death and reoccurrence of disease. Any significant difference in the outcomes can attributed to the intervention and not to some other unidentified factor.

3.2 STEPS INVOLVED IN PHARMACOVIGILANCE STUDY OF VACCINES:

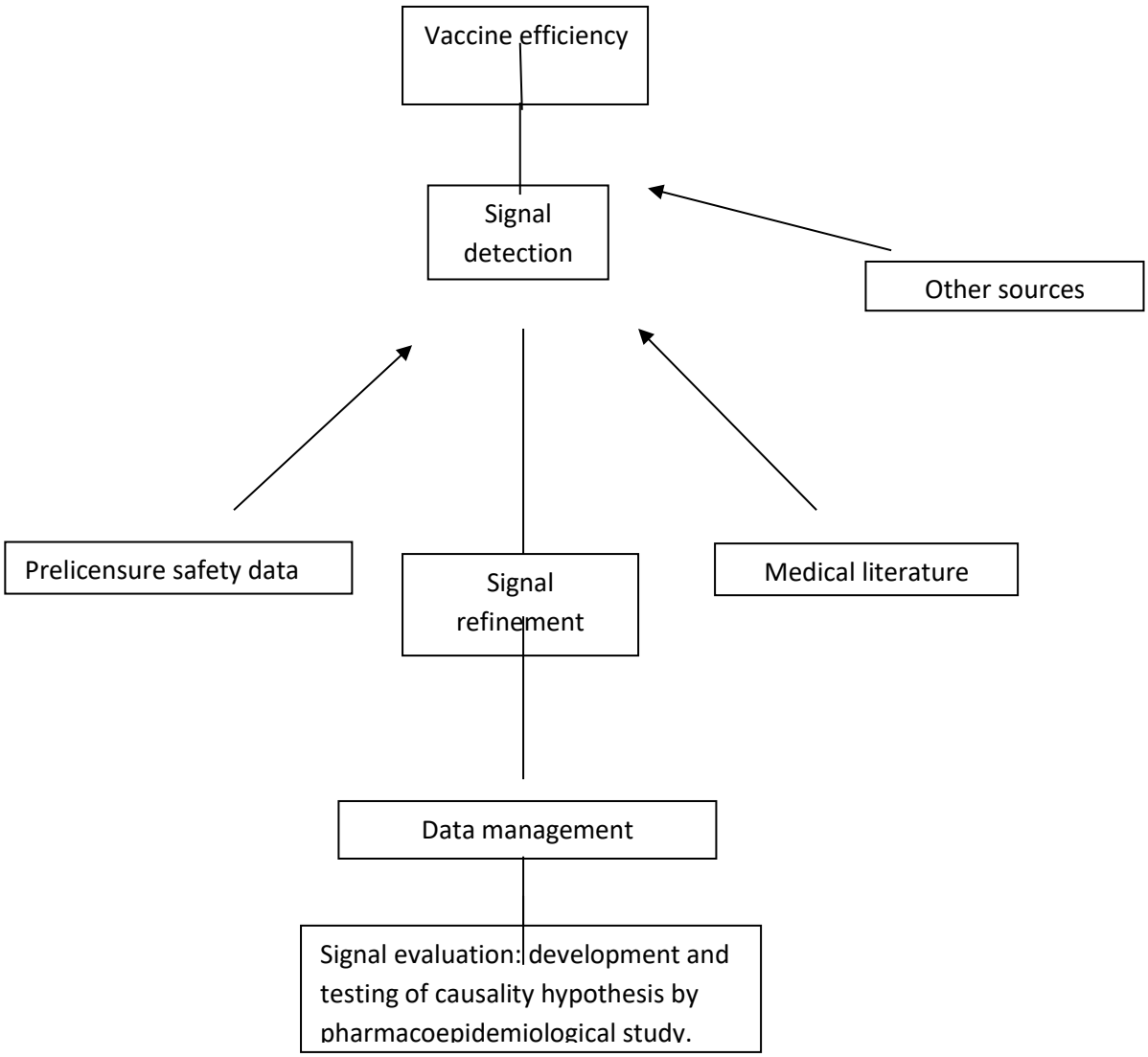

Fig 5. steps involved in pharmacovigilance study of vaccines

Vaccine effectiveness:
All vaccines effectiveness study involves the comparison of the relative risk of the vaccinated group with the unvaccinated group. The vaccine effectiveness (VE) is calculated in percentage (%). The standard equation for calculating vaccine effectiveness (VE) is-

$$VE(\%) = \left[\frac{ARU - ARV}{ARU}\right] \times 100$$

Where, ARU is the attack rate in the unvaccinated group and
ARV is the attack rate in the vaccinated group.
Rearranging the formula gives the following,

$$VE(\%) = \left\{1 - \left[\frac{ARV}{ARU}\right]\right\} \times 100$$

Where, $\frac{ARV}{ARU}$ is the equivalent to the relative risk? In case-control studies the relative risk is approximated by the odds ratio.

