

Vaccine adverse events reporting system globally

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Abstract

Worldwide reporting of vaccines adverse event following immunization is a challenging problem because of absence of well framed reporting system in maximum countries of the world. In Past ten years fear of disease like polio, measles, tetanus, diphtheria etc was important concern in the mind of both parents & doctors than adverse reactions of the vaccinations, but today with the availability of effective vaccines and associated adverse reaction, lead to change in the thinking towards safe use of vaccine through vaccine pharmacovigilance. Hence there is need of effective vaccine adverse reaction reporting system in countries to find rare, serious adverse event following vaccination.

This article reviews on vaccine adverse event reporting Systems (offline or /& online reporting) in different countries like U.S.A, U.K, Australia, Singapore, India, Newzealand, Saudi, Srilanka, Canada that have a somewhat effective vaccine phamacovigilance system and also focuses on efforts of WHO in enhancing reporting of adverse event following immunization globally. Death or any type of harm to pediatric population can only be minimized if serious to non serious ADRs be reported with joint effort of health care professionals including doctors, nurses, pharmacist and consumer.

Keywords: Vaccines, Adverse event following immunization, Pharmacovigilance, spontaneous reporting.

1. Introduction

1.1 Adverse event following immunization & its classification

Adverse event following immunization (AEFI) is any untoward medical occurrence which follows immunization and which does not necessarily have causal relationship with the usage of the vaccine [1]. The AEFI can be broadly classified into five categories as vaccine induced; vaccine quality defect induced programmatic error induced, coincidental events and injection events [2]. Vaccine induced AEFI include event due to direct effects of vaccine i.e. rare event caused by inherent properties of vaccine or vaccine component and/or due to underlying medical condition or idiosyncratic response in recipient. Vaccine quality defect induced AEFI due to one or more quality defect of the vaccine product e.g., failure by manufacturer to completely inactivate a lot of inactivated polio vaccine. Programmatic errors include event caused by error in vaccine selection, storage, preparation, handling, or administration (95% & Preventable) e.g. Incorrect doses or routes, wrong diluents, Wrong vaccine used, Vaccine reconstituted incorrectly, Needle left in vial, Wrong technique used, Expired vaccine used, Reconstituted vaccine not discarded after 4 hours,

Freezing of freeze-sensitive vaccines (DPT, TT) .Coincidental events include event happened by chance not caused by the vaccine . Injection event include event as a result of injection itself, not the vaccine e.g. pain, anxiety. AEFI may also be classified as serious or non serious. A *serious adverse event* (SAE) is defined as that which results in death, is life threatening, requires in patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability /incapacity, is a congenital anomaly/birth defect, or require intervention to prevent permanent impairment or damage.[2] Based on causal association, AEFI may also be classified as i) definitely /very likely ii) probably iii) possibly iv) unlikely v) unrelated vi) unclassifiable. Adverse vaccine reactions are those that are causally related to vaccines and may be classified as local, systemic or allergic. *Local reactions:* Most parenteral vaccines induce some degree of local reactions including pain, erythema and induration. Local reactions may be partly ameliorated by ice application and paracetamol. *Systemic reactions:* Fever is the most common systemic reactions. Administration of paracetamol at the time of vaccination and later on a regular basis is helpful. *Severe allergy:* Severe allergy or anaphylaxis or anaphylaxis like

reactions including generalized urticaria or hives, wheezing, swelling of the mouth and throat, difficulty breathing, hypotension, and shock occur rarely at a frequency of 1 per 10,00,000 vaccines. These reactions are rarely due to the vaccine antigen; they are usually due to other vaccine constituents including residual animal protein, stabilizers, antimicrobials or preservatives.[3]

2. 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 vaccine- or immunization-related issues, and to the prevention of untoward effects of the vaccine or immunization [4]”. Vaccine pharmacovigilance relies mainly on three parameters as signal detection (on the basis of data collected through reported AEFI), generation of causal hypothesis and lastly testing of causal hypothesis [5]. It is extremely important to distinguish vaccine reactions that are causally related to the vaccine (vaccine adverse reactions) from other adverse events so that compliance to vaccines does not drop. The goal of vaccine pharmacovigilance is the early detection of and appropriate and timely response to AEFIs in order to minimize negative effects to the health of individuals and lessen the potential negative impact on immunization of the population [6]. The most important tool for gathering the safety information of vaccine is Spontaneous reporting. *An ideal Vaccine pharmacovigilance system must have following objective:*

