The Importance of Epidemiologic Indicators in HTA

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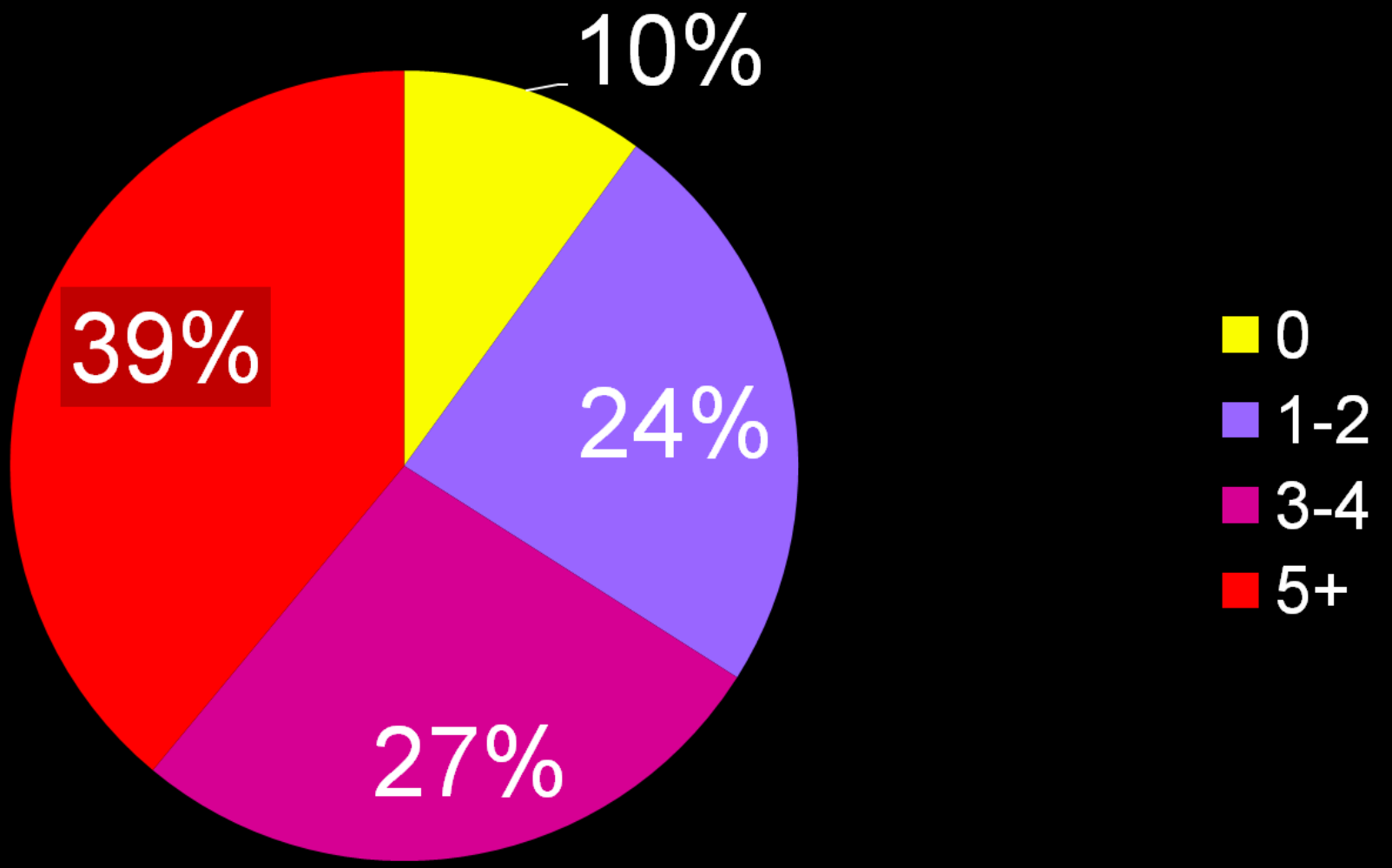
“What do you do for a living?”

“I use Big Data to study the safety of medications.”

