GUIDELINES ON PHARMACOVIGILANCE FOR PUBLIC HEALTH PROGRAMMES

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1. HISTORY

This is the first edition of this document.

2. APPLICATION - Guidance for Public Health Programs

This document is generally applicabe to the Public Health Programmes (PHPs) active in Pakistan to ensure safety of drugs, vaccines and other therapeutic goods used in these programs using pharmacovigilance tool as an essential component of public health.

3. PURPOSE

This guidance document is intended to assist the programme managers, administration and staff of Public Health Programmes (PHPs) regarding the establishment of active pharmacovigilance in all PHPs. This document will also explains communication channels among PHPs and Pharmacovigilanc Centres for cllaobrative working to synergize activities within the National Pharmacovigilance system of Pakistan. The key objectives of pharmacovigilance activities in public health programs are:-

i. To improve public health and safety in relation to the use of therapeutic goods in PHPs;

ii. To detect problems related to the use of therapeutic goods and associated risk communication in a timely manner

iii. To encourage the safe, rational and more effective use of therapeutic goods.

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4. INTRODUCTION

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems is Pharmacovigilance.

Drug Regulatory Authority of Pakistan (DRAP) aims at providing a holistic system of Pharmacovigilance in the country. There are multiple stakeholders involved in the reporting, assessment and risk communication of various un-wanted effects arising after the use of medicine. One of the important stakeholders in this system is organizational structure involved in protecting public health through provision and administration of medicine and vaccines to the public. These programs are known as Public Health Programs (PHPs) and are aimed at prevention and eradication of a disease(s) and prolong health through organized efforts of the society. The documentation and reporting of AEs following therapeutic goods (drugs, vaccines, biologicals etc.) exclusively being used by PHPs are essential to a pharmacovigilance system.

1. Establishment of pharmacovigilance centre under the public health programme
2. Collection assessment and reporting of ADR/AEFIs
3. Coordination and collaboration with pharmacovigilance stakeholders at the national and international level

Risk versus benefit assessment of any therapeutic good is based on evidence of risks and effects including known/intended and unknow/unwanted effects. This risk-benefit profile, early identification of unexpected adverse reactions and risk factors is given due importance when the products have been newly developed and data on extensive and diverse use is scarce, so that patients, public and healthcare professionals are fully informed and chances of harm can be minimized.

In the presence of a good pharmacovigilance system in a public health programme (PHP), risks and associated factors with the specific treatments, are timely identified and effectively communicated resulting in evidence-based use of therapeutic goods with the potential for preventing many adverse reactions. It can also provide evidence of other types of medicine-related problems including treatment failure, incorrect or irrational use, counterfeit, poor quality therapeutic goods, interactions between therapeutic goods and food.

The traditional division between the safe use of therapeutic goods and provision of public health hinders in achievement of the objective of PHPs which is improvement of health.

5. DEFINITION AND ACRONYMS

Abuse of therapeutic good:	means persistent or sporadic, intentional excessive use of therapeutic good which is accompanied by harmful physical or psychological effects;

ADR:	**"***Adverse Drug Reaction*" or "ADR" means response to drug or therapeutic goods which is noxious and unintended that occurs at doses normally used for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function. A response in this context means that a causal relationship between a therapeutic good and an adverse event is at least a reasonable possibility. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a therapeutic good and an occurrence is suspected.
AE:	**"***Adverse Event" or "AE"* means any untoward medical occurrence in a patient or clinical investigation subject administered a drug or therapeutic good and which does not necessarily have a causal relationship with this treatment
AEFI:	*"adverse event following immunizations" or "AEFI"* means any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine
AESI:	**"***adverse event of special interest"or "AESI"* means
Causality Assessment:	means the evaluation of the likelihood that medicine or therapeutic good was the causative agent of an observed adverse reaction;
DRAP:	Drug Regulatory Authority of Pakistan
EPI:	Expanded Programme on Immunization
ESRP:	Expert Safety Review Panel
HCP:	Healthcare Professionals such as physicians, pharmacists, nurses etc.
Incidence:	The number of new cases (e.g., of disease, adverse event) occurring in a defined population during a given time interval, often one year.
Injection reaction	An AEFI classification that refers to an event resulting from anxiety about, or pain from, the act of injection rather than the vaccine.
Medication Error:	means any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient or consumer
NPC:	National Pharmacovigilance Centre
Occupational Exposure	means situations where the therapeutic good or drug is intentionally and inappropriately used not in accordance with the

	registered therapeutic good information.
Off Label Use:	refers to the use of an approved medicine under the direction or supervision of a healthcare professional for an unapproved indication, age group, dosage, route or form of administration
Overdose of Therapeutic good:	means administration of a quantity of a therapeutic good given per administration or cumulatively which is above the maximum recommended dose according to the registered therapeutic good information
PHPs:	Public Health Programmes
PRAEC:	Pharmacovigilance Risk Assessment Evaluation Committee
PV:	Pharmacovigilance
Serious ADRs or AEs:	means any untoward medical occurrence that at any dose result in patient death, is life-threatening, require inpatient hospitalization or results in prolongation of existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect or is judged to be a medically important event or reaction;
Therapeutic Goods:	Includes drugs or alternative medicine or medical devices or biologicals or other related product as may be notified by DRAP.
WHO-PIDM:	World Health Organization's Programme on International Drug Monitoring
WHO-UMC:	World Health Organization Uppsala Monitoring Centre.

6. PHARMACOVIGILANCE SYSTEM OVERVIEW

6.1 WHO-PIDM

The WHO-Programme for International Drug Monitoring (WHO-PIDM) is a global network of countries to monitor drug safety and adverse events. Currently 149 national pharmacovigilance centres across the world are networking in a strong international programme in coordination with the World Health Organization (WHO) and its Collaborating Centre for International Drug Monitoring (the Uppsala Monitoring Centre). These national centres collaborate in the WHO-PIDM, to collect reports of suspected adverse drug reactions (ADRs) and after review, send them to the WHO database maintained by the Uppsala Monitoring Centre. This is the largest database of ADR reports in the world (over 28 million reports of adverse reactions) and is a prime resource for generating signals of previously unrecognized ADRs and for the study of questions on the safety of medicines.

6.2 National Pharmacovigilance Centre, DRAP

In Pakistan the National Pharmacovigilance Centre (NPC), is established under

the Division of Pharmacy Services, at DRAP headquarters, Islamabad, to monitor the safety of therapeutic goods across the country.

NPC collects reports from Healthcare professionals, Patients, Provincial Pharmacovigilance Centres, Public Health Programmes and Registration holders of therapeutic goods. In addition, NPC is also responsible to communicate with national and global stakeholders and detecting signals; recommending regulatory actions; integrating provincial, public health programmes, hospitals and regional pharmacovigilance centres; issuing safety communication; publishing newsletters; and performing other functions as elaborated in pharmacovigilance rules.

Pharmacovigilance Risk Assessment Expert Committee [PRAEC] is the advisory committee working under the Division of Pharmacy Services at the National level. PRAEC is responsible to evaluate risks associated with the use of therapeutic goods; signal detection, prioritization and assessment; risk management; risk minimization; failure mode effect analysis; and evaluation of periodic reports.

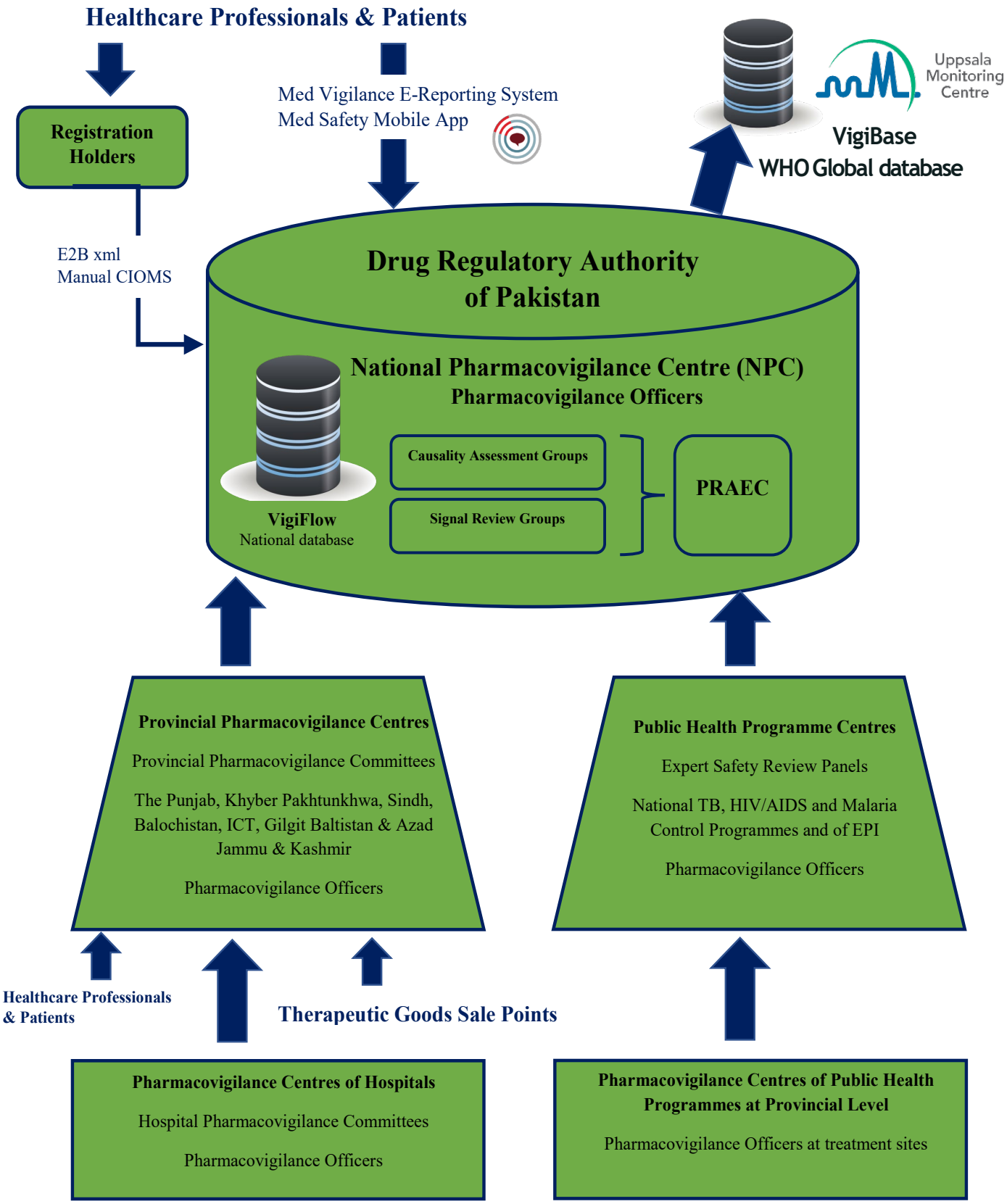


Figure.1 Information Process Flow in National Pharmacovigilance System

6.3 National Database, Collection and Assessemnt Tools

NPC, DRAP started national and international coordination for the development and promotion of pharmacovigilance in Pakistan. Pakistan became 134th Full member of the World Health Organization Programme for International Drug Monitoring (WHO-PIDM) in 2018 with endeavours of DRAP. The NPC subscribed to VigiFlow for transferring ADRs/AEFIs to VigiBase (Global database) and is supporting provincial governments and public health programmes in the establishment of their pharmacovigilance centres.

VigiFlow is a web-based ICSR data management system, which collects, structures, evaluates and shares ADRs/AEFIs and is accessible to National Pharmacovigilance Centres (the access can be extended to other affiliated centres at regional and sub-regional level). Adverse Event reports about therapeutic goods used in PHPs are a valuable resource for the programmes themselves and add value to the international database as well.