- 1) Timingly detect problems in vaccine lots or brands leading to vaccine reactions caused by the inherent properties of a vaccine,
- 2) Detect, correct and prevent immunization errors caused by errors in vaccine preparation, handling, storage or administration,

- 3) Prevent false blame arising from coincidental adverse events following immunization, which may have a known or unknown cause unrelated to the immunization,
- 4) Reduce the incidence
- 5) Maintain confidence by properly responding to parent/community concerns, while increasing awareness (public and professional) about vaccine risks,
- 6) Generate new hypotheses about vaccine reactions that are specific to the population of particular country/region,
- 7) Estimate rates of occurrence of AEFIs in the local population compared with trial and international data, particularly for new vaccines that are being introduced.

3. Spontaneous reporting

In current scenario spontaneous reporting method is the best method for rapid & easy collection of data for effective pharmacovigilance system in any country, which mainly depends upon voluntarily reporting by prescribers. In all countries (low, middle or high income), national pharmacovigilance systems rely heavily on spontaneous (or voluntary) reporting in which Vaccine suspected adverse drug reactions (ADRs) are reported to a national coordinating centre by health professionals, manufacturers or directly by patients[7]. Spontaneous reporting system has many benefits (cover large population, may generate rapid alerts, low set-up/costs) along with some limitations (under reporting, incomplete data, bias).

The most important function of spontaneous reporting systems is the early identification of signals [8] and formulation of hypotheses, leading to further confirmatory investigations or sometimes regulatory warnings and changes of product information leaflets. In some instances, withdrawals of marketing authorizations are also based on Individual case safety reports (ICSR)[9].

Table I: Advantages and disadvantages of spontaneous reporting

Advantages	Disadvantages
Include large population i.e. not specific to patient groups	Under reporting
Include all hospital and out-patient care	Difficult to detect: delayed reactions, reactions with high background incidence.
May leads to generation of rapid alerts	Number of exposed unknown
Don't much influence prescribing behavior of prescriber	Bias
Low set-up/costs	Data collected are incomplete both in terms of quality and quantity
Provides safety surveillance throughout the marketed life of all medicines	Special studies will need to be set up to obtain accurate information on areas of particular interest, e.g. pregnancy, children and specific events of concern.

Table II: Detailed WHO Classification of AEFI

TYPE OF AEFI	OVERVIEW
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. Eg: Extensive limb swelling following DTP vaccination
Vaccine quality 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. Eg: Failure by manufacturer to completely inactivate a lot of inactivated polio vaccine
Immunization error related reaction	An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable. Eg: Transmission of infection by contaminated multidose vial.
Injection related reaction	An AEFI arising from as a result of injection itself, not the vaccine i.e, pain & anxiety. Eg: Vasovagal syncope in an adolescent during / following vaccination.
Coincidental events	An AEFI that is caused by something other than vaccine product, immunization error or injection anxiety Eg: A fever occurs at the time of the vaccination (temporal relationship) but is in fact caused by malaria.

Figure I: Different Classification of AEFI [10]

