

PART I
PHARMACOEPIDEMIOLOGY

PHARMACOEPIDEMOLOGY AND PHARMACOECONOMICS

CONCEPTS AND PRACTICE

*Pharmacoepidemiology is the application of epidemiological methodologies for the study of drugs focusing on their use and effects in a large number of people.
It is drug epidemiology.*

CHAPTER 1

Background and Introduction of Pharmacoepidemiology

Chapter Mission

After learning this chapter you may be able to know:

- Background, definition, concepts and scope of *epidemiology*.
- Background, definition, concepts and scope of *clinical epidemiology*.
- Definition, concepts and scope of *pharmacoepidemiology*.
- Relationship between *epidemiology*, *clinical epidemiology* and *pharmacoepidemiology*.

Background and Introduction

In 1900 AD, there was only one potent analgesic - Morphine, three analgesic antipyretics- Aspirin, Acetanilide and Antipyrin, one antispasmodic- Belladonna, one antimalarial - Quinine and only one heart drug - Digitalis. Anticancer drugs, antibacterials, anti-TB drugs, anti-hypertensive drugs, psychopharmacological agents, antidiabetic medicines, sulpha drugs etc., were not at all available. There were only limited number of medicines and most of them were processed from natural sources. During the second half of the twentieth century we got a large number of medicines which helped the doctors to treat and manage the diseases that were earlier untreated.

Today modern medicine is blessed with pharmaceutical armamentarium that is much more powerful than the past. We can see that the volume, potency and complexity of modern medicines are increasing day by day and medicines are becoming highly sophisticated and potential items. As medicines became potential, they became more and more toxic and started to harbor with them lot of hazards if not prudently used. If the patients are not made aware of the medicines prescribed to them, they may not be able use them safely. Knowledge of the benefits and risks of medicine use in human population is essential to make the practice of pharmacotherapy safe and effective. There is a paramount need to compare the therapeutic efficacy or benefits of medicines with their potential to cause harm or risks .

However our understanding about the efficacy, safety and risks of the medicines relies heavily on the studies conducted during the developmental process and approval of the drug product. Only after the drug product is introduced for marketing, it will be used widely by the general and ordinary population. Such a wide use will help to identify many additional risks and sometimes some additional benefits. These risks and benefits may range from minor or trivial to major or serious effects. There are number of medicines that were once accepted as highly useful but became dangerous subsequently as earlier unknown risks were subsequently identified when used in large population. Penicillin is a classical example. We could also identify newer uses to the existing medicines and Aspirin is a classical example. German apothecary Felix Hoffman in 1898 gave acetyl salicylic acid to his father who was suffering from both arthritis and the bad effects of salicylic acid used to treat arthritis. When the drug was found highly effective, the Bayer Pharmaceuticals started marketing it under the trade name 'Aspirin' which later became its generic name. By the time Aspirin celebrated its hundred years of its use as an analgesic and anti-inflammatory drug, it was found very much useful as a cardiac protective agent (Anti platelet).

Chemie Grunenthal, the German firm started marketing 'thalidomide' in October 1957 under the name 'countergan'. Thalidomide was synthesized in the Company in 1956 by Dr Muckter and his colleagues. On 16th December 1961,

Lancet published first report in Medical Press indicating that thalidomide might be a human teratogen (Mc Bride 1984). Thousands of deformed babies were born to mothers who were given thalidomide to cure their 'morning sickness' during early periods of pregnancy. Epidemiologic studies established its cause to be in utero exposure to thalidomide and the drug was withdrawn from the world market. The adverse effects on human fetus can be estimated only through observational methods, not through experimental methods. In 1996, a relation between appetite suppressant drugs and the risks of primary pulmonary hypertension was reported (Abenheim L 1996). In the next year another report came out showing the relationship between the drug and valvular heart disease (Connolly HM 1997). These are only some examples of serious adverse effects discovered after the drugs were put in wide use. Such cases help us to remind about the inherent limitations of the drug development process and the need to study populations receiving medications through routine prescriptions of doctors. Today we have subjects like Epidemiology, Clinical Epidemiology and Pharmacoepidemiology in health sciences helping the authorities to frame effective policies in health care including drug usage, surveillance and other medicine related aspects.

Epidemiology

Epidemiology is the rigorous and scientific study of occurrence, patterns, causes, distribution and determinants of diseases

in defined human populations. Epidemiology helps to shape policy decisions and evidence based practice by identifying the risk factors for the diseases. Epidemiology has two major areas - one is the study of infectious diseases in large populations called epidemics and the second is the study of chronic diseases. Epidemiological studies help diagnose such health problems and provide a basis for the care of people. During its progress and development, epidemiology has made available precise and strict methodologies for the study of diseases.

