

# Introduction to Pharmacoepidemiology

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# Epidemiology

- Epidemiology is the study (scientific, systematic, data-driven) of the distribution (frequency, pattern) and determinants (causes, risk factors) of health-related states and events (not just diseases) in specified populations (patient is community, individuals viewed collectively), and the application of this study to the control of health problems.
1. Last, JM. *A dictionary of Epidemiology*, 4<sup>th</sup> ed.. New York, NY: Oxford University Press; 2001.
  2. CDC. May 2012

# Disease Distribution

- Analysis of disease patterns according to person, place, and time
  - Who is getting the disease?
  - Where is it occurring?
  - When is it occurring? How is it changing overtime?
- Variations in disease frequency by the three characteristics provide useful information that helps:
  - Understand the health status of a population;
  - Formulate hypothesis about the determinants;
  - Plan, implement and evaluate health programs

# Disease Determinants

- Factors that bring about a change in a person's health
- Determinants include both causal and preventive factors
- Determinants also include individual, environmental, and societal

# Disease control



EPIDEMIOLOGY PROVIDES INFORMATION  
FOR ACTION

# The objectives of Epidemiology

## 1. Causation:

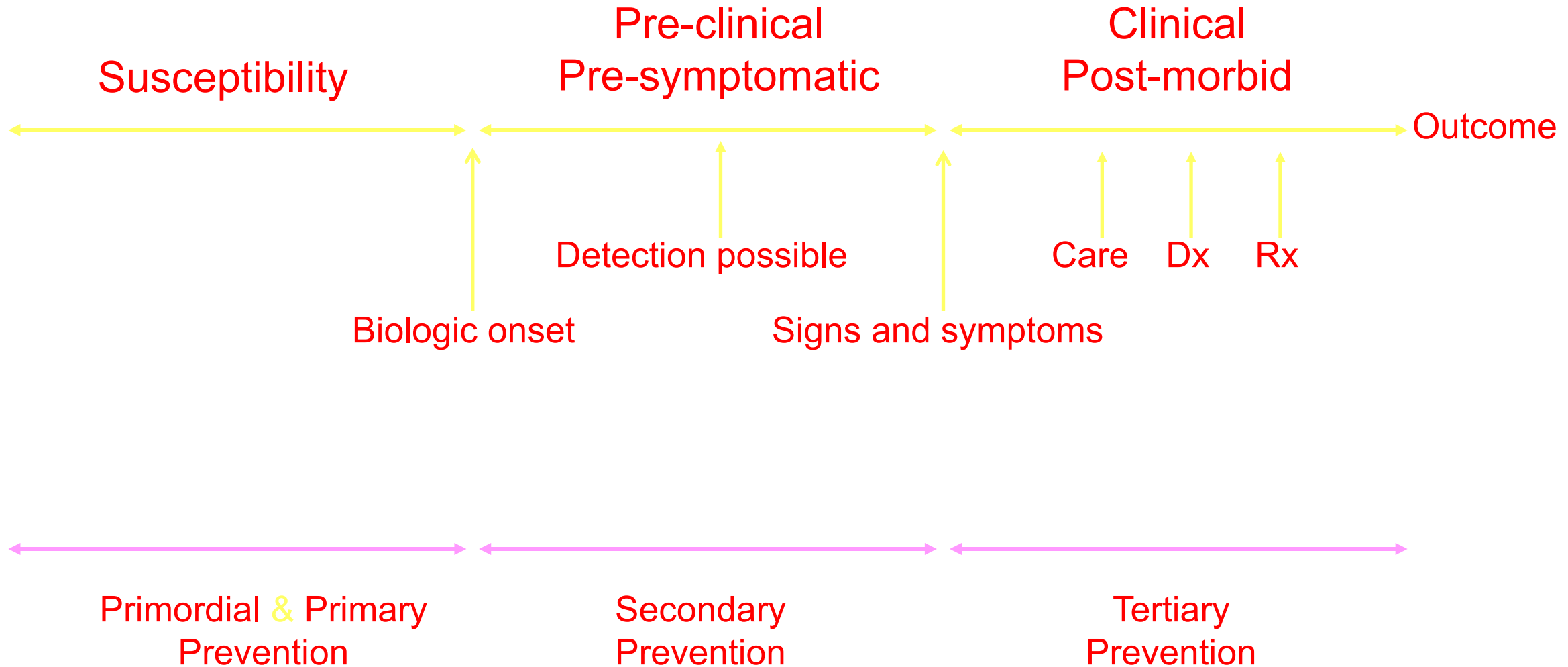
- To identify the etiology or cause of a disease and relevant risk factors;
  - example, description of disease in terms of the kind of people affected and its geographic distribution led to discover the association of pellagra and maize diet.
- Knowing how the disease is transmitted would enable us to intervene , reduce morbidity & mortality.
  - Example, John Snow's removal of the pump handle and withdrawal of brand of tampon that was linked to toxic shock syndrome.