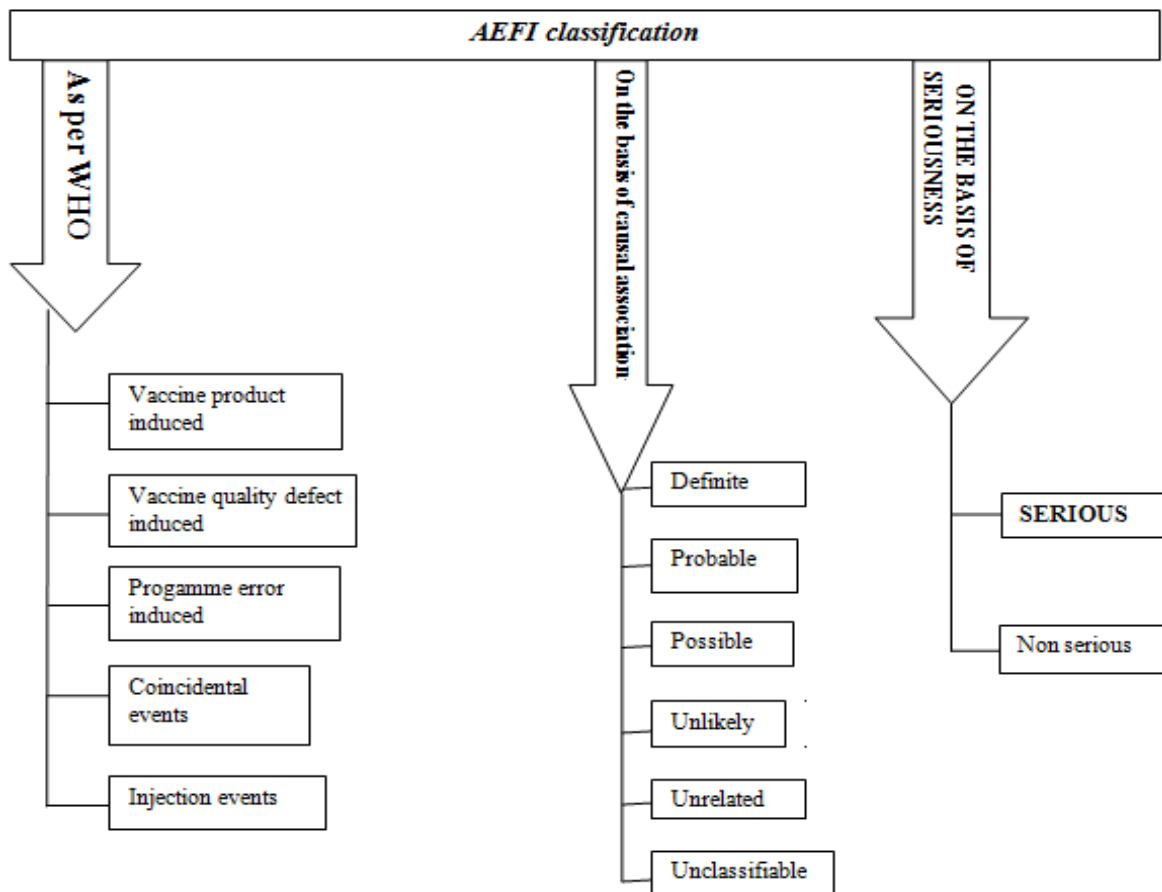


Table III: Countries with their AEFI reporting agency & reporting mode.

	Country	AEFI Reporting Agency	AEFI Reporting mode (Offline: AEFI reporting form, Online or both)
1.	United Kingdom (U.K)	MHRA & CHM - Yellow card	Both
2.	United States of America(U.S.A)	CDS &FDA-VAERS	Both
3.	Australia	TGA-Australian govt. SAEFIC-Victorian govt.	Both
4.	Singapore	HSA	Both
5.	India	CDSCO-IPC	Both
6.	Saudi	SFDA	Both
7.	Newzealand	NZPhvC-CARM	Both
8.	Srilanka	CDDRA	Offline
9.	Canada	CAEFISS	Offline

3.1 United Kingdom (U.K) - Yellow card Reporting system

The Yellow Card Scheme is the UK system for collecting information on suspected adverse drug reactions (ADRs) to medicines & vaccines. Yellow card was started in 1964 after the thalidomide disaster. The Yellow Card Scheme is run by the Medicines and Healthcare Products Regulatory Agency (MHRA) and the Commission on Human Medicines (CHM), and is used to collect information from both health professionals and the general public [11].

3.2 United States of America (U.S.A) - Vaccine Adverse Event Reporting System (VAERS)

VAERS is United States program for vaccine safety, co-managed by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration IJBR (2016) 7(03)

(FDA). VAERS is a post-marketing safety surveillance program, collecting information about adverse events (possible side effects) that occur after administration of vaccines [12].

Each year the VAERS receives 10,000–20,000 reports of adverse events following immunization of more than 10 million vaccines [13] by spontaneous reporting system. Both (offline, online) mode of reporting AEFI is available for doctor & report can be submitted voluntarily by anyone, including healthcare providers, patients or family members.

3.3 Australia - Therapeutic Goods Administration (TGA)

The TGA is part of the Australian Government Department of Health, and is responsible for regulating therapeutic goods including prescription medicines, vaccines,

sunscreens, vitamins and minerals, medical devices, blood and blood products [14]. Each year the TGA receives more than 12,000 reports of suspected adverse events to medicines and vaccines.

Surveillance of adverse events following vaccination in the community (SAEFIC)

It is a part of Victorian immunization program funded by department of health, Victoria for AEFI reporting.

3.4 Singapore - Health Sciences Authority (HSA)

It is the authority which uses number of post marketing risk assessment approaches to ensure the continued safe use of vaccine in Singapore. These include mandatory reporting from pharmaceutical manufacturers, spontaneous reporting from healthcare professionals, literature reviews and the exchange of regulatory information with other national drug regulatory bodies. HSA also contributes to the World Health Organisation (WHO) International Drug Monitoring Programme by submitting anonymised local adverse events reports to the WHO Uppsala Monitoring Centre in Sweden for international surveillance of adverse drug reactions [15].