Currently, the following tools have been made available by the NPC, DRAP for reporting ADRs/AEFIs:

Sr.	Tool	Access/link	Reporter
1	Paper form	https://primaryreporting.who-umc.org/Reporting/Reporter?OrganizationID=PK	HCPs
7.	Med Vigilance E-Reporting link	https://primaryreporting.who-umc.org/Reporting/Reporter?OrganizationID=PK	Patients /HCPs
8.	Med Safety Mobile App	Apple store & Google Play store	Patients /HCPs
9.	Email id	npc@dra.gov.pk	Patients /HCPs
10.	Landline contacts	051-9107413 / 9107299	Patients /HCPs
6.	E2B XML & CIOMS form	--	Therapeutic goods companies
7.	VigiFlow accounts	--	Regional Centres (Provinces, PHPs, & Administrative territories)

Figure.2 Schemtic flow of Data Collection and Assessment in National Database

6.4 Integrating of PHPs in the Pharmacovigilance System:

Integration of pharmacovigilance into public health programmes at national and international level is important for the successful operation of the PHPs and is essential for provision of safe healthcare to the community. The network of pharmacovigilance involving PHPs can be better understood from the given flow diagram:

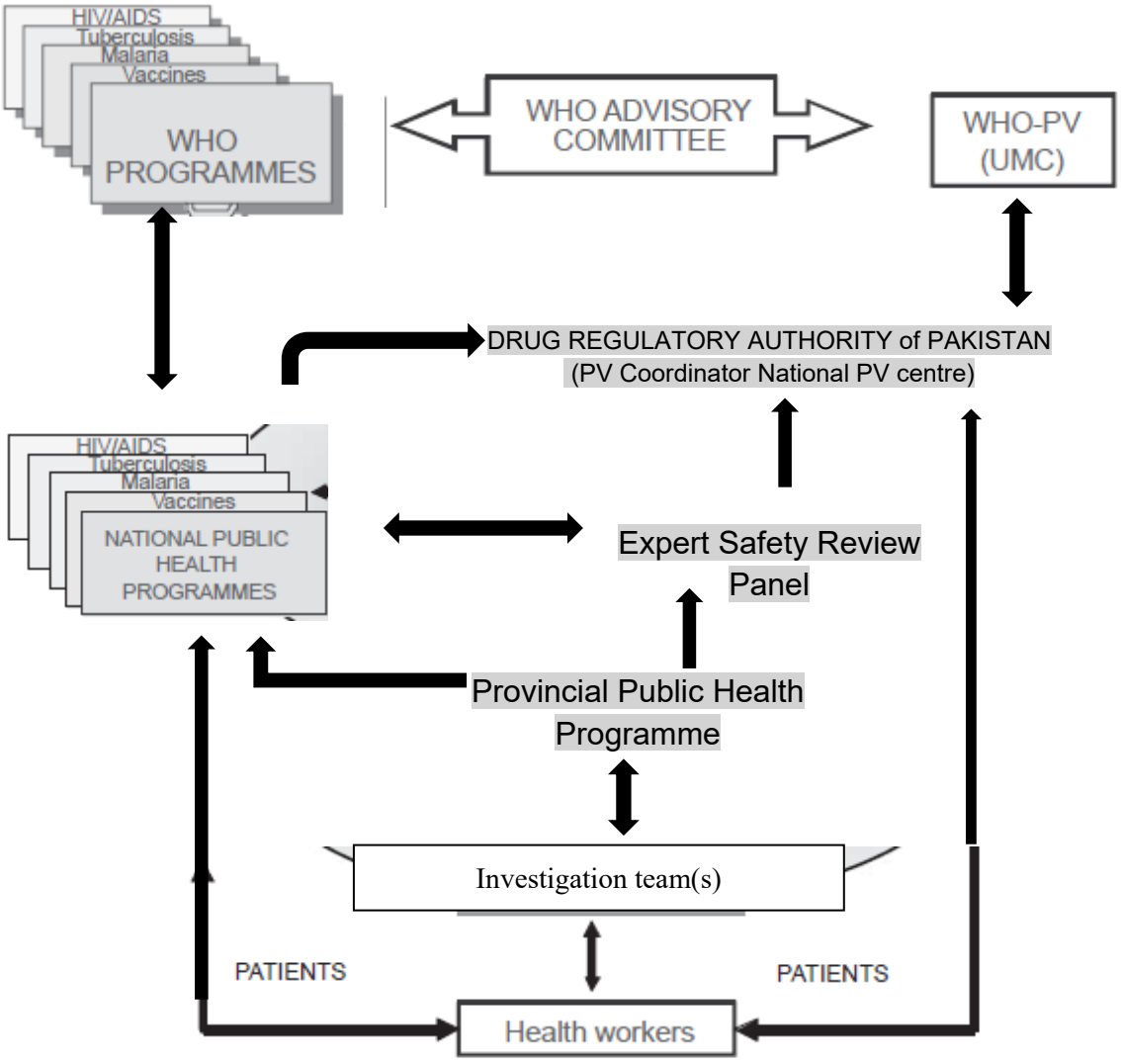


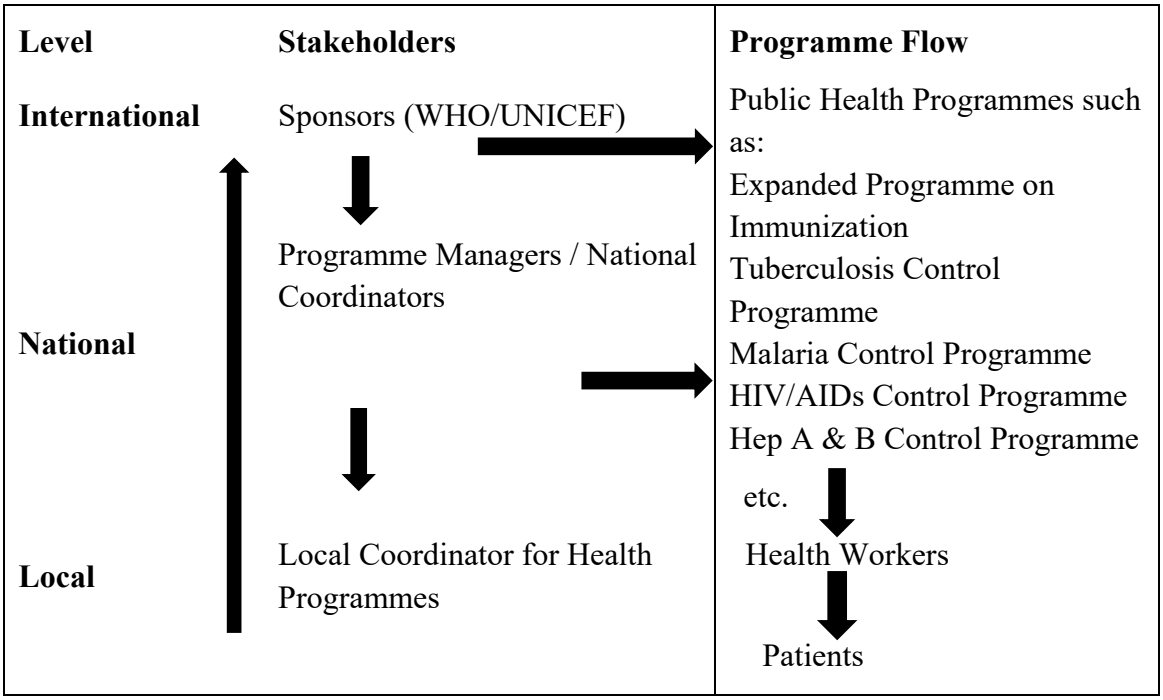
Figure.3 Public Health Programs (PHPs) integeration in National Pharmacovigilance System

7. PUBLIC HEALTH PROGRAMS AND REQUIREMENTS OF PHARMACOVIGILANCE

Public health is defined as the organized efforts of society to protect, promote and restore people's health. It is the combination of science, skills and beliefs that is directed to the maintenance and improvement of health of all the people through focused and collective activities and community efforts. The activities are supported and monitored internationally and nationally in the form of education, mass free distribution of drugs or vaccines, behavioural & lifestyle changes etc.

PHPs are vertical programmes with intensive activities towards specific health problems, employing the methods of prophylaxis, treatment and eradication through drugs or vaccines with direct administration. Interventions aimed at achieving the assigned goal (i.e. reduction of morbidity and mortality rates) include mobilization of resources both nationally and internationally to support the different aspects of the programme, including the mass distribution of free medicines.

The organization of a PHP can be better understood:



The scope of monitoring by PHPs involves:

i. Incidence and prevalence of disease
ii. Morbidity and mortality rates due to the disease
iii. Number of patients treated
iv. Number of drug units delivered

The scope of this monitoring needs to be broadened for including the risk and effectiveness of the drugs/vaccines being used to detect, evaluate and prevent ADRs/AEFIs related to:

i. Harm
ii. Acceptance and tolerance
iii. Misuse

iv. Dependence
v. Effect in special population/condition (elderly, children, pregnancy etc.)
vi. Therapeutic failures (resistance, quality defects, counterfeits)

7.1 Strengths and Weaknesses of PHPs

PHPs have some distinct advantages for undertaking pharmacovigilance, and in turn also benefit pharmacovigilance systems from gained experience. In public health model the strengths of the pharmacovigilance and PHPs should be utilized to operate the pharmacoviglance, hence avoiding duplication of efforts and un-necessary expenditure on resources.

When a PHP and NPC function independently of each other, it leads to duplication of efforts, lack of harmonized terminologies, data collection methods and causality assessment. The information that is collected is not added to the international database for pharmacovigilance and therefore the international community derives no benefit from it.

7.1.1 *Strengths*

Public health programmes:

i. well-established roles through essential health care work with large populations, engaging in preventive and curative interventions through the use of medicines;
ii. better resource support than pharmacovigilance programmes including support from international sources;
iii. proper guidelines or protocols;
iv. established performance monitoring and evaluation procedures;
v. established information systems to process epidemiological data;
vi. data on denominators (numbers of patients treated) is available, which can be used for the calculation of rates or incidence of ADRs; and
vii. good training programmes for health care providers.

In contrast the particular *strengths of pharmacovigilance programmes* are in the development of new methods for assessing the safety of medicines, including better analyses of data and signal-detection processes.

Another strength of pharmacovigilance programmes of considerable importance to PHPs is the training and expertise in effectiveness–risk evaluation and its communication.

7.1.2 *Weaknesses*

In most developing countries, there are insufficient resources within the public health system to undertake training and capacity building and to invest in systems for monitoring drug efficacy and safety. The major resources are often concentrated on developing PHPs to reduce disease morbidity and mortality and very few of these countries have a well-established pharmacovigilance system.

i. Insufficient training and awareness of PHP managers in the need to

detect and report adverse reactions to the medicines that are used in their programmes.

ii. False assumption of universal safety of medicines disregarding the need to monitor or re-evaluate the use.

iii. Lack of training in staff working within PHPs to assist in monitoring the safety of medicines.

iv. Wrong perception of ADRs having a negative impact on the PHP, leading to ignorance of the significance of adverse reactions for the projection of the safety of medicines and ascertain good adherence.

7.2 Establishment of Federal & Provincial Centres by PHP

The major aims of pharmacovigilance in public health will be the same as those of the national pharmacovigilance centre. These are:

i. Rational and safe use of medicines by health professionals;

ii. Assessment and communication of the risks and effectiveness of medicines used; and

iii. Educating and informing patients.

The essential role players are:

i. patients;

ii. primary health-care workers/professionals;

iii. district hospital;

iv. district health officer;

v. district investigation team;

vi. tertiary care referral hospital;

vii. programme manager;

viii. national pharmacovigilance coordinator/pharmacovigilance centre; and

ix. expert safety review panel.

7.2.1 *Focal Person Pharmacovigilance*

In any pharmacovigilance centre whether national, provincial or sub-regional/district a pharmacovigilance coordinator or focal person is essential. The focal person will coordinate and integrate pharmacovigilance activities between the PHP at the national and provincial levels and with the NPC. The person appointed at the Federal level should be a member or secretary of the Expert Safety Review Panel (ESRP). The person should be knowledgeable about pharmacovigilance concepts and be a useful resource officer to develop and maintain the PHPs PV system as per international standards. The focal persons at the provincial level will coordinate with the focal persons PHPs at the national and sub-regional or district level of the programme.

7.2.2 *Procedures for Pharmacovigilance*

It is vital to have defined procedures within the PHP for coherent Pharmacovigilance activities describing the practical details of the intended information flow. The procedures should be harmonized with

these guidelines and set protocols of the PHP. The following minimum information should be addressed in pharmacovigilance procedures:

i. What constitutes a reportable adverse reaction?
ii. Who is expected to report an observation of a suspected therapeutic good-related problem?
iii. The availability and practicalities of filling in a reporting form.
iv. Procedures for submission or collection of reports.
v. Routines for assessment, follow-up and processing of case reports at the pharmacovigilance centre.
vi. Procedures for the analysis of aggregated information and options for action.
vii. Good communication practices.
viii. A description of indicators by which the progress of the monitoring system may be measured.

7.2.3 *Role and Responsibilities*

Being part of the National Pharmacovigilance System, the responsibilities of a PHP as a regional pharmacovigilance centre are as under:

i. Pharmacovigilance centres are established by each PHP at the national level and integrated with the provincial chapters of the said public health programme.
ii. The signing of MoU with NPC, DRAP for collection and submission of pharmacovigilance data.
iii. Effective coordination with NPC, DRAP by properly nominating a Focal Person for this purpose.
iv. Notification of Pharmacovigilance Officers at National, Provincial and site-level of PHP for collection and assessment of data.
v. Collecting, receiving and processing of reports from provincial chapters of PHP and treatment sites (with verification, interpretation, coding of therapeutic goods and ADRs, and case causality assessment) and case management;
vi. Regular submission of pharmacovigilance data to NPC, DRAP.
vii. Constitution of an Expert Safety Review Panel (ESRP) at the National level, which shall perform functions such as causality assessment, signal detection, and establish procedures for pharmacoepidemiological studies and cohort event monitoring.
viii. Develop a system of active surveillance for all new drugs and other drugs that are specific to that public health programme and are associated with risks i.e. priority drugs. Conduction of pharmacoepidemiological studies, cohort event monitoring, targeted spontaneous reporting etc.
ix. Strengthening of the healthcare system with emphasis on clinical observation for suspected adverse reactions to know about patient's underlying conditions and contraindications.

x. Training of POs of PHP and awareness campaigns for patients in all aspects of pharmacovigilance. Training of health care workers in reporting adverse reactions;

xi. Decision-making, risk management, follow-up;

xii. Good communication;

xiii. Coordination between pharmacovigilance, regulatory and public health activities;

7.3 Core Indicators for Pharmacovigilance of a PHP

PHPs are targeted at combating specific diseases and health issues. The majority of these programmes use medicines for the prevention and /or treatment of diseases. A good pharmacovigilance strategy is required to be in place in a PHP to monitor the safety and safe use of the high volumes of specific therapeutic goods and the vulnerability of the population receiving these treatments.