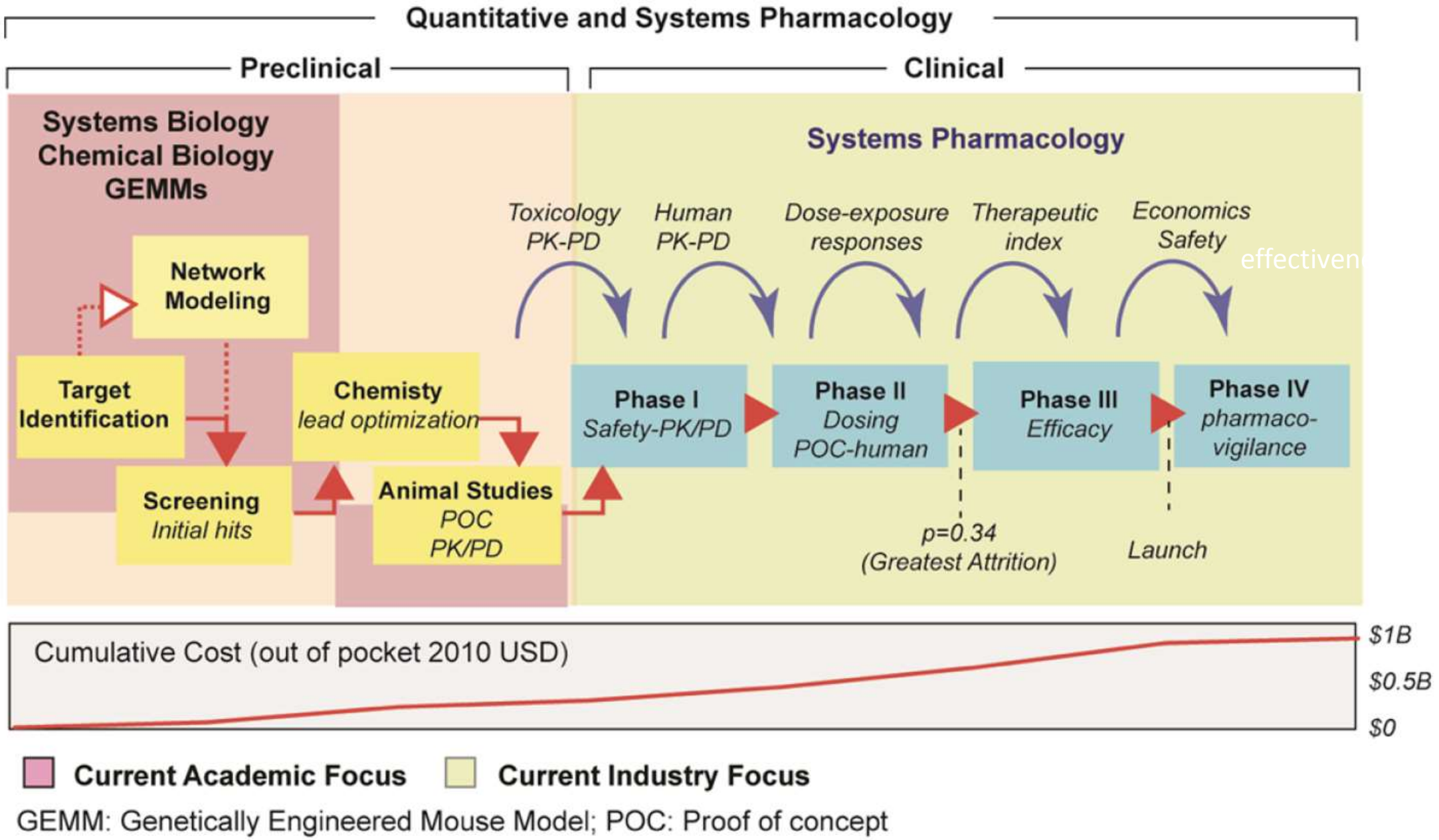
Pharmacoepidemiology

- the study of the health effects of drugs and other medical products (biologicals, medical devices) in populations
- the science underlying the public health practice of drug safety surveillance

of Rx Medications Used in the Past Month by US Residents age ≥ 65 (2005-08)



Kit BK et al. Ann Epidemiol 2012;22:112-9.

