From Clinical Observations to Experimental Research

Hierarchy of Study Designs

Dr. Dick Menzies

July 14th, 2014

Hierarchy of study designs

- Descriptive studies
  - Case reports, and case series
  - Reported data, and Prevalence surveys
- Analytic studies
  - Observational
    - Cross-sectional
    - Ecologic studies
    - Case control studies
    - Cohort studies
  - Experimental studies
    - Uncontrolled trials
    - Randomized or quasi-randomized controlled trials
      - Individual level
      - Field trials - community or group level

The starting point – an Observation

- Usually a clinical observation
  - An unusual case (young woman with PE)
  - An unusual cluster (3 homosexual men with PCP)
  - An unusual complication (ICU admissions for C Dif)
- Or, an observation based on reported data
  - Temporal trend (Increase in Lung cancer rates)
  - Geographic clustering (MS, gastric Ca)

Case Reports

- Report of a single occurrence of new disease or unusual occurrence of a known disease
  - Pulmonary embolus in young woman on oral contraceptives
  - Myocardial infarction in a child
- Strengths –
  - Rapid and cheap
  - Useful to alert community to a new disease
  - Particularly if others are seeing the same thing.
- Weaknesses –
  - Rare events do happen - Someone always wins the lottery
  - Clinicians have to recognize that the problem seen is unusual. Requires genuine expertise

Case series

- This means 3 or more of the same condition
  - Unusual events - as for case reports
  - Generally adds a little more than case reports
  - More cases equals potentially more weight
- But, rare events can also happen together
  - 3 cases of Angiosarcoma in workers from a PVC factory
  - Lightning strikes the same person twice
  - Three people on same street win lottery
  - All have occurred. Was one NOT due to chance?

Case series – example

Extensively drug-resistant tuberculosis as a cause of death in patients with TB and HIV in rural South Africa

Neel R Gandhi, Anthony Moll, A Willem Sturm, Robert Pawinski, Thiloshini Govender, Umesh Lalloo, Kimberly Zeller, Jason Andrews, Gerald Friedland

- Among 475 patients with culture-confirmed TB:
  - 39% (185 patients) MDR-TB
  - 6% (30 patients) XDR-TB.
- Of XDR-TB:
  - 45% had been previously treated for TB ;
  - 67% had a recent hospital admission.
  - 100% of tested for HIV were co-infected.
  - 98% died, with median survival of 16 days

Large Case Series

- Description of a large number of patients with a new disease, or receiving a new treatment or new operation .
- Advantages – Comprehensive - Includes all cases
- Disadvantages – No controls or comparison population
  - Implicit comparison with standard, or previous therapy
  - Historical controls or concurrent non-randomized controls
- Thus better results can be because:
  - The new treatment IS better,
- BUT could be,
  - Better selection of patients
  - Other improvements in care, or better care at specialized centre

After the case report/case series. Need to review and understand disease

1. Case definition
   - Who gets it, clinical features, outcomes?
2. What appears to be the biology?
   - Apparent latency
   - Manifestations - what organs affected
   - Pathogenesis - probable or known
3. Review the literature
   - This is often forgotten, or under-utilized
   - But is essential to avoid mistakes and wasting time

Population characteristics – who gets the disease?

