Pharmacovigilance of Vaccines

- ✓ THE QUIZ
- ✓ INTRODUCTION: WHAT? WHY? WHO?
- ✓ REGULATION
- ✓ FUNDEMENTALS OF EFFECTIVE PHARMACOVIGILANCE
- ✓ SIGNAL IDENTIFICATION AND ASSESSMENT
- ✓ PERIODIC SAFETY UPDATE REPORTS
- ✓ RISK MANAGEMENT PLAN
- ✓ THE QUIZ REVISTED
- ✓ GAP ANALYSIS WORKSHOP

What? Why? Who?

- Definition
- Why do we need it ?
- What is a Pharmacovigilance system ?
- Roles and responsibilities

What is Pharmacovigilance?

- "A medical discipline crucial in preventing medicine related adverse effects in humans promoting patient safety and the rational use of medicines"
- "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine- related problem"

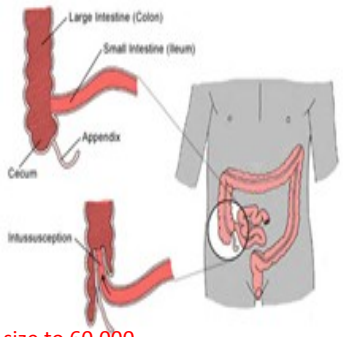
Ref: WHO Pharmaceutical indicators

WHY DO WE NEED PHARMACOVIGILANCE

- Rare AEFI may only be picked up after large cohorts are immunised.
- Clinical trial data for registration are limited
- Sub-groups are sometimes excluded from trials.
- Clinical efficacy needs to be continually monitored.
- Errors in manufacture can occur.
- Errors in administration can occur.
- False assumptions can have a profound impact on vaccination programs.
- Legal requirement in most countries.

Clinical trial data is limited

- Rotavirus vaccine and intussusception associated with receipt of Rotashield vaccine is estimated to be low (<1 in 10 000 vaccine recipients (Murphy et al., 2001;Murphy et al., 2003).



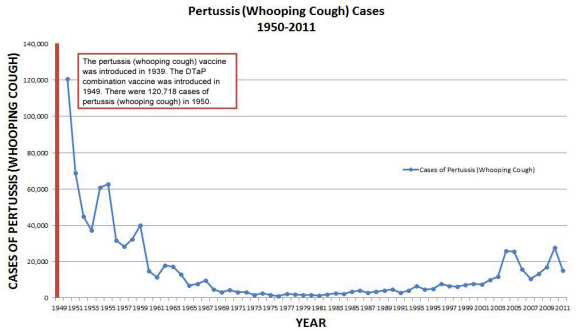
Resulted in WHO increasing trial size to 60,000

SUB-GROUPS ARE SOMETIMES EXCLUDED FROM TRIALS

- The 2010 trivalent influenza vaccine (TIV) manufactured by CSL Biotherapies (CSL) was associated with increased febrile reactions, including febrile convulsions, among Australian children.

- 57% OF 209 6 months- 5 years 2010 season
- 17% OF 109 6 months- 5 years 2009 season

CLINICAL EFFICACY NEEDS TO BE CONTINUALLY MONITORED



VAERS : Vaccine Error Codes N=11

Accidental
- Accidental exposure
- Accidental exposure to product
- Accidental needle stick

Administration errors
- Drug administered at inappropriate site
- Drug administration error
- Incorrect drug dosage form administered
- Incorrect drug administration duration
- Incorrect route of drug administration
- Multiple use of a single-use product
- Wrong technique in drug usage process

Contraindication
- Contraindication to vaccination
- Documented hypersensitivity to administered drug
- Labeled drug-drug interaction medication error

Equipment
- Injury associated with device
- Medical device complication
- Needle issue
- Syringe issue

General
- Medication error
- Vaccination error

Inappropriate schedule
- Inappropriate schedule of drug administration
- Drug administered to patient of inappropriate age

Incorrect dose
- Accidental overdose
- Drug dose omission
- Extra dose
- Incorrect dose administered
- Underdose
- Overdose
- Multiple drug overdose

Product quality
- Product contamination,
- Product contamination microbial
- Product contamination physical
- Product quality issue

Product labeling/packaging
- Drug name confusion
- Product label confusion
- Product name confusion
- Product container issue
- Product label issue
- Product label on wrong product
- Product outer packaging issue
- Product packaging issue
- Product packaging confusion

Storage and dispensing
- Drug dispensing error
- Expired drug administered
- Incorrect product storage
- Incorrect storage of drug
- Poor quality drug administered
- Product reconstitution issue

Wrong drug
- Drug dispensed to wrong patient
- Wrong drug administered

False assumptions can have a profound impact on vaccination programs

What is a Pharmacovigilance System

- Effective collection of safety information.
- System for storage of data.
- A process for analysing data.
- A strategy or process for conducting investigations.
- A process for assessing risk verses benefit of a vaccine.
- A process for defining knowledge gaps and how these gaps are to be addressed.