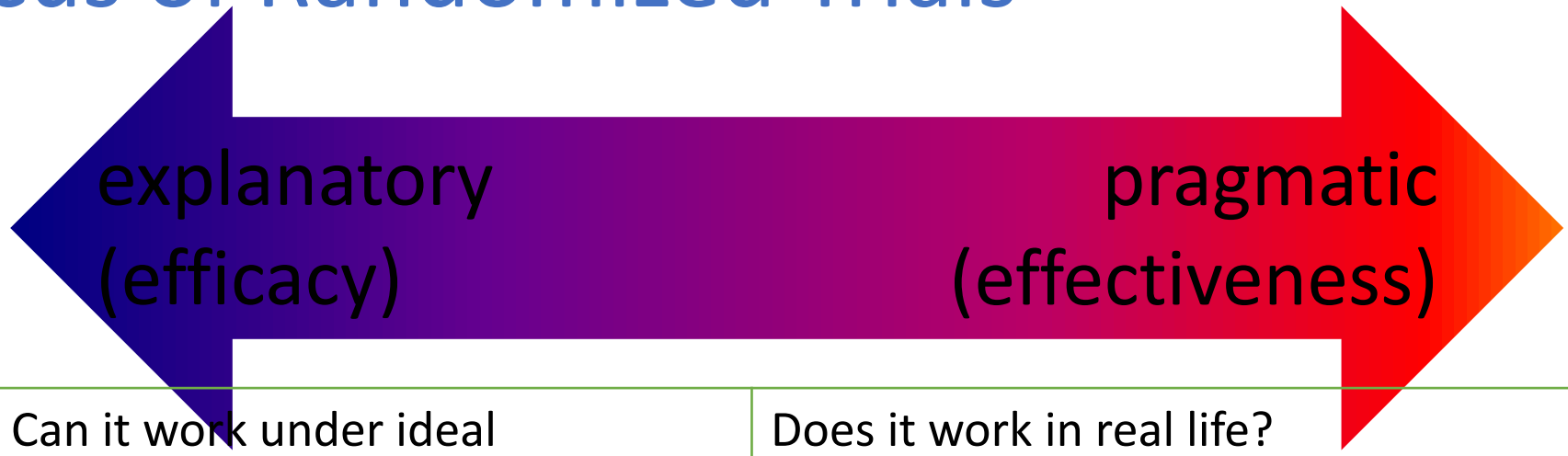


http://www.nigms.nih.gov/training/documents/systemspharmawpsorger2011.pdf

Phase 3 Clinical Trials

- Subjects: usually 500-3000 patients with target disease
- Purpose:
  - To demonstrate efficacy (not effectiveness)
  - To identify and measure the incidence of adverse effects

Focus of Randomized Trials



Question	Can it work under ideal conditions?	Does it work in real life?
Study subjects	Carefully selected, most likely to respond, adherent	All participants with condition of interest
Control intervention	Placebo	Best available alternative
Adherence	Monitored and encouraged	Unobtrusive or no monitoring; no encouragement
Outcome	Direct and immediate effect of intervention; often surrogate	Clinically meaningful; assessed under clinical conditions

Limitations of Pre-marketing Trials

- Carefully selected subjects may not reflect real-life patients in whom drug will be used
- Study subjects may receive better care than real-life patients
- Short duration of treatment
- Surrogate endpoints

Limitations of Randomized Clinical Trials

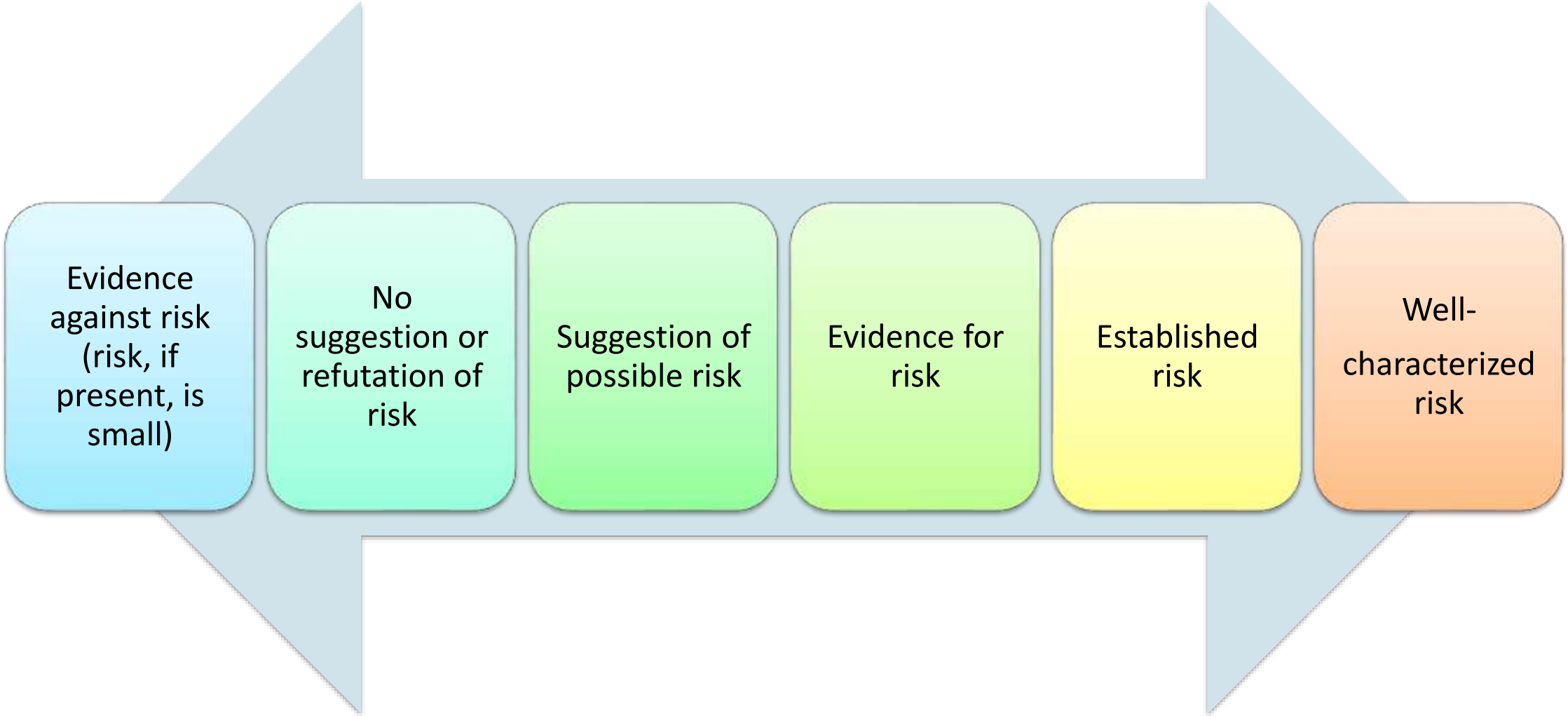
- Internal validity is excellent
- External validity may be limited
- RCT determines an average effect across a disease
- Within disease, there may be differential benefits to patients with more or less severe disease
  - E.g. oseltamivir for influenza
  - Different cancer mutations is a specific cancer may differ by population and therefore impact response to a specific therapy

