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2nd Edition

Textbook of
Pharmacovigilance
Ensuring the Safe Use of Medicines







Editors
SK Gupta
Sushma Srivastava

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4

Current Methods of Pharmacovigilance

Arani Chatterjee, Manoj Sharma, SK Gupta

Information for the readers for their better understanding on various methods adopted for the conduct of Post Marketing Surveillance has been provided in the chapter entitled "Post Marketing Surveillance". This chapter envisages in providing further detailed information on various methods used to conduct pharmacovigilance.

Here, it should be noted that the term Pharmacovigilance is an umbrella term and covers the "Post Marketing Surveillance" also.

Pharmacovigilance is defined by the World Health Organization (WHO) as 'the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.'

The role of pharmacovigilance can be divided into three main areas:

- To identify, quantify and document drug-related problems
- To contribute to reduce the risk of drug-related problems in healthcare systems
- To increase knowledge and understanding of factors and mechanisms which are responsible for drug-related injuries.

PHARMACOVIGILANCE METHODS

As per the ICH-E2E[1] guidelines the pharmacovigilance method can be categorized as:

- Passive surveillance
  - Spontaneous reporting
  - Case series
- Stimulated reporting
- Active surveillance
  - Sentinel sites
  - Drug event monitoring
  - Registries
- Comparative observational studies
  - Cross-sectional study (survey)
  - Case-control study
  - Cohort study
- Targeted clinical investigations
- Descriptive studies
  - Natural history of disease
  - Drug utilization study.

Pharmacoepidemiological *(Pharmacoepidemiology is the science concerned with the benefit and risk of drugs used in populations and the analysis of the outcomes of drug therapies)* methods are also used as tools in pharmacovigilance for generating initial suspicions (Hypothesis generation methods) or testing hypotheses (Hypothesis testing methods) about changes in adverse effect profiles of medicines. The details of these two methods is provided as below:

- Hypothesis-generating methods
  - Spontaneous ADR reporting
  - Prescription event monitoring (PEM)

  Hypothesis-generating studies, with a recently marketed drug, aim to provide unexpected ADRs.

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- Hypothesis-testing methods
  - Case control studies
  - Cohort studies
  - Randomized controlled trials

  Hypothesis-testing studies aim to prove whether any suspicions that may have been raised are justified.

Passive Surveillance

Spontaneous Reports

"A spontaneous report is an **unsolicited** communication by healthcare professionals or consumers to a company, regulatory authority or other organization (e.g. WHO, Regional Centres, Poison Control Centre) that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme.[1] *This type of report is voluntary in nature (voluntary reporting), i.e. it may be initiated by the health care professionals or consumers as and when they become suspicious of any adverse reaction by any medication.*

Doctors (prescribers) or other health care professionals (e.g. pharmacists, nurses) are provided with a form (*see* annexures 1,2,3,4 for the suspected ADR reporting forms) for filling the details of the suspected ADR experienced by the patient along with the details of the suspected medication, patient details and the details of the doctor (or prescriber). These forms are generated by the concerned regulatory authority or the organizations working under the aegis of the government regulatory authorities; these are either provided on the websites or distributed to the health care professional through various training programmes conducted by the personals working in the area of pharmacovigilance or distributed by the sponsors which in most of the cases is a pharmaceutical company or a medical device manufacturing company. These filled forms are then notified to the central authority (country's governmental body) which is usually the drug regulatory authority (e.g. DCGI i.e. Drug Controller General India for India; USFDA for United States of America; TGA, i.e. Therapeutic and Goods Administration for Australia; MHRA for UK; BfARM for Germany; AFFSAPS for France, etc.).

In India, the form used for the spontaneous reporting is known as "Suspected Adverse Drug Reaction Reporting Form (Annexures 1A and 1B)" generated by CDSCO (Central Drug Standard Control Organization) working under the aegis of Directorate General of Health Services (DGHS), Government of India.

In the United Kingdom the form used for the spontaneous reporting is known as "Yellow Card". This has been used for the purpose of spontaneous reporting since 1964. The form is available separately for the **patients (patient reporting form)** and for the **health care professionals (health care professional reporting form)** (*see* Annexures 2A and 2B).

In the United States, the "Med Watch" form (Annexures 3A and 3B) is used in two different categories:

- **Form FDA 3500-Voluntary Reporting:** For use by health professionals, consumers and patients.
- **Form FDA 3500A-Mandatory Reporting:** For use by IND reporters, manufacturers, distributors, importers, user facilities personnel.