A set of pharmacovigilance indicators dedicated to PHPs will help programme managers plan, monitor, and evaluate the effectiveness of pharmacovigilance within their programmes. It is required that the pharmacovigilance activities being planned and conducted by PHPs are in close collaboration with the National Pharmacovigilance Centre, DRAP to avoid duplication of efforts and optimize the use of resources. There are nine pharmacovigilance indicators identified by the World Health Organization for public health programmes, which should be used as guidance to set up an operational PV system and measure performance:

i. The operational document of a PHP includes pharmacovigilance activities

ii. All main treatment guidelines or protocols in use within the public health programme systematically consider pharmacovigilance

iii. Adoption of ADR/AEFI reporting form and reporting tools of NPC, DRAP and their easy access. The reporting of following:-
   a. Suspected medication errors
   b. Suspected counterfeit / substandard medicines
   c. Therapeutic ineffectiveness
   d. Suspected misuse, abuse of and /or dependence on medicines

iv. Data of ADR/AEFI reports collected within the public health programme

v. Data of ADR/AEFI reports per 1000 individuals exposed to medicines in the public health programme

vi. Data of reports on therapeutic ineffectiveness

vii. Percentage of completed reports submitted to the National Pharmacovigilance Centre.

viii. Percentage of reports submitted to WHO database from the reports satisfactorily completed and submitted to NPC, DRAP

ix. Data of medicine-related hospital admissions per 1000 individuals exposed to medicines in the public health programme.

x. Data of medicine-related deaths per 1000 individuals exposed to medicines in the public health programme.

7.4 Training, Awareness and Education

The healthcare workers in Public Health Programmes require guidance and training, to prevent patients from increased risk of medication errors and/or preventable ADRs/AEFIs. PHPs, therefore, need to have in place continuous training, education and awareness programmes for all their employees. The following points should be encompassed to address risks and factors of different aspects:

i. Disease management and diagnosis (proper diagnosis, evidence-based treatment and follow up with patients)

ii. Population characteristics when treating large numbers (en masse, case contact or individual treatment methods etc.) in a short period (not having the disease, contraindications, use in the special population, community habits i.e literacy, food habits, nutrition etc. for treatment effectiveness, adherence and safety)

iii. Aspects related to therapeutic goods for prevention of avoidable treatment failures, antimicrobial resistance, morbidity & mortality and limited clinical experience:

   a. Rational & evidence-based use and avoiding irrational practices (prescribed, dispensed or sold incorrectly):
      - use of too many medicines per patient (polypharmacy);
      - inappropriate use of antimicrobials, often in inadequate dosage and frequently for non-bacterial infections;
      - overuse of injections when oral formulations would be more appropriate;
      - failure to prescribe in accordance with clinical guidelines; and
      - inappropriate self-medication, often using prescription-only medicines.
   b. Assurance that therapeutic goods received or purchased from any source meet quality standards
   c. Identification of counterfeit, substandard & falsified therapeutic goods, etc.
   d. Proper manufacturing, packaging, storage and distribution
   e. Access to therapeutic goods through qualified personnel or authentic sources
   f. Drug-drug interactions, drug-food interactions and interactions between therapeutic goods from different systems of treatment (e.g. alternative and allopathic systems etc.)
   g. WHO guidelines for good donation practices

iv. Focused training of health workers (non-medical workers of the community) regarding disease symptoms and identification and reporting ADRs/AEFIs.

v. Planned Good Pharmacovigilance Practice courses, training, education and orientation for all the healthcare professionals and health workers.

vi. Awareness and education of the community regarding reporting.

7.5 The Expert Safety Review Panel (ESRP)

The ESRP occupies a very special position in causality assessment. A preliminary assessment should have been undertaken and follow-up conducted if necessary before reports are presented to the ESRP.

The panel should be constituted as follows:

i. the Programme Manager;
ii. Pharmacovigilance Coordinator / Focal Person of the PHP;
iii. a clinical pharmacologist or a clinician who has an interest in medicines;
iv. a physician and disease expert;
v. a pharmacist;
vi. a member of the NPC, DRAP;
vii. other members with specific expertise as required e.g. a paediatrician or a gynaecologist; and
viii. a representative of a consumer organization may be included.

The functions of the ESRP will be to:

i. review reports referred by the PHP's pharmacovigilance coordinator or programme manager;
ii. assess safety issues from reports of serious ADRs and/or cumulative data;
iii. assess safety issues that, although not serious, may affect adherence;
iv. assess reports that may suggest lack of efficacy and determine the likely cause;
v. assess potential causal links between ADR/AEFI and therapeutic good/vaccine;
vi. monitoring reported ADR/AEFI data for potential signals of previously unrecognized therapeutic good /vaccine-related adverse events;
vii. recommend further follow-up and investigation when indicated; and
viii. recommend appropriate action to the pharmacovigilance coordinator, programme manager or DRAP. This will include communication with healthcare professionals and/or the public.

The ESRP should be disease or programme-specific. The National Pharmacovigilance Centre has subscription of VigiFlow as National Dtabase for collection, management, assessment and reporting of ADRs and AEFIs with the option to integrate Provincial / Regional Centres of the country. On establishment of proper pharmacovigilance centre at the Level of Public Health Programmes the National Pharmacovigilance Centre provides VigiFlow Logins to the nominated officers for carrying out PV related tasks.

The recommendations of the ESRP should be submitted to the regional or national programme director and the National Pharmacovigilance Centre, DRAP for their decisions.

8. PHARMACOVIGILANCE PROCESS

8.1 Suspected ADR /AEFI Reporting

The success or failure of any pharmacovigilance activity depends on the reporting of suspected adverse events/reactions.

Safety Information is collected through various methods. The most common method is spontaneous reporting whereby adverse events are reported by health professionals and patients and pharmaceutical companies voluntarily. It is the reporting of a suspected adverse reaction on the initiative of the health professional who becomes aware of the problem, or on the patient's initiative.

The other methods of collecting safety information are pharmacoepidemiological in nature which address important safety questions and limitations of reporting. These are Prescription Event Monitoring, record linkage and case-control studies, cohort event monitoring etc. Details on the methods are given in the National Pharmacovigilance Guidelines.

As PHPs are disease-specific programmes hence require more focused and intensive reporting. Prospective monitoring or active surveillance systems can be implemented to complement spontaneous reporting for a more systematic and robust pharmacovigilance system.

A standardized reporting form should be available to the primary healthcare worker at the treatment sites, who should report the ADRs/AEFIs to the District Health Office/Provincial Health Programme (or equivalent) as the case may be. The District Health Office or Programme Manager, in association with the investigation team, will follow up reports of serious ADRs/AEFIs or other AEs of interest and submit details to the PHP at the Federal level for review by the ESRP.

The primary healthcare worker should manage suspected ADRs/AEFIs. Patients with serious or severe AEs should be referred immediately to the nearest hospital with required facilities for investigation and management. The details of management and outcome should be included in the report submitted by the District Health Officer or Programme Manager. Staff from the PHP already performing the function of health-care delivery are best suited to detect, investigate and manage ADRs and therefore would need extra training in the identification and reporting of ADRs/AEFIs.

8.1.1 *Reporting*

An ADR reporting form developed by the National Pharmacovigilance Centre, DRAP is available for HCPs, which can be adopted with changes in mailing address and made accessible at various reporting points in yellow colour for distinction. (**Annex-I**).

The AEFI reporting form of WHO should be adopted for any adverse event after immunization.

The Mandatory information to be filled in the reporting form includes:

Mandatory Information	**Essentially Required Information.**
i. Patient Information. ii. One or more suspected reaction	i. Patient initials, and age at the time of reaction. ii. Sex of the patient.

(s). The reaction terms must be given.
iii. One or more suspected drug (s).
iv. Reporter Information.

iii. Reaction term (s).
iv. Time-to-onset of reaction (start date/time of suspected drug +start date/time of reaction)
v. Suspected drug (s) (dose, strength, dosage)
vi. Indication for use.
vii. Seriousness of reaction
viii. Outcome of reaction
ix. De-challenge
x. Re-challenge (not always ethical to perform)
xi. Reporter information (designation, contact details)
xii. Case Narrative in free text (chronology of happening of ADRs)
xiii. Date of report.

A reporting form should contain the maximum possible information available regarding ADRs/AEFIs. In case of incomplete information essentially required fields be filled at the first try. In case of incomplete essentially required information, it should be made sure that the reporting form contains all the mandatory information so that it can be considered a valid report.

8.1.1.1 Patient Information

i. *Patient Initial or Name*: here healthcare professionals can either write initials of a patient name like for example "MA" for Muhammad Arif or can write full name. If Healthcare professionals provide full names it would be kept confidential.

ii. *Identification Number*: Here hospital or ward admission numbers can be provided so that Healthcare professionals can easily access patient files in case follow up information is required.

iii. *Sex*: Mention the gender of the patient. If the patient is female, then the healthcare professional must provide information, whether she is pregnant or not.

iv. *Age at the time of reaction:* The age of the patient should be provided in this section along with a proper unit for example hours, days, weeks, months, years etc. Suppose an infant is of 8 hours then the reporter needs to mention hours unit with a numerical value.

8.1.1.2 Suspected Drug (s)/Vaccine (s)/ Alternative Medicine(s)

i. *Drug/ Vaccine/Alternative Medicine Name:* Both generic and brand shall be provided.

ii. *Batch No:* Batch number shall be provided in case the drug has a quality problem, it would be helpful to trace the drug and recall it.

iii. *Manufacturer Importer:* if the reporter has provided a generic name then he must provide details of the manufacturer/ importer.

iv. *Route of Administration and daily doses:* Route through which the drug was given

v. *Dosage and Strength:* dosage form the therapeutic good and the strength used

vi. *Start date: administration date of the drug.* It would be helpful to build a relationship between the drug and event and will determine a time to onset of reaction.

vii. *Stop Date: when the drug was withdrawn.* It would also help in the assessment of reports by providing information on Dechallenge of a drug.

viii. *Prescribed for:* the indication for which the drug was administered.

8.1.1.3 Suspected Reaction (s)

i. *When Reaction started:* Mention the date on which reaction started, it would be helpful to determine the casual relationship of reaction with drug and will determine the time to onset of reaction.

ii. *When Recovery Started:* Mention the date on which the reaction ended or recovery started, it would be helpful to determine whether the reaction subsides when the suspected medicine is stopped.

iii. *Describe the reaction(s):* Complete narrative/ description of reaction should be provided; who the patient developed the reaction, nature, localization etc.

iv. *Other relevant histories of the patient (Allergies, Smoking, Alcohol Use, Hepatic/Renal Problems, and Pre-Existing Medical Problems etc.:* write the relevant history persistent to a patient including pre-existing conditions (allergies, smoking, alcohol use, hepatic or renal dysfunction, surgical procedure, risk factors etc.) and current medical condition if any.

v. *Relevant tests/Laboratory data with dates:* write all tests and procedures performed to diagnose or confirm the reaction/event, including those tests done to investigate a non-drug cause.

vi. *The seriousness of the reaction:* If the reporter considers the reaction to be serious then he must tick all that apply out of the following:

a. *Death of patient*: If the patient died due to an adverse event. It would be appropriate to mention the cause of death in the reaction narrative along with the date of death.

b. *Life-Threatening:* If the patient was at substantial risk of dying at the time of the adverse event.

c. *Involved or Prolonged Inpatient Hospitalization:* if due to adverse the patient was hospitalized or already hospitalized patient stay was prolonged.

d. *Disability or incapacity:* If due to an adverse event the patient normal life function are affected.

e. *Congenital Anomaly/ Birth Defect:* when exposure to drug during pregnancy has resulted in adverse outcome in the infant in the form birth defect.

f. *Other serious events:* Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

vii. *De-challenge details:* Withdrawal of a medicine from a patient following an adverse event.

a. *Yes:* if reaction abate/ subside after the suspected drug is stopped or dose reduced.

b. *No:* if reaction does not abate/ subsides after the suspected drug is stopped or dose reduced.

c. *Does not apply:* If de-challenge is not applicable as in case of vaccines, anaesthesia, where a single dose is given, in case of death, or in case where treatment is completed prior to reaction or event. De-challenge

is also meaningless in case of myocardial infarction and stroke

viii. *Re-Challenge details:* Reintroduction of the medicine under the same conditions as previously (same dose, form, route of administration), following withdrawal and recovery from the adverse event.
   a. *Yes:* when the suspected drug is reintroduced the reaction again appeared.
   b. *No:* when the suspected drug is re-introduced the reaction does not appear.
   c. *Does not apply:* if re-challenge is not applicable as in case of anaphylaxis.

ix. *Outcome:*
   a. *Fatal:* if the patient dies.
   b. *Recovering:* If the patient is recovering from the reaction.
   c. *Unknown:* if the outcome is unknown.
   d. *Continuing:* if the patient is continuing to experience the reaction/event.
   e. *Recovered:* if the patient has completely recovered from the reaction/event.

x. *Cause of the Reaction:*
   a. *Quality problem:* if the reaction patient experience was due to quality problem.
   However, healthcare professionals can also inform NPC about the visible sign of quality defects.
   b. *Medication Error:* Inappropriate medication use or patient harm, when the medicine was in control of healthcare professional or consumer.
   c. *Adverse Event/ Reaction:* if the patient develops reaction or event in spite of the fact that medicine has no quality defect and the healthcare professional does not use the medicine inappropriately.

xi. *Causality Assessment:* the reporter (if trained) must perform the causality assessment and justify the assessment.

