I. [redacted] of Vaccine Safety

- Vaccines are immunobiological substances designed to produce specific protection against or other immune mechanisms.
- The vaccine mimics infection with the respective pathogen, but without risk of the disease
- The goal of all vaccines is to promote a primary immune reaction so that when the organism is again exposed to the antigen, a much stronger secondary immune response will be elicited. No vaccine is perfectly safe or effective, however, and concerns over adverse events (AEs) after immunizations have often threatened the stability of immunization programs.

Types of vaccines:

- Live (attenuated)
- Inactivated (killed)
- Toxoids
- Subunit and recombinant.

Adverse event following immunization:

AEFI is a medical incident that takes place after immunization, causes concern, and is believed to be caused by immunization, can be either True Adverse Event i.e. really a result of the vaccine or immunization or COINCIDENTAL EVENTS that are not due to vaccine or immunization prcess

Classification of adverse events following immunization

Vaccine reaction	Event or ppt caused by the vaccine when given correctly
Programmed error	Event caused by an error in vaccine preparation, handling or administration
coincidental	Event that happens after immunization but not caused by the vaccine- a chance associated
Injection reaction	Event from anxiety about, or pain from, the injection itself rather than the vaccine.
unknown	Event's cause cannot be determined.

Clinical problems to be Addressed by pharmacoepidemiologic Research:

- The tolerance for adverse reactions to vaccines given to healthy persons-especially healthy babies - is lower than to products administered to persons already sick A higher Standard of safety is required for

vaccines because of the large number of persons who are exposed, some of whom are compelled to do so by law or regulation for public health reasons. These issues lead often to a need to investigate much rare adverse events following vaccinations than for unlike many classes of drugs for which other effective therapy may be substituted, vaccines generally have few alternative choices, and the decision to withdraw a vaccine may have wide ramifications.

Establishing associations of adverse events with vaccines and prompt definition of the attributable risk are critical in placing adverse events in the proper risk/benefit perspective.

By virtue of vaccines being relatively universal exposures, deposite the relative rarity of serious true vaccine reactions, the absolute number of clinically significant vaccine adverse event reports received annually in the US now averages ~15 000

Research in vaccine safety can help to distinguish true vaccine reactions from coincidental events,

estimate their attributable risk, identify risk factors that may permit development of valid contraindications, and, if the pathophysiologic mechanism becomes known, develop safer vaccines.

oMethodologic Problems to be Addressed by pharmacoepidemiologic Research.

.An Institute of Medicine (IOM) review of vaccine safety found that the US knowledge and research capacity has been limited by:

i- inadequate understanding of biologic mechanisms underlying adverse events

ii- insufficient or inconsistent information from case reports and case series

iii- inadequate size or length of follow-up of many population based epidemiologic studies

iv- limitations of existing surveillance systems to provide persuasive evidence of causation; and

v. few experimental studies published relative to the total number of epidemiologic studies published.

In ensuing attempts to overcome these limitations, epidemiology has been vital in providing the scientific methodology for assessing the safety of vaccines.

Methodologic problems:

Epidemiology has been vital in providing the scientific methodology for assessing the safety of vaccines.

- Signal detection
- Assessment of casuality
- Measurement accuracy
- Confounding and bias
- Sample size

Signal Detection:

High profile vaccine adverse events, such as intussusception following Rotavirus vaccination, demonstrate the need for surveillance systems able to detect potential aberrations in a timely manner. Some factors make identification of true signals difficult however, for example, many vaccines are administered early in life, at a time when the baseline

risk is constantly evolving. Until the recent advent of systematic analyses of automated data and data mining of spontaneous reports methods, detection of a vaccine safety signal occured as much due to a persistent patient as from data analysis..

Assessment of causality:

Assessing whether any adverse event was actually caused by vaccine is generally not possible unless a vaccine specific clinical syndrome (e.g. myopericarditis in healthy young adult recipient of small pox vaccine), recurrence upon rechallenge (e.g. alopecia and hepatitis B vaccination), or a vaccine-specific laboratory finding (e.g Urabe mumps vaccine virus isolation) can be identified. When the adverse event also occurs in the absence of vaccination (e.g seizure), epidemiologic studies are necessary to assess whether vaccinated persons are at higher risk than unvaccinated persons.

Measurement Accuracy:

Misclassification of exposure status may occur if there is poor documentation of vaccinations. Documentation of exposure status has been fairly good through school age, but difficulty has been encountered in ascertaining vaccination status in older persons.