Similar forms are provided in the FP10 prescriptions pads, the British National Formulary, and other sources.

Although physicians and other health care professionals are encouraged to report new and unusual adverse drug reactions to the FDA, the system relies heavily on pharmaceutical manufacturers, whose field representatives and headquarters regulatory personnel are often the first to identify a potential reportable event. Here it should be noted that a pharmaceutical manufacturer is legally

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required to report serious unlabeled (not mentioned in the package insert or summary of product characteristic) adverse reactions to the Food and Drug Administration (FDA) with in 15 working days (or as per the applicable regulatory procedures) of learning of adverse reactions. Approximately, 80% of spontaneous reports about adverse drug reactions come to the FDA through drug companies.

Reporting of adverse reactions fluctuates with the length of time the drug has been on the market. The marketing of a new drug usually involves a slow release onto the market, which causes a slow rise in ADR reports. According to Weber,[2] the total number of ADR report increases until two year after the introduction and declines thereafter.

Spontaneous reports play a major role in the identification of safety signals once a drug is marketed. This has the potential to capture rare, unexpected adverse reactions more quickly than other study designs. In many instances, a company can be alerted to rare adverse events that were not detected in earlier clinical trials or other pre-marketing studies. Spontaneous reports can also provide important information on at-risk groups, risk factors, and clinical features of known serious adverse drug reactions. Caution should be exercised in evaluating spontaneous reports, especially when comparing drugs. The data accompanying spontaneous reports are often incomplete, and the rate at which cases are reported is dependent on many factors including the time since launch, pharmacovigilance-related regulatory activity, media attention, and the indication for use of the drug (Box 4.1).[3-6]

The various strengths and weaknesses of a spontaneous reporting system has been dealt in a separate chapter on "Postmarketing Surveillance"

Case Series

Case report describes the particular outcome or experience of a person who has been exposed to a drug. These reports are useful for generating hypotheses about the effects of the drug, and may lead to further studies to test these hypotheses. A case series, reports on two or more people with common exposure to a drug, or a common outcome.

Series of case reports can provide evidence of an association between a drug and an adverse event, but they are generally more useful for generating hypotheses than for verifying an association between drug exposure and outcome. There are certain distinct adverse events known to be associated

Box 4.1: Methods for the evaluation of spontaneous reports

More recently, systematic methods for the detection of safety signals from spontaneous reports have been used. Many of these techniques are still in development and their usefulness for identifying safety signals is being evaluated. These methods include the calculation of the proportional reporting ratio, as well as the use of Bayesian and other techniques for signal detection.[7-8] Data mining techniques have also been used to examine drug-drug interactions.[7-8] Data mining techniques should always be used in conjunction with, and not in place of, analyzes of single case reports. Data mining techniques facilitate the evaluation of spontaneous reports by using statistical methods to detect potential signals for further evaluation. This tool does not quantify the magnitude of risk, and caution should be exercised when comparing drugs. Further, when using data mining techniques, consideration should be given to the threshold established for detecting signals, since this will have implications for the sensitivity and specificity of the method (a high threshold is associated with high specificity and low sensitivity). Confounding factors that influence spontaneous adverse event reporting are not removed by data mining. Results of data mining should be interpreted with the knowledge of the weaknesses of the spontaneous reporting system and, more specifically, the large differences in the ADR reporting rate among different drugs and the many potential biases inherent in spontaneous reporting. All signals should be evaluated recognizing the possibility of false positives. In addition, the absence of a signal does not mean that a problem does not exist.

False positives: *A test result that shows evidence of a disease or an abnormal condition although it (the condition being tested for) is not present. In statistics it is also known as type I error or* α*- error.*

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more frequently with drug therapy, such as anaphylaxis, plastic anemia, toxic epidermal necrolysis and Stevens-Johnson syndrome.[10,11] Therefore, when events such as these are spontaneously reported, sponsors should place more emphasis on these reports for detailed and rapid follow-up.

Example of Case Series:

For the evaluation of the preliminary efficacy and safety of alefacept in the treatment of moderate to severe mucosal lichen planus (LP)[12] seven subjects were randomly selected to receive either alefacept 15 mg or placebo every week for 12 weeks. Endpoints of the case series were the Physician Global Assessment (PGA) of disease severity, mucosal pain (MP) severity, and itch severity (IS). Two of the subjects receiving alefacept achieved significant improvement during the study. There were no serious adverse events during the course of the study period. In this small case series, alefacept may have conferred a modest therapeutic response in erosive LP. It was concluded that larger multicentric prospective studies will be needed to determine whether alefacept can improve erosive LP in a statistically significant way.