Post-Approval Safety Info

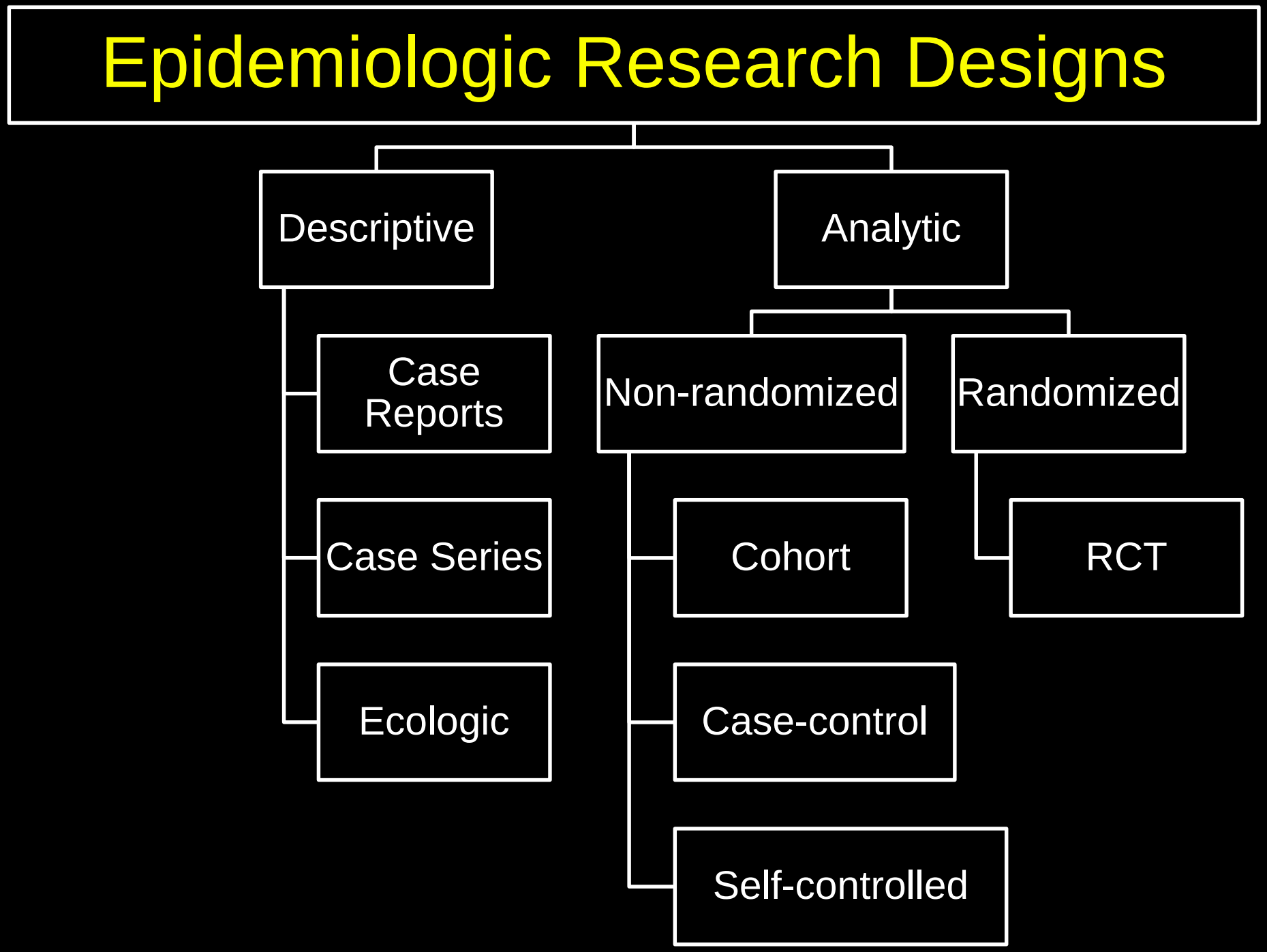
- ~20% of drugs get a new “black box” warning after marketing
- ~4% of drugs are ultimately withdrawn for safety reasons