Sample Size:

Because outcome events (e.g encephalopathy) are often extremely rare, it may be a challenge to identify enough cases for a meaningful study. The difficulty with adequate study power is further compounded in assessing rare events in populations less frequently exposed (e.g. subpopulations with special indications). For studies of rare outcomes, Case-control designs are the most efficient. Such studies typically sample the source population of cases, identify appropriate control group, and assess the exposure status of both groups

to estimate the risk associated with exposure.

Example

Let us take a hypothetical examples where isoniazid chemoprophylaxis and development of tuberculosis is studied.

The information gathered is set in the form of table.

Exposure	Outcome		
	Developed TB	Didn't	total
ISONIAZID (INTERVENTION GROUP)	3	42	45
Control group	9	36	45
total	12	78	90

Example:

Study of Vaccination Risk in multiple sclerosis

Background:

The occurrence of relapses in multiple sclerosis is highly variable and unpredictable. Vaccines, particularly for hepatitis B, have been suspected to induce relapses in multiple sclerosis.

Question:

- Does vaccination increase the rate of relapse in multiple sclerosis?

Approach

- A case-crossover study within the European Database for Multiple Sclerosis network. Cases with a relapse after a 12-month relapse-free period were questioned on vaccinations. Exposure to vaccination in the two month risk-period immediately preceding the relapse was compared with that of the four previous two months control periods to estimate the relative risk.

- Results:

- The prevalence of exposure during the two-month risk period was similar to that of the four control periods

- The relative risk of relapse associated with exposure to any vaccination was thus unity.

Strengths

- Large clinical population with extensive computerized information.
- Efficient study design using only cases for this acute event and transient drug exposure.
- Confounding factors that do not change over time are inherently controlled for by the within-subject matched analysis.

limitations

- Low vaccination prevalence in this clinical population does not permit assessment of the risk for shorter effect periods, such as a week.
- Confounding by factors that change over time, such as infections, could not be controlled.

Pharmacoepidemiology and risk management:

Pharmacoepidemiology:

Pharmacoepidemiology is the study of the utilization and effects of drugs in large numbers of patients It can be viewed as an epidemiological discipline with particular focus on drugs.

Risk Management:

Risk management is the overall and continuing process of minimizing risks throughout a product's lifecycle to optimize its benefit/risk balance. Risk information emerges continuously throughout a product's lifecycle, during both the investigation and marketing phases through both labeled and off-label uses.

- FDA considers risk management to be a continious process of

1. learning about and interpreting a product's benefits and risks
2. Designing and implementing interventions to minimize a product's risks
3. Evaluating interventions in light of new knowledge that is acquired over time

4. Revising interventions when appropriate.

Goals of RM:

1. Goal of risk management is to enhance the safe use of medicines by optimizing the balance of benefit and risk.

2. This can be accomplished by increasing the benefit and/or decreasing the risk associated with the use of drug product.

3. The most common method use to attend to improve the balance of benefit to risk of specific drug products include professional labeling and package insert, special letters send to health care professional and training programs.

Clinical problems:

- Post marketing
- Product usage
- Case report view
- Risk identity and characterization

1. Postmarketing:

. In the early Stages of marketing of a new drug, observational Studies using computerized databases are often not practicable because there has not been sufficient patient exposure to the drug of interest. From an RM perspective, this means that during the early post-marketing phase most information about risk will be obtained from spontaneous or published case reports.

2. Product usage:

. From the start of marketing, drug use can be monitored Drug use in inappropriate age groups, at higher dose, for longer lengths of time than labeled, or for off-label use might signal the emergence of a potential safety problem requiring RM.

3. Case Reports:

. Review of well-documented case reports can provide useful insight into the spectrum, severity, and

natural history of an adverse drug effect, as well as its reversibility, predictability and preventability. Understanding these factors should be a critical component of any decision to design or implement an RM program.

4. Risk Identification and characterization:

Randomized controlled trials (RCTs) have a number of limitations, including relatively small size, short duration, and recruitment of highly selected and hence unrepresentative patients. Consequently, well-designed epidemiologic studies frequently offer the only way to characterize the safety risks associated with a given drug.

Drug-induced birth defects

Drug Induced Birth Defects

Major birth defects, typically defined as those that are life-threatening, require major surgery, or present a significant disability, affect approximately 2-4% of live born infants.

Minor malformations are of lesser clinical importance, and vary considerably in their definition, detection and prevalence.

Teratogenesis is a unique adverse drug effect, affecting an organism (the fetus) other than the one for whom the drug was intended (the mother). Whatever benefit/risk accrues to the mother, only the fetus is at risk for birth defects.