The objectives of Epidemiology include application of the information or findings to improve the structure, activities, programs and the outcomes of public health care and for that purpose develop health policies rooted in evidence. Epidemiology helped to develop methodologies that can be used in clinical research, public health and also basic research in health and biological sciences. Major areas of epidemiology include surveillance and screening of diseases, disease etiology and transmission, outbreak related studies, management and monitoring and comparison of treatment effects including clinical trials. Application of scientific principles of biology helps to understand the disease process better. Application of statistics helps to make efficient and effective use of data and arrive at appropriate conclusions. Application of principles of social science helps to understand the proximate and distal causes and engineering for exposure assessment.

Box 1.1 Selected Milestones in the History of Epidemiology

1849-54	John Snow formed and tested hypothesis on the origin of cholera in London - one of the first studies in analytic epidemiology
1920	Goldberger published a descriptive study report showing the dietary origin of pellagra
1940's	Fluoride supplements added to public water supplies in randomized community trials
1949	Initiation of the Framingham study of risk factors for cardiovascular disease
1950	Epidemiological studies link cigarette smoking and lung cancer, demonstrating the power of case-control study design
1954	Field trial of the polio vaccine (Salk), the largest formal human experiment
1959	Mantel and Haenszel developed a statistical procedure for stratified analysis of case-control studies
1960	Mac Mahon published first epidemiologic text with a systematic focus on study design
1964	US Surgeon General's Report on Smoking and Health establish criteria for evaluation of causality
1970's	Large community based trials implemented for worldwide eradication of smallpox
1980's	Chronic disease, injury and occupational epidemiology; HIV epidemic
2000's	Genetic and molecular epidemiology; health disparities; racialism;
2002	bioterrorism; anthrax and smallpox threat and vaccinations
2003	SARS quarantines and public health law; and world-wide epidemiology; BSE in Canada
2004	SARS recurrence; BSE in USA; flu epidemic
2009	2009 H1N1 pandemic

Epidemiological studies can be divided into two main types:

Descriptive Epidemiology

Descriptive epidemiology deals with disease and/or exposure and may consist of calculating rates like incidence and prevalence. Such descriptive studies help to generate hypotheses, but not test them. Studies of drug use would generally fall under descriptive studies.

Analytic Epidemiology

Analytic epidemiology includes two types of studies: observational studies, such as case-control and cohort studies, and

experimental studies which include clinical trials or randomized clinical trials (RCT). The analytic studies compare an exposed group with a control group and usually designed as hypothesis testing by studies. Only during the second half of 20th century that the discipline drifted apart, with separate schools, training, journals, and opportunities for employment.

Clinical Epidemiology

'Clinical epidemiology' is the application of epidemiologic principles and methods to problems and issues encountered in clinical medicine. It studies the determinants and effects of clinical decisions. Clinical

epidemiology guides clinical decision-making based on quantitative analyses of previous research findings. The term clinical epidemiology originated from two parent disciplines - clinical medicine and epidemiology. It is “clinical” because it seeks to answer clinical questions and to guide clinical decision making with the best available evidence and is “epidemiologic” because many of the methods used to answer these questions have been developed by epidemiologists.

The International Clinical Epidemiology Network (INCLLEN) was established in 1980 as a project of The Rockefeller Foundation registered in USA. It is converted into an independent non profit organization in 1988. It is helping clinicians and other health care scientists obtain knowledge and tools to improve health of people in developing countries. Today INCLLEN is spread over to 34 countries in the world and membership includes 89 institutes, 59 Clinical Epidemiology Units and 31 Clinical Epidemiology Research and Training Centers (CERTCs). It promotes research and training in clinical epidemiology and biostatistics and carry out multidisciplinary collaborative research works. IndiaCLEN is one of the seven regional networks of INCLLEN established in 1991 at Trivandrum Medical College. Its units are established in selected medical colleges in India.

Definition and Scope of Pharmacoepidemiology

Patients and health care providers increasingly rely on pharmacists to

appropriately evaluate the benefits and risks of drug therapy. It indicated a need for pharmacoepidemiology training and education in pharmacy schools and colleges. Although epidemiologic terms and statistics often appear in the clinical literature, pharmacy students were not accurately understood such terms till 1980s even in US where PharmD was in existence since 1950s.