Lasser KE. et al. JAMA 2002; 287:2215-201.
Bakke OM et al. Clin Pharmacol Ther. 1995;58:108-17

Continuum of Evidence that a Drug Causes or Does Not Cause a Given Outcome



Hennessy S, Strom BL. Ann Rev Pharmacol Toxicol 2015;55:75-87


Epidemiologic Research Designs
Descriptive
Analytic
Case Reports
Case Series
Ecologic
Non-randomized
Randomized
Cohort
Case-control
Self-controlled
RCT

Do we have any pharmacoepidemiologists in the room or in the country?

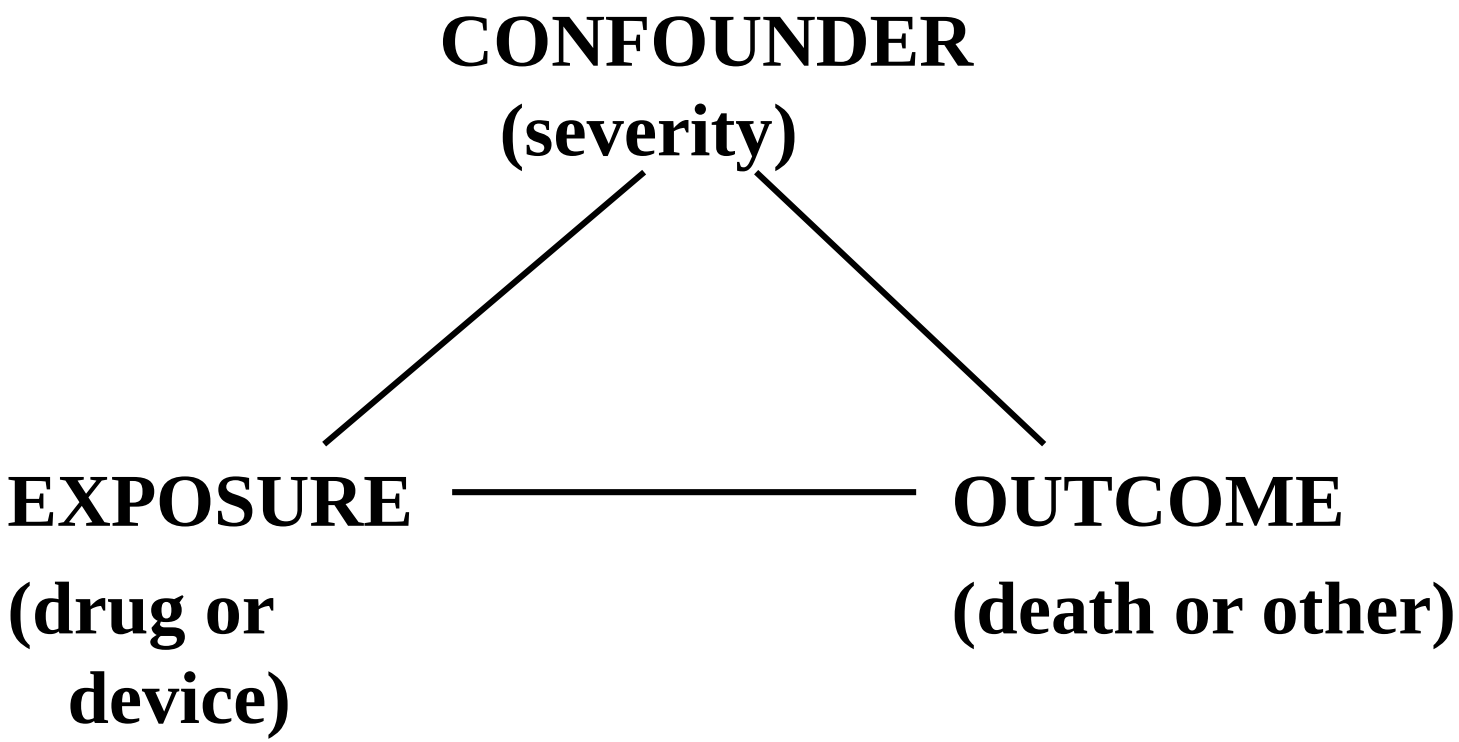
Need for data!