Stimulated Reporting

Stimulated reports are those that may have been motivated, prompted or induced and can occur in certain situations, such as notification by a Health Care Professional Communication (HCPC), public advisory, literature report, publication in the press, or questioning of health care professionals by MAH representatives. These reports should be considered unsolicited in nature and as a form of spontaneous reporting. Data obtained from stimulated reporting cannot be used to generate accurate incidence rates, but can be used to estimate reporting rates. Several methods have been used to encourage and facilitate reporting by health professionals in specific situations (e.g. in-hospital settings) for new products or for limited time periods.[13] Such methods include on-line reporting of adverse events and systematic stimulation of reporting of adverse events based on a pre-designed method. Although, these methods have been shown to improve reporting, they are not devoid of the limitations of passive surveillance, especially selective reporting and incomplete information.

During the early postmarketing phase, companies might actively provide health professionals with safety information and at the same time encourage cautious use of new products and the submission of spontaneous reports when an adverse event is identified. A plan can be developed before the product is launched (e.g. through site visits by company representatives, by direct mailings or faxes, etc.). Stimulated adverse event reporting in the early postmarketing phase can lead companies to notify healthcare professionals of new therapies and provide safety information early in use by the general population [e.g. early postmarketing phase vigilance (EPPV) in Japan].

Active Surveillance

Active surveillance, in contrast to passive surveillance, seeks to ascertain completely the number of adverse events via a continuous preorganised process. An example of active surveillance is the follow-up of patients treated with a particular drug through a risk management programme. Patients who fill a prescription for this drug may be asked to complete a brief survey form and give permission for later contact.[13] In general, it is more feasible to get comprehensive data (complete or widespread data) on individual adverse event reports through an active surveillance system rather than through a passive surveillance system. The various methods to get the comprehensive data through active surveillance are depicted below.

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Sentinel Sites

Active surveillance can be achieved by reviewing medical records or interviewing patients and/or physicians in a sample of sentinel sites to ensure complete and accurate data on reported adverse events from these sites. The selected sites can provide information, such as data from specific patient subgroups that would not be available in a passive spontaneous reporting system. Further, information on the use of a drug, such as abuse, can be targeted at selected sentinel sites.[14] Some of the major weaknesses of sentinel sites are problems with selection bias, small numbers of patients, and increased costs. Active surveillance with sentinel sites is most efficient for those drugs used mainly in institutional settings such as hospitals, nursing homes, hemodialysis centres, etc. Institutional settings can have a greater frequency of use for certain drug products and can provide an infrastructure for dedicated reporting. In addition, automatic detection of abnormal laboratory values from computerized laboratory reports in certain clinical settings can provide an efficient active surveillance system. Intensive monitoring of sentinel sites can also be helpful in identifying risks among patients taking orphan drugs.

Drug Event Monitoring

Drug event monitoring is a method of active pharmacovigilance surveillance. In drug event monitoring, patients might be identified from electronic prescription data or automated health insurance claims. A follow-up questionnaire can then be sent to each prescribing physician or patient at pre-specified intervals to obtain outcome information. Information on patient demographics, indication for treatment, duration of therapy (including start dates), dosage, clinical events, and reasons for discontinuation can be included in the questionnaire.[15-18]

Limitations of drug event monitoring may include:

- Poor physician and patient response rates
- Unfocused nature of data collection, which can obscure important signals.

In addition to the above mentioned limitations maintenance of patient confidentiality might be a concern. On the other hand, more detailed information on adverse events from a large number of physicians and/or patients might be collected.

Registries

A registry is a list of patients presenting with the same characteristic(s). This characteristic can be a disease (disease registry) or a specific exposure (drug registry). Both types of registries, which only differ by the type of patient data of interest, can collect a battery of information using standardized questionnaires in a prospective fashion. Disease registries, such as registries for blood dyscrasias, severe cutaneous reactions, or congenital malformations can help collect data on drug exposure and other factors associated with a clinical condition. A disease registry might also be used as a base for a case-control study comparing the drug exposure of cases identified from the registry and controls selected from either patients with another condition within the registry, or patients outside the registry.

Exposure (drug) registries address populations exposed to drugs of interest (e.g. registry of rheumatoid arthritis patients exposed to biological therapies) to determine if a drug has a special impact on this group of patients. Some exposure (drug) registries address drug exposures in specific populations, such as pregnant women. Patients can be followed over time and included in a cohort study to collect data on adverse events using standardized questionnaires. Single cohort studies can measure incidence, but, without a comparison group, cannot provide proof of association. However, they can be useful

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for signal amplification, particularly for rare outcomes. This type of registry can be very valuable when examining the safety of an orphan drug indicated for a specific condition.

