School of Pharmacy—Drug Information

Literature Evaluation II

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Outcome

- Structures of research articles
- Criteria for evaluating a clinical trial

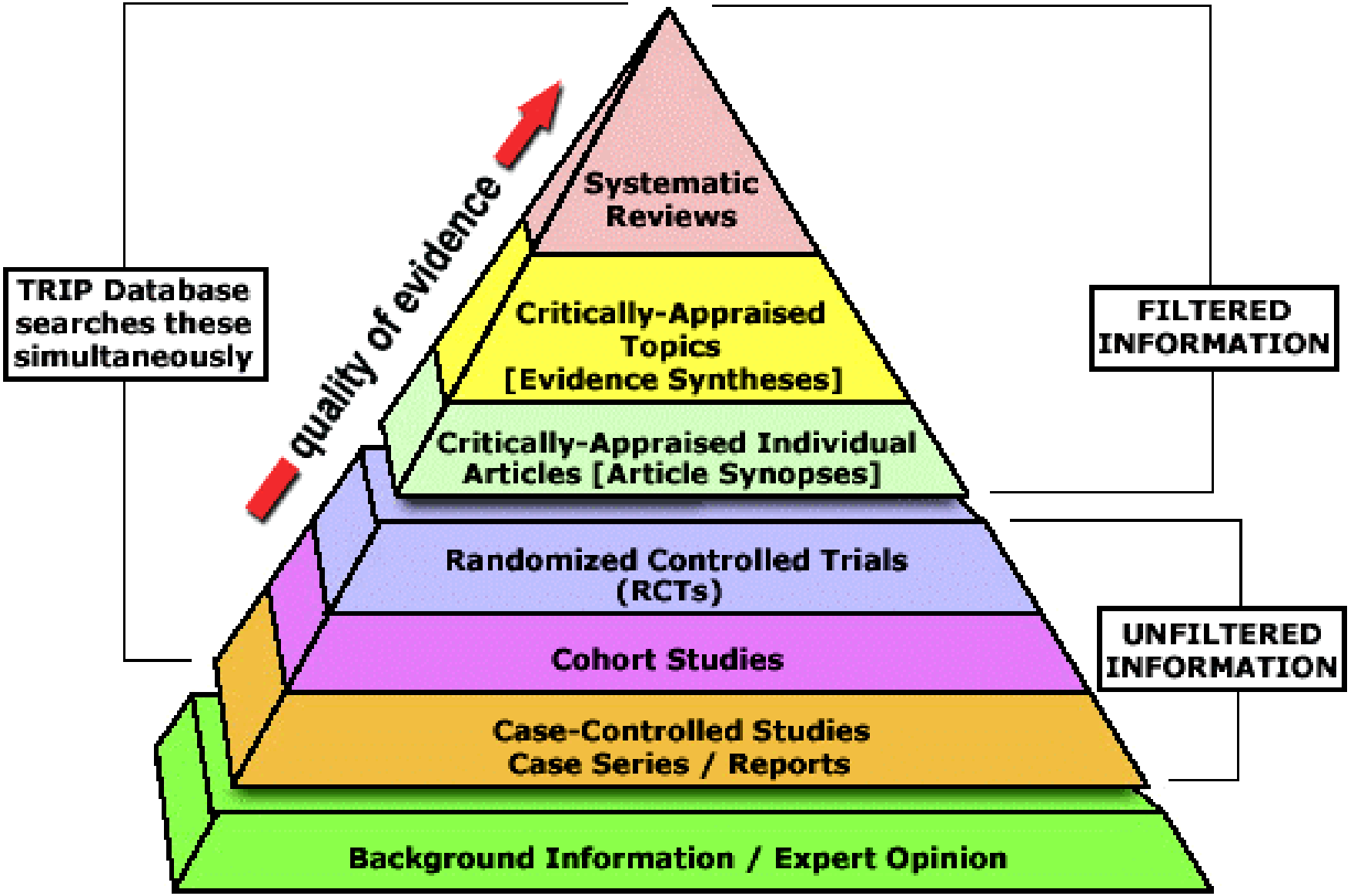
- Evidence-Based Pyramid
- Types of Study Designs
  - Observational study
  - Experimental study