We are usually completely unaware of a drug's teratogenic potential when it is first marketed. Ignorance about embryologic mechanisms constrains development of predictive in vitro tests, and testing in animals is only rarely predictive. Premarketing clinical studies do not provide this information either. Traditionally, women of childbearing age

were excluded from clinical studies, specifically because of concerns about potential teratogenicity; newer guidelines encourage their enrolment, but most studies assure that they are at minimal risk of becoming pregnant.

Clinical Problems to be addressed by pharmacoepidemiologic research:

As noted, the fetus is the "innocent bystander" with respect to its mother's therapy. Further, since roughly half of pregnancies (at least in the US) are unplanned, teratogenic concerns extend to women who might become pregnant while taking a medication. Finally, unlike other adverse outcomes, teratogenic effects can be prevented by avoidance of pregnancy, and the birth of a malformed infant can be avoided by termination of pregnancy. Our understanding of a drug's teratogenic risk, therefore, has important consequences for how a given drug is used clinically.

Drugs known to be teratogenic:

- Human teratogens tend to fall into two broad categories. Drugs that produce major defects in a high proportion (roughly, 25%) of exposed pregnancies can be considered "high risk" teratogens (e.g, thalidomide and isotretinoin).
- More common are "moderate risk" teratogens, which increase the rate of specific birth defects by perhaps 5-20-fold (e.g. carbamazepine and neural tube defects).

The differences b/w high-risk and moderate risk. --- teratogens are relevant to how these drugs are considered in the clinical setting. Various approaches may be applied to the few drugs known to be human teratogens. Such drugs may be prohibited or removed from the general market, as was the case for thalidomide in the 1960s, given its high teratogenic risk without offsetting therapeutic benefits. Most known teratogens, such as phenytoin and valproic acid, pose moderate risks balanced by clinical benefits.

Physicians are expected to discuss the benefits and risks with their patients. Sometimes, a drug may be restricted to prescription by selected physicians.

. The third, more recent, approach utilizes a formal risk management program involving education of physicians and patients combined, in some cases, with restricted access to the drug (e.g; thalidomide, isotretinoin).

□ Methodologic problems to be Addressed by pharmacoepidemiologic Research:

. Birth defects is not a single, homogeneous outcome, and teratogens do not uniformly increase the rates of all birthdefects, but rather increase the rates of selected defects. Defects vary widely in terms of gestational timing, embryologic tissue of origin, and mechanism of development. Thus, one would predict that malformations produced by a drug would vary according to the timing of exposure, the sensitivity of the end organ (i.e. embryologic tissue), and the teratogenic mechanism.

The need to focus on specific birth defects dramatically affects sample size requirements. For example, a cohort study of a few hundred exposed pregnancies might be sufficient to identify a doubling of the overall rate of birth defects; resulting out a doubling of the overall rate would require larger numbers, but is still within the same order of magnitude. However, any specific defect is rare, affecting 1 per 1000 live births (e.g. oral clefts) to 1 per 10,000 or fewer (e.g biliary atresia). For a cohort study to detect a doubling of risk for a relatively common specific birth defect (e.g 1/1000) requires over 20,000 exposed pregnancies To rule out a doubling of risk for the same defect, one would need a far larger sample size of exposed pregnancies.

Exposure

Non-Prescribed Drugs:

Over-the-counter (OTC) drugs present a unique situation.

By definition, use of OTC drugs does not require physician involvement. Like consumers and physicians, women of childbearing age view OTC drugs as safer than prescription products, and they may assume that the same is true for use of these drugs in pregnancy.

Though prescription drugs generally become OTC based on a history of wide use and safety, this history rarely includes systematic information on potential human teratogenicity. This is particularly true for drugs that became available OTC decades ago.

Although the teratogenic effects of OTC drugs are largely unstudied, these agents have been used widely in pregnancy for decades, and the more recent increase in herbal product use has raised additional concerns. These exposures should be a focus of pharmacoepidemiologic research.

Examples of Drugs causing birth defects:

Thalidomide	Phocomelia, multiple birth defects
Anticancer drugs	Multiple birth defects, fetal death
Androgens	Virilisation, limb, esophagal and cardiac defects
Corticosteroids	Cleft palate, cleft lip, cardiac defects
Warfarin	Nose, eye, hand defects, growth retardation
Isotretinoin	Craniofacial, heart and CVS defects
Aspirin, Indomethacin	Premature closure of ductus arteriosus
Valproate Sodium	Spina bifida, neural tube defects
Tetracyclines	Discolored, deformed teeth, retarded bone growth
Lithium	Fetal goitre, cardiac and other abnormalities