3.5 India - Central drug standard control organization- Indian pharmacopoeia commission (CDSCO-IPC):

IPC, Ghaziabad is the National coordinating centre (NCC) under Pharmacovigilance programme of India (PvPI) in India that monitors the ADRs among Indian population, which help the regulatory authority of India (CDSCO) in taking decision for safe use of vaccines [16]. Mainly depend on spontaneous reporting system for AEFI data collection. Both (offline, online) mode of reporting AEFI is available to doctors. .

Indian academy of pediatrics (IAP):

IAP has integrating IAP disease surveillance project (IDSURV) with AEFI reporting for a web based and integrated voice recording reporting [17].

VIGIVAC reporting:

It provides On-line reporting of AEFI to practitioner and is based on CDSCO-FIR form & PIR form. VIGIVAC reporting system is developed under guidance of Dr. Ambrish Gupta GSVM Medical College, Kanpur.

3.6 Saudi - Saudi Food & Drug Authority (SFDA):

In Saudi, vigilance and Crisis Management Executive Directorate is concerned with detection, assessment and prevention of adverse drug reaction associated with vaccines [18]. Single common form (offline mode) of ADR reporting for medicine & vaccine is available and also online reporting is possible.

3.7 New Zealand - New Zealand pharmacovigilance centre (NZPhvC) - Centre for Adverse Reactions Monitoring (CARM):

Suspected AEFI are reported directly to the CARM within the New Zealand Pharmacovigilance Centre & CARM asks to report all suspected reactions (including minor reactions). Spontaneous reporting is particularly valuable for

recognising possible new hazards rapidly for newly introduced medicines and vaccines [19].

3.8 Srilanka - Cosmetics, Devices & Drugs Regulatory Authority (CDDRA):

It is the authority to ensure that the Pharmaceutical vaccines, available to the public meet the required standards of quality and are within the existing legislative framework with respect to the production, marketing and dispensing of these items and for AEFI reporting [20]. Srilanka has single common form of ADRs reporting for Medicine and vaccines & only offline mode of reporting exist.

3.9 Canada - Canadian Adverse Event Following Immunization Surveillance System (CAEFISS):

It is a public health post-market vaccine safety monitoring system of Canada[21] for identifying previously unknown adverse events following immunization(AEFI) that could possibly be related to vaccine (unexpected AEFI)[22].

3.10 World Health Organization (WHO):

WHO plays multiple roles in vaccine safety and vaccine pharmacovigilance at the global level as:

- 1) By providing technical support to its Member States to develop and maintain capacity for post-licensure vaccine safety monitoring as part of countries' responsibility for vaccine regulation and ensuring delivery of safe and effective vaccines,
- 2) By Operating the Programme for International Drug Monitoring (through its Collaborating Centre, the Uppsala Monitoring Centre (UMC) for maintaining a global database of adverse drug reactions, including those for vaccines,
- 3) By providing technical support for the investigation of vaccine safety issues in order to minimize any potential risks to vaccinated persons while avoiding unnecessary disruptions to the immunization programmes.
- 4) By providing advice to Member States about vaccine safety concerns of global, regional or national importance [23].
- 5) By providing Global Vaccine Safety Initiative (GVSI), a document on vaccine safety. This document sets out indicators that aim to ensure that all countries have at least a minimal capacity to ensure vaccine safety [24].

4. Conclusion

AEFI Surveillance is a important part of national immunization programme of every country. Vaccine adverse event reporting system is required in all countries for the safe use of vaccine, to prevent death or harm caused by vaccine. The countries like U.K, U.S.A. Australia, New Zealand, Saudi, India, Srilanka, Singapore & Canada have effective AEFI reporting system, where either online or offline (AEFI reporting form) method or both methods are available for healthcare professional & patient. In these countries AEFI data is mainly collected through spontaneous reporting from doctors .The major drawback of this reporting system is underreporting & bad quality of report. All countries have nearly similar reporting details in their prescribed form of reporting. WHO is also successfully playing major role in

spreading AEFI surveillance programme globally. Practicing pediatrics and educated parents are not aware of these reporting systems hence underreporting of AEFI is in all countries. Global learning programs / CMEs are recommended for doctors for more awareness of AEFI & smart use of reporting system in curbing dangerous AEFI.

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