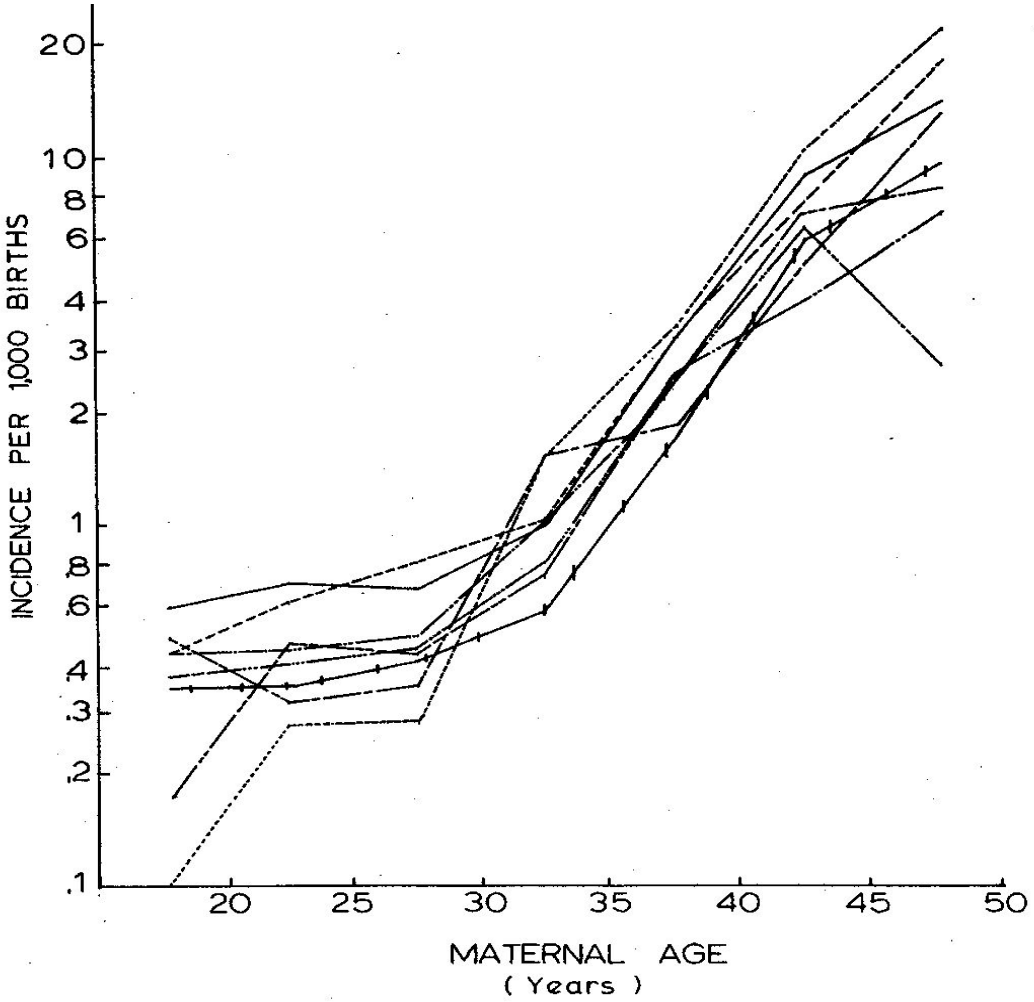


Figure 7–12. Incidence rates of mongolism by maternal age at birth from selected studies, 1923–1964