Signal detection:
The expected and unexpected adverse reactions are observed and recorded as a signal by a source of any preclinical and clinical data including the data obtained from spontaneous reporting from healthcare professionals, epidemiological studies and clinical trials.

In the first step of signal detection it is examined by statistical methods by using comparators groups and can also be determined by the use of stratification including geographical region and by considering the age factor. In some time seasonability of vaccine administration is also considered. A most simple method of investigating a signal is to compare the number of cases observed in temporal relationship to a suspected exposure during a period of time to the number of natural incidences of the disease estimated to occur in the same period of time observed means reporting by spontaneous reporting. When a signal is evaluated, vaccination policy (target group to be immunized), incidences of natural disease in the target population, public information and seasonability should also be considered.

Signal refinement:
When a decision making safety concern is required and if there is a small time period for review the individual cases then the observed vs. expected analysis for signal validation and preliminary signal evaluation is used.

Data management:
It is very important that data is managed according to age groups in such a manner that data retrieval and analysis of number of doses, different vaccination schedule, different risk factors, according to disease and adverse event reporting system. In future if the same cases are observed with the same type of preparation then the available data can provide useful information about the adverse effect and process of avoiding such adverse drug reactions.

Risk evaluation:
The main aim of pharmacovigilance study is to determine the rare or new adverse events. In this step the frequency of the adverse event generation and the severity of the adverse event are mainly recorded. Errors in manufacturing, handling and administration should be considered. In risk evaluation the rate of occurrence of the disease is mainly evaluated.

Development of causality hypothesis:
On the basis of the reported signal the causal hypothesis is prepared by developing a causal relationship between the adverse event and the vaccine which is vaccinated.

Testing of hypothesis:
In case of vaccine pharmacovigilance study the cohort study and case controlled study is sometimes not suitable when a large population is vaccinated and a large population remains un-vaccinated. So hypothesis testing provides a rational data for pharmacovigilance study of vaccines. In hypothesis testing socioeconomic status, health status and other factors which influences the probability of vaccination are considered. The following are the three methods which are basically used for hypothesis testing.

- The case coverage method
- The case crossover method
- The self controlled case series

Hypothesis testing is performed by using epidemiological methods including the study of available data sets.

Audit and outcome assessment:
There is a need to ensure effective follow-up of the pharmacovigilance process and measurements of the outcomes of any actions taken.

4. PHARMACOVIGILANCE PROGRAM IN INDIA: [5]

The pharmacovigilance exertion in India is organized by the Indian Pharmacopoeia Commission (IPC) and conducted by the Central Drugs Standard Control Organization (CDSCO). The main responsibility of the Indian Pharmacopoeia Commission (IPC) is to maintain and develop the pharmacovigilance database

consisting of all suspected serious adverse reactions to medicines which are observed. The Indian Pharmacopoeia Commission (IPC) is functioning as a National Coordination Centre (NCC) for pharmacovigilance program of India. The National Coordination Centre is operating under the observation of steering committee which recommends procedures and guidelines regulatory interventions. The main duty of National Coordination centre is to monitor all the adverse reactions of medicines being observed in the Indian population and to develop and maintain its own pharmacovigilance database.