# Objectives contd..

## 2. Study the natural history and prognosis of diseases

Some diseases are more severe than others; some may be rapidly lethal and others may have longer/shorter duration of survival. Defining the baseline natural history of a disease in quantitative terms help to develop new treatment/ prevention modalities.

# Natural History of Disease





# Levels of Prevention

Level of Prevention	Phase of Disease	Target
Primordial	Underlying conditions leading to causation	Total population and selected groups
Primary	Specific causal factors	Total population, selected groups and healthy ind's
Secondary	Early stage of disease	Patients
Tertiary	Late stage of disease	Patient

# Objectives contd.

## 3. Description of health status of the population

– Determine the extent of disease found in the community:

- What are the actual and potential health problems in the community?
- Where are they?
- Who is at risk?
- Which problem is declining/increasing over time?
- How these patterns relate to the level of and distribution of services available?

# Objectives contd.

## 4. Evaluation of intervention

Example: Effectiveness of residual DDT spraying is measured by reduction in the incidence of malaria.

# Exercise

- Match the term to the activity that best describes it.

- **Distribution, Determinants, Application**

\_\_\_\_\_ Compare food histories between persons with Staphylococcus food poisoning and those without

\_\_\_\_\_ Mark on a map the residences of all children born with birth defects within 2 miles of a hazardous waste site

\_\_\_\_\_ Recommend that close contacts of a child recently reported with meningococcal meningitis receive Rifampin

# Pharmacoepidemiology

# Why are new drugs needed?

- **unmet medical need**; new diseases (AIDS, Alzheimer's; obesity); low efficacy (dementia, cancer); side effects (antidepressants, antipsychotics)
- **downstream health costs**;
  - cost of therapy
- **sustain industrial activity**; pharmaceutical industry employs thousands and makes a massive contribution to overseas earnings); patent expiry

# Overview of Drug Development Process

# DISCOVERY

## PHARMACEUTICAL RESEARCH & DEVELOPMENT PROCESS

### Pre-discovery

**Goal:** Understand the disease and choose a target molecule.

**How:** Scientists in pharmaceutical research companies, government, academic and for-profit research institutions contribute to basic research.

3 - 6 YEARS

### Discovery

**Goal:** Find a drug candidate.

**How:** Create a new molecule or select an existing molecule as the starting point. Perform tests on that molecule and then optimize (change its structure) it to make it work better.

### Preclinical

**Goal:** Test extensively to determine if the drug is safe enough for human testing.

**How:** Researchers test the safety and effectiveness in the lab and in animal models.

# DEVELOPMENT

6 - 7 YEARS

### IND

**Goal:** Obtain FDA approval to test the drug in humans.

**How:** FDA reviews all preclinical testing and plans for clinical testing to determine if the drug is safe enough to move to human trials.

### Clinical Trials

**Goal:** Test in humans to determine if the drug is safe and effective.

**How:** Candidate drug is tested in clinical setting in three phases of trials, beginning with tests in a small group of healthy volunteers and moving into larger groups of patients.

0.5 - 2 YEARS

### Review

**Goal:** FDA reviews results of all testing to determine if the drug can be approved for patients to use.

**How:** The FDA reviews hundreds of thousands of pages of information, including all clinical and preclinical findings, proposed labeling and manufacturing plans. They may solicit the opinion of an independent advisory committee.