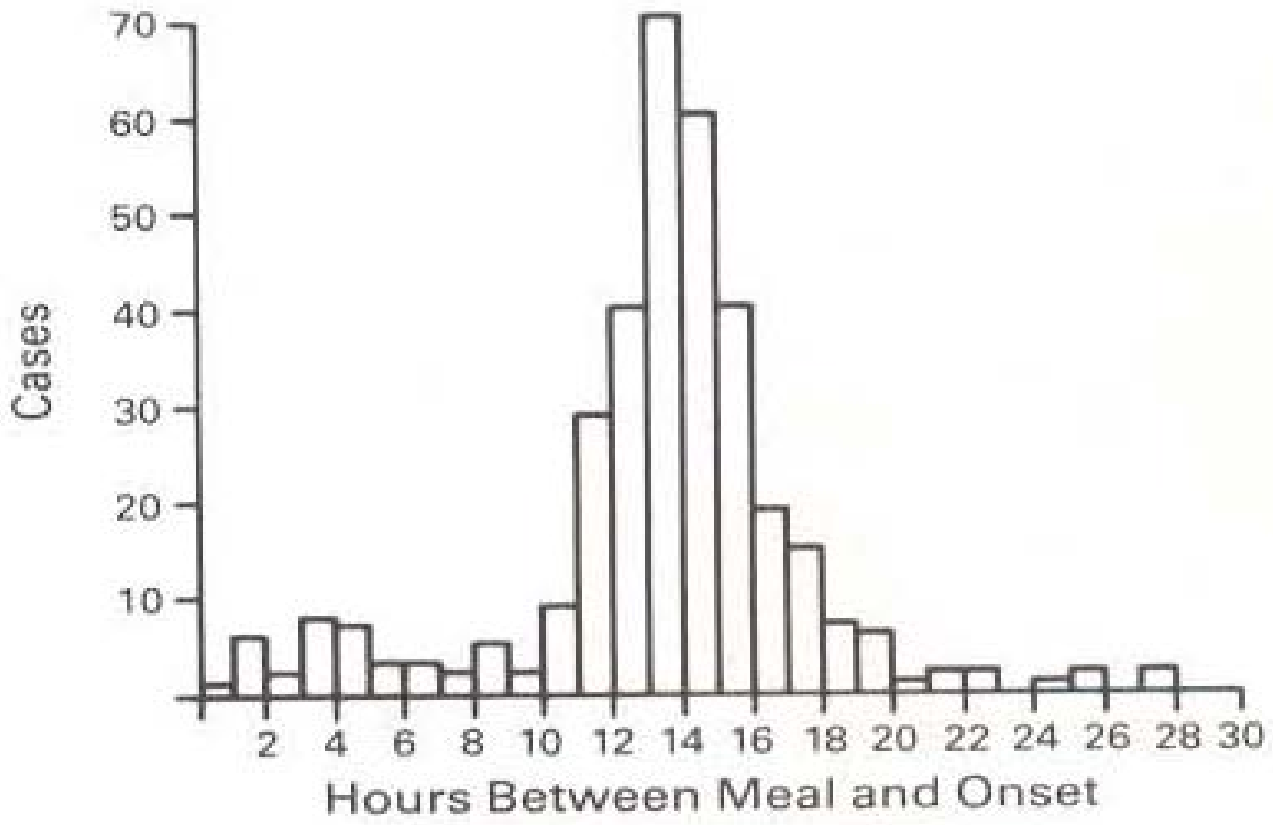
Source: **Lilienfeld (20). Copyright © 1969, The Johns Hopkins University Press.**

Understanding the disease - latency and duration

- Latency refers to interval between exposure and disease.
- Plausible that exposure leads to disease if interval from exposure to disease fits with known latency

Latency and clinical acumen

- The shorter the latency the easier to link exposure and disease
  - Immediate – eg Grain workers and asthma
  - <24 hours “must have been the egg salad”
  - < 1 week – “I think I caught this from Fred”
  - If longer it gets harder. “So many exposures, so much time, and so little memory” (recall)
    - Asbestos and mesothelioma
    - Smoking and most diseases