A pharmacovigilance system must therefore have the ability to….

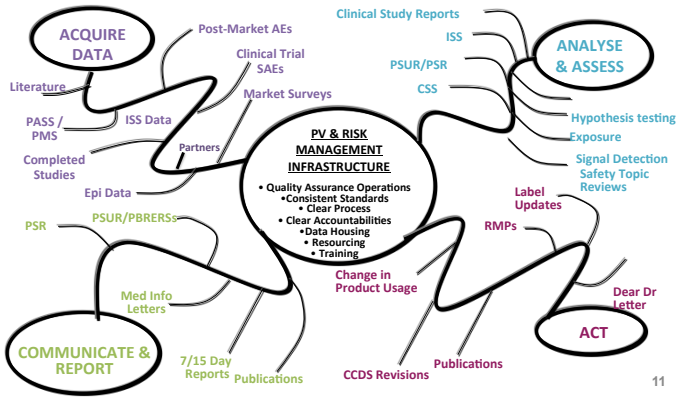
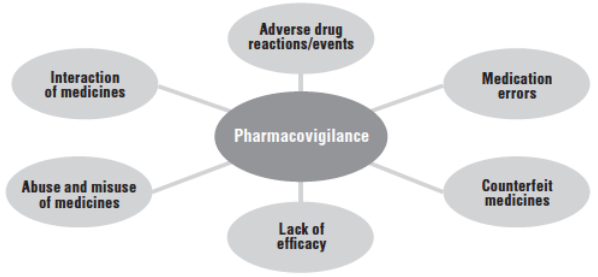


Figure 1. Scope of pharmacovigilance



Ref WHO Pharmacovigilance Indicators

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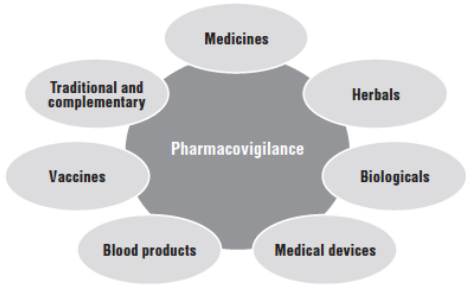
Figure 2. Products covered by pharmacovigilance



2 WHO PHARMACOVIGILANCE INDICATORS

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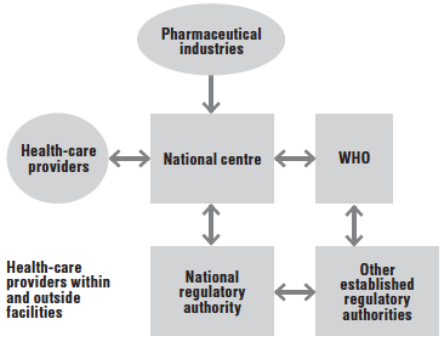
Figure 3. Diagrammatic representation of the pharmacovigilance system



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The minimum functions of a national Pharmacovigilance (PV) system

1. To promote PV in the country, notably, to collect and manage adverse drug reaction (ADR) reports, reports of medication errors and suspected counterfeit/substandard drugs
2. To collaborate and harmonize with existing ADR collection activities within the country (National disease control programmes, Ministry of Health etc.) as well as international cohorts monitoring ADRs in defined patients or populations
3. To identify signals of medicine safety i.e. unknown or poorly characterized adverse events in relation to a medicine or a combination of medicines and/or its use
4. To undertake assessment of risk and options for risk management

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The minimum functions …continued

5. To identify if there are quality problems in medicines resulting in ADRs; and more generally, support the identification of medicine quality issues
6. To provide effective communication on aspects related to medicine safety, including dispelling unfounded rumors of toxicity attributed to medicines and/or vaccines
7. To apply resulting information from pharmacovigilance for the benefit of public health programmes, individual patients and national medicines policies
8. To develop and maintain drug utilization information
9. To identify issues associated with unregulated prescribing and dispensing of medicines

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The minimum requirements of a national PV system