Pharmacoepidemiology developed as speciality sometime in the late 1970s at a time when it became increasingly evident, that factors affecting drug use by the community played a critical role in the success or failure of drug therapy. However it was first described and defined in 1984 when it was proposed that a new discipline was necessary to integrate epidemiology and drug-related events.

Since then, pharmacoepidemiology research has evolved into an important discipline that analyses information pertaining to areas such as adverse drug events, drug utilization patterns, drug efficacy, and post-marketing surveillance research. The World Health Organization (WHO) started to promote research in pharmacoepidemiology by conducting workshops, publishing manuals, training investigators and encouraging research by funding projects as they identified it as a ‘research tool of global importance’.

The term Pharmacoepidemiology has with it two components, namely ‘pharmacology’ and epidemiology which makes it clear that it is the epidemiology of drugs or medicines. Pharmacoepidemiology is the amalgamation of the

terms 'Pharmacology' and 'Epidemiology'. Some authors state that Pharmacoeconomics is the child obtained after the 'marriage' of clinical epidemiology and clinical pharmacology.

Most of the initial works related to Pharmacoeconomics were done by Professors and Researchers of Medicine who were trained in Epidemiology and Biostatistics. Founders of epidemiology and early authors of Pharmacoeconomics were from the field of medicine, mostly clinicians.

Definition of Pharmacoeconomics

Pharmacoeconomics is the epidemiological study of the uses and effects of drugs or medicines in a defined human population. Pharmacoeconomics uses all the techniques of epidemiology to study the use of and the effects of medicines. It is one of the most useful non-experimental methods of research in drug usage and related aspects. It helped to generate a number of product liability suits against pharmaceutical manufacturers.

Pharmacoeconomics gives the health care professionals significant information about the health care and cost outcomes of medicines and similar items used in health care after their approval for clinical use. Pharmacoeconomics is drug epidemiology and applies epidemiological methodologies for the study of drugs focusing on their use and effects in a large number of people. It aims at studying the effects of drugs in people.

The field of Pharmacoeconomics uses the techniques of chronic disease epidemiology to study the use of and effects of drugs. It helps to get an estimate of probability of beneficial effects as well as probability of adverse effects on populations. It applies all the principles of biological sciences, clinical pharmacology, clinical epidemiology, biostatistics and social sciences. The pharmacoeconomic studies principally concentrate on the period after the drug enters the market known as post marketing surveillance (PMS) period. Traditionally the Pharmacoeconomic studies were concerned with the study of adverse effects of drugs. The growing concern related to adverse effects of medicines and their increasing cost helped considerably for the popularization of pharmacoeconomic studies in recent times.

Pharmacoeconomics can contribute body of knowledge that promotes the optimal use of medications. It also helps clinicians to take better-informed drug therapy decisions. Pharmacoeconomics today plays an important role in the drug-approval process in many countries including the United States, Canada, Australia and France with regard to drug safety. Withdrawals of marketed medications during the last few decades were primarily due to findings from pharmacoeconomic studies. The significance of pharmacoeconomics is also demonstrated by its inclusion in one of the objectives of US Health Policies. Healthy People 2010 published by the US Department of Health and Human Resources highlights pharmaco-

epidemiological databases as resources that can be used by health care organizations to monitor and report adverse events related to medical therapies.

The US Accreditation Council for Pharmacy Education (ACPE) later took a decision that education in US pharmacy programs should provide students with the sufficient background in understanding bio-statistical and clinical epidemiological concepts. The 2006 ACPE standards and guidelines recommended the inclusion of pharmacoepidemiology in the social, behavioural, and administrative sciences component of the pharmacy curriculum. While the ACPE has adopted new standards for pharmacoepidemiology curricula taught in US colleges of pharmacy, they have only provided general guidelines for incorporating pharmacoepidemiology topics into pharmacy curriculum. It subsequently increased the extent of Pharmacoepidemiology in pharmacy education.

Education and Training facilities Global Vs India

Pharmacoepidemiology is emerging as an important component of pharmacy education throughout the world, particularly when Doctor of Pharmacy (PharmD) evolved as the global program in pharmacy education, replacing B.S (Pharmacy) and B.Pharm. Since the M.Pharm Pharmacy Practice and the Doctor of Pharmacy (PharmD) programs in India have incorporated Pharmacoepidemiology as a topic or subject in the syllabus it is important

to provide didactic and practical training on Pharmacoepidemiology in global versus national situations during their courses and promote research in the areas. Pharmacoepidemiology is an important component of pharmacist education and training as the pharmacists' role in drug therapy decision-making and monitoring is expanding in India in recent times.