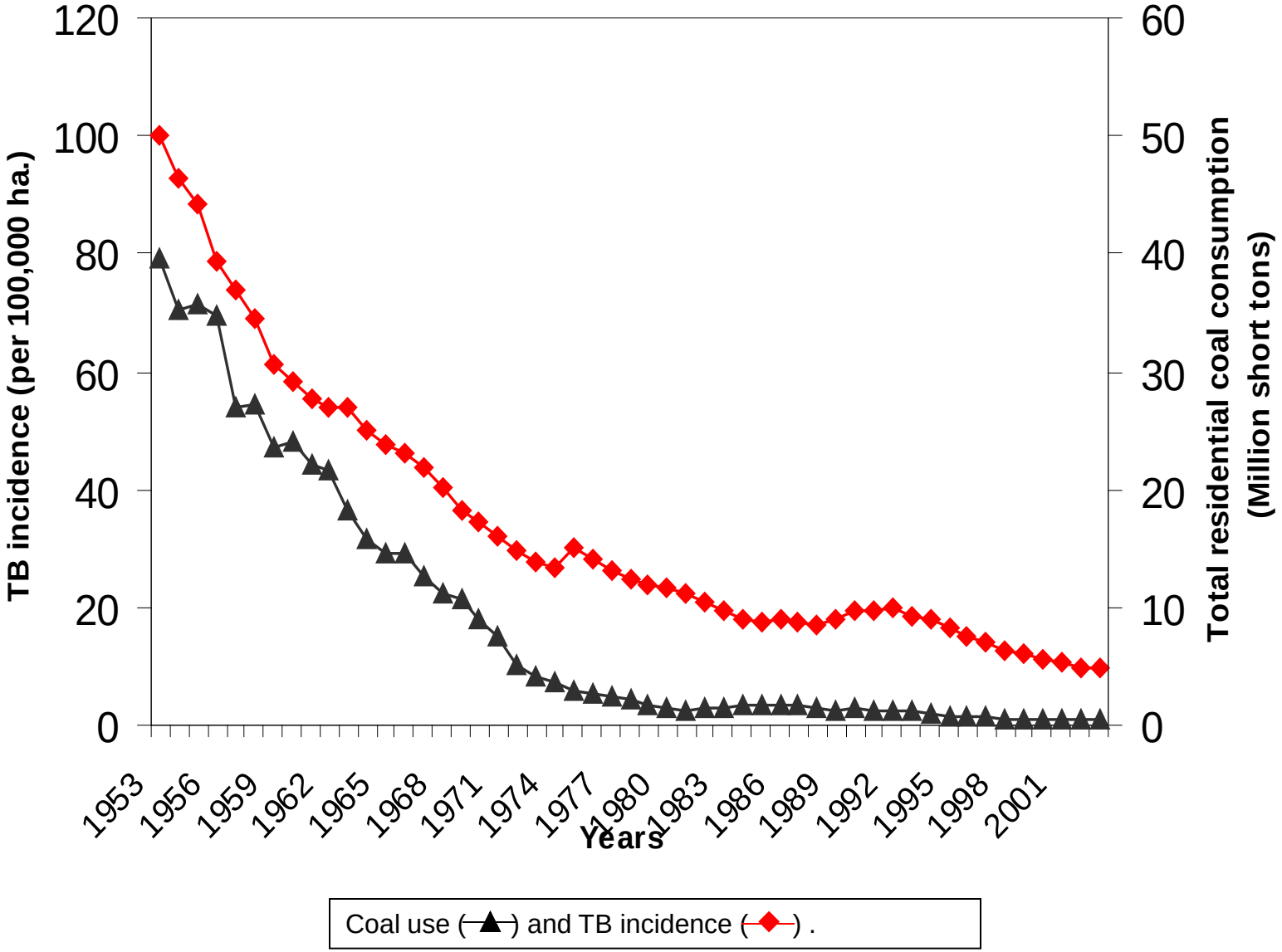
Distribution of incubation in common-source outbreak from gravy contaminated with *Clostridium perfringens*.