1. A ***national pharmacovigilance centre*** with designated staff (at least one full time), stable basic funding, clear mandates, well defined structures and roles and collaborating with the WHO Programme for International Drug Monitoring

2. The existence of a ***national spontaneous reporting system*** with a national individual case safety report (ICSR) form i.e. ADR reporting form

The Minimum Requirements …continued

3. A ***national database*** or system for collating and managing ADR reports

4. A national ADR or pharmacovigilance ***advisory committee*** able to provide technical assistance on causality assessment, risk assessment, risk management case investigation and where necessary crisis management including crisis communication

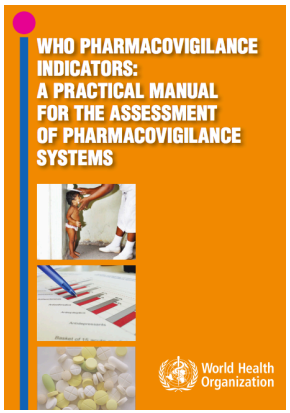
5. Clear ***communication strategy*** for routine communication and crises communication

The 'follow-on' after the "minimum requirements"

- The 'advanced' requirements of a PV system relate to broad higher levels of PV practice (*full details in meeting report available from WHO/GF*)
  - **Policy and Governance** including existence of national laws and policies related to pharmacovigilance – in particular legal requirements on companies holding marketing authorizations to report ADRs, provide data on drug utilization, and produce risk management plans; and to empower the national authority to suspend, revoke or vary marketing authorizations
  - **Methodologies** highlighting what PV methods may be appropriate in specific situations
  - **Information management** including data management, crisis management, communication and public perception surveillance
  - **Monitoring and Evaluation** including availability of a set of PV indicators

WHO Pharmacovigilance indicators: Purpose

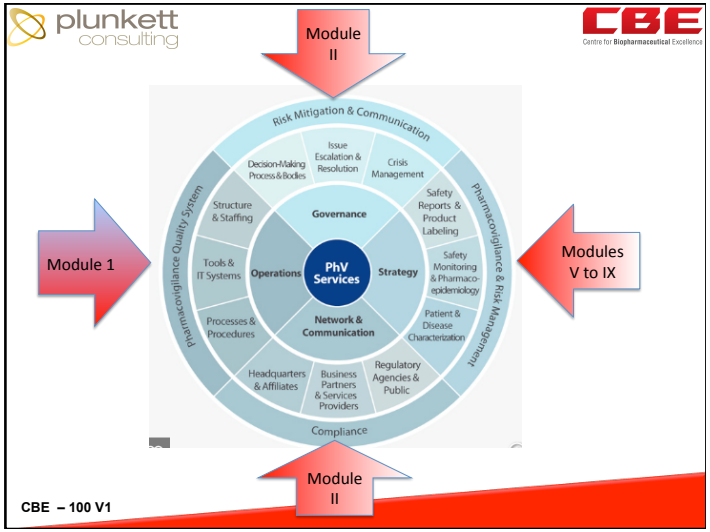
- provide objective measures to describe the pharmacovigilance situation in a country;
- assess pharmacovigilance activities – at the global (national), regional and health-care facility levels;
- assess capacity of (and for) pharmacovigilance at these levels;
- provide tools for supervision and monitoring of pharmacovigilance activities;
- assess progress and enable the prioritization of efforts, based on this assessment;
- enable comparison of pharmacovigilance activities between geographical regions and health facilities at a given time and at different times;
- provide tools for measuring the impact of interventions; and
- provide information for governments and other stakeholders to enable them to take appropriate action in ensuring drug safety.



http://www.who.int/medicines/areas/quality_safety/safety_efficacy/EMP_PV_Indicators_web_ready_v2.pdf?ua=1

European Medicines Agency: Good pharmacovigilance practice modules

- Module I: Pharmacovigilance systems and their quality systems;
- Module II: Pharmacovigilance systems master files;
- *Module III – Pharmacovigilance inspections (Rev 1)*\
- *Module IV – Pharmacovigilance audits*
- Module V: Risk management systems;
- Module VI: Management and reporting of adverse reactions to medicinal products;
- Module VII: Periodic safety update reports;
- Module VIII: Post-authorisation safety studies;
- Module IX: Signal management.