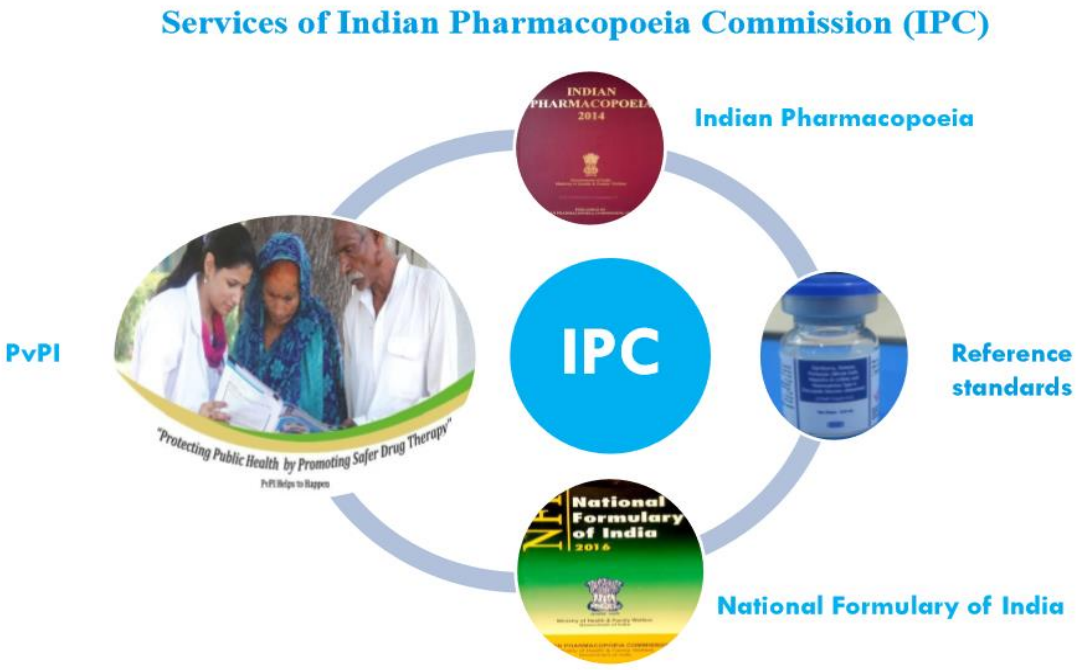

Fig No- 6 Services of IPC

The Central Drugs Standard Control Organization (CDSCO), Directorate General of Health Services under the agencies of Ministry of Health and Family Welfare, Government of India in association with Indian Pharmacopoeia Commission, Ghaziabad is initiating a nation-wide pharmacovigilance program for protecting the health of patients by promising drug safety. The pharmacovigilance program of India was started by the government of India on 14th July 2010 with the All India Institute of Medical Science (AIIMS), New Delhi as a National Coordination Centre for monitoring adverse drug reactions in the country for safe – guarding public health. In the year 2010 there are 22 ADR monitoring centers including AIIMS, New Delhi. To safeguard implementation of this program in a more effective way, the National Coordination centre was shifted from the All India Institute of Medical Science (AIIMS), New Delhi to the Indian pharmacopoeia commission, Ghaziabad, Uttar Pradesh on 15th April 2011.

Main objectives:

- To create a nation - wide system for patient safety reporting.
- To support regulatory agencies in the decision making process on use of medications.
- To emerge as a national centre of excellence for pharmacovigilance activities.
- To collaborate with other national centers for the exchange of information and data management.
- To communicate the safety information on the use of medications to various stakeholders to minimize the risk.
- To provide training and consultancy support to other national pharmacovigilance centers located globally.

For the first time a national centre for pharmacovigilance program is established in 2004. The Central Drugs Standard Control Organization (CDSCO) is started with the aim to coordinate all pharmacovigilance programs in India. The Central Drugs Standard Control Organization (CDSCO) establishes a National Pharmacovigilance Advisory Committee to works in India for ADR reporting. The Indian pharmacovigilance program is prepared like a pyramid in which the peripheral centre reports to the regional centre and the regional centre reports to two zonal centers which are responsible for maintaining the national pharmacovigilance program.