8.1.1.4 Other Concomitant Drug(s)/ Vaccine (s)/ Alternative Medicines (s)

This information detail is the same as that of suspected drug. But, this section is required to only include additional medication being used by the patient.

8.1.1.5 Suspected Medical Devices (s)

i. *Medical Device Common Name/ Brand Name:* Brand name is on a label attached to a durable device; on a package of a disposable device; or is on the labelling materials of an implantable device. The generic or common name of the suspect medical device or a general descriptive name (e.g., urological catheter, heart pacemaker, patient restraint). Please do not use broad generic terms such as "catheter", "valve", "screw", etc.
ii. *Lot No/ Batch Name:* This number can be found on the label or packaging material and help in tracking the device in the market and its production record at the time of recall.
iii. *Manufacturer/ Importer:* The name of registration/enlistment holder is on the label.
iv. *Model No:* The exact model number found on the device label or accompanying packaging.
v. *Unique Identifier No:* This number can be found on the device, its label, or accompanying packaging. The number is located below the barcode and begins with one of the following three elements: 01; +; or =. Record all numbers, letters, parentheses, and symbols included in the UDI Number
vi. *Serial No:* it is assigned by the manufacturer, and should be specific to each device.
vii. *Implantation date* of the device
viii. *Explantation date* of the device

8.1.1.6 Reporter Details

i. *Name of Reporter:* The reporter needs to mention his name on the form.
ii. *Professional Address:* The reporter must also mention his professional address for communication.
iii. *Speciality:* Clinician, Pharmacist, Nurse, Physiotherapist.
iv. *Telephone No:* For communication, if any information is required by the officers of PNPC.
v. *Email Address:* for communication
vi. *Date of this report:* mention the date on which she/he report the adverse reaction/ event.
vii. *Signature:* sing of the reporter
viii. *Reporting to other stakeholders:* the reporter needs to mention whether he or she has reported the same ADR/ AE to PPC and Registration holder of therapeutic good or is reporting directly to PNPC.

8.1.2 *Collection of reports*

Reports of adverse reactions/events should be submitted to the provincial or national PHPs.

Public health programmes may receive adverse event reports from patients and healthcare professionals through spontaneous reporting. Likewise, healthcare workers or pharmacovigilance officers of public health programmes should report to the provincial or national PHPs as identified by the respective PHPs. Furthermore, pharmacovigilance officers/healthcare workers should be involved in the active surveillance of PHP specific therapeutic goods and report as per the design of the study. All the collected reports are submitted to the national database i.e VigiFlow managed by the National Pharmacovigilance Centre. Reports can be collected through reporting tools available with the PHP and should be versatile in nature to ensure maximum reporting i.e

Sr #	Tools of PHP	Reporters	
i.	Yellow printed reporting form	HCPs	Reporting form made available by DRAP must be adopted with the relevant addresses of the PHP
ii.	E-reporting link	HCPs/Patients	
iii.	Dedicated phone number	HCPs/Patients	
iv.	Email	HCPs/Patients	

The suspected adverse drug reaction/event-related information collected can be:

i. Known or unknown serious/non serious spontaneous AE or ADR reports with therapeutic goods;
ii. AEFI reports with Vaccines and immunization errors;
iii. Lack of therapeutic efficacy in the case of vaccines, contraceptives, antibiotics, and medicines used in critical conditions or life-threatening; and
iv. AEs with medication errors;
v. AEs with quality problems.
vi. AE or ADR reports associated with adverse outcomes as a result of an overdose, abuse, misuse, off-label use, occupational exposure and medication error of therapeutic goods.

8.1.3 *Where, How and When to Report?*

The PHP is required to enter the collected reports in the national database maintained by the NPC, DRAP. For this purpose on the establishment of a PV system and notification of PV Officers in the PHP, VigiFlow logins are provided, which enable entry of ADRs/AEFIs collected directly in the National Database.

Timelines for reporting:

	To PHPs	By PHPS to NPC
Serious ADRs/AEFIs	As soon as possible by patients and HCPs or POs of PHPs	within 15 calendar days
Non-Serious ADRs/AEFIs	At the earliest by patients and HCPs	within 30 calendar days

8.1.4 *Assessment / Processing of collected reports*

The reports received are checked for data quality, completion and proper coding of the reaction and suspected therapeutic good. If PHP is integrated into the Pakistan VigiFlow database, the data is entered into the Pakistan VigiFlow database using terminologies.

When the data from paper forms is entered into VigiFlow, the POs select the appropriate MedDRA and WHODrug terminologies for coding.

Pharmacovigilance officers (PO) of PHP working at the treatment site who receive the reports from different sources will ensure collection of maximun information and perform initial assessment of the reports. Where required serious cases or in public health emergencies a detailed investigation is performed and POs will assist the investigation team in the matter.

An Expert Safety Review Panel (ESRP) is constituted at the Federal Level of PHP, which consists of pharmacists, physicians, disease experts and other members which it may desire. This panel performs intial or review of causality assessment of the collected reports and signal detection of programme specific drugs referred by the Focal Person PV of the PHP.

For further details on assessment refer to Chapter 6 of the National Pharmacovigilance Guidelines.

8.1.5 *Causality assessment*

It is evaluation of the likelihood that medicine or therapeutic good was the causative agent of an observed adverse reaction". In other way, it is a structured approach to determine the relationship between reported events and therapeutic good.

Nevertheless, causality assessment has become a common routine procedure in pharmacovigilance. These systems are largely based on four considerations:

i. The association in time (or place) between drug administration and event
ii. Pharmacology (including current knowledge of nature and frequency of adverse reactions).
iii. Medical or pharmacological plausibility (signs and symptoms, laboratory tests, pathological findings, mechanism).
iv. Likelihood or exclusion of other causes.

These systems mainly fall into three categories which are described in detail in National PV Guidelines.

i. Algorithms e.g. Naranjo, RUCAM;
ii. 'Global introspection' qualitative (e.g. WHO-UMC) or quantitative (e.g. French imputability system); and
iii. Probabilistic methods e.g. Bayesian.

8.1.6 *Signal Detection*

Signal is defined as reported information on a possible causal relationship between an adverse event and a therapeutic good. The information is previously unknown incomplete. Usually, more than one report are required to generate a signal and also depends upon the seriousness of the event and quality of information. When a signal is generated it requires review of safety or regulatory action.

Signal Management (chapter 7 of NPV Guidelines) is a set of activities based on analysis of ICSRs, data from active surveillance or studies or other data sources like scientific literature. This process comprises of the following steps:

i. Signal detection
ii. Signal validation
iii. Signal prioritization
iv. Signal assessment
v. Recommendation for action
vi. Communication

9. VACCINOVIGILANCE

According to the CIOMS/WHO Working Group on Vaccine Pharmacovigilance, Vaccine pharmacovigilance is defined as:

"the science and activities relating to the

- *Detection,*
- *Assessment,*
- *Understanding and*
- *Communication*

of adverse events following immunization and other vaccines- or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization" (7).

It aims for the earlier detection of adverse events to trigger accurate risk assessment and the appropriate response (risk-management) to the problem ensuring the minimization of negative effects on individuals. Another goal of vaccine pharmacovigilance is to lessen the potential negative impact on immunization programmes.

Vaccine pharmacovigilance relies on three steps:

Signal detection, Development of Causality Hypothesis and Testing of Causality Hypothesis.

9.1 Categorization of AEFIs

Reported adverse events can either be true adverse events – i.e. resulting from the vaccine or immunization process – or coincidental events that are not due to the vaccine or immunization process but are temporally associated with immunization.

Cause-specific type of AEFI	**Definition**
Vaccine product-related reaction	An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.
Vaccine quality defect-related reaction	An AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product, including its administration device as provided by the manufacturer.
Immunization error related reaction (formerly "programme error")	An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable.
Immunization anxiety-related reaction	An AEFI arising from anxiety about the immunization.
Coincidental event	An AEFI which is caused by something other than the vaccine product, immunization error or immunization anxiety, but a temporal association with immunization exists.

Based specifically on 1) cause and on 2) seriousness and frequency, vaccine reactions may be grouped into two broad categories:

1. Cause-specific vaccine reactions:
   - vaccine product-related reaction;
   - vaccine quality defect-related reaction;
2. Vaccine reactions by seriousness and frequency:
   - common or minor reactions;
   - rare or serious reactions.

9.2 AEFI Surveillance:

DRAP is mandated to ensure the safety, efficacy and quality of vaccines therefore AEFI surveillance is a key function of the NPC, DRAP. Monitoring the safety of vaccines requires involvement and interaction of the NPC and National Immunization Programme i.e EPI, Pakistan.

Role	NPC, DRAP		EPI
Monitoring safety of vaccines	✔	⟷	✔
Integrating AEFI surveillance with the system of vaccine delivery	✔	⟷	✔
Clear distribution of roles in reporting and detection	✔	⟷	✔

9.2.1 *Types of Surveillance*

9.2.1.1 Routine passive surveillance (spontaneous reporting).

This involves detection of the AEFI by anyone (immunization service providers/hospitals/patients to the first administrative level (e.g. divisional, municipality, township) in the surveillance system) and reporting them to any health care worker within the health care system.

9.2.1.2 Active Vaccine Safety Surveillance (AVSS):

Collection of data from all individuals within a defined population, thereby minimizing the risk of under-reporting. AVSS is done via sentinel sites or through cohort event monitoring. Active surveillance aims at collecting AESIs and is used for characterization of the AEFI profile, rates and risk factors, but logistical and resource constraints limit its wide application. e.g Cohort Event Monitoring

9.2.1.3 Ad Hoc Studies:

Epidemiological studies (e.g. cohort study, case-control study, case series studies) may be conducted to further expand immunization safety surveillance activities. These studies are focused on selected vaccine safety concerns (e.g. testing causality hypotheses).

9.2.2 *Affecting Factors*

Two major factors need to be specially considered due to their effect on the type and outcome of surveillance. These are organizational and functional factors.

9.2.2.1 Organizational factors include:

i. training of front line health workers on how to detect, report and respond to adverse events and communicating with the patients/their relatives, community and media.
ii. Review of special events by a group of independent experts with a wide range of specialities. The Committee should have support from and work in close communication with NPC, DRAP.

9.2.2.2 Functional factors

Affect surveillance due to challenges in systematic procedures and vaccine safety monitoring systems and may result in adverse events due to the following:

i. information on "dechallenge and rechallenge" is usually missing;
ii. vaccines are given to most of the country's birth cohort at an age when coincidental diseases are likely;
iii. several vaccines are likely to be administered at the same immunization visit;
iv. vaccine storage, handling, transport and administration must adhere to specific conditions.

Investigation of the possibility of immunization errors and causality assessment is therefore required for meaningful outcomes.

9.2.3 *Objectives and Components of AEFI Surveillance*

The objectives of AEFI Surveillance are:

i. *identify problems with vaccine lots or brands* leading to vaccine reactions caused by the inherent properties of a vaccine;
ii. *detect, correct and prevent immunization errors* caused by errors in vaccine preparation, handling, storage or administration;
iii. prevent false blame arising from *coincidental adverse events* following immunization, which may have a known or unknown cause unrelated to the immunization;
iv. *reduce the incidence of injection reactions* caused by anxiety or pain associated with immunization, by educating and reassuring vaccinees, parents/guardians and the general public about vaccine safety;
v. *maintain confidence* by properly responding to parent/community concerns, while increasing awareness (public and professional) about vaccine risks;
vi. *generate new specific hypotheses* about vaccine reactions in the country or region's local population;
vii. *estimate rates of occurrence of AEFIs* in the local population compared with trial and international data, particularly for new vaccines that are being introduced.