Adverse Event Reporting: Individual Case Safety Report Form (ICSR)

1 .Patient details

- Identifier- eg. Initials/patient number
- Gender
- Age/Age category/Date of Birth
- Concomitant medications
- Medical history including relevant past drug history
- Relevant family history
- Weight and height of patient
- Ethnicity

Adverse Event Reporting: Individual Case Safety Report Form (ICSR)

2. Suspected medicine(s)

- Drug identifiers: Brand name, International Non-Proprietary Name (INN) or Country Approved Name, Registration No on label
- Active ingredients
- Batch/lot number
- Indication(s) for which suspect medicine was prescribed o
- Dosing information
  - form and strength/ Daily dose &regimen/Route of administration /Starting date and time /Stopping date and time, or duration of treatment
- Actions taken with drug (e.g., drug withdrawn, dose reduced, dose increased, dose not changed, unknown, not applicable)
- Additional information on drug

  For suspected drug/drug, drug/food, or drug/alcohol interactions, the names and active ingredients of the suspected interacting products or substances

Adverse Event Reporting: Individual Case Safety Report Form (ICSR)

3. Other treatment(s)

The same information as in item 2 should be provided for the following:

- Concomitant medicines (including non-prescription, over-the-counter medicines, herbal remedies, dietary supplements, complementary and alternative therapies, etc.);and
- Relevant medical devices.

Adverse Event Reporting: Individual Case Safety Report Form (ICSR)

4 Details of adverse reaction(s)

- Full description of reaction(s), including
  - body site and severity
  - *as reported by the primary source*
  - *reaction in MedDRA terminology (lowest level term)*
- The criterion (or criteria) for regarding the report as serious
  - Description of the reported signs and symptoms
  - Specific diagnosis for the reaction
- Timing of the reaction
  - Onset date/time/Stop date/time
  - Time interval between suspect drug administration and start of reaction
- Relevant diagnostic test results and laboratory data
- Setting (e.g., hospital, out-patient clinic, home, nursing home)
- Outcome of reaction at the time of last observation (e.g., recovered/ resolved, recovering/resolving, not recovered/ not resolved, recovered/resolved with sequelae. Describe sequelae)

Adverse Event Reporting: Individual Case Safety Report Form (ICSR)

In the event of a Death

- Date/Stated cause/ autopsy-post mortem finings-

Relatedness of product to reaction(s)/event(s)

- Assessment of reaction:
  - Source of assessment (e.g., initial reporter, investigator, regulatory agency, company),
  - Method of assessment (global introspection, algorithm, Bayesian calculation) and result
  - Case narrative including clinical course, therapeutic measures, outcome and any additional relevant information
  - Sponsor's comments (e.g., diagnosis/syndrome and/or reclassification of reaction/event)
  - Medical confirmation?- Lab or other test date?- health care professional opinion- on causal or not? Were there reactions with other subjects?

Adverse Event Reporting: Individual Case Safety Report Form (ICSR)

5 Details about the person reporting the adverse reaction to sponsor

- Name/Contact Details/Profession-speciality

6 Administrative and sponsor details

- Source of report (spontaneous, epidemiological study, patient survey, literature, etc.)
- Date the event report was first received by manufacturer/company
- Country in which the event occurred
- Contact Details
- Product registration number
- Company's identification number for the case
- The AR identification number (if known) of possible duplicate reports initially submitted to the TGA by a consumer, healthcare professional or other primary source

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last) | 1a. COUNTRY | 2. DATE OF BIRTH (Day / Month / Year) | 2a. AGE (Years) | 3. SEX | 4-5 REACTION ONSET (Day / Month / Year) | 6-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)

- PATIENT DIED
- INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY
- LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name) | 20. DID REACTION ABATE AFTER STOPPING DRUG? YES NO NA

15. DAILY DOSE(S) | 16. ROUTE(S) OF ADMINISTRATION | 21. DID REACTION REAPPEAR AFTER REINTRODUCTION? YES NO NA

17. INDICATION(S) FOR USE

18. THERAPY DATES (from/to) | 19. THERAPY DURATION

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

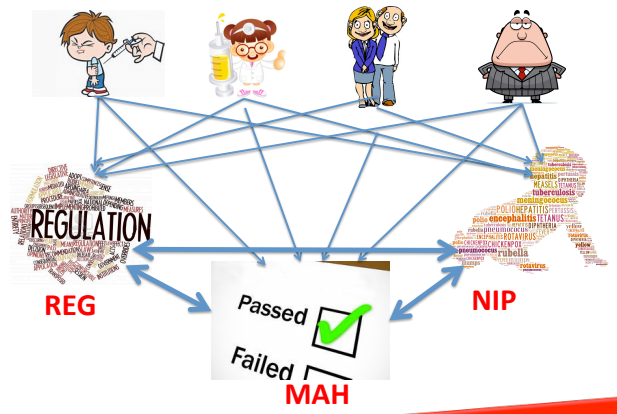
IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER

24b. MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER | 24d. REPORT SOURCE: STUDY, LITERATURE, HEALTH PROFESSIONAL

DATE OF THIS REPORT | 25a. REPORT TYPE: INITIAL, FOLLOWUP



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Adverse Event Reporting

Who has overall responsibility for PV in your organisation ?