### Manufacturing

**Goal:** Formulation, scale up and production of the new medicine.

### Ongoing Studies

**Goal:** Monitor the drug as it is used in the larger population to catch any unexpected serious side effects.

### TOTAL

**How much:** \$800 million – \$1 billion

**How long:** 10 – 15 years



# Phase IV clinical trials: post marketing studies

What would happen to the drug after being marketed?

# What is **Pharmacoepidemiology**?

- study of the **frequency** and **distribution** of health and disease as a result of the use and effects (beneficial and adverse) of drugs in human populations
- the science of measuring drug mediated **health events** in well defined large number of populations:
  - therapeutic gain, length of life, quality of life or adverse events for any appropriate sub-groups in any selected medicines

# Cont'd

- it is a growing discipline that applies epidemiological techniques to study **drug use** in a large population
  - **aims:**
    - describe
    - explain
    - control
    - predict
- uses and effects of drugs in a defined time, space and population

# Scope

- Pharmacoepidemiology Vs Clinical Pharmacology
- clinical pharmacology is the study of the effects of drugs in humans
- in attempting to optimize the use of drugs
- central principle of clinical pharmacology is that therapy should be individualized, or tailored, to the needs of the specific patient at hand

# Cont'd

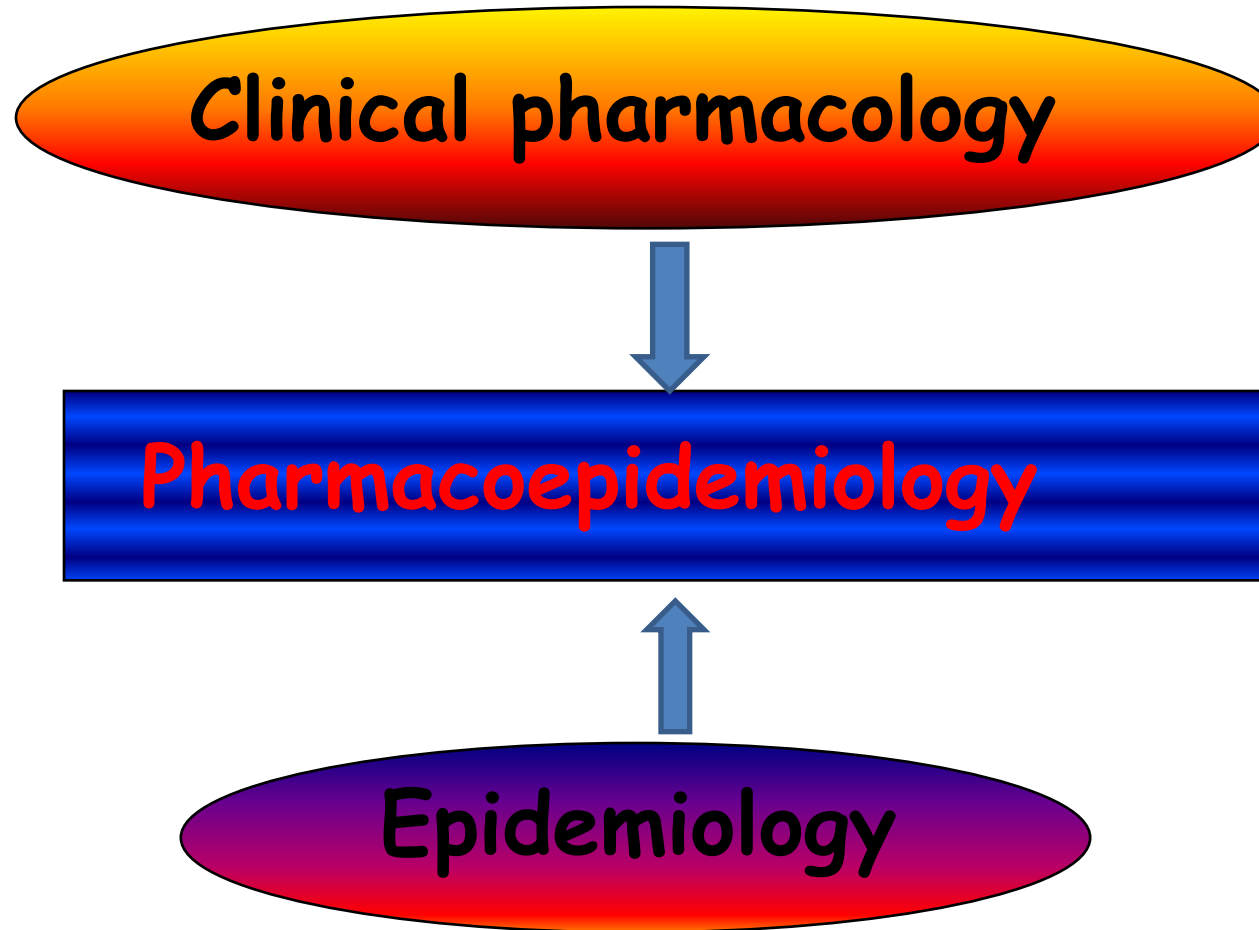
- this individualization of therapy requires determination of **risk/benefit ratio** specific to the patient
- thus pharmacoepidemiology is useful in providing information about the **beneficial** and **harmful effects** of any drugs permitting a better assessment of the **risk/benefit balance**