Reported Data

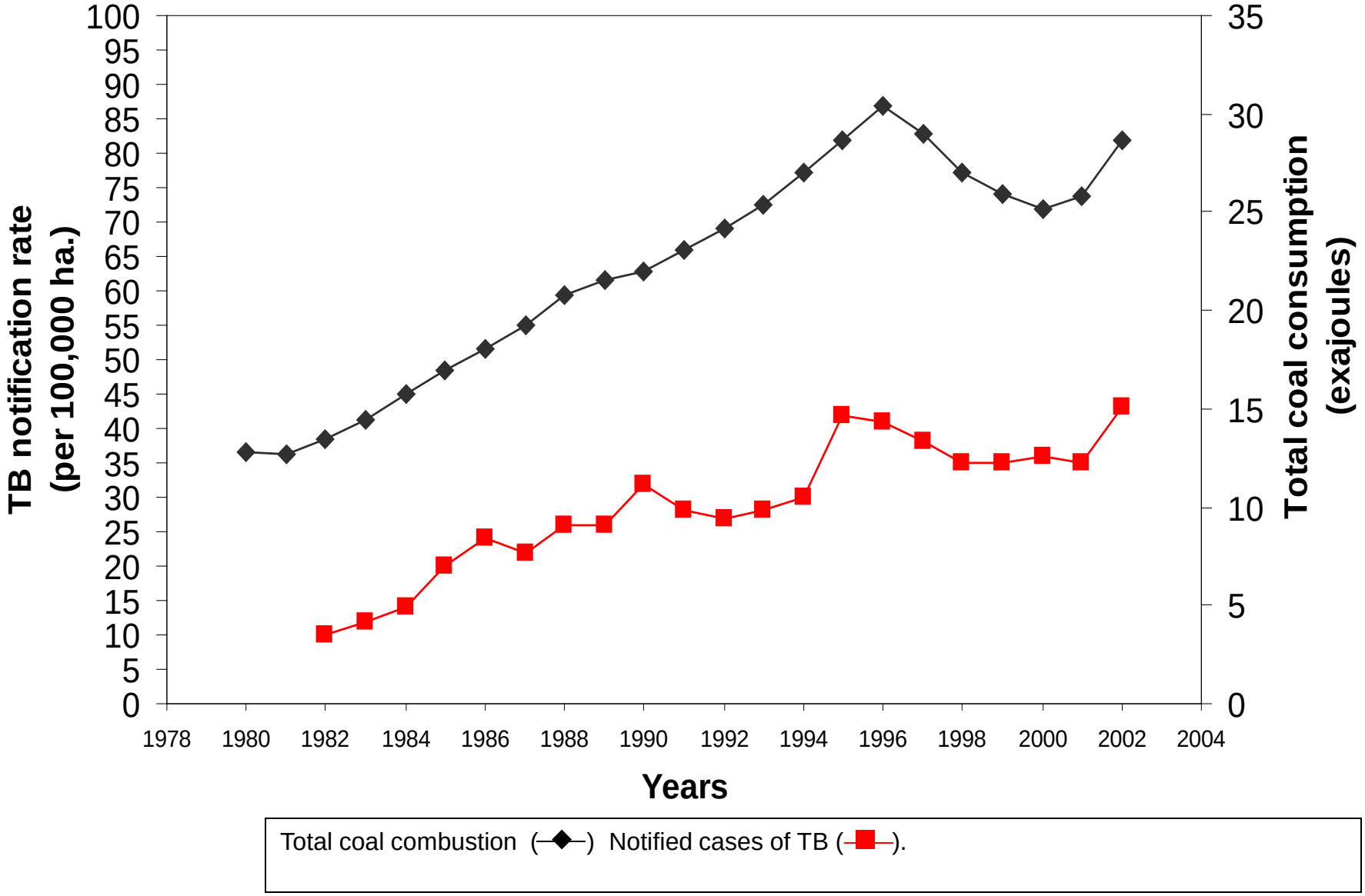
- Reported data commonly used
  - TB, HIV, Cancers
  - Useful if this is COMPLETE
- Useful to:
  - Define incidence/prevalence
  - Identify geographic or temporal differences
  - Describe clinical characteristics
  - Describe outcomes.
- Implicit comparison with general population
  - Risk factors can be identified.

Temporal trends may indicate clues to causal exposure

Coal use and TB in USA: 1953 – 2003



Temporal trends may indicate clues to causal exposure
Coal use and TB in China: 1978 - 2004



Ecologic Studies

Advantages

- Usually very easy and quick studies
- Take advantage of already gathered data
  - Exposures
  - Diseases

Disadvantages

- Relationship may be due to completely unmeasured factors
- VERY substantial potential for confounding

Ecologic study – Geographic distribution may indicate clues to exposures: Skin test sensitivity to coccidiomycosis and place of residence