Example of registry:

Survival trends between the years 2000 and 2004 for 20 common cancers based on follow-up data from **12 cancer registries** *(disease registry)* from diverse areas of Europe using model-based period analysis techniques were examined.[19] Between 2000 and 2004, marked rises were seen in 5-year relative survival amongst patients with prostate, breast and colorectal cancer, which were statistically significant in 10, 8 and 7 of the 12 participating cancer registries, respectively. For cancer sites amenable to effective early detection and treatment, major geographical differences in patient prognosis still persisted, with a lower survival generally observed in Eastern European countries. It was concluded that model-based period analysis enables the timely monitoring of recent trends in population-based cancer survival. For colorectal and breast cancers, the identified rises in survival are probably (at least partly) explained by the improvements in clinical care and the management of the disease. Nevertheless, persisting geographic differences do point to the potential for a further reduction in the burden of cancer throughout Europe, towards which improvements in diverse areas of care, including secondary prevention, access to advances in treatment as well as subspecialization and regionalization of oncologic care may all contribute.

Comparative Observational Studies

Traditional epidemiologic methods are a key component in the evaluation of adverse events. There are a number of observational study designs that are useful in validating signals from spontaneous reports or case series. Major types of these designs are cross-sectional studies, case-control studies, and cohort studies (both retrospective and prospective). [15,16]

Cross-sectional Study (Survey)

Data collected on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status constitute a cross-sectional study. These types of studies are primarily used to gather data for surveys or for ecological analyses. The major drawback of cross-sectional studies is that the temporal relationship between exposure and outcome cannot be directly addressed. These studies are best used to examine the prevalence of a disease at one time point or to examine trends over time, when data for serial time points can be captured. These studies can also be used to examine the crude association between exposure and outcome in ecologic analyses. Cross-sectional studies are best utilized when exposures do not change over time.

Case-control Study

In a case-control study, cases of disease (or events) are identified. Controls, or patients without the disease or event of interest, are then selected 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 represents the prevalence of exposure in the source population. The exposure status of the two groups is then compared using the **odds ratio**, which is **an estimate of the relative risk of disease in the two groups**. Patients can be identified from an existing database or using data collected specifically for the purpose of the study of interest. If safety information is sought for special populations, the cases and controls can be stratified according to the population of interest (the elderly, children, pregnant women, etc.). For rare adverse events, existing large population-based databases are a useful and efficient means of providing

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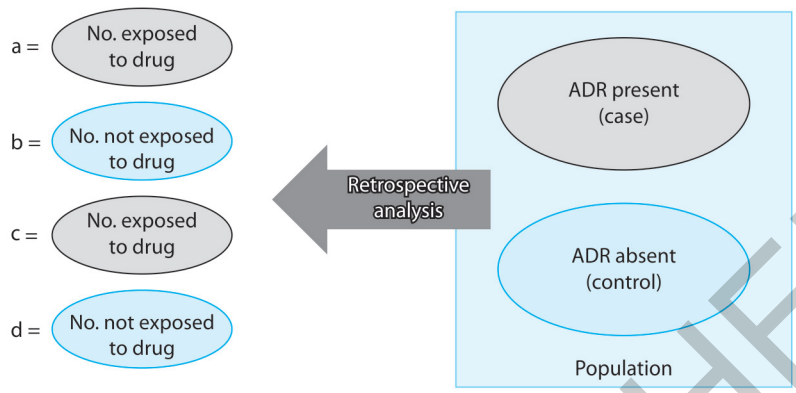

The odds ratio (OR) is a measure of the strength of association between the risk factor (exposure to the drug) and the disease or outcome (presence of a suspected adverse reaction), and is measured as odds or exposure among the cases against the odds of exposure among the controls

$$OR = \frac{a/(a+c)/\ c\ (a+c)}{b/(b+d)/\ d\ (b+d)} = \frac{ad}{bc}$$

Fig. 4.1: Retrospective case-control study

needed drug exposure and medical outcome data in a relatively short period of time. Case-control studies are particularly useful when the goal is to investigate whether there is an association between a drug (or drugs) and one specific rare adverse event, as well as to identify risk factors for adverse events. Risk factors can include conditions such as renal and hepatic dysfunction that might modify the relationship between the drug exposure and the adverse event. Under specific conditions, a case-control study can provide the absolute incidence rate of the event. If all cases of interest (or a well-defined fraction of cases) in the catchment area are captured and the fraction of controls from the source population is known, an incidence rate can be calculated (Fig. 4.1).