Objectives

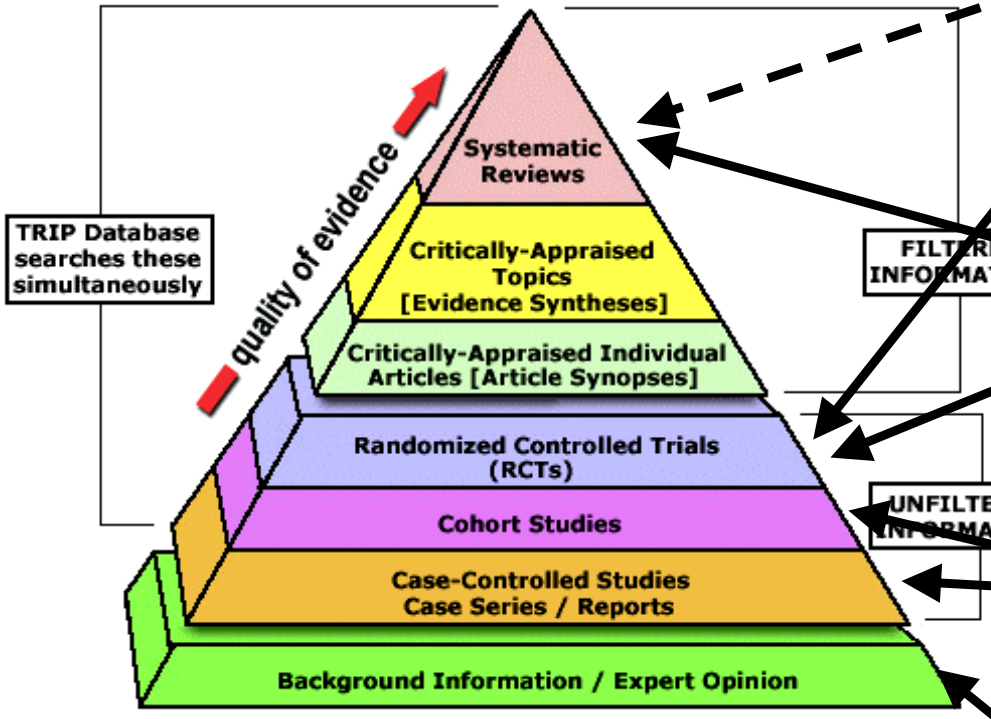
- After the current lecture you should be able to…
  - Draw a figure of evidence-base pyramid
  - Tell the difference between…
    - Case-control study v.s. cohort study
    - Longitudinal study v.s. cross-sectional study
    - Cross-sectional study v.s. cross-over design

Evidence-Based Pyramid

Evidence-Based Pyramid*



NCEP ATPIII for Hyperlipidemia



A

Major randomized controlled clinical trials (RCTs)