The components of AEFI Surveillance are:

i. Detection, recording and reporting;
ii. Investigation & causality assessment of AEFIs;
iii. risk/benefit assessment and corrective actions
iv. communication

9.2.4 *Responsibilities Tiers*

Administrative level	**Responsibilities/Activities**	**AEFI Classification status**
Peripheral level	**Health workers /immunization service provider level** • AEFI detection and recording • Triage and reporting of serious AEFIs to intermediate level • Routine reporting and line listing • Investigation • Corrective action • Public education / Communication	Preliminary classification: • Non-serious • serious

Intermediate level	**Surveillance units at sub-national level**
	• Support peripheral level
	  ○ Investigation of serious AEFI
	  ○ Clinical and laboratory assessment
	• Causality Assessment of AEFI (preliminary)
	• Report to the national expert committee
	• Data analysis and search for additional cases
	• Corrective action
	• Monitoring and supervision/training
	• Public education / Communication
		Provisional classification of serious AEFI
		For referral to national level
		• Vaccine reaction
		• Coincidental
		• unknown
		For local action
		• Immunization error related
		• Immunization anxiety related

National level	**National program (EPI / Supporting institutes including National Pharmacovigilance Centre DRAP)** • Provide expert support for field investigation	Final classification of all serious AEFI Maintain a repository of all cases; Serious and non-serious

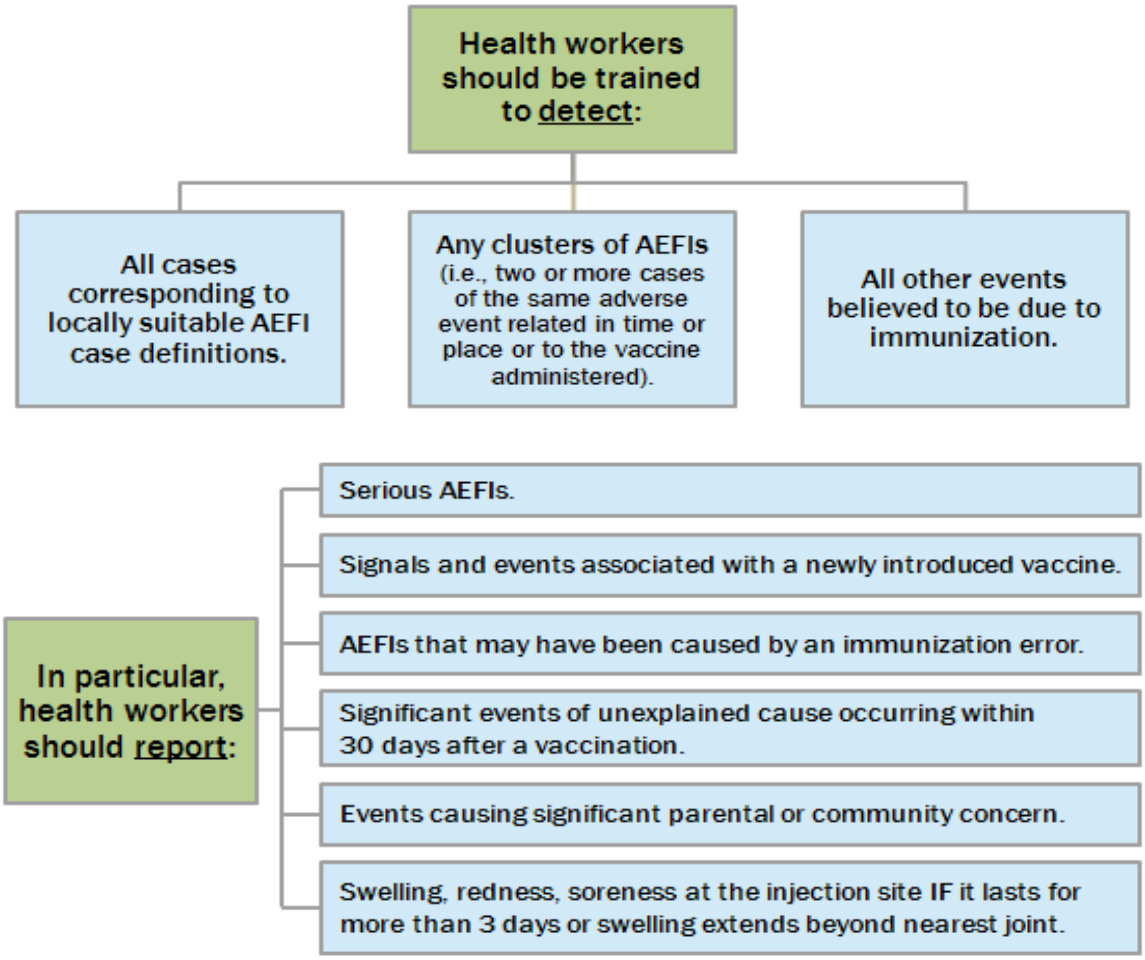
	• Monitor information collection and assess serious AEFI • Causality Assessment of AEFI (Final - National AEFI • committee) • Data analysis and search for signals • Recommend decisions for policy • Provide guidance on feedback to all levels • Conduct research studies • Guide Monitoring/supervision & training • Define contents for Public education / Communication • At the global level share/ obtain expertise and assistance	

9.3 Tools for AEFI Surveillance

Description	Purpose	Electronic tool
AEFI reporting form	To collect basic reports of all AEFI cases that have been notified	WHO recommends Vigiflow
AEFI linelist	To collate the details in the reporting form	WHO recommends Vigiflow
AEFI investigation form	To collect detailed information when serious AEFI cases are investigated	WHO AEFI investigation assistance software WHO AEFI investigation aide mémoire
AEFI causality assessment (available here)	To determine case classification of serious AEFI cases	Global Vaccine Safety online causality assessment tool

9.4 Components of AEFI Surveillance

9.4.1 *Detection and Reporting:*



Example of reportable AEFIs:

The following list can be expanded/range of events can be broadened to increase global harmonization of AEFI data. The time interval to onset will depend on the antigen and the adverse reaction.

Reportable AEFI	**Time onset following immunization**
• Acute flaccid paralysis for OPV recipient • Acute flaccid paralysis for the contact of OPV recipient	• 4-30 days following immunization • 4-75 days following immunization
Anaphylaxis (after any vaccine)	Within 48 hours of immunization
Brachial neuritis (after tetanus-containing vaccine)	2-28 days following immunization
Disseminated BCG infection after BCG vaccine	Between 1 and 12 months
Encephalopathy • after measles/MMR vaccine • after DTP vaccine	 • 6-12 days following immunization • 0-2 days following immunization

Hypotonic hyporesponsive episode (HHE) after DTP/PVV vaccine	Median time is 3-4 hours after immunization but ranges from immediate to 48 hours. However, it can occur even after 48 hours
Injection site abscess (bacterial/sterile) after any injectable vaccine	Not specific. However, commonly within the first 14 days of immunization
Intussusception (after rotavirus vaccines)	Commonly within 21 days, the risk increased after the first 7 days and usually first dose
• Lymphadenitis after BCG vaccine • Osteitis/osteomyelitis after BCG vaccine	Between 1 and 12 months
Persistent (more than 3 hours) inconsolable screaming after DTP/PVV vaccine	Common immediately and up to 48 hours of immunization. However, it can occur even after 48 hours
Sepsis (after any injectable vaccine)	Within 7 days following immunization
Seizures, including febrile seizures • after measles/MMR • after DTP/PVV	 • 6-12 days following immunization • 0-2 days following immunization
Severe local reaction (after any injectable vaccine)	Within 7 days following immunization
Thrombocytopaenia (after measles/MMR)	Median time is 12-25 days after immunization, but the range is 1-83 days
Toxic shock syndrome (TSS) (after any injectable vaccine)	Commonly within 72 hours following immunization
Death Hospitalization Disability Any other severe and unusual events that are attributed to immunization by health workers or the public	No time limit, but in general those within 30 days following any immunization

9.4.2 *Investigation*

Some AEFI reports will need further investigation. The purpose of an AEFI investigation is to:

i. confirm the diagnosis (or propose other diagnoses) and determine the outcome of the adverse event;

ii. identify specifications of implicated vaccine(s) used to immunize patient(s);

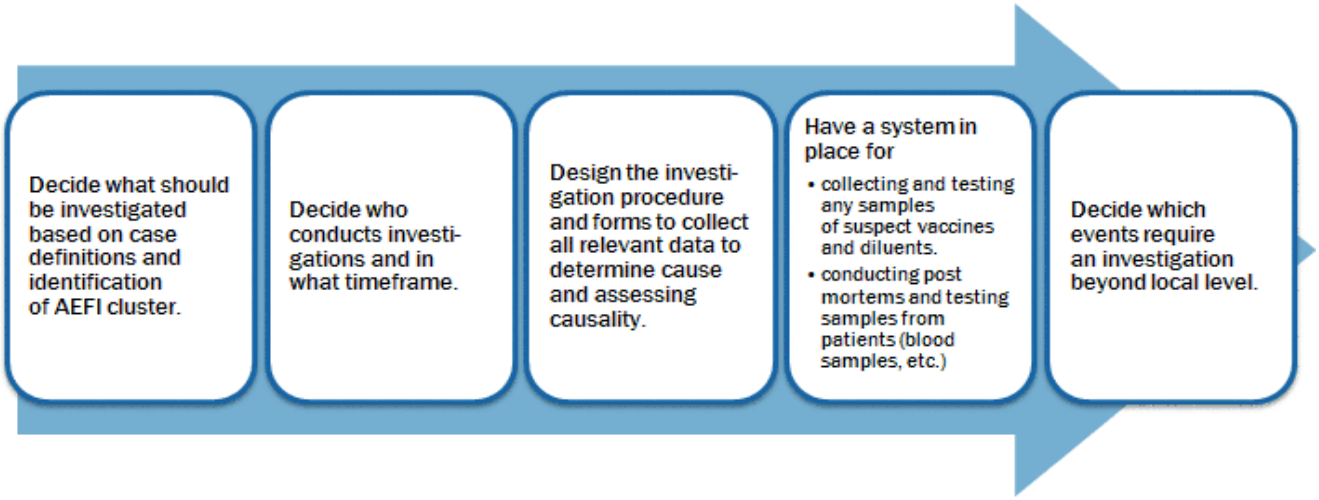
iii. examine operational aspects of the immunization programme, which may have led to immunization errors;

iv. justify the search for other AEFI cases/clustering;

Cluster investigation begins by establishing a case definition for the

AEFI and related circumstances and by identifying all cases that meet the case definition.

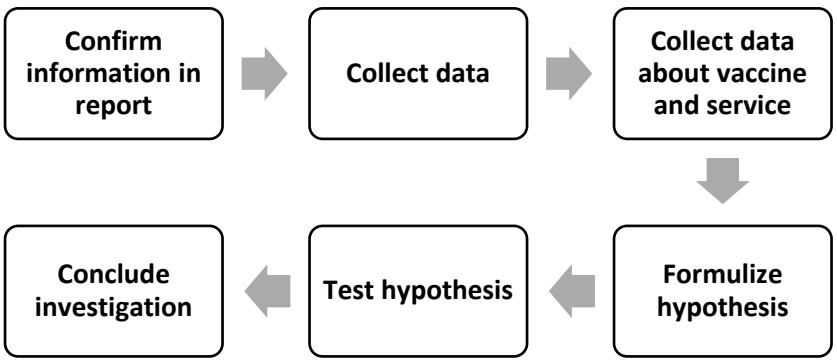
v. compare background risk of adverse events (occurring in unimmunized people) to the reported rate in the vaccinated population.



The reported AEFI must be investigated if it:

i. appears to be a serious event (as defined by WHO) of known or unknown cause;
ii. belongs to a cluster of AEFI;
iii. is a previously unrecognized event associated with an old or newly introduced vaccine;
iv. involves an increased number or rates of known cause;
v. is a suspected immunization error;
vi. appears on the list of events defined for AEFI surveillance; and
vii. causes significant parental or public concern.