Cohort Study

In a cohort study, a population-at-risk for the disease (or event) is followed over time for the occurrence of the disease (or event). Information on exposure status is known throughout the follow-up period for each patient. A patient might be exposed to a drug at one time during follow-up, but non-exposed at another time point. Since, the population exposure during follow-up is known, incidence rates can be calculated. In many cohort studies involving drug exposure, comparison cohorts of interest are selected on the basis of drug use and followed 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 of adverse events. Multiple adverse events can also be investigated using the same data source in a cohort study (Fig. 4.2). However, it can be difficult to recruit sufficient numbers of patients who are exposed to a drug of interest (such as an orphan drug) or to study very rare outcomes. Like case-control studies, the identification of patients for cohort studies can come from large automated databases or from data collected specifically for the study at hand. In addition, cohort studies can be used to examine safety issues in special populations (the elderly, children, patients with comorbid conditions, pregnant women) through over-sampling of these patients or by stratifying the cohort if sufficient numbers of patients exist. There are several automated databases available for pharmacoepidemiologic studies.[15,16,20]

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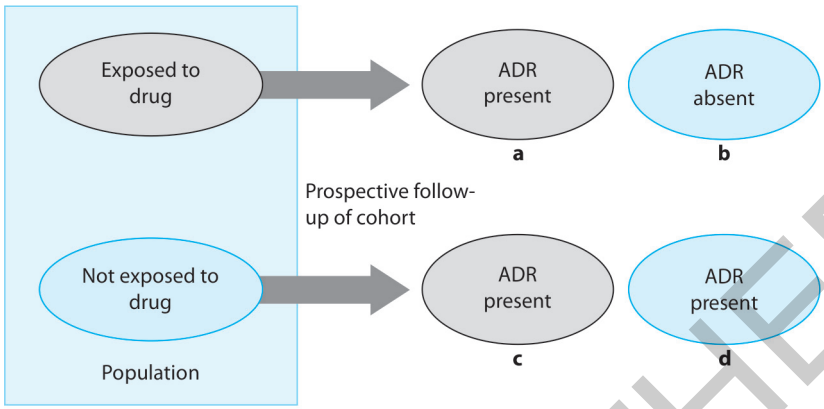

Fig. 4.2: Cohort study

They include databases which contain automated medical records or automated accounting/billing systems. Databases that are created from accounting/billing systems might be linked to pharmacy claims and medical claims databases. These datasets might include millions of patients. Since, they are created for administrative or billing purposes, they might not have the detailed and accurate information needed for some research, such as validated diagnostic information or laboratory data. Although, medical records can be used to ascertain and validate test results and medical diagnoses, one should be cognizant of the privacy and confidentiality regulations that apply to patient medical records.

Targeted Clinical Investigations

When significant risks are identified from pre-approval clinical trials, further clinical studies might be called for to evaluate the mechanism of action for the adverse reaction. In some instances, pharmacodynamic and pharmacokinetic studies might be conducted to determine whether a particular dosing instruction can put patients at an increased risk of adverse events. Genetic testing can also provide clues about which group of patients might be at an increased risk of adverse reactions. Furthermore, based on the pharmacological properties and the expected use of the drug in general practice, conducting specific studies to investigate potential drug-drug interactions and food-drug interactions might be called for. These studies can include population pharmacokinetic studies and drug concentration monitoring in patients and normal volunteers. Sometimes, potential risks or unforeseen benefits in special populations might be identified from pre-approval clinical trials, but cannot be fully quantified due to small sample sizes or the exclusion of subpopulations of patients from these clinical studies. These populations might include the elderly, children, or patients with renal or hepatic disorder. Children, the elderly, and patients with comorbid conditions might metabolise drugs differently than patients typically enrolled in clinical trials. Further clinical trials might be used to determine and to quantify the magnitude of the risk (or benefit) in such populations. To elucidate the benefit-risk profile of a drug outside of the formal/traditional clinical trial setting and/or to fully quantify the risk of a critical but relatively rare adverse event, a large simplified trial might be conducted. Patients enrolled in a large simplified trial are usually randomized to avoid selection bias. In this type of trial,

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though, the event of interest will be focused to ensure a convenient and practical study. One limitation of this method is that the outcome measure might be too simplified and this might have an impact on the quality and ultimate usefulness of the trial. Large, simplified trials are also resource-intensive.