B

Smaller RCTs and meta-analyses of other clinical trials

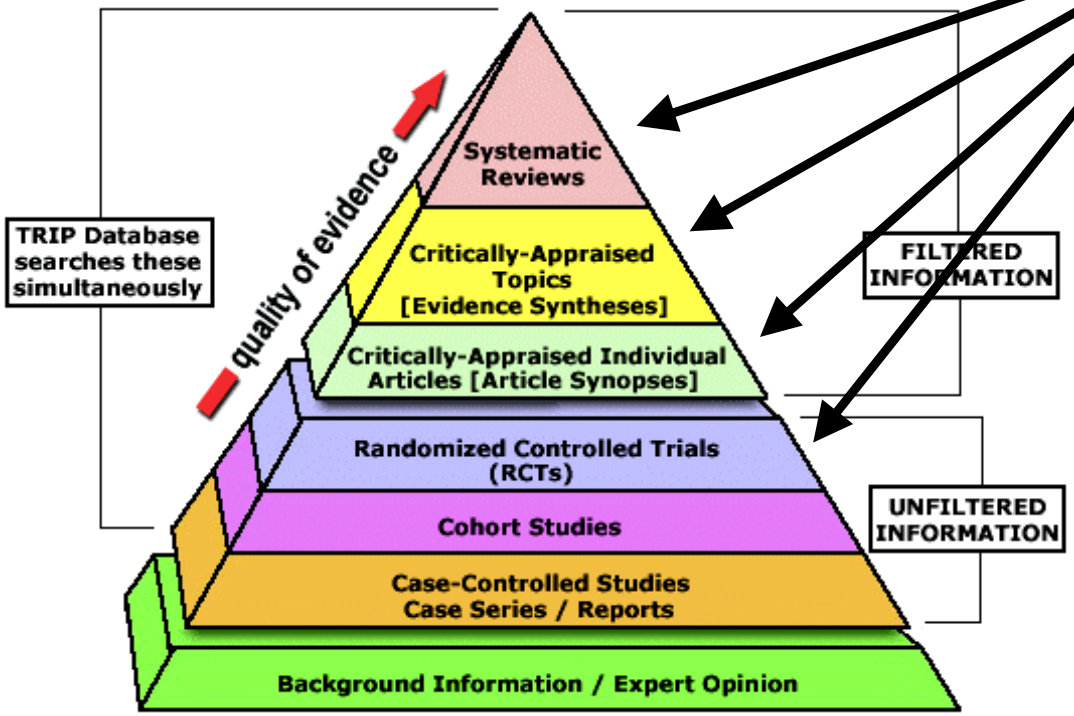
C

Observational and metabolic studies

D

Clinical experience

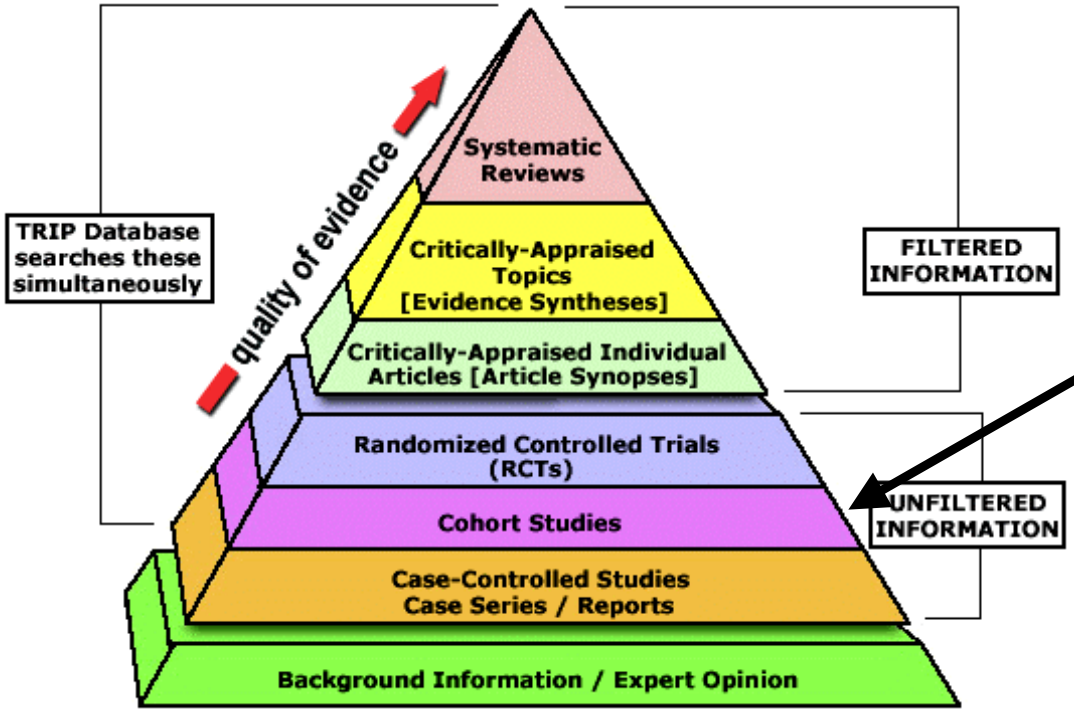
Standards of Medical Care in DM$_{(1/4)}$



A

Well-conducted, generalizable, randomized controlled trials that are adequately powered: Multicenter trial, meta-analysis that incorporated quality ratings in the analysis, critical appraised nonexperimental evidence, well-conducted randomized controll trials

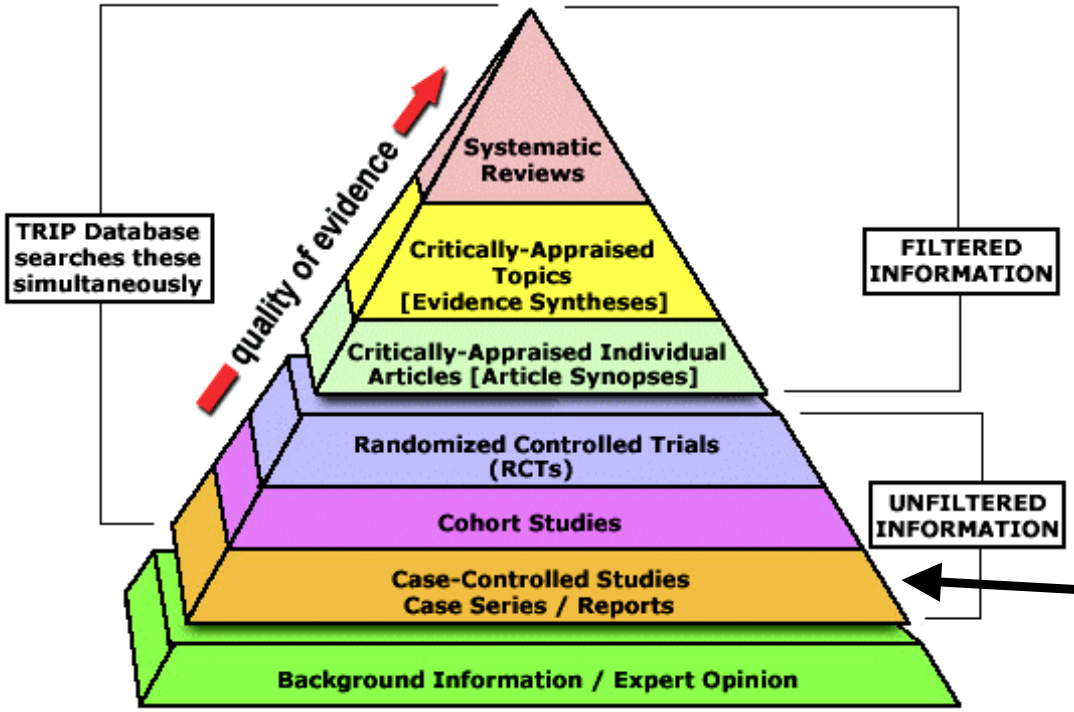
Standards of Medical Care in DM$_{(2/4)}$