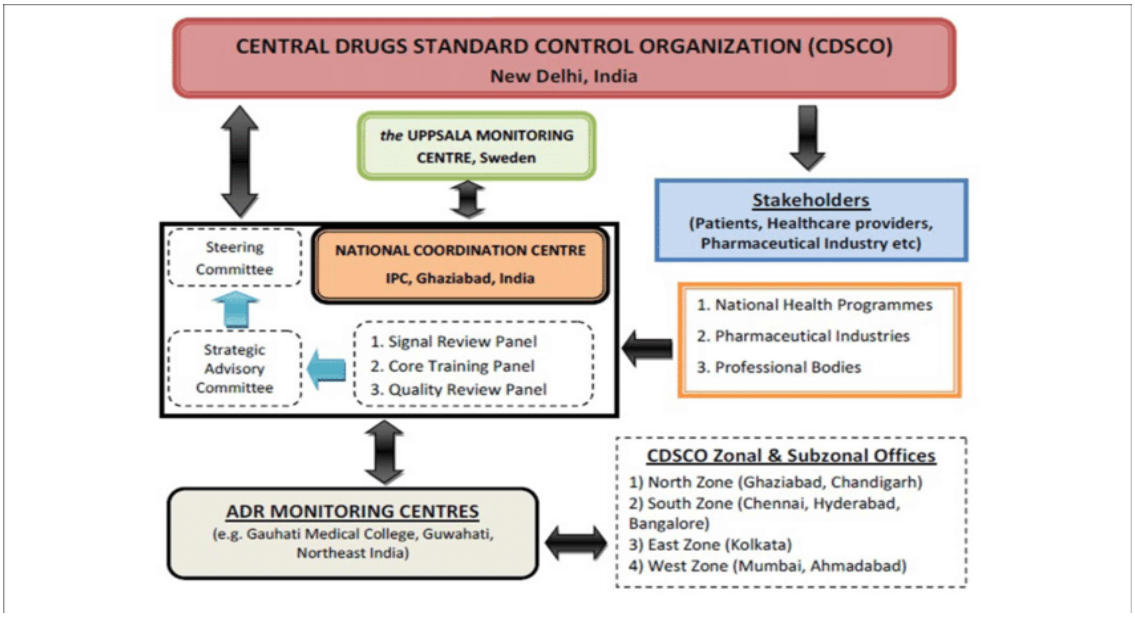

Fig.No 7 - CDSCO flow chart

In many diseases oriented public health programs large amount of medicines and vaccines are distributed in the public. So the public health programs are operated separately and in isolation of the normal health care system that is patient centric. It is the most important requirement for upgrading the pharmacovigilance activity in many public health programs and this requires training in methodology and data analysis.

The recent development in the pharmacovigilance program (schedule Y amendment) for pharmaceutical companies to submit the suspected Adverse Drug Reaction (ADR) from clinical trials performed in India to the regulatory authority. The major companies establishing their own units for post marketing safety surveillance; while the smaller companies uses the Contract Research Organizations (CROs) for assisting the pharmacovigilance activities. The major multinational companies are increasing their phase 2 and phase 4 clinical trials for the management of pharmacovigilance program.

4.1 Cause for failure of pharmacovigilance program in India:

Many new drugs and new vaccines are being introduced in the country, so there is a need to improve the pharmacovigilance system in India in order to protect the Indian population from potential harm that may be caused by some of the new drugs and also due to the some ingredients which are present in the vaccines. However, there are numerous issues and problems that have prevented building a strong pharmacovigilance system, which are discussed below:

1. Pharmacovigilance systems are not well-funded and systematized for a vast country like India to serve patients and the public.
2. Involvement of healthcare professionals i.e. both in rural areas and urban cities and hospitals and knowledge and motivation for pharmacovigilance is negligible. There little encouragement from the department of health to provide more training and create more awareness amongst them for better reporting.
3. The data obtained to date in the zonal centers from various peripheral centers is often poor and not well-analyzed. There is inadequate research on ADRs in India, so the exact incidence of specific ADRs is unknown.
4. In India, there are several consumers' groups who encourage patients to report any adverse reactions encountered by them, although there is no information for patients to report ADRs directly to the regulatory authority.

4.2 Global vaccine safety program:

Hundreds of millions of doses of vaccines are used every year in developing countries. However, assessments of regulatory authorities conducted by WHO demonstrate that few of these countries programs have the ability to monitor and assure the safe use of vaccines by studying the current performance of vaccine pharmacovigilance systems in low and middle income countries, and of existing inter-country and global support mechanisms, WHO has developed a global vaccine safety blueprint strategy in an inclusive drafting process.

The global vaccine safety blueprint is a strategic framework aiming of the establishment of effective vaccine pharmacovigilance system in all countries. It defines indicators of a minimal capacity for

ensuring vaccine safety activities by combining the efforts of major pharmacovigilance stakeholders.
The global vaccine safety blueprint has 3 main goals:

1 .Minimal capacity for vaccine safety activities:
The first goal aims at assisting low income and middle income countries to have at least minimal capacity for vaccine safety activities.