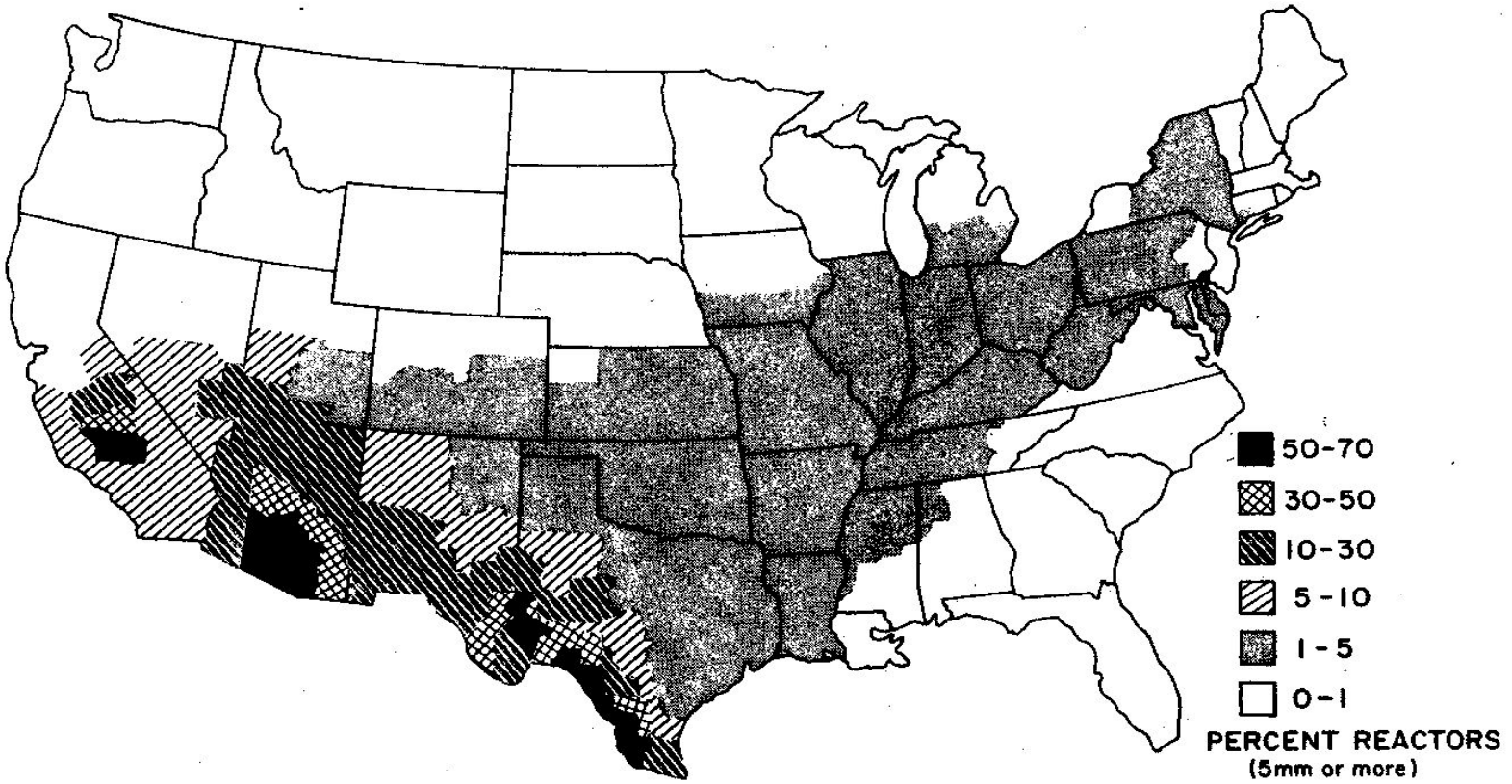


Figure 7–9. Percent reactors to coccidioidin skin test among white men and women, 17–21 years of age, by county of residence, United States, 1945–1951

Source: Edwards and Palmer (11).

Directionality in research - Backward

- Retrospective: Start with a persons with disease and ‘look backward’ in time to ascertain exposures.
- Advantages: Biggest is convenience – do not have to wait a long time, because disease HAS happened.
  - Makes these studies much quicker to complete, and much cheaper.

Observational studies – You gather the data:

- Prevalence surveys – Easy to design, Moderately time consuming and expensive to conduct
- Case-control – hard to design,

  Quick and easy to conduct
- Cohort studies – moderately hard to design. Very time-consuming and expensive to conduct

Directionality in research - Forward

- Prospective: Start with a population and observe them ‘going forward’ in time. Exposures are measured first, and health events are measured afterward, as they occur.
- Advantages: Biggest is accuracy of exposure
  - Also certainty that exposure is followed by disease, not simply coincidental

Retrospective designs: Prevalence or cross-sectional studies

General approach:

- Pick a disease (can pick several)
- Identify the possible exposures (can pick several)
- Pick a population (one time survey)
- Data gathering:
  - Measure who has the disease
  - Measure who has the exposure.
- Analysis: Association of disease presence with exposure presence (Prevalence odds ratio)

Cross-sectional or Prevalence Studies
(continued)

Advantages

- Good for common/chronic diseases
- Also good for fairly common exposures
- Allows one to measure multiple disease or conditions and multiple exposures