B

Well-conducted cohort studies or their meta-analysis

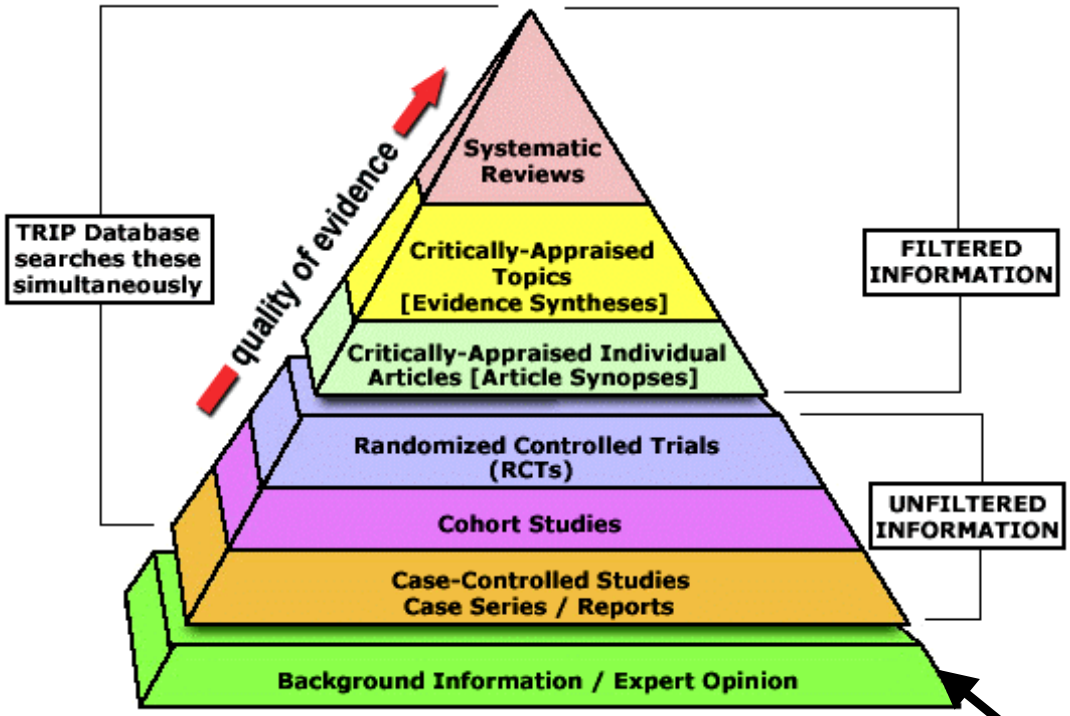
Standards of Medical Care in DM$_{(3/4)}$



C

Poorly controlled or uncontrolled studies (with methodological flaws), case series or case reports

Standards of Medical Care in DM$_{(4/4)}$



D

Expert consensus or clinical experience

Types of Study Designs

Observational Studies

Experimental Studies

Frameworks of Studies

Assignment	Selection of individuals for study groups
Assessment	Determination of the outcomes of interest in the study groups
Analysis	Comparison of the results between (or among) the study groups
Interpretation	Drawing conclusions about the meaning of the differences for those subjects within the study
Extrapolation	Drawing conclusions about the meaning of the study for individuals or situations not included in the study

Observational Studies

Case Report / Case Series

- Observations of a single (case report) or small number (case series) of patients
- Used to report rare/unique situations occurring in practice
- Lead to new hypothesis

- ✖ No comparable group
- ✖ No research hypothesis
- ✖ Interpretation and application must be done cautiously

Paragraphs of Case Report

- Introduction
- Case report(s)…the main story
  - History
  - Clinical features
  - Investigations
  - Treatment and outcome
  - Progress
- Discussion…review of literatures
  - Arguments, Message
  - Recommendation from the authors
- Conclusion or summary

Quiz 1

- Dr. L has a DM patient with cellulites treated with Linezolid. After taking Linezolid for 10 days, the patient's teeth color turned darker and darker.
- He is concerning if this effect can be cause by medications. The only possible and time-relevant drug is Linezolid.