Who do you report AEFIs to..Contact details ?

What is included in your ICRF?

Are all elements of the Pharmacovigilance system familiar with ICRF? (Manufacturer, Distributer, MAH, Regulator)?

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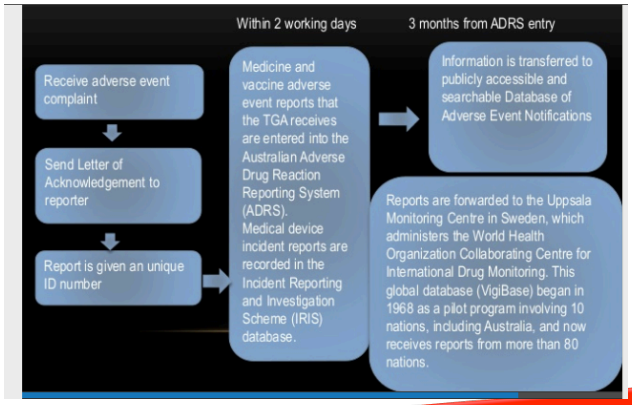
What happens to reports received by the regulator ?



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FLASH QUIZ
True or False?

An effective pharmacovigilance system:

- is a system that facilitates the systematic collection, storage and ongoing analysis of safety information associated with a medicinal product
- allows periodic analysis of the Benefit/Risks profile associated with vaccines.
- enables the effective communication of Benefit/Risk information to customers in order to prevent harm and minimize risks to the patients
- evaluates the effectiveness of any specific risk mitigation steps
- identifies gaps in the knowledge on drug/vaccine safety profile and defines measures to address these gaps

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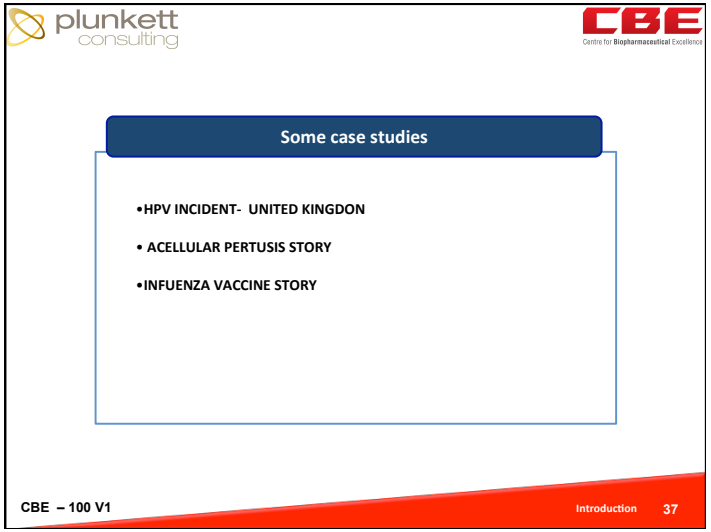
FLASH QUIZ
Match the Group with the Function

Group	Function
A. WORLD HEALTH ORGANISATION	1. TRAINS STAFF ON CORRECT WAY TO ADMINISTER A VACCINE
B. NATIONAL IMMUNISATION PROGRAM	2. PROVIDES SUMMARY INFORMATION ON AEFIs IN THE FORM OF A PERIODIC SAFETY UPDATE REPORT
C. WHO- UPPSALA MONITORING COMMITTEE	3. COLLECTS AND ASSESSES CASE REPORTS ON AEFIs FROM MEMBER COUNTRIES
D. NATIONAL REGULATOR	4. GRANTS PRE-QUALIFICATION AFTER CONDUCTING QA TESTS ON VACCINES AND INSPECTING MANUFACTURING SITES
E. VACCINE MANUFACTURER	5. LICENSES AND APPROVES VACCINES THAT ARE SAFE AND EFFECTIVE AND OF GOOD QUALITY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Some case studies
•HPV INCIDENT- UNITED KINGDON
• ACELLULAR PERTUSIS STORY
•INFUENZA VACCINE STORY
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