Steps in Investigation:



i. Confirm the information in report

a. Obtain patients medical records
b. Check detail about patients and events from medical records
• Verify from AEFI report form, obtain missing details
c. Identify other cases to be included in the investigation

ii. Collect data

About patient and event

a. Immunization history
b. previous medical history, including prior history similar reaction or other allergies
c. family history of similar events
d. clinical description, any relevant laboratory results about the AEFI and diagnosis event
e. treatment, whether hospitalized and outcome

iii. Collect data about vaccine and service

a. Vaccine storage (including open vials), distribution, and disposal
b. Diluents storage and distribution
c. Reconstitution (process and time kept)
d. Use and sterilization of syringe and needles
e. Immunization of procedures (reconstitution, drawing vaccine, injection technique, safety of needles and syringes, disposal of opened vials)
f. Do any open vials look contaminated

iv. Formulize hypothesis

a. On the likely /possible cause(s) of the event

v. Test hypothesis

a. Does case distribution match the working hypothesis?
b. Occasionally, laboratory tests may help

vi. Conclude investigation

a. Conclude the cause
b. Complete AEFI investigation form
c. Take corrective action and recommend further action

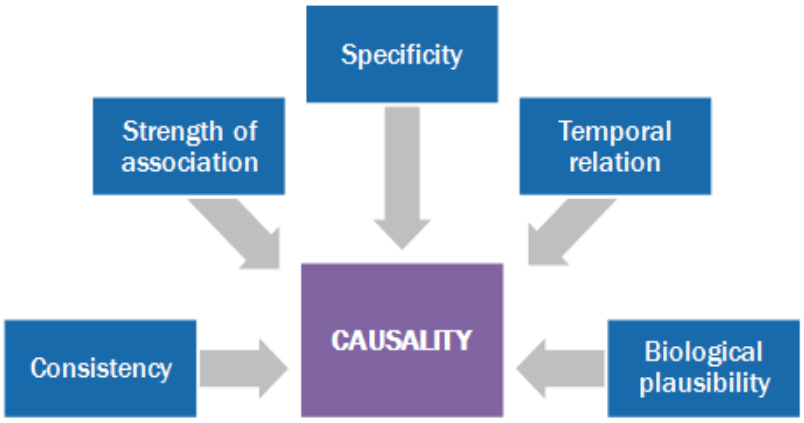
9.4.3 *Causality Assessment of AEFIs*

Causality assessment outcomes help raise awareness of vaccine-associated risks among healthcare workers. This, combined with knowledge of the benefits of immunization, forms the basis of vaccine information for parents and/or vaccines.

The quality of a causality assessment depends on the:

i. quality of AEFI case report;
ii. effectiveness of AEFI reporting system;
iii. quality of the causality review process.

Five principles underpin the causality assessment of vaccine adverse events.



The WHO checklist Aide-Memoire on causality assessment and software serve as a guide to a systematic, standardized causality assessment process for serious adverse events following immunization (including clusters).
There are four steps in causality assessment. The steps and their purpose are outlined below:

Step 1. Eligibility: To determine if the AEFI case satisfies the minimum criteria for causality assessment as outlined below.

AEFI Case: all details and investigation are complete with details available in a retrievable database.

Identify Vaccine: administered before the event

Valid Diagnosis: unintended event abnormal lab findings, symptoms of disease to be causally linked

Case definition: to ascertain the diagnosis

Create the causality question:
Has the _____vaccine/vaccination caused_____?

Step 2. Checklist: To systematically review the relevant and available information to address possible causal aspects of the AEFI.

Step 3. Algorithm: To obtain direction as to the causality with the information gathered in the checklist.

Step 4. Classification: To categorize the AEFI's association to the vaccine/vaccination based on the direction determined in the algorithm.

9.5 Monitoring/Evaluating the AEFI Surveillance System:

The EPI should prepare annual data report:

To monitor performance;

i. Rate of AEFI reporting per 100,000 population
ii. Rate of AEFI reporting per 100,000 under 5 population
iii. Rate of AEFI reporting per 1,000,000 distributed doses of vaccines
iv. Rate of AEFI reporting per 1,000,000 administered doses of vaccines
v. Percentage of serious cases versus total AEFI reports;

To monitor the quality of AEFI reporting; &

i. Completeness of reports (% of AEFI report forms with complete mandatory information)
ii. Timeliness of reports (% of serious AEFI reports received as per specified time)

To monitor the response to serious AEFI

i. Timeliness of case investigation (% of serious AEFI cases investigated within 48 hours of occurrence)

9.6 AESI Surveillance

AESIs (Adverse Events of Special Interest) should be identified, irrespective of exposure to vaccines, based on a unique pre-specified list for Pakistan. The diagnosis of each AESI case identified should match an approved case definition.

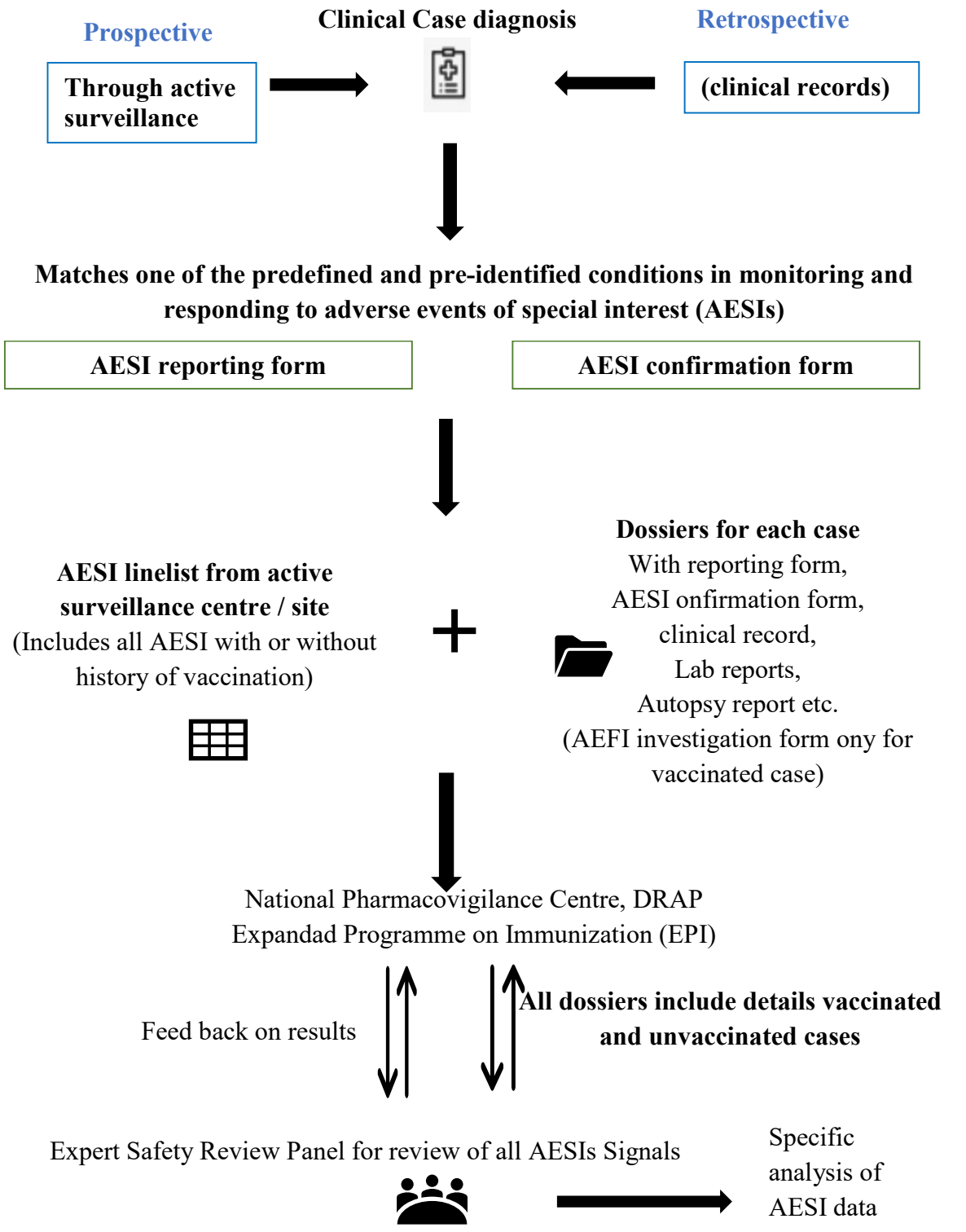
These pre-specified AESIs should be identified through an active process and then reported, investigated and analysed to:

i. Identify signals
ii. Determine the rate of an event in a defined population
iii. Determine the relative risk of the event
iv. Determine the occurrence of events in both vaccinated and unvaccinated population

Depending on the AESI surveillance methodology and the protocol (master protocols) adopted by the EPI, AESIs can be detected through:

i. *prospective surveillance*, which requires that health care workers are trained to detect AESIs, using simplified case definitions, as they occur;
ii. *retrospective surveillance*, which requires designated surveillance staff to conduct systematic searches for pre-specified AESIs, using a simplified case definition, in the target population by examining patient records at facilities; or
iii. *other electronic methods*.

The following flow chart is intended to provide a general understanding surveillance and analysis of AESIs.



9.6.1 *Tools for AESI Reporting & Surveillance*

Any AESI matching the list of pre-specified AESI conditions should undergo detailed investigation unless specified otherwise.

A variety of tools can be developed and employed in reporting and surveillance of AESIs like protocols, case definitions, AESI reporting form**,** AESI confirmation form, AESI line list, AESI investigation form, tabular checklists, automated tools for assessments.

9.7 AEFI vs AESI

	AEFI	AESI
What	Any untoward medical occurrence that follows immunization, and that does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.	A pre-specified event that has the potential to be causally associated with a vaccine product that needs to be carefully monitored and confirmed by further special studies.
Purpose of collecting information	To identify all events after vaccination determine if serious, investigate (serious) and do causality assessment.	To identify pre-specified specific events by a set criterion and determine if the event is associated with COVID-19 vaccination.
Identification method	Identified via spontaneous reporting by vaccine recipients or their parents, or health care workers or other persons who first notice the event.	Identified via an active surveillance system in sentinel sites or electronic health record by a health care worker or other staff in the system
Case definitions	Important	Critical
Training	All frontline immunization staff in health care facilities (public and private); and other relevant staff for reporting, investigation, data analysis, and causality assessment	Immunization staff and other health care workers in sentinel sites and predefined active surveillance systems, NIP/EPI mangers, NRA, research staff, national AEFI committee.
Users	Health care workers, NIP/EPI managers, NRA, surveillance and information managers, epidemiologists, surveillance and information managers, vaccine safety partners including the community	Sentinel site staff, NIP/EPI managers, NRA, epidemiologists, national AEFI committees, study teams.

9.8 Case Definitions

A standardized case definition is:

A globally harmonized set of criteria for ***the identification*** *and* ***assessment*** *of a given AESI,* ***including guidelines for data collection, analysis, and presentation***

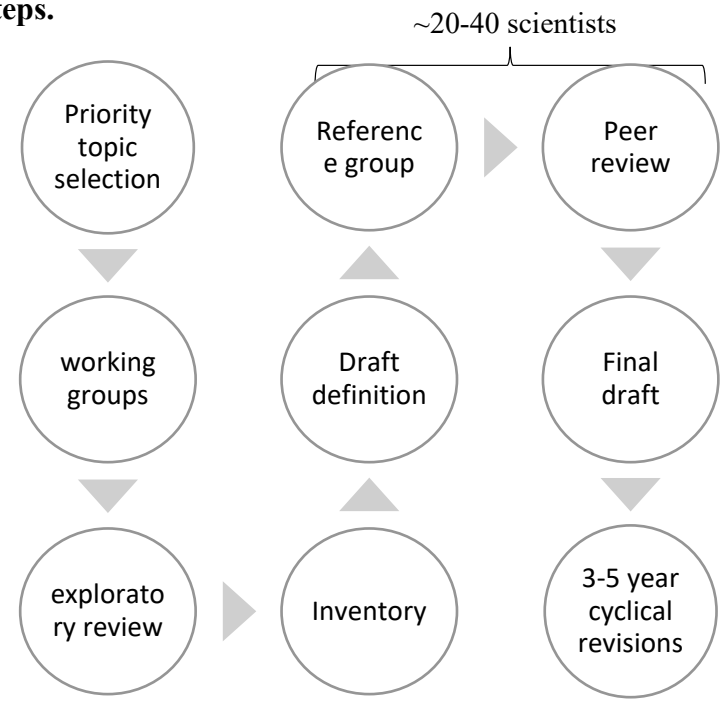
These are of critical importance in AESI Surveillance therefore it is essential to avoid variations in case definitions across studies/surveillance systems which lead to inconsistent findings (e.g., 120 vaccine safety studies using 9 different fever cut-off temperatures).

Appropriate definition like Brighton Collaboration definition, standard literature definition, national definition or other approved definition are used to assess diagnostic certainty of any adverse event. Case definitions can also be set out during the investigation of an event. Standardization enables comparability of vaccine safety data from different study designs**,** including clinical trials and observational studies.

As recommended by the WHO Global Advisory Committee on Vaccine Safety (GACVS), review of new vaccines is required be based on the appropriate Brighton Collaboration standardized templates for benefit-risk assessment.