Pharmacoepidemiology topics include:

- ▶ Application of principles of epidemiology to the study of drug use and outcomes in large populations
- ▶ Studies that provide an estimate of the probability of beneficial effects in populations, or the probability of adverse effects in populations, and other parameters relating to drug use benefit
- ▶ Methods for continual monitoring for unwanted effects and other safety-related aspects of drugs.

At the global level, training programme in field of epidemiology are conducted by more than 40 countries, mostly of two-year duration. Three member states of South East Asia Region of WHO namely India, Indonesia and Thailand are conducting the two year training programme in Field Epidemiology. In India two year's training programme in field epidemiology (MPH) is being conducted by National NICD, Delhi and NIE, Chennai, each having an enrolment capacity of 15 students per year. The goal of the course is to strengthen public health services by developing a cadre of professional field epidemiologists.

Some of the topics or areas given for advanced course work in Pharmacoepidemiology for PharmD students and researchers in Pharmacy Practice in Hospital and community pharmacies in certain Universities are noted in Box 1.2.

Box 1.2 Topics or areas for advanced studies

- ▶ Introduction to Pharmacoepidemiology
- ▶ Fundamentals of Epidemiology
- ▶ Pharmacoepidemiology and Risk Management
- ▶ Epidemiology Research Methods
- ▶ Epidemiology of Infectious Disease
- ▶ Epidemiology, Prevention, and Control of Chronic Diseases
- ▶ Epidemiology of Aging
- ▶ Measurement in Epidemiology & Outcomes Research
- ▶ Epidemiology critical, Literature Review & Critique
- ▶ Design & Conduct of Clinical Trials
- ▶ Cancer Epidemiology, Prevention, Early Detection, and Control
- ▶ Grant Writing Skills in Epidemiology and Clinical Research
- ▶ Molecular and Genetic Epidemiology
- ▶ Cardiovascular Disease Epidemiology
- ▶ Paediatric Epidemiology
- ▶ Epidemiology, Prevention, and Control of Infectious Diseases
- ▶ Management for Epidemiologic & Clinical Research

The National Institute of Communicable Diseases (NICD) is situated in New Delhi and is now renamed as National Center for Disease Control. It was established in July 1963, by Government of India to expand and reorganize the activities of the Malaria Institute of India (MII). The reorganized Institute was established to develop a national centre for teaching and research in various disciplines of epidemiology and control of communicable diseases. The Institute is affiliated to Guru Govind Singh Indraprastha University Delhi. The Institute was also entrusted with the task of developing reliable rapid economic epidemiological tools which could be effectively applied in the field for the control of communicable diseases. The objectives of the Institute broadly cover three activities viz., training, service and operational research in the field of communicable diseases and their prevention and control in the country.

National Institute of Epidemiology (NIE) was established in 1999 July at Chennai under the control of ICMR. The main objectives of the NIC include development of human resources in epidemiology and biostatistics, networking of the various ICMR and non-ICMR institutes at the national level for epidemiological purposes and Consultancy services. The Institute offers 2-year Post Graduate course (M.Sc.) in Epidemiology and Doctorate programme (Ph.D.). Post graduate course in Epidemiology was started in the year 2001 for graduates in Medicine / Dental / Indian

Medicine / Allied Health Sciences. The courses are affiliated to DR. MGR University, Chennai. Today NIE is under the control of Department of Health Research (DHR), Government of India.

The Indian Institute of Public Health – Delhi (IIPH-D) commenced its operations in November 2008 with the launch of the Post Graduate Diploma in Health Economics, Financing and Policy. Since then, the institute has expanded its activities and launched Post Graduate Diploma in Public Health Management and Post Graduate Diploma in Clinical Research. IIPH Delhi has successfully conducted many short-term training Programmes and workshops in various fields related to public health and is still conducting such programs regularly. The activities get funding support from the Ministry of Health and Family Welfare, Department of AYUSH, Indian Council of Medical Research, Central

Council for Research in Unani Medicine, Department of Science and Technology, Medical Council of India and similar agencies.

The INCLIN centres in India conduct courses and training programs on various aspects of clinical epidemiology in about 17 Medical Colleges. However the Indian Universities are yet to start specialised programs like masters in Pharmacoepidemiology or Pharmacoeconomics. However research studies at PhD and M.Phil levels are undertaken by scholars in many Indian Universities. At the global level, many Universities currently offer specialised programs and training in Pharmacoepidemiology. Many American Universities including Johns Hopkins and Harvard took Pharmacoepidemiology at post graduate/ masters and PhD levels in recent decades.