- Please try to find a primary literature regarding this issue and give an answer.
  - Keywords: Linezolid, tooth discoloration

Quiz-1 Answer

Tooth Discoloration After Treatment with Linezolid

Kelly L. Matson, Pharm.D., and Susan E. Miller, Pharm.D.

With the increasing frequency of methicillin-resistant *Staphylococcus aureus* in immunocompromised hosts, clinicians are increasingly prescribing the oral treatment option of linezolid. Linezolid is the first of a new class of antibiotics, the oxazolidinones. The drug is generally well tolerated. However, mild-to-moderate adverse effects have been reported, such as gastrointestinal effects (most frequent), myelosuppression, skin eruptions, elevated liver enzymes, and tongue discoloration. As with any new drug on the commercial market, not all adverse effects are elucidated during preclinical trials. An immunocompromised 11-year-old girl with cellulitis of the toe experienced tooth discoloration after receiving a 28-day course of linezolid. The discoloration was present on the enamel of her lower anterior teeth and was superficial and reversible with dental cleaning.
(Pharmacotherapy 2003;23(5):682–685)

Cross-Sectional Studies

- Prevalence studies
- Providing information for particular condition, disease stage or diagnosis

- ✕ Single point of time; no follow-up
- ✕ Association, not causal relationship

Example

Melamine-Contaminated Powdered Formula and Urolithiasis in Young Children

Na Guan, M.D., Ph.D., Qingfeng Fan, M.D., Ph.D., Jie Ding, M.D., Ph.D., Yiming Zhao, Ph.D., Jingqiao Lu, Ph.D., Yi Ai, M.D., Guobin Xu, M.S., Sainan Zhu, M.S., Chen Yao, M.D., Lina Jiang, M.D., Jing Miao, M.D., Han Zhang, M.D., Dan Zhao, M.D., Xiaoyu Liu, M.D., and Yong Yao, M.D.

Epidemiologic Studies

- Include case-control and cohort studies

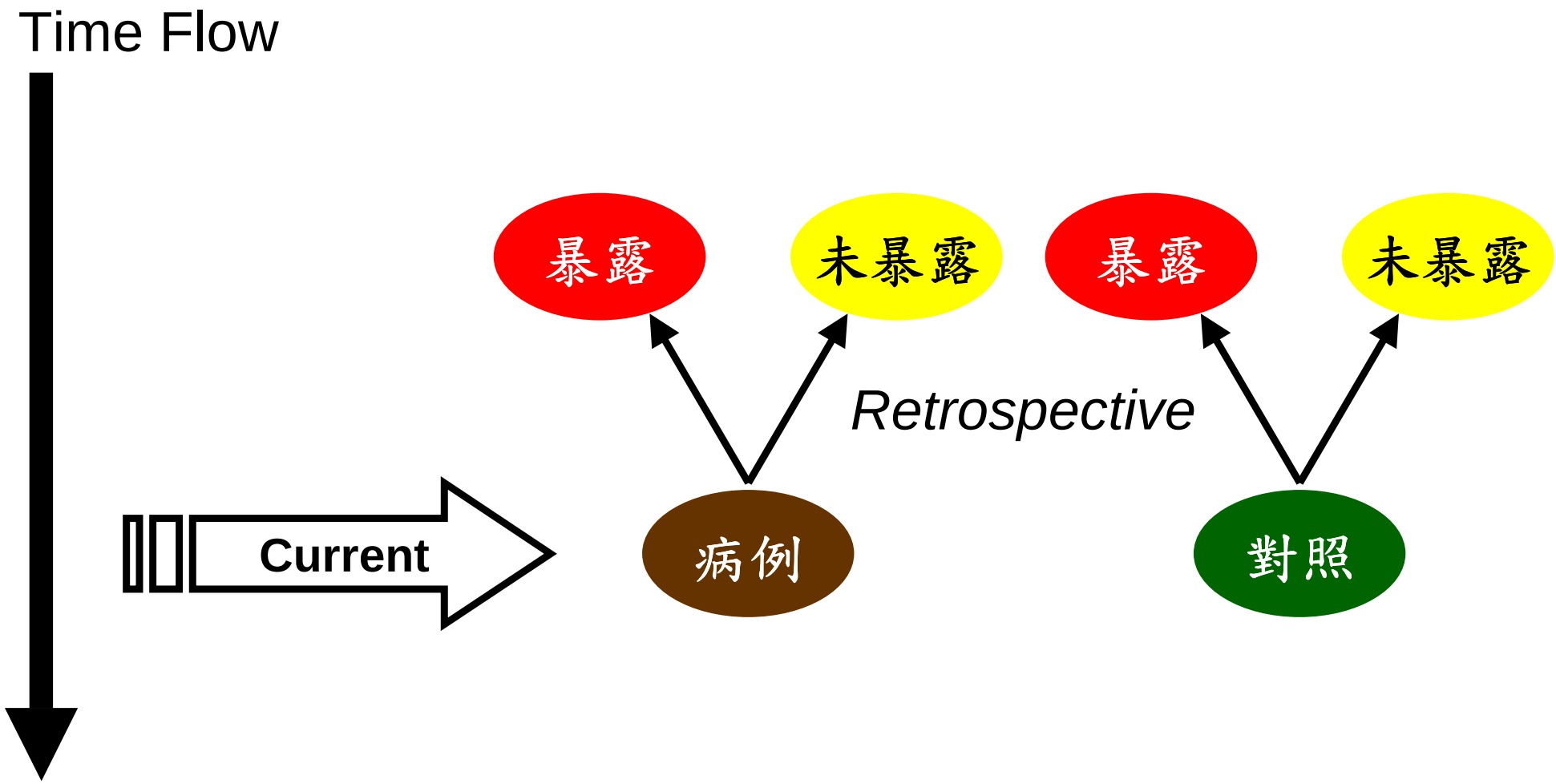
- Done either retrospectively or prospectively
- Designed to identify associations between exposure to certain factors and development of diseases
- Results must be considered in the context of possible confounding variables