# Cont'd

- Pharmacoepidemiology Vs Epidemiology
- Epidemiology is the study of the factors that determine the occurrence and distribution of diseases in populations
- Pharmacoepidemiology as the study of the use and effects of drugs in large number of people, falls within epidemiology, as well to study the content area of clinical pharmacology
- pharmacoepidemiology uses the methods of epidemiology

# Cont'd

- Pharmacoepidemiology serves as a **bridging science** between clinical pharmacology and epidemiology



# Cont'd

- The broad purposes of pharmacoepidemiology are to advance our knowledge of the risks and benefits of medication use in real-world populations, and to foster improved prescribing and patient health outcomes.



# Potential contributions of P'coepidemiology

- provides:
  - information which **supplements** the information available from premarketing studies
  - new types of information **not available** from pre marketing studies

# 1. Information which supplements the information available from premarketing studies

- pre-marketing studies of drug effects are **limited in size** and **time**
  - few drugs are studied in < 4,000 subjects, 15-20 yrs
- after marketing, non-experimental epidemiologic studies can be performed in an ongoing basis
  - **cost effective** accumulation of much larger number of patients than those studied prior to marketing
  - results in a **more precise measurement** of incidence of adverse and beneficial drug effects

## Supplementary info...cont'd

- to release **critically important drugs** more quickly by taking advantage of the work that can be performed after the drugs are being marketed
  - in recent years regulatory authorities have occasionally released a particularly important drug after essentially only **Phase II testing**, assuming that additional data would be gathered during **post marketing testing**

## Supplementary info...cont'd

- Example, zidovudine was released for marketing after only limited testing, and only later were additional data gathered on both **safety** and **efficacy** data which indicated, among other things, that the doses initially recommended were **too large**
- important sub-group of patients are usually not included before drug marketing for ethical reasons

Example: **elderly, children** and **pregnant women** are often excluded

## Supplementary info...cont'd

- **post marketing studies** can explore how factors such as other **illnesses** and **other drugs** might modify the effects of drugs as well as looking at the effects of differences in **drug regimens**, **compliance**, etc.