- Most HTAs include epidemiology data in some form.
- This is often included in order to understand the impact of the technology on the entire health care system within a country, assessments of disease prevalence and severity will be used to estimate budget impact on a system, alternatively hospital or other data that can indicate number of patients that could benefit from the technology is used.

The Need for Accurate Epidemiology Data to drive a Higher Success Rate with Health Technology Assessments

Elizabeth A Griffiths, Janek K Hendrich, Samuel DR Stoddart, Sean CM Walsh, **Acceptance of health technology assessments submissions with incremental cost-effectiveness ratios above the cost-effectiveness threshold**, ClinicoEconomics and Outcome Research 2015:7 463-476.

Central Paradigm of Modern Clinical Epidemiology



Disease Prevalence and Severity

- Prevalence of disease but also prevalence of different subtypes of a specific disease
- Severity metrics
  - In order to address cost effectiveness or cost benefit need to understand severity
  - Severity as defined by healthcare utilization burden
  - Number of outpatient visits
  - Number of urgent care visits
  - Number of hospitalizations
  - Duration of hospitalization
  - Intensity of hospitalization – ICU, etc

Definition of Outcome

- Need to clearly define the outcomes of interest
- Is it death, hospitalization, healthcare utilization, quality of life?
- Should be a validated outcome
- What is important to our society, culture, values, healthsystem?

Need to understand local epidemiology

- Classic Example is Infectious Diseases and Antimicrobial Use
- Empiric therapy and Definitive Therapy is guided by the local epidemiology
- Local could be defined as hospital, city, region, country, etc