Case-Control Studies

- Retrospective
- Two types of subjects:
  - Case: individual with the disease or outcome
  - Control: individual without the disease or outcome
- Can be matched or unmatched
- Rare disease, conditions developed over a long-period of time, investigating risk factors

- ✕ With a preliminary hypothesis
- ✕ Depends on high-quality medical records and availability of control

Epidemiologic Studies
Case-Control Studies*



Epidemiologic Studies

Case-Control Studies*

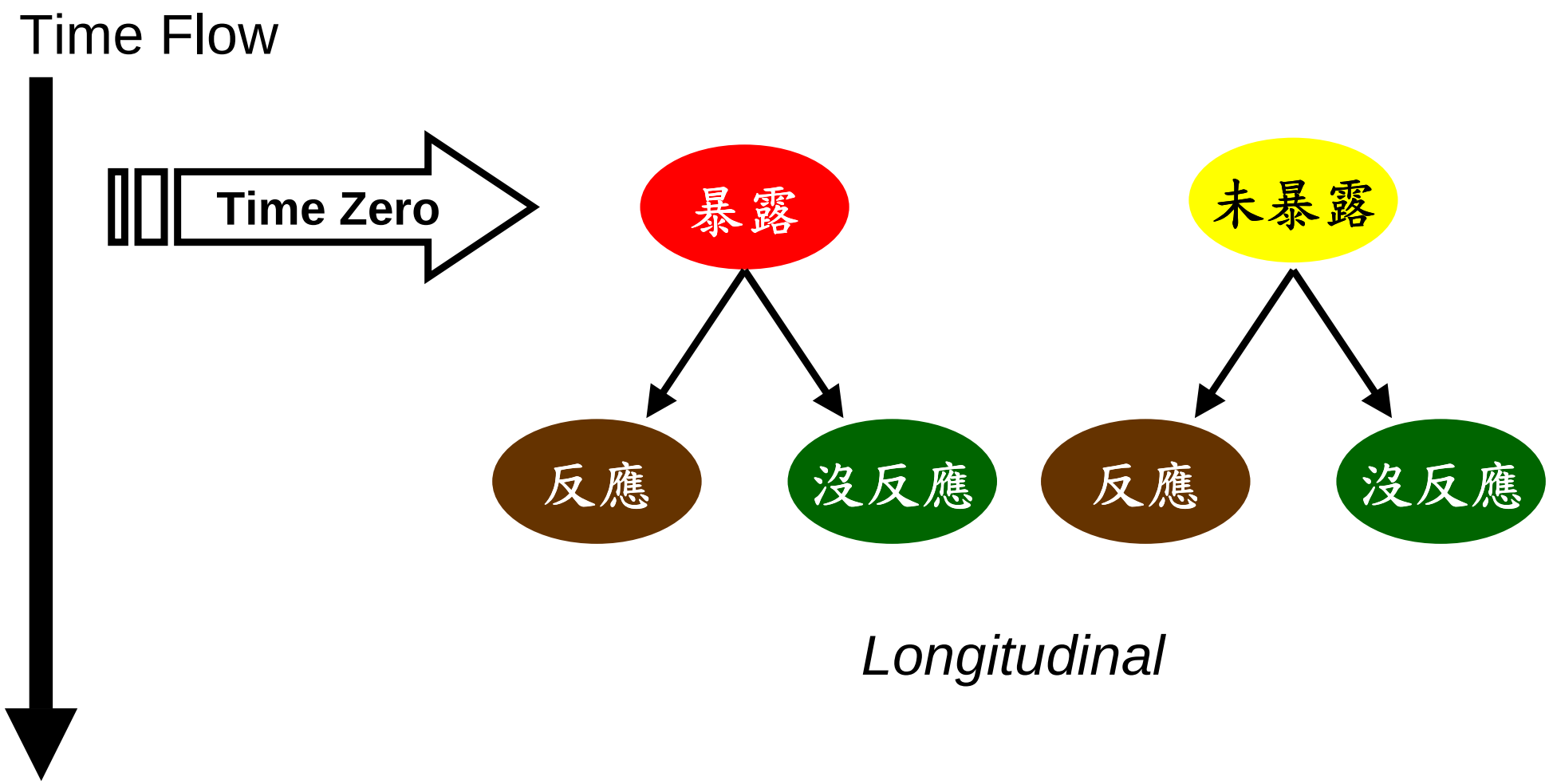
Assignment	Case: currently endometrial cancer Control: No endometrial cancer
Assessment	Determine whether and how each woman took estrogen previously
Analysis	Calculate the odds
Interpretation	Draw conclusions about the meaning of unopposed estrogen use for women included in the study
Extrapolation	Draw conclusions about the use for women not included in this study, e.g. different dosages or with different characteristics