Descriptive Studies

Descriptive studies are an important component of pharmacovigilance, although not for the detection or verification of adverse events associated with drug exposures. These studies are primarily used to obtain the background rate of outcome events and/or establish the prevalence of the use of drugs in specified populations.

Natural History of Disease

The science of epidemiology originally focused on the natural history of disease, including the characteristics of diseased patients and the distribution of disease in selected populations, as well as estimating the incidence and prevalence of potential outcomes of interest. These outcomes of interest now include a description of disease treatment patterns and adverse events. Studies that examine specific aspects of adverse events, such as the background incidence rate of or risk factors for the adverse event of interest can be used to assist in putting spontaneous reports into perspective.[16] For example, an epidemiologic study can be conducted using a disease registry to understand the frequency at which the event of interest might occur in specific subgroups, such as patients with concomitant illnesses.

Drug Utilization Study

Drug utilization studies (DUSs) describe how a drug is marketed, prescribed, and used in a population, and how these factors influence outcomes, including clinical, social, and economic outcomes.[15] These studies provide data on specific populations, such as the elderly, children, or patients with hepatic or renal dysfunction, often stratified by age, gender, concomitant medication, and other characteristics. DUS can be used to determine if a product is being used in these populations. From these studies denominator data can be developed for use in determining rates of adverse drug reactions. DUS have been used to describe the effect of regulatory actions and media attention on the use of drugs, as well as to develop estimates of the economic burden of the cost of drugs. DUS can be used to examine the relationship between recommended and actual clinical practice. These studies can help to determine whether a drug has the potential for drug abuse by examining whether patients are taking escalating dose regimens or whether there is evidence of inappropriate repeat prescribing. Important limitations of these studies can include a lack of clinical outcome data or information of the indication for use of a product.

It should be noted that the best method to address a specific situation can vary depending on the product, the indication, the population being treated and the issue to be addressed. The method chosen can also depend on whether an identified risk, potential risk or missing information is the issue and whether signal detection, evaluation or safety demonstration is the main objective of further study. When choosing a method to address a safety concern, the most appropriate design should be employed.

METHODS FOR VACCINE SAFETY[21-23]

A vaccine is a biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism, and is often made from weakened or killed forms of the microbe, its toxins or one of its

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surface proteins. The agent stimulates the body's immune system to recognize the agent as foreign, destroy it, and "remember" it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters.

Each year, vaccines prevent more than 2.5 million child deaths globally. Although, vaccines used in national immunization programmes (NIPs) are considered as safe and effective when used correctly, however vaccines are not risk-free as adverse events will occasionally occur following vaccination.

Although most adverse events are minor (e.g. redness at injection site, fever), more serious reactions (e.g. seizures, anaphylaxis) can occur at a very low frequency.

The general public has low tolerance to any adverse events following vaccination because vaccines are given to healthy persons to prevent disease. For this reason, a higher standard of safety is expected of immunizations compared with medications that are used to treat people who are sick (e.g. antibiotics, insulin). This lower tolerance for risks from vaccines translates into a greater need to detect and investigate any adverse event following immunization (AEFI) than is generally expected for other pharmaceutical products.

An AEFI is defined as a medical incident that takes place after an immunization, causes concern, and is believed to be caused by immunization.

Types of AEFI

AEFIs can be classified into five types:[21]

1. Vaccine reaction
2. Programme error
3. Coincidental reactions
4. Injection reaction
5. Unknown

Isolated and Clusters of AEFI[21]

Isolated AEFI

This is a solitary medical incident that takes place after immunization, causes concern and is believed to be caused by immunization.

Table 4.1: Types of AEFIs[21]

Type	*Definition*	*Example*
	**1. Vaccine reaction:** An event caused or precipitated by the active component or one of the other components of the vaccine (e.g. adjuvant, preservative and stabilizer). This is due to the inherent properties of the vaccine	• High-grade fever following DPT vaccination • Anaphylaxis
	**2. Programme error:** An event caused by an error in vaccine preparation, handling or administration	Bacterial abscess due to unsterile injection/ wrong diluent
	**3. Coincidental:** An event that occurs after immunization but is not caused by the vaccine. This is due to a chance temporal association	Pneumonia after oral polio vaccine administration
	4. Injection reaction: Event caused by anxiety about, or pain from the injection itself rather than the vaccine	Fainting spell after immunization
	5. Unknown The cause of the event cannot be determined	Does not fit into any of the above four types