2 .Enhanced capacity:
The second goal aims to enhance capacity for vaccine safety assessment in countries that introduce newly developed vaccines, that introduce vaccines in setting with novel characteristics, or that both manufacture and use prequalified vaccines.

3 .International collaboration:
The third goal looks to establish a global vaccine safety support structure so that countries can benefit from international collaboration, training and information exchange.

Blueprint objectives-

- To strengthen vaccine safety monitoring in all countries.
- To strengthen the ability of countries to investigate vaccine safety signals.
- To develop vaccine safety communication plans, understand perceptions of risk, and prepare for managing any AEFI and crises promptly.
- To develop internationally harmonized tools and methods for vaccine pharmacovigilance.
- To promote a legal, regulatory and administrative framework for the safety of vaccines at national, regional and international levels.
- To strengthen regional and global technical support platforms for vaccine pharmacovigilance.
- To make international expert scientific advice on vaccine safety issues available.
- To put in place systems for appropriate interaction between national governments, multinational agencies, and manufactures at national, regional and international levels.

The blueprint consists of eight complementary objectives in them. The main aim of the first four objectives is to improve the technical aspects of spontaneous reporting, active surveillance and risk communication and to ensure the availability of harmonized methods and tools. The objective of remaining four is to promote the establishment of effective managerial principles to facilitate international collaboration and information exchange relating to the vaccine safety monitoring.

5. FUTURE PERSPECTIVES FOR PHARMACOVIGILANCE PROCESS IN INDIA: [6, 7, 8]

A suitably working pharmacovigilance system is vital if medicines are to be used safely. It will advantage all parties including healthcare professionals, regulatory authorities, pharmaceutical companies and the consumers. It aids pharmaceutical companies to monitor their medicines for risk and to devise and implement effective risk management plans to save their drugs in difficult circumstances.
Having considered the problems and challenges facing the development of a robust pharmacovigilance system for India, the following proposals might be follows:

- Building and maintaining a robust pharmacovigilance system.
- Making pharmacovigilance reporting mandatory and introducing pharmacovigilance inspections.
- High-level discussions with various stakeholders.
- Strengthen the drug control general of India office with trained scientific and medical assessors for pharmacovigilance.
- Creating a single country-specific adverse event reporting form to be used by all.
- Creating a clinical trial and post marketing database for SAEs / SUSARs and ADRs for signal detection and access to all relevant data from various stakeholders.
- List all new drugs / indications by maintaining a standard database for every pharmaceutical company.
- Education and training of medical students, pharmacists and nurses in the area of pharmacovigilance.
- Collaborating with pharmacovigilance organizations in enhancing drug safety with advancements in information technology, there has been the emergence of new opportunities for national and international collaborations that can enhance postmarking surveillance programs and increase drug safety.
- Building a network of pharmacovigilance and pharmacopeidemiologists in India.

6. REFERENCES:

1. Vaccines Side effects and Adverse Events: The History of Vaccine, A Project of the College of Physician Of The Phyladelphia.
2. Report of CIOMS/WHO Working Group: definition and Application of Terms for Vaccine Pharmacovigilance on Vaccine Pharmacovigilance, 2008; p 32.

3. The Safety of Medicines in Public Health Programs: Pharmacovigilance an essential tool world health organization, 2002; p 9-21.
4. Chitkara A.J, Thacher N., Vashishtha V.M, Bansal C.P, Gupta S.G, Adverse Event Following Immunization Surveillance in India position paper of Indian Academy of Pediatrics. Indian Pediatrics, 50(8): 739 - 41
5. Thorvaldsen Siranda and McIntyre Peter B. Observational methods in epidemiologic assessment of vaccine effectiveness Communicable Diseases Intelligence, 2002: 26: 453.
6. Guideline on the conduct of pharmacovigilance for vaccines for pre- and post-exposure prophylaxis against infectious diseases: European Medicines Agency London, [updated on 22 July 2009] p-16.
7. Sten Olsson, Pharmacovigilance training with focus on India, Indian Journal of Pharmacology, 40(suppl 1): S28 – S30
8. The GVS Initiative "Strengthening Global Capacity For Vaccine Pharmacovigilance" World Health Organization, Africa Pharmacovigilance Meeting 2012.