For comparison of safety data collected in trials and surveillance systems, standard case definitions for assessing AEFIs & AESIs are provided by Brighton's Collaboration

The Brighton Collaboration is an independent body with >500 experts from >50 countries, currently funded by Coalition for Epidemic Preparedness Innovations (CEPI), with many partners incl. WHO, EMA and FDA. It aims to provide standardized, validated and objective methods for monitoring safety profiles and benefit/risk ratios of vaccines. The workflow to develop BC case definitions includes **8 steps.**



These case definitions are structured, 3-component documents i.e preamble (explains decisions made on case definition, body of the case definition and guidelines (data collection, analysis and presentation).
These are not based on the classic "definite, probable and possible" assessment categories and are not used as filters. The events with the lowest certainty are also required to be analysed.
A complete list of case definitions can be found on the following web page:
https://brightoncollaboration.us/category/pubs-tools/case-definitions/

Examples of AEFI case definitions and treatments

Adverse Event	Case definition	Treatment
Anaphylactic reaction (Acute hypersensitivity reaction)	Exaggerated acute allergic reaction, occurring within 2 hours after immunization, characterized by one or more of the following: • Wheezing or shortness of breath due to bronchospasm • Laryngospasm/ laryngeal oedema • One or more skin manifestations e.g. hives, facial oedema or generalized oedema **Less severe allergic reactions do not need to be reported**	Self-limiting: anti-histamines may be helpful
Anaphylaxis	Severe immediate (within 1 hour) allergic reaction leading to circulatory failure with or without bronchospasm and/or laryngospasm/laryngeal oedema	Adrenaline injection
Encephalopathy	Acute onset of major illness characterised by any two of the following three conditions: • Seizures • Severe alteration in level of consciousness lasting for one day or more • Distinct change in behaviour lasting one day or more	No specific treatment available; supportive care

	Needs to occur within 48 hours of DTP vaccine or from 7 to 12 days after measles or MMR vaccine, to be related to immunization	
Fever	The fever can be classified (based on rectal temperature) as mild (38 to 38.9 ºC), high (39 to 40.4 ºC) and extreme (40.5 ºC or higher). Fever on its own does not need to be reported	Symptomatic; paracetamol
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 not.	Incise and drain; antibiotics if bacterial
Seizures	Occurrence of generalized convulsions that are not accompanied by focal neurological signs or symptoms. **Febrile seizures:** if temperature elevated >38 ºC (rectal) **Afebrile Seizures:** if temperature normal	Self limting; supportive care; paracetamol and cooling if febrile; rarely anticonvulsants.
Sepsis	Acute onset of severe generalized illness due to bacterial infection and confirmed (if possible) by positive blood culture. Needs to be reported as a possible indicator of programme error	Critical to recognize and treat early. Urgent transfer to hospital for parenteral antibiotics and fluids.
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 duration Requires hospitalization	Settles spontaneously within a few days to a week. Symptomatic treatment with analgesics. Antibiotics are inappropriate.

	Local reactions of lesser intensity occur commonly and are trivial and do not need to be reported	
Thrombocytopenia	Serum platelet count of less than 50,000/ml leading to bruising and/or bleeding	Usually mild and self-limiting; occasionally may need steroids or platelet transfusion.
Toxic shock syndrome (TSS)	Abrupt onset of fever, vomiting and watery diarrhoea within a few hours of immunization. Often leading to death within 24 to 48 hours. Needs to be reported as a possible indicator of programme error.	Critical to recognize and treat early. Urgent transfer to hospital for parenteral antibiotics and fluids.

10. RISK COMMUNICATION

Risk communication is an important part of pharmacovigilance. When a therapeutic goods safety investigation is underway as a result of a report of an ADR/AEFI, communications involve keeping the public informed about the investigation, results, and actions already taken or to be taken regarding the ADR/AEFI. At the same time, it is crucial to highlight the benefits of the treatment/immunization even while communicating about an investigation. PHPs are required to establish storng communication channels and effective communication strategies considering the following points:

i. Communication with parents, community, staff, other stakeholders and the media is necessary and important.
ii. During communication make sure to build confidence in the programme. Be aware of the risks and benefits of the treatment/immunization and the progress and findings of the investigation. Any overconfidence about risk estimates that are later shown to be incorrect contributes to a breakdown of trust among the people involved.
iii. Communication needs assurance from someone in authority with knowledge and expertise in the subject.
iv. Uncertainty about AEFI should be acknowledged, there should be a full investigation, and the community should be kept informed. Premature statements about the cause of the event before the investigation is complete should be avoided.
v. If the cause is identified as immunization-related error, it is vital not to lay personal blame on anyone, but to focus on system-related problems that resulted in the error(s) and the steps being taken to correct them.

vi. It is recommended to prepare a communication plan in advance, as this will minimize the negative impact of AEFI-related matters.

There are principles of communication that apply to most if not all audiences. These include the need to:

i. listen empathetically to concerns;
ii. reassure and support but do not make false promises;
iii. communicate frequently;
iv. build-up and maintain the relationship among the stakeholders;
v. inform audiences about possible common adverse events and how to handle them;
vi. prepare fact sheets on adverse events and other key information for all audiences;

Communication with staff by public health authorities and investigators should be sensitive to their needs. Therefore:

i. Communication should include all levels of health authorities involved.
ii. Reassure the staff of their knowledge, ability, skills and performance.
iii. Do not blame health worker(s) but focus on the correction and quality of the national immunization programme.
iv. Keep health workers updated on the investigation process, progress, and findings.

Communication may be done in two stages:

i. sharing preliminary information at the initial stage and sharing
ii. the final data/report after completion of the investigation/causality assessment.

10.1 Crisis Management

Aside from risk communication it is vital to be prepared for any future emergency situations. A crisis is a situation in which a real or potential loss of confidence in the therapeutic good or the public health programme is triggered by information about an ADR/AEFI. Crises can often be avoided through foresight, care and training. If managed properly, the investigation and management of a therapeutic good safety situation will boost public confidence and acceptance and ultimately strengthen the immunization programme.

Anticipate. Do not wait until a crisis occurs. Prepare for the unavoidable. Develop a good relationship with the media. Good public awareness and understanding of the public health programme is necessary.

i. Train staff at all levels to respond adequately. Develop confidence in responding to the public and the media (particularly the local media) properly and correctly.
ii. Confirm all facts and prepare (see steps for a press conference or press release) before making any public comments.
iii. Prepare a plan to react to a crisis when it occurs. This has to be done in advance, identifying responsible persons to handle the crisis and preparing all supporting documents and information.

11. REFERENCES

1. Pakistan National Pharmacovigilance Guidelines.
2. The Importance of Pharmacovigilance Safety Monitoring of Medicinal Product
3. The WHO-UMC standardized method for causality assessment.
4. Brighton Collaboration Case Definitions
5. Vaccine Safety Basics
6. The safety of medicines in public health programmes by WHO (2006)
7. Definition and Application of Terms for Vaccine Pharmacovigilance (2012).
8. Global Manual on Surveillance of Adverse Events Following Immunization (2014)

ANNEXURE I

WHO Aide Memoire on AEFI Investigation

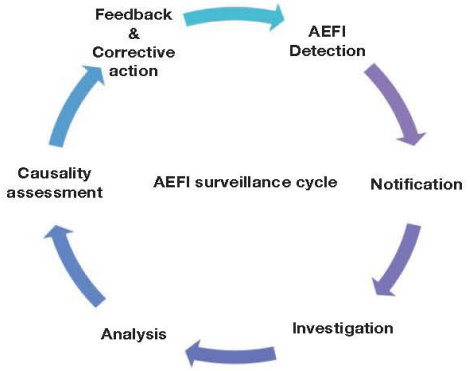
World Health Organization

ADVERSE EVENT FOLLOWING IMMUNIZATION

AIDE-MÉMOIRE ON AEFI INVESTIGATION

Purpose: This aide-mémoire proposes a systematic, standardized process to investigate reported serious adverse events following immunization (AEFI) and ascertain the underlying cause of the AEFI by:

- confirming a diagnosis and timing
- identifying details of vaccine(s) administered
- documenting the outcome of the reported adverse event
- determining whether the reported event is solitary or part of a cluster
- reviewing the operational aspects of the programme



DETECTION AND REPORTING

Vaccine recipients themselves and/or parents of vaccine recipients who identify AEFI should notify the same to the health care provider. All notified AEFI cases should be documented and reported in a simple standard reporting form by the health care provider.

WHICH OF THE REPORTED AEFI SHOULD BE INVESTIGATED IN MORE DETAIL?

A detailed AEFI investigation to assess causality is necessary if:

- it is serious[i]
- it is part of a cluster[ii]
- it is part of a suspected signal[iii]
- it is a suspected immunization error[iv]
- it appears on the list of events defined for AEFI investigation or
- it causes significant parental or public concern

WHO SHOULD INVESTIGATE AEFI?

Detailed AEFI field investigation can be done based on the program's operational structure and the expertise available. A basic preliminary investigation by local programme managers may be sufficient if the cause of the reported AEFI is very clear; otherwise, investigation should be done by next/higher administrative level, by a trained/skilled person/ team, depending on the nature of event, its seriousness and impact to the programme.

WHEN TO INVESTIGATE AEFI?

If a detailed investigation is warranted, it should be initiated as soon as possible, ideally within 24 to 48 hours of the case being first reported.

CHECKLIST FOR AEFI INVESTIGATION

1. PRELIMINARY STEPS

- ☐ Develop national guidelines with case definitions for reportable AEFIs, reporting forms, investigation procedures, roles and responsibilities
- ☐ Develop resource documents and training material on reporting, management and investigation of AEFIs
- ☐ Designate and train staff to conduct an AEFI investigation using the investigation form and guidelines
- ☐ Train staff on how to collect and store specimens
- ☐ Have a functioning National AEFI Review Committee with suitable representation
- ☐ Establish procedure, criteria and designate focal persons for notifying and communicating with WHO and UNICEF (if UN- supplied vaccine) or other relevant party depending on procurement mechanism
- ☐ Identify a spokesperson for public communications

2. RECEIVING A REPORT

- ☐ Provide rapid attention to all reports received and immediate response to serious events
- ☐ Verify the information in the report, confirm the diagnosis, classify and assess the AEFI using established case definitions. Decide whether it needs further detailed investigation.
- ☐ If investigation is warranted, travel to the location of the AEFI, or delegate responsibility to another trained person

3. INVESTIGATE AND COLLECT DATA

- ☐ Obtain information from patient or relatives directly/ use available records
- ☐ Obtain information from immunization service providers and medical care service providers (hospital staff)/ use available records
- ☐ Ask about the vaccine(s) administered and other drugs potentially received
- ☐ Establish a more specific case definition if needed
- ☐ Ask about other vaccinees who may have received the same or other vaccines
- ☐ Observe the service in action
- ☐ Ask about cases in unvaccinated persons
- ☐ Formulate a hypothesis as to what may have caused the AEFI (see table below)
- ☐ Collect specimens (if indicated by investigation, but not as a routine):
  - ✓ from the patient
  - ✓ the vaccine and diluent if applicable
  - ✓ the syringes and needles

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- ☐ Dispatch specimens to appropriate testing facility (laboratory, regulatory authority, etc.)

4. ANALYSE THE DATA

- ☐ Review epidemiological, clinical, and laboratory findings
- ☐ Share findings with national AEFI committee for expert advice
- ☐ Summarize and report findings

5. TAKE ACTION

The local response after an AEFI investigation should be based on findings (data/information) and local practices.. The highest priority is to treat patient. Suspending vaccination at the locality of the event temporarily pending investigation outcome may be necessary but is uncommon. Broader suspension of vaccination is only very rarely necessary. When taking action, it is important to

- ☐ Provide feedback to health staff
- ☐ Communicate findings and action to the parents and public – during all stages of the investigation
- ☐ Correct problem (based on the cause) by improving training, supervision and/or distribution of vaccines/injection equipment
- ☐ Replace vaccines if indicated

INVESTIGATING DEATHS AFTER IMMUNIZATION

After informing higher authorities, field investigation should be conducted by a team of clinical, laboratory and forensic experts supported by programme managers. A decision on autopsy should be taken within the local sociocultural, religious, political context. Autopsies should be done with adequate information of the circumstances of the event using standard autopsy protocols. Appropriate specimens should be collected for testing.

If an autopsy is not possible, a verbal autopsy can be carried out using established guidelines and protocols.

OUTCOME OF AEFI INVESTIGATION

On concluding the investigation, the documents and evidence collected should be compiled, a report prepared and submitted to a group of experts to determine/evaluate causality.

POSSIBLE CAUSES OF AEFI
Related to vaccine or vaccination
Vaccine product-related
Vaccine quality defect-related
Immunization error-related
Immunization anxiety-related
Coincidental adverse event

KEY RESOURCES FOR AEFI INVESTIGATION

- WHO standard AEFI reporting form http://www.who.int/vaccine_safety/REPORTING_FORM_FOR_ADVERSE_EVENTS_FOLLOWING_IMMUNIZATION.pdf?ua=1
- WHO standard AEFI investigation form http://www.who.int/vaccine_safety/initiative/investigation/AEFI_Investigation_form_2Dec14.pdf?ua=1
- Global manual on surveillance of AEFI http://www.who.int/vaccine_safety/publications/aefi_surveillance/en/
- User manual for the revised WHO AEFI causality assessment classification http://www.who.int/vaccine_safety/publications/gvs_aefi/en/
- Brighton Collaboration standard case definitions https://brightoncollaboration.org/public.html
- Verbal autopsy standards: ascertaining and attributing causes of death http://www.who.int/healthinfo/statistics/verbalautopsystandards/en/index1.html

[i] An AEFI is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.