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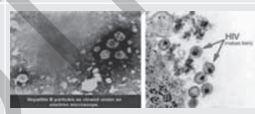
Table 4.2 : Common programme errors leading to AEFIs[21]

Programme errors		*Possible AEFI*
Non-sterile injection		
	• Contact of needle with unsterile surface e.g. finger, swab, table, etc. • Contaminated vaccine or diluent Administering injection over clothes • Improper handling of vaccine vials like touching of septum	Infection, e.g. local abscess at site of injection, sepsis
	• Use of reconstituted vaccines beyond the stipulated time (4 hours for BCG and measles, 2 hours for Japanese encephalitis) • Reuse of reconstituted vaccine at subsequent sessions	Toxic shock syndrome or death
	• Reuse of disposable syringe and needle • Improper storage and handling of syringes and needles leading to loss of sterility. • Syringes and needles used after expiry date	 Blood-borne infections, e.g. Hep B, HIV, Hep C, etc. Abscess
Reconstitution error/ Wrong vaccine preparation		
	• Reconstitution with incorrect diluent • Reuse of the reconstitution syringe • Use of expired vaccine or diluents • Drug substituted for diluent • Inadequate shaking of T-series vaccines	• Less vaccine effectiveness • Drug reaction; Death • Local abscess
Injection at incorrect site/route		
	Injection into gluteal region (buttocks)	Sciatic nerve damage, paralysis
	BCG/T series vaccine given subcutaneously	Local reaction or abscess
Vaccine transportation/storage incorrect		
	Improper storage of vaccines like freezing of T-series vaccines and subsequent administration of frozen and thawed freeze-sensitive vaccine	Increased local reaction such as sterile abscess Less vaccine effectiveness
Contraindications ignored		
	DPT2 given after history of convulsions with DPT1	More severe convulsions

Cluster AEFI

A cluster is defined as two or more cases of the same or similar event, which is related in time, and has occurred within the same district or geographical unit, or associated with the same vaccine, same batch number administered or same vaccinator.

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Vaccine Adverse Event Reporting System (VAERS),[24] is the national postmarketing safety monitoring system that accepts reports about adverse events that occur after administration of US licensed vaccines.

In India, Ministry of Health and Family Welfare Government of India has developed Standard Operating Procedures for Investigation of Adverse Event Following Immunization (AEFI).[21] The details of reporting system of AEFI has been provided in the National AEFI Surveillance and response Operational Guidelines, 2010. The non-serious AEFI should be reported "routinely" on a monthly basis and the serious AEFI should be reported immediately and also included in the monthly report and the line list

There are two channels of reporting AEFIs:

1. Monthly routine reporting
2. Immediate serious AEFI reporting

Monthly Routine Reporting

This includes reporting of all non-serious and serious AEFIs from the level of Health worker (Auxiliary Nurse Midwife or ANM) up to the National level (coordinated by the district) through monthly progress reports using existing immunization monthly progress reports/forms (vary from state to state). It is necessary for the ANM to submit "Nil" report in case no AEFI case detected from her area during the month. This information is collated and compiled by health workers in monthly reporting formats under the heading of "Any untoward reactions or reportable AEFIs" and forwarded to the next level. These include:

1. Deaths
2. Injection site abscesses
3. High-grade fever (>102° F)
4. Persistent inconsolable screaming (>3 hours)
5. Seizure
6. Hypotonic hyporesponsive episode (HHE)
7. Other complications (including the cases not listed above such as severe local reaction, brachial neuritis, thrombocytopenia, lymphadenitis, disseminated BCG infection, osteitis/osteomyelitis and any untoward incident that the vaccinator, ANM, Medical Officer think is a result of immunization.

Immediate Notification of Serious AEFI

The serious AEFI is defined as "any untoward medical occurrence that results in death, hospitalization or prolongation of hospitalization, persistent or significant disability/incapacity, or is life-threatening". All serious AEFI are to be immediately notified by the first person who identifies the event. This 'first' person should notify the case to the nearest government Primary Health Centre (PHC), Community Health Centre (CHC) and or the District Immunization Officer (DIO)/ by quickest means of communication, e.g. telephone, messenger, etc. All persons involved in reporting AEFI should be aware of the timeline and channels of reporting. Notification should be followed up with a First Information Report (FIR) as mentioned in Annexure 4.

The Process of Reporting Serious AEFIs

In India, the following reporting reports are used to guide AEFI investigation and causality assessment.

1. First Information Report (FIR): Annexure 4.
2. Preliminary Investigation Report (PIR): Annexure 5.
3. Detailed Investigation Report (DIR): Annexure 6.
4. AEFI- Laboratory Requisition Form: Annexure 7

The case definitions of some reportable adverse events are mentioned in Table 4.3.