Example: after marketing the ophthalmic preparation of timolol, it was noted that it caused many serious episodes of heart block and asthma resulting deaths

- these effects were **not detected** prior to marketing as patients with underlying cardiovascular or respiratory diseases were **excluded** from premarketing studies

## 2. New types of information not available from pre marketing studies

- premarketing studies are limited in size
  - usually < 4,000
  - Cases that occur with a frequency of 1/10,000 are difficult to detect
- sample size in post marketing studies permits the study of drug effects that may be uncommon but important
  - e.g. drug-induced agranulocytosis

## New types of info...cont'd

- premarketing studies are limited in time
  - they must come to an end or the drug could never be marketed
- post marketing studies allow the study of **delayed drug effects**
- the patterns of **physician prescribing and patient drug utilization** often cannot be predicted prior to marketing

- In most cases, premarketing studies are performed using **selected patients** who are closely observed
  - thus rarely can there be overdoses in these populations
  - Hence the study of effects of drugs when ingested in **extremely high dose** is possible in post marketing p'coepidemiologic studies



- cost of medical care: the exploration of the cost of drug use requires consideration of much more than just cost of the drug themselves.
  - the **costs of drug side effects** may be more than the costs of the drug if these adverse effects result in additional medical care and possibly hospitalization

# Reasons to Perform pharmacoepidemiology studies

- Regulatory
- Marketing
- Legal
- Clinical

# Cont'd

## A. Regulatory

- Requirement: a plan for post marketing pharmacoepidemiology study is required before the drug will be **approved for marketing**.
- This is designed to clarify residual questions about drug's efficacy and toxicity

- to obtain earlier approval for marketing:
  - if the drug regulatory agency believed that serious problems **could reliably and rapidly detected** after marketing, it could feel more comfortable releasing the drug sooner
- as a response to questions by regulatory agency:
  - some post marketing studies of drugs arise in response to **case reports** of adverse reactions reported to the regulatory agency

- to assist application for approval for marketing elsewhere
  - drugs are obviously marketed at different times in different countries
  - a post marketing study conducted in a country which marketed a drug relatively early could be useful in demonstrating the safety of the drug to regulatory agencies in countries which have not yet permitted the marketing of the drug.

## B. Marketing

- to assist market penetration by documenting the safety of the drug
- to increase name recognition:
  - the fact that a study is underway will often be known to prescribers as well its results once it is publicly presented and published increased name recognition

- to assist in repositioning the drug
  - this means to develop **new markets** for the drug

### i. different outcomes

- one can explore **different outcomes** resulting from the use of drugs for approved indication

For Example: the impact of the drug on the cost of medical care and on patients' quality-of-life

### ii. different types of patients:

- one could also explore the use of drugs for the approved indication in **types of patients other than those included in premarketing studies.**

Example: children and elderly

### iii. new indications:

- by exploring **unintended beneficial effects, or even drug efficacy**, one could obtain clues to and supporting information for new indications for drug use



iv. less restrictive labeling:

- because of questions about efficacy or about toxicity, drugs are sometimes approved for initial marketing with restrictive labeling.
  - additional data may be obtained from Pharmacoepidemiologic studies that help to make the labeling **less restrictive**
  - Example, bretylium was initially approved for marketing in the US only for the treatment of life-threatening arrhythmias

- to protect the drug from accusations about adverse effects
  - when a question about drug toxicity arises, it often needs **an immediate answer** or else the drug may lose market share or even be removed from market
  - Example, the experience of Pfizer Pharmaceuticals, when the question arose about whether piroxicam (Feldene®) was more likely to cause deaths in the elderly from gastrointestinal bleeding than the other NSAIDs

# Cont'd

- although Pfizer did not fund studies in anticipation of such a question, it was fortunate that several Pharmacoepidemiologic research groups had [data available on this question](#) because of other studies that they had performed
- But McNeil was not as fortunate when questions were raised about anaphylactic reactions caused by zomepirac.
  - ❖ If the data they eventually were able to have had been [available at the time of the crisis](#), they might not have removed the drug from the market

## C. Legal

- post marketing surveillance studies can theoretically be useful as legal prophylaxis to defend against product liability suits
- Even if the drug did cause the adverse outcome in question, a manufacturer certainly can document that it was performing state-of-the-art studies to attempt to detect whatever toxic effects the drug had

# Cont'd

## D. Clinical

- Hypothesis generating
- Hypothesis testing
  - problem hypothesized on the basis of **drug structure**, suspected on the basis of **pre-clinical or premarketing human data**, suspected on the basis of **spontaneous reports** and **need to better quantify the frequency** of ADRs

# Any question?

