

## Epidemiological Methods for Pharmaco-Vigilance: The Case of Vaccine Safety

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### Introduction

Pharmacovigilance is defined by WHO as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem” [1]. Though the system of adverse event monitoring started for drugs now it is well established for vaccines also. There is criticism that drug safety reporting in medical research is inadequate [2]. Though safety may be a concern in phase I or II trials of vaccine development, efficacy is their prime concern and adverse events being so rare, need not be picked by such studies. These studies usually have limited number of sample size and this is why adequate monitoring of large number of population in the community is needed for safety data [3]. This is effectively done through post marketing surveillance. Vaccine safety monitoring is done before and after the licensure of the vaccines [4]. Epidemiological studies for safety monitoring are essentially observational in nature. Epidemiological studies on vaccine safety have many methodological challenges. The basic issues are measurement problems which can be threat to validity of conclusions. Every epidemiological exercise can be considered as a measurement exercise. Validity is the extent to which the measurement is correctly undertaken so that it measures only what it is intended to measure. In the process of measurement anything other than the truth is called error. The errors which can occur randomly are called random errors. These errors are reduced by increasing the precision of measurement process or increasing the sample size. Errors that are repeatedly occurring are called bias or systematic errors. Bias is basically of two types, selection bias and information bias and the third identical threat to validity is confounding.

There is possibility of many types of bias in vaccine safety studies especially in the diagnostic process, at investigator level and in the process of recall. In the diagnostic process misclassification can occur. The major selection bias is healthy vaccine effect and confounding by indication [5]. During the signal detection or AEFI reporting many types of misclassification, ascertainment bias and reporting bias or recall identical to berksonian can occur. This can be due to incomplete disclosure of information by parents or health functionaries. The pre-licensure safety assessment is undertaken by properly conducted epidemiological studies. These studies are mostly vaccine trials. For identification of the specific type of vaccine adverse event the case definitions by Brighton collaboration is useful [6].

### Safety Concerns

Sometimes safety concerns are made unnecessarily sensational by media and proactive critics: This then becomes an issue of vaccine related mis-propaganda. The method of countering this is by enhancing vaccine confidence in the community. In fact propaganda cannot be countered by scientific arguments and this is where authorities need to be assertive and decisive. For example take the situation of Vaccine preventable disease control in India. There are twenty-seven million new births in India each year-the largest birth cohort in the world. However, fewer than 44 percent of these children receive the full schedule of immunizations.

According to recent estimates, the 81,275 annual deaths from measles in India account for three-quarters of the global deaths from

this disease. It is estimated that two-thirds of the children who die of measles and the other preventable childhood diseases would have survived if they had been immunized.

In India the large number of unimmunized or incompletely immunized remains as the urgent priority to be addressed. Sometimes the concerns on safety are expressed as propaganda against the vaccine, demoralize the program and dilute the spirit of universal immunization. The story of pentavalent vaccine is an example [7].

You can imagine how many children in India would have died of vaccine preventable causes if the vaccination Program was not there. The adverse event unless weighed in the light of benefits, is a meaningless concept.

### Pre-Licensure Issues: Design Considerations

#### Randomization

Vaccine development takes a very long inception period ranging from 10-15 years. There are exceptions like Ebola vaccine which happened in a short time due to the urgency of a vaccine development [8].

The justification for an experimental study is usually evident, as we need a vaccine to prevent the disease. The gold standard in such study designs is said to be the randomized controlled trial [9]. Meta-analysis and systemic reviews give maximum evidence for recommendation. The justification for a randomized clinical trial is defined in terms of concept of clinical equipoise. The requirement is satisfied if there is genuine uncertainty within the expert medical community, not necessarily on the part of the individual investigator about the preferred treatment. Clinical equipoise is the assumption that there is not one ‘better’ intervention present (for either the control or experimental group) during the design of a randomized controlled trial. A true state of equipoise exists when one has no good basis for a choice between two or more care options.