Cohort Studies

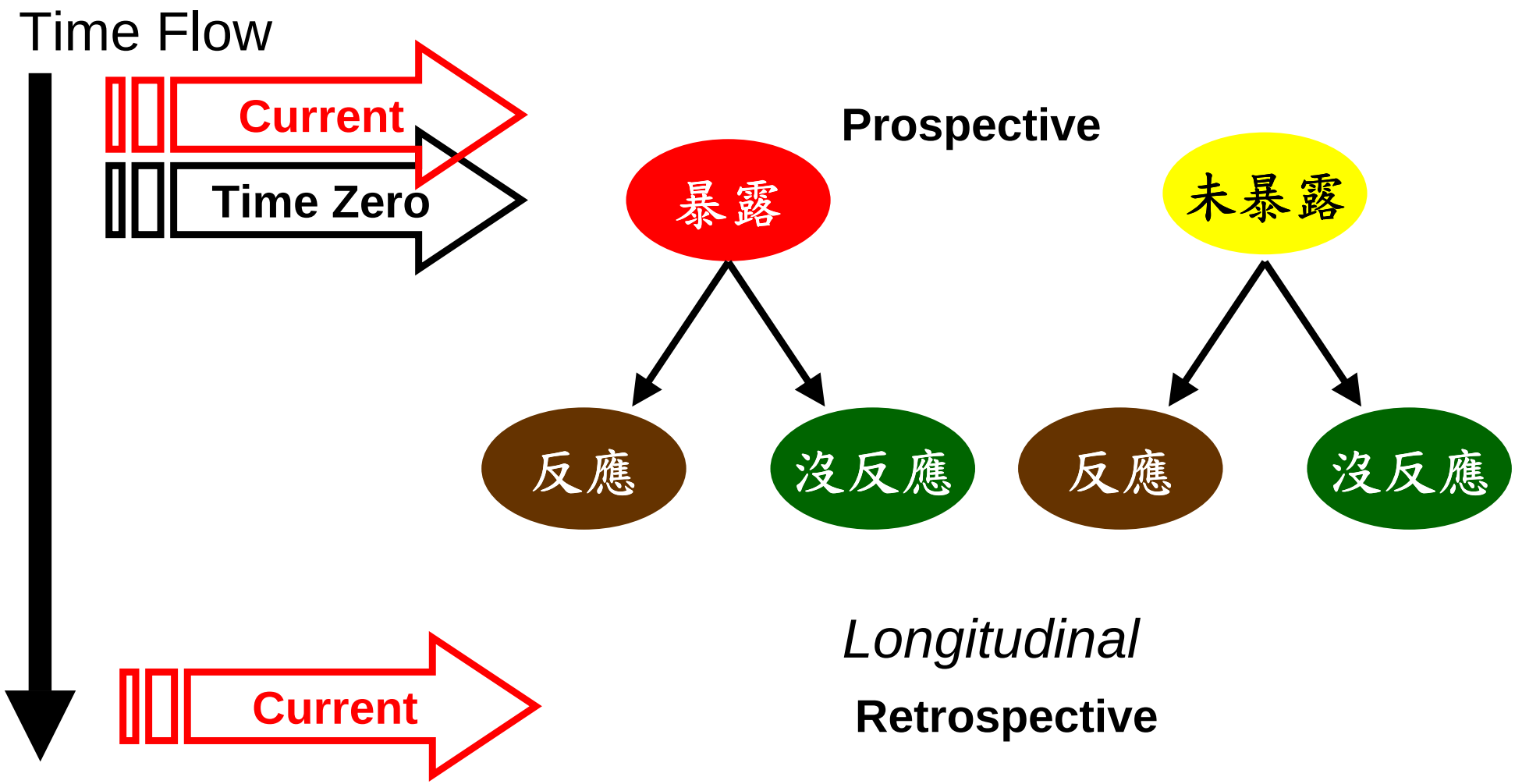
- Prospective mostly; some retrospective
- Cohort: a group of individuals who share a common experience
- Cohort study: follow two groups from the start of the study
  - A cohort with the characteristics under study
  - A cohort without that particular characteristics
- Appropriate if interesting in the causes, course, and possible risk factors of a disease