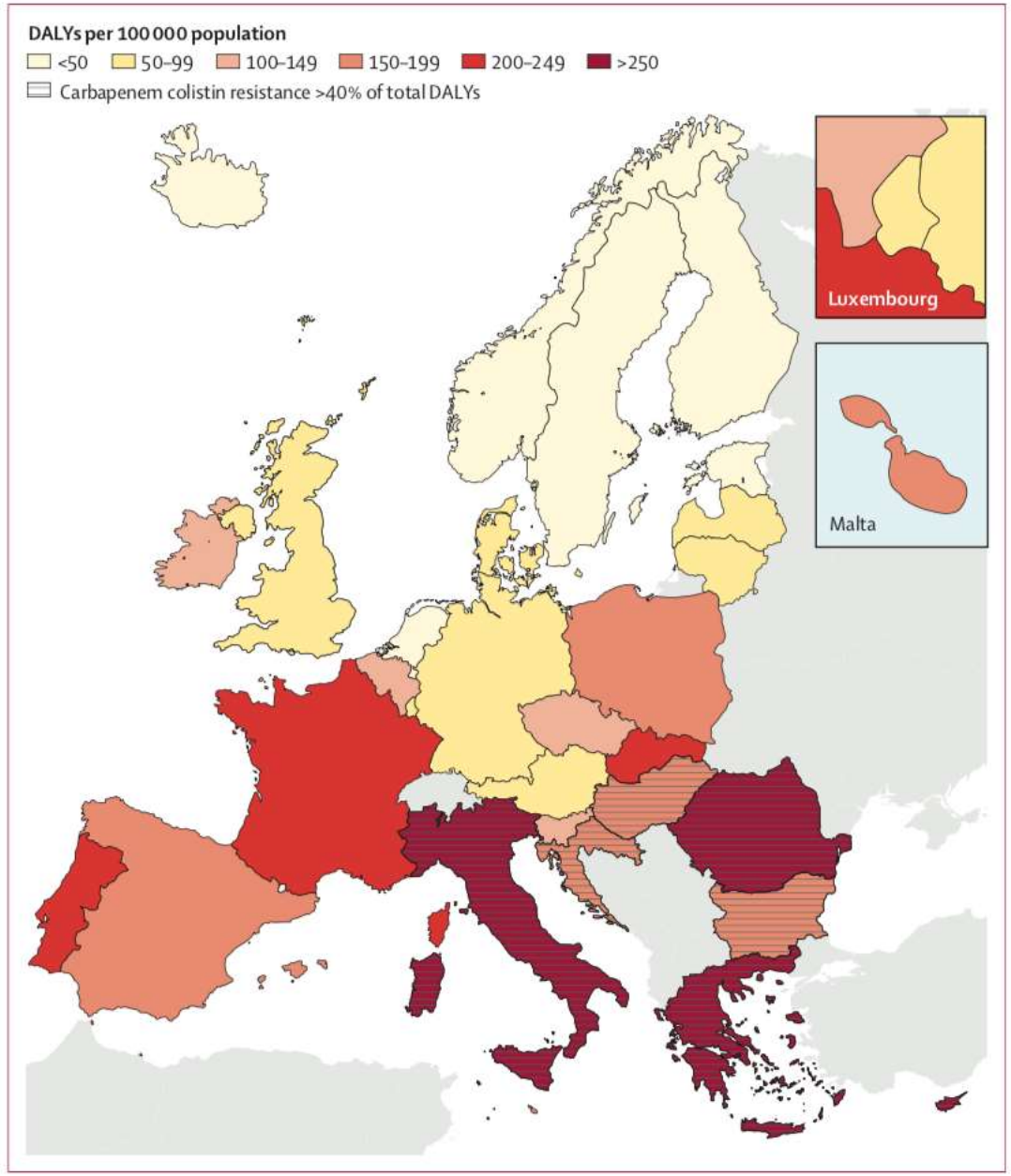
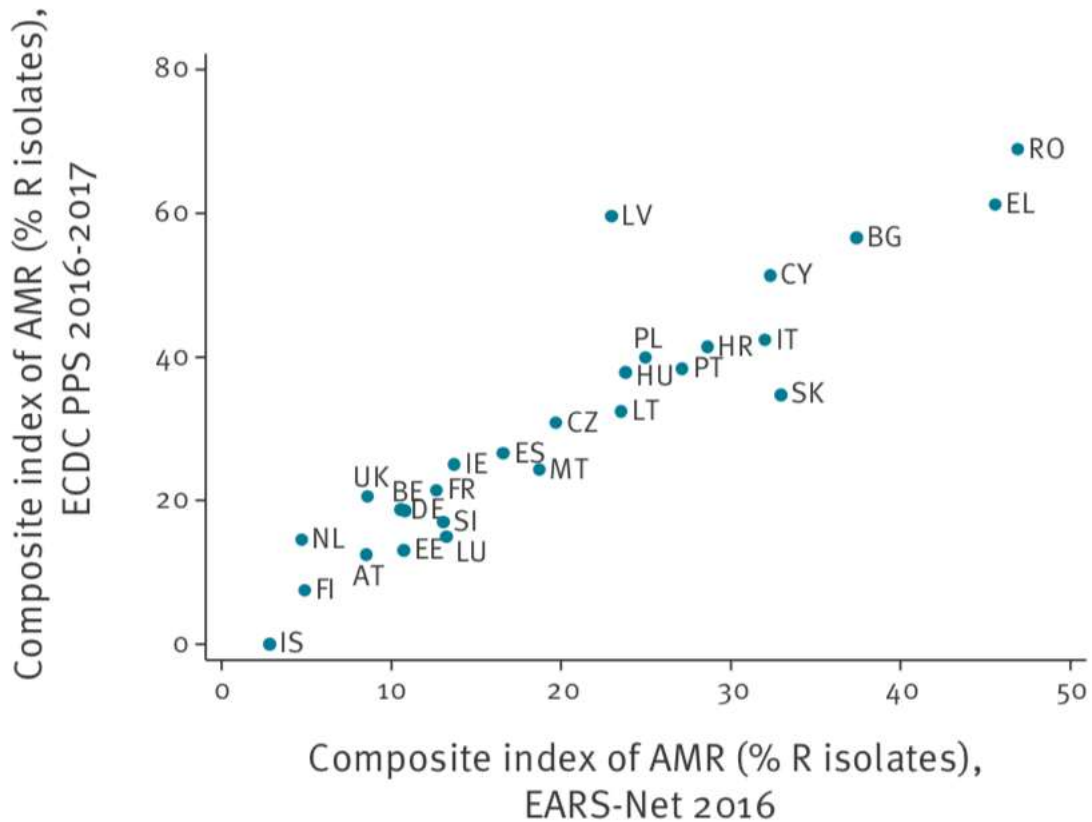


Figure 4: **Model estimates of the burden of infections with selected antibiotic-resistant bacteria of public health importance in DALYs per 100 000 population, EU and European Economic Area, 2015**
Greece did not report data on *S pneumoniae* isolates to the European Antimicrobial Resistance Surveillance Network in 2015. DALYs=disability-adjusted life-years.