Randomized clinical trials pose a number of fundamental ethical problems; the most important one is randomization. If a trial has the desired outcome, and proves one option more effective or less toxic, then some patients (typically half) will have had suboptimal treatment. The randomized double-blind clinical trial is ethically justified and the preferred method of demonstrating therapeutic effectiveness and

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Received May 15, 2015; Accepted May 22, 2015; Published June 02, 2015

Citation: Pillai RK (2015) Epidemiological Methods for Pharmaco-Vigilance: The Case of Vaccine Safety J Pharmacovigilance 3: 164. doi:10.4172/2329-6887.1000164

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safety. Alternate methods such as crossover and self-controlled designs, the use of historical controls, observational methods, and practitioner's clinical trials also exist and have their place in certain circumstances. The use of randomized double-blind clinical trials must assure adequate explanation of the research plan to the patient, the documentation of informed consent, adequate consideration of safety, and an acceptably low risk/benefit ratio.

### Placebo

A placebo has been defined as a simulated or otherwise medically ineffectual treatment for a disease intended to deceive the recipient. It can be Pharmacological substances, Sham surgery, sham electrodes implanted in the brain, and sham acupuncture, either with sham needles or on fake acupuncture points, have all exhibited placebo effects. The physician has even been called a placebo. In the case of vaccine studies there is inherent difficulty in including placebo.

### Ethical Considerations

#### Informed consent

- Participants must be informed about the rationale for the trial and must understand that they may be assigned to a placebo condition
- Participants must be informed of any risks of the interventions and the risks associated with delaying treatment if assigned to a placebo condition In the case of vaccine studies the uncertainty is more and informed consent sometimes is more difficult

### Towards evidence based immunization practice

The hierarchy of evidence has been widely used as a scheme for assessing the strength of evidence [10]. Quantitative research is concerned with 'precise measurement, replicability, prediction and control. In RCT the researcher, systematically and rigorously studying cause-and-effect relationships between variables and ensuring that the results obtained (the effect) can only be attributed to the intervention or cause. In the hierarchy of research designs, the results of randomized controlled trials are considered the highest level of evidence. Randomization is the only method for controlling for known and unknown prognostic factors between two comparison groups. Lack of randomization predisposes a study to potentially important imbalances in baseline characteristics between two study groups. There is a hierarchy of evidence, with randomized controlled trials at the top, controlled observational studies in the middle, and uncontrolled studies and opinion at the bottom. This hierarchy has not been supported in two recent publications in the New England Journal of Medicine which identified non-significant differences in results between randomized, controlled trials, and observational studies patient care. Justifications for the argument: Randomization, controlled observation (experimental setting), prospective nature of the study conduct, valid comparison with control group. Though RCT is considered the gold standard for testing a therapeutic intervention, the conduct of an RCT is not without numerous obstacles. The barriers can be attributed to randomization, recruitment, retention, blinding and sampling procedures, and conduct of experiment.

### Safety monitoring through surveillance system

This is also called post-marketing surveillance. The surveillance system is a public health tool and different platforms are used for surveillance data collection. Though surveillance system for individual diseases has been reported, the integrated disease surveillance is the

order of the day [11]. VAERS is a system which is an establishment within the health system where the health system functionaries will collect data on routine basis [12]. Routine disease reporting, analysis of hospital administration reports and ad-hoc surveys are other modes of data collection on vaccine safety. The quality of data collected is important and there are many challenges. Changing disease epidemiology and varying prevalence of diseases can influence inference from data collected. Web based surveillance has now become common practice [13]. The credibility of source of information and the completeness of information are other challenges. Lack of facilities for laboratory confirmation is another big challenge. Many a time's phenomenal amount of data is collected and not bothered to be analyzed completely. Case definition and ascertainment bias is another challenge. Prior treatment influencing diagnostic certainty is another big challenge.

Causality assessment in relation to vaccine adverse event following immunization is another important epidemiological activity. Cause and effect relationship is disentangled through established epidemiological techniques. Association only means statistical dependence between two variables. Association can be causal or non-causal. Causality is established by step by step approach and for this there are many guidelines [14]. A WHO tool for global assessment has been practiced in this regard [15] now the WHO-UMC causality assessment system is more popular [16].

### Conclusions

Vaccines generally have two primary concerns. Clinical research is the method for establishing both. Epidemiology is the methodology for research and is the foundation for evidence based vaccine delivery in the community in the clinical practice mode as well as immunization program mode.

The major methodological challenges are in the pre-licensure phase of vaccine development regarding design and conduct of intervention studies and challenges unique to observational research especially during post marketing surveillance. A methodologically unsound study is always unethical and hence inappropriate design is a major ethical concern. Validity and precision issues are other methodological considerations for both experimental studies as well as surveillance.

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