✕ Long follow-up

Epidemiologic Studies
Cohort Studies*



Epidemiologic Studies
Cohort Studies*



Epidemiologic Studies

Cohort Studies*

Assignment	Cohort A: estrogen user Cohort B: women who are not used estrogen
Assessment	Follow the subjects to see the development of endometrial cancer
Analysis	Calculate the probability of cancer in two cohorts
Interpretation	Draw conclusions about the meaning of estrogen use for women in this study
Extrapolation	Draw conclusions about the use for women not included in the study

Quiz-2

- What kind of epidemiologic study could this be?
  1. Case-control study
  2. Cohort study

Table 2. Crude incidence rate and HR for hospitalization for myocardial infarction after initiation of pioglitazone or rosiglitazone

	Pioglitazone ($n = 14\,807$)	Rosiglitazone ($n = 15\,104$)	HR (95%CI)	
			Unadjusted	Adjusted*
No. of hospitalizations for MI	161 (1.1%)	214 (1.42%)		
Total person-time (years)	17 256	19 229		
Crude IR (95%CI) per 10 000 patient-years	93.3 (80.0–108.8)	111.3 (97.0–127.1)		
HR for pioglitazone *versus* rosiglitazone			0.82 (0.67–1.01)	0.78 (0.63–0.96)

IR, incidence rate; HR, hazard ratio.
*Adjusted for all variables in Table 1 (age as continuous covariate).

Quiz-2 Answer

Cohort 1: Subjects who initiate pioglitazone (for DM)

Cohort 2: Subjects who initiate rosiglitazone (for DM)

Table 2. Crude incidence rate and HR for hospitalization for myocardial infarction after initiation of pioglitazone or rosiglitazone

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Response: Hospitalization for MI

Types of Study Designs

Observational Studies

Experimental Studies

Crossover Design

- Subjects itself as their own comparison
- Less sample size required

- ✕ Carry-over effect→ Wash-out period required
- ✕ Time effect

Experimental Studies

Randomized Controlled Trial

- Gold standard of clinical research
- Designed to determine causal relationships
- More verifiable, reproducible
- Enrollment of subjects
- Randomly assignment
- Control group: active control > placebo > null
- Sometime blinded: patient, evaluator

- ✕ Resources consuming: time, economic, human
- ✕ Selection of study sample

Experimental Studies

Randomized Controlled Trial*

Assignment	Treatment: estrogen given Control: placebo given
Assessment	Follow the subjects to see the development of endometrial cancer
Analysis	Calculate the probability of cancer in two groups
Interpretation	Draw conclusions about the meaning of estrogen use for women in this study
Extrapolation	Draw conclusions about the use for women not included in the study

Experimental Studies

Randomized Controlled Trial

ORIGINAL ARTICLE

Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis

Anne B. Rossebø, M.D., Terje R. Pedersen, M.D., Ph.D.,
Kurt Boman, M.D., Ph.D., Philippe Brudi, M.D., John B. Chambers, M.D.,
Kenneth Egstrup, M.D., Ph.D., Eva Gerdts, M.D., Ph.D.,
Christa Gohlke-Bärwolf, M.D., Ingar Holme, Ph.D.,
Y. Antero Kesäniemi, M.D., Ph.D., William Malbecq, Ph.D.,
Christoph A. Nienaber, M.D., Ph.D., Simon Ray, M.D.,
Terje Skjærpe, M.D., Ph.D., Kristian Wachtell, M.D., Ph.D.,
and Ronnie Willenheimer, M.D., Ph.D., for the SEAS Investigators*

Reference

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- Guyatt GH, Sackett DL, Cook DJ. User's Guides to the medical literature: II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? *JAMA* 1994;271(1):59-63.

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- Etminan M, Samii A. Pharmacoepidemiology I: a review of pharmacoepidemiologic study designs. *Pharmacotherapy* 2004;24(8):964-9.

Thank You