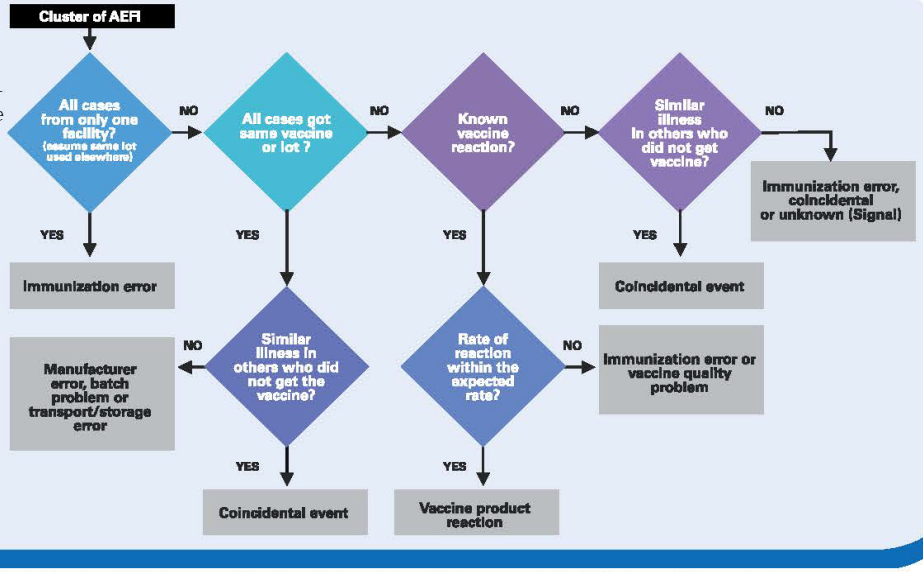
[ii] Serious AEFI include death, hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, congenital anomaly/birth defect or is life-threatening

[iii] A cluster of AEFIs is two or more cases of the same adverse event related in time, place or vaccine administered

[iv] Information (from one or multiple sources) which suggests a new and potentially causal association, or a new aspect of a known association, between an intervention and an adverse event or set of related adverse events, that is judged to be of sufficient likelihood to justify verificatory action.

INVESTIGATING AEFI CLUSTERS

Suggested steps for identifying the most likely cause of a cluster of AEFI



ANNEXURE II

WHO Aide Memoire on Causality Assessment

World Health Organization

ADVERSE EVENT FOLLOWING IMMUNIZATION

AIDE-MÉMOIRE ON CAUSALITY ASSESSMENT

Purpose: This aide-mémoire serves as a guide to a systematic, standardized process of assessing whether serious adverse events following immunization (AEFI[1]) are causally linked to vaccines/immunization or not.

Definition: AEFI causality assessment determines if a causal relationship exists between a vaccine (and/or vaccination) and an adverse event.

Rationale: Safety requirements for vaccines are stricter than those for drugs since vaccines are biological products that are more prone to lot variation and instability, they are used in healthy populations and the target groups are vulnerable. Vaccines therefore require a causality assessment process that responds in a timely manner and with scientific rigour to AEFI.

WHO SHOULD ASSESS AEFI CAUSALITY?

Ideally an AEFI review committee should be in place backed by written terms of reference. It should consist of independent experts who have no conflicts of interest. As far as possible, the experts should cover a broad range of expertise: infectious diseases, epidemiology, microbiology, pathology, immunology, neurology, forensics and vaccine programming. The committee should be supported by a secretariat (usually the national regulatory authority [NRA] and the immunization programme) that can provide supporting evidence and investigation findings to enable causality to be determined.

WHAT ARE PREREQUISITES FOR AEFI CAUSALITY ASSESSMENT?

- AEFI case investigation should be completed. Premature assessments may mislead classification.
- All relevant information should be available, including documents of investigation, laboratory and postmortem findings (if applicable).
- Valid diagnosis (unfavourable or unintended sign, abnormal laboratory finding, symptom or disease) for the AEFI must be defined, be well-founded and correspond accurately to the event being assessed.
- Information that could bias results (patient name, hospital name, etc.) should be anonymized.

POSSIBLE CAUSES OF AEFI
Related to vaccine or vaccination **Vaccine product-related** **Vaccine quality defect-related** **Immunization error-related** **Immunization anxiety-related**
Coincidental adverse event

AT WHAT LEVELS IS AEFI CAUSALITY ASSESSED?

AEFI causality assessment could be performed:

- **At population level** (is there a causal association between usage of a vaccine and a particular AEFI in the population?)
- **For an individual** (is the adverse event in the individual patient causally linked to the vaccine/vaccination?)

CONSIDERATIONS FOR ASSESSING CAUSALITY OF A SOLITARY AEFI:

- **Temporal relationship:** is it certain that the vaccination preceded the adverse event?
- **Alternate explanations:** is the event coincidental, i.e. is it due to something other than the vaccine product, immunization error or immunization anxiety?
- **Proof of association:** is there clinical or laboratory proof that the vaccine caused the event?
- **Prior evidence:** has a similar AEFI been previously reported in studies/literature or other sources?
- **Population-based evidence:** does the rate of event occurrence exceed the expected rate of the event in the population? (Refer to WHO information sheets on observed rates of known vaccine reactions.)
- **Biological plausibility:** can the association be explained by the natural history, biological mechanisms of the disease, laboratory evidence or animal studies? However this is not an important consideration.

WHICH AEFI TO SELECT FOR CAUSALITY ASSESSMENT?

All reported AEFI require verification of diagnosis, coding, review, information collation and storage. Causality assessment needs to be done for:

- **Serious AEFI** (i.e. events that are life-threatening or lead to death, hospitalization, significant disability or congenital anomaly)
- **Clusters of AEFI** (the cause for each case in the cluster should be determined separately). Line-listing of data may identify patterns that could constitute a signal
- Occurrence of **events above the expected rate** or of **unusual severity**

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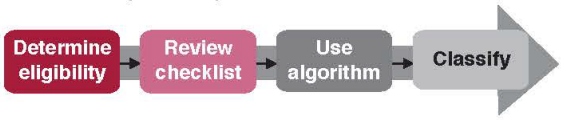
- **Signals** resulting from single or cluster cases
- Other AEFI as decided by the review committee or an investigation team such as **immunization errors**, significant **events of unexplained cause** occurring within 30 days after a vaccination (not listed in the product label), or events causing **significant parental or community concern.**

WHAT ARE THE STEPS[2] OF A CAUSALITY ASSESSMENT?

- Determine the eligibility of the case
- Review the checklist to ensure that all possible causes are considered
- Use algorithm to determine trend of causality
- Classify causality.



HOW ARE CASES CLASSIFIED AT THE END OF THE ASSESSEMENT?

I. Case with adequate information

A. Consistent with causal association to immunization

A1. Vaccine product-related

A2. Vaccine quality defect-related

A3. Immunization error-related

A4. Immunization anxiety-related

B. Indeterminate

B1 Consistent temporal relationship but insufficient definitive evidence for vaccine causing the event

B2. Reviewing factors result in conflicting trends of consistency and inconsistency with causal association to immunization

C. Inconsistent with causal association to immunization (coincidental)

Underlying or emerging condition(s) or condition(s) caused by exposure to something other than vaccine

II. Case without adequate information

It is categorized as "unclassifiable" since it requires additional information to determine causality (the available information on such cases should be archived in a repository or an electronic database and classified when additional information becomes available)

WHAT ARE THE ACTIONS AFTER CAUSALITY ASSESSMENT?

They include providing feedback, training, modifying systems, refining tools, research, etc. to avoid and/or minimize recurrences. Based on outcomes of assessment, the following need to be considered:

A. Consistent with causal association to immunization

A1 Vaccine product-related reaction: Follow protocols adopted by each country.

A Vaccine quality defect-related reaction: Inform the NRA, manufacturer and relevant stakeholders. Take decision on existing vaccine stock.

A3 Immunization error-related reaction: Training and capacity-building are critical to avoid recurrences.

A4 Immunization anxiety-related reaction: Vaccinating in an ambient and safe environment.

B. Indeterminate

B1 The temporal relationship is consistent but there is insufficient evidence for vaccine causing the event: A national database of such AEFI cases could help to identify signals.

B2 Reviewing factors result in conflicting trends of consistency and inconsistency with causal association to immunization: If additional information becomes available, the classification can move into more definitive categories; if not, they are to be archived.

C. Inconsistent with causal association to immunization (coincidental)

Confirm diagnosis; information on why the case is classified as coincidental to be provided to the patients, relatives, care provider and community.

KEY RESOURCES FOR CAUSALITY ASSESSMENT

Causality assessment of an AEFI - User manual for the revised WHO classification
http://www.who.int/vaccine_safety/publications/gvs_aefi/en/

WHO vaccine reaction rates information sheets
http://www.who.int/vaccine_safety/initiative/tools/vaccinfosheets/en/

Brighton Collaboration
https://brightoncollaboration.org/public.html

[1] AEFI definition: any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease. http://whqlibdoc.who.int/publications/2012/9789290360834_eng.pdf

[2] For detailed description of the steps, please refer to the Causality assessment of an AEFI - User manual for the revised WHO classification shown in key resources

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ADVERSE EVENT FOLLOWING IMMUNIZATION

STEP 1 (ELIGIBILITY)

Name of the patient	Name of one or more vaccines administered before this event	What is the Valid Diagnosis? (The case diagnosis of the AEFI)	Does the diagnosis meet a case definition?

Create your question on causality here

Has the _____ vaccine/vaccination caused _____ ?(The event for review in step 2)

STEP 2 (EVENT CHECKLIST) [✔ check all boxes that apply]

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

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

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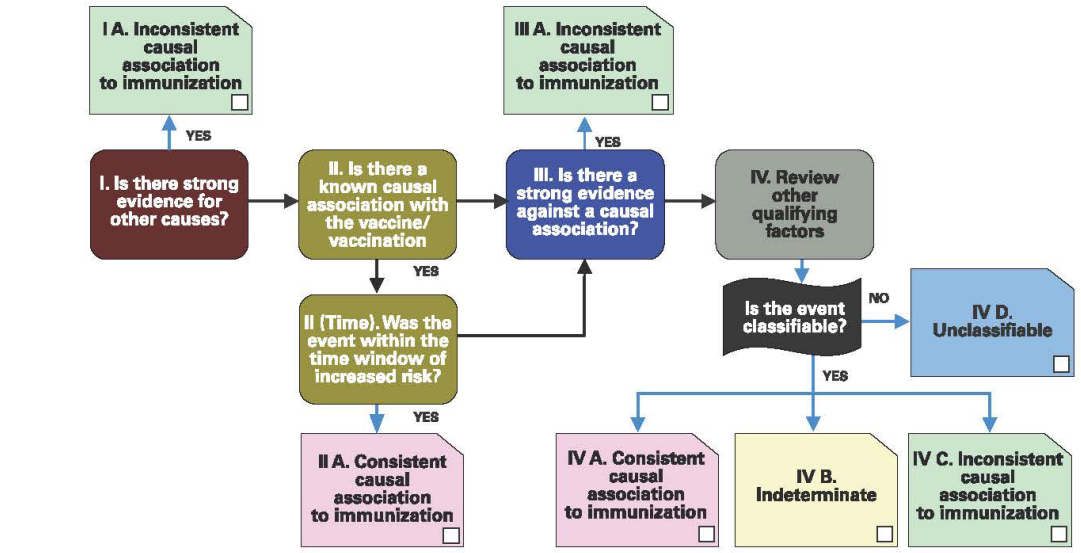
ADVERSE EVENT FOLLOWING IMMUNIZATION

STEP 3: (ALGORITHM) REVIEW ALL STEPS AND ✓ ALL THE APPROPRIATE BOXES



Notes for Step 3:

STEP 4: (CLASSIFICATION) ✓ ALL BOXES THAT APPLY

	A. Consistent causal association to immunization	B. Indeterminate	C. Inconsistent causal association to immunization
Adequate information available	☐ A1. Vaccine product-related reaction (As per published literature) ☐ A2. Vaccine quality defect-related reaction ☐ A3. Imminization error-related reaction ☐ A4. Immunization anxiety-related reaction	☐ *B1. Temporary relationship is consistent but there is insufficient definitive evidence for vaccine causing event (may be new vaccine-linked event) ☐ B2. Qualifying factors result in conflicting trends of consistency and inconstistency with causal association to immunization	☐ C. Coincidental Underlying or emerging condition(s), or condition(s) caused by exposure to something other than vaccine
Adequate information not available	Unclassifiable ☐ Specify the additional information required for classification		

*B1: Potential signal and maybe considered for investigation

Summarize the classification logic

With available evidence, we could conclude that the classification is _____ because:

FEEDBACK AND CORRECTIVE ACTION RECOMMENDED:

DRUG REGULATORY AUTHORITY OF PAKISTAN

Telecom Foundation Complex, G-9/4, Islamabad, Pakistan

Email: npc@dra.gov.pk Phone:92-51-9107413 / 9107299

www.dra.gov.pk