Disadvantages

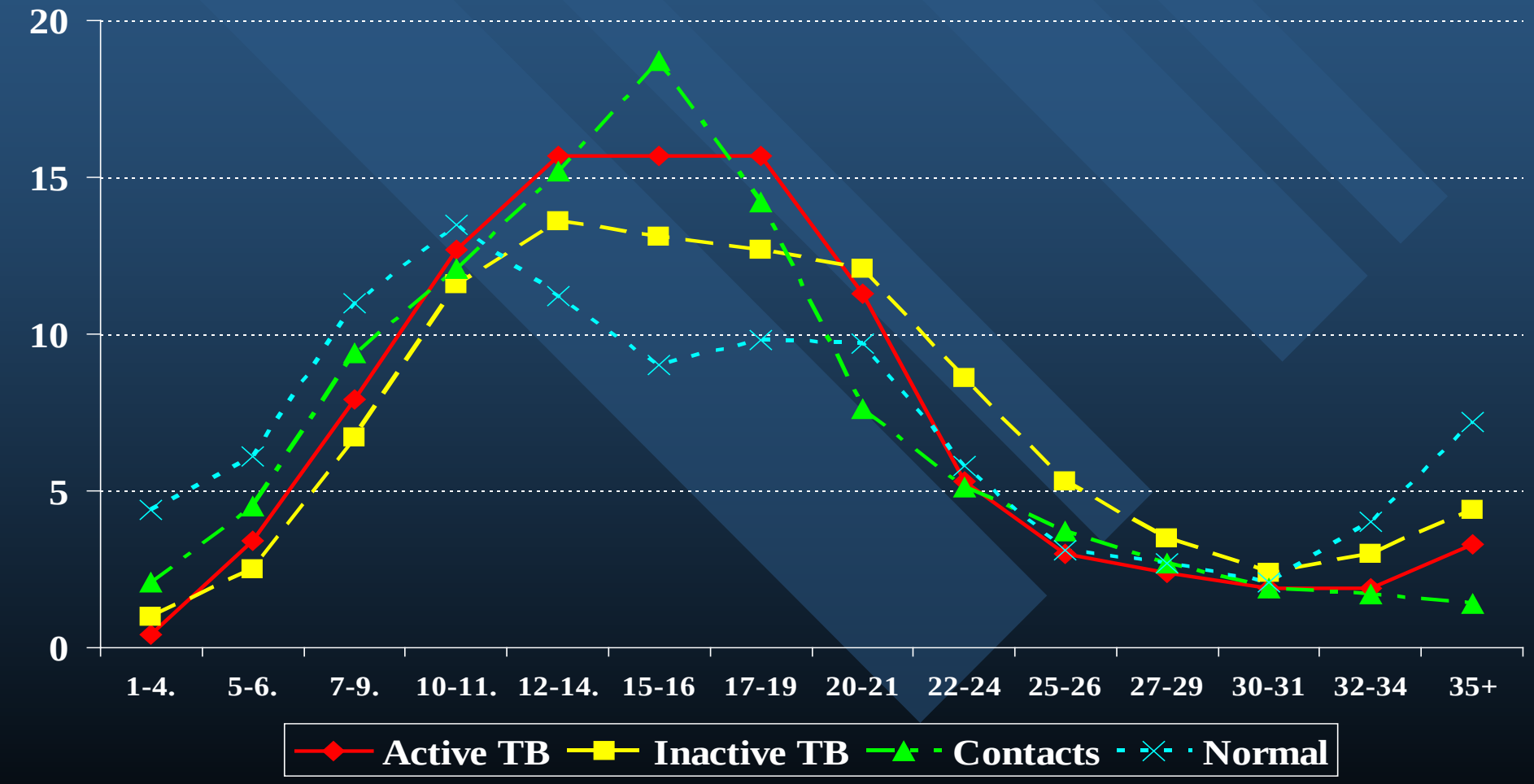
- Measurement of exposure often difficult
  - Recall problems if long latency
  - May change over time (Alcohol, smoking, blood pressure)
- Can not distinguish cause and effect
  - (Tobacco Industry defense)