A. Correlation between the composite indices of AMR from the PPS in acute care hospitals, 2016-2017 and EARS-Net, 2016 (n = 27 countries)



HTA Rejections

- Rejection rates of between 24%-58%, depending on reviewing agency.
- Discrepancy between the results calculated by the evidence review group versus the submitting manufacturer.
- Key reason was related to issues with the study population.
- Application of data not relevant to the country or population under consideration.
- Study populations did not reflect intended population in clinical practice.

RCT vs Real World Data

- The RCTs are considered as “gold standard” in clinical efficacy studies.
  - relatively short term studies
  - very well defined population
  - conducted within a controlled environment, with the sole aim of establishing clinical efficacy and safety.
- Data from RCTs is not enough.
- It needs to be supplemented with data from the ‘Real World’.
  - uncontrolled data from the general population,
  - clearer idea as to what happens when treatment or technology is made available to the public at large.

What is Real World Data (RWD)?

- The International Society of Pharmacoeconmics and Outcomes Research (ISPOR Real World Task Force Report) defines RWD as “data used for decision making that as not collected in conventional RCTs” RWD comes from the confines of a natural environment. As such, it gives a better insight into the epidemiology of a disease, patient compliance and adherence to treatment and the costs involved; information which is more relevant to policy makers.

Sources of Real World Data

- ISPOR
  - Supplementary information collected during RCTs
  - Large simple trials (also called practical clinical trials)
  - Registries
  - Administrative data
  - Health surveys
  - Electronic Health Records (EHRs) and Medical Chart Reviews

Registries as Sources of Real World Data

- Agency for Healthcare Research and Quality (AHRQ) defines a patient registry as ‘an organized system that uses observational study methods to collect uniform data, to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes.
  - comprehensive compilations of all cases of a particular disease or condition which happen in a given population.
  - registries store data for large number of patients, and follow up these patients over long periods of time, usually spanning a few decades.

Registries as Sources of Real World Data

- Integrates data from various sources.
- Primary data is collected for its defined purpose of listing.
- Secondary data is collected for purposes supplementary to, or not related to the registry.
  - from medical records systems
  - institutional or organizational databases
  - administrative and health insurance claims data
  - death and birth records, census databases, and related existing registry databases.
  - **Thus this secondary data is invaluable for epidemiological, social and economic research.**

Registries for Pharmacoeconomic Analyses

- Data on clinical outcomes, admission and discharge, resource utilization and other data used for burden of illness, cost-utility and cost-effectiveness studies.
  - Prostate cancer, radiotherapy, colorectal cancer, esophageal cancer
- Prospective HTA of new technologies after coverage to make decision makers aware of the real world implications of the new technology.
- Clinical registries are the most efficient tool for collection of such data.
- Registries important in treatment of rare diseases and orphan drugs.
- Given the low prevalence of these diseases, not possible to conduct statistically significant RCTs.

Limitations of Registries

- lack of established methodology and protocol for designing registries.
- Poor conceptualization can lead to inaccurate data.
- Definitions need to be defined at the time building the registry.
- The data collected by registries is not validated as compared to traditional RCTs.
- Beside, as the data collected is non- randomized, there is a potential for bias.

Key Features in Developing Registries

- A sound implementation plan
- Well defined and documented inclusion/exclusion criteria and data sources
- Data collection protocol and appropriate tools to record data
- Data processing procedures and software
- Quality Control Procedures
- Data access policy
- Data and outcome dissemination network for optimum utilization of data

Policy Decisions Favoring Registries for HTA

- Governments have taken up commitment
- US Centers for Medicare and Medicaid Services (CMS) released guidance in 2014
- NICE conducts HTAs for NHS uses modeling studies using RWD
- Many other developed nations realizing this need

Conclusions

- In this era of “Big Data”, we are realizing the potential for real world data stored in registries to affect policy
- We need to unlock the potential behind clinical registries and better registries and better data capture tools are developed.
- This is a unique time and opportunity for Greece to develop these tools given the financial imperatives to appropriately use drugs and devices.

- "If the whole materia medica, as now used, could be sunk to the bottom of the sea, it would be all the better for mankind , and all the worse for the fishes."

Oliver Wendell Holmes
Medical Essays, "Comments and Counter"
Currents in Medical Science

CCEB

Centers for ™ Education & Research on Therapeutics

Acknowledgement