These events are an emergency and need to be immediately investigated, managed and reported on standardized AEFI formats. Each serious event(s) should be followed up to determine the cause for its occurrence (causality assessment).

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Table 4.3: Case definitions of some reportable adverse events[21]

AEFI	*Case definition*	*Vaccine*
Vaccine associated paralytic poliomyelitis (presenting as AFP)	An acute flaccid paralysis 4–30 days following receipt of OPV, or within 4–75 day after contact with a recipient of OPV, with neurological deficits remaining 60 days after onset, of death	OPV
Anaphylactoid reaction (acute hypersensitivity reaction)	Exaggerated acute allergic reaction, occurring within 2 hours after immunization, characterized by one or more of the following: • Wheezing and shortness of breath due to bronchospasm • Laryngospasm/laryngeal edema • One or more skin manifestation, e.g. hives, facial edema, or generalized edema Do not report less severe allergic reactions	All
Anaphylaxis	Severe immediate (within 1 hour) allergic reaction leading to circulatory failure with or without bronchospasm and/or laryngospasm/laryngeal edema	All
Disseminated BCG infections	Widespread infection occurring within 1 to 12 months after BCG vaccination of confirmed by isolation of *Mycobacterium bovis* BCG strain. Usually in immunecompromised individuals	BCG
Encephalopathy	Acute onset of major illness characterized by any two of the following three conditions: • Seizures • Severe alteration in level consciousness lasting for one day or more • Distinct change in behavior lasting one day or more. Needs to occur within 48 hours of DPT vaccine of from 7 to 12 days after measles vaccine, to be related to immunization	Measles, pertussis
Fever	The fever can be classified (based on temperature) such as • Mild fever: 100.4°F to 102°F (38 to 38.9°C) • High fever: 102°F to 104.7° (39 to 40.4°C) • Extreme fever: 104.7°F or higher (> 40.5°C)	All
Hypotonic, hyporesponsive episode (HHE or shock-collapse)	Event of sudden onset occurring within 48 [usually less than 12] hours of vaccination and lasting from one minute to several hours, in children younger than 10 years of age. All of the following must be present: • Limpness (hypotonic) • Reduced responsiveness (hyporesponsive) • Pallor or cyanosis or failure to observe/recall	Mainly DPT, rarely others
Injection site abscess	• Fluctuant or draining fluid filled lesion at the site of injection • Bacterial if evidence of infection (e.g. purulent, inflammatory signs, fever, culture), sterile abscess if no evidence of bacterial infection on culture. Sterile abscesses are usually due to the inherent properties of the vaccine	All injectable vaccines
Lymphadenitis (includes suppurative lymphadenitis)	• Either at least one lymph nodes enlarged to >1.5 cm in size (one adult finger width) or a draining sinus over a lymph node • Almost exclusively caused by BCG and then occurring within 2 to 6 months after receipt of BCG vaccine, on the same side as inoculation (mostly axillary)	BCG
Osteitis/Osteomyelitis	Inflammation of the bone with isolation of *Mycobacterium bovis* BCG stain	BCG
Persistent inconsolable screaming	Inconsolable continuous crying lasting 3 hours or longer accompanied by high pitched screaming	DPT, pertussis

Contd...

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Contd...

AEFI	*Case definition*	*Vaccine*
Seizures	Occurrence of generalized convulsion that are not accompanied by focal neurological signs or symptoms. Febrile seizures: if temperature elevated >100.4°F or 38°C (rectal) Afebrile seizures: If temperature is normal	All, especially pertussis, measles
Sepsis	Acute onset of severe generalized illness due to bacterial infection and confirmed (if possible) by positive blood culture. Needs to be reported as possible indicator of programme error	All injectable vaccines
Severe local reaction	Redness and/or swelling centred at the site of injection and one or more of the following: • Swelling beyond the nearest joint • Pain, redness, and swelling of more than 3 days • Requires hospitalization Local reactions of lesser intensity occur commonly and are trivial and do not need to be reported	All injectable vaccines
TSS	Abrupt onset of fever, vomiting and watery diarrhea within a few hours of immunization. Often leading to death within 24 to 48 hours. Report as a possible indicator of programme error.	All injectable vaccines

Abbreviations: BCG, Bacillus-Calmette-Guerin; OPV, oral polio vaccine; DPT, diphtheria, pertussis tetanus; TSS, toxic shock syndrome

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