Tuberculin (or IGRA) Surveys
A special type of cross-sectional survey

- Once TST or IGRA convert to positive with TB infection – they remain positive lifelong
- Cross-sectional survey – detects all with positive tests – from recent or remote
- From prevalence of positive test at a given age – can calculate average annual risk of TB infection.
- Can compare prevalence in different populations
- If different ages, or different exposure periods can estimate trends in infection

Does Size matter? Relationship of patient's diagnosis to size of TST

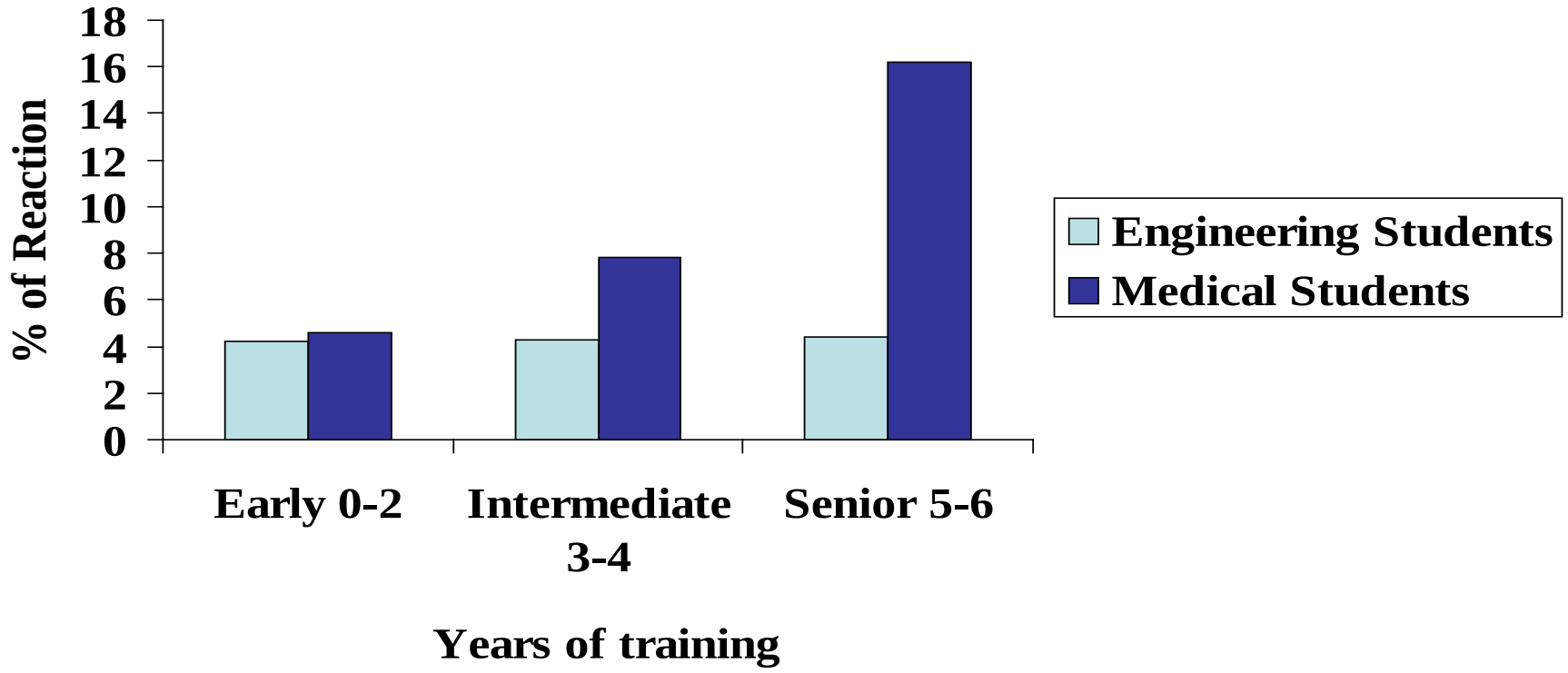
(from Al-Zahrani et al AJRCCM, 2000)



University students in Brazil

(All BCG vaccinated in infancy)

Silva et.al. IJTLD2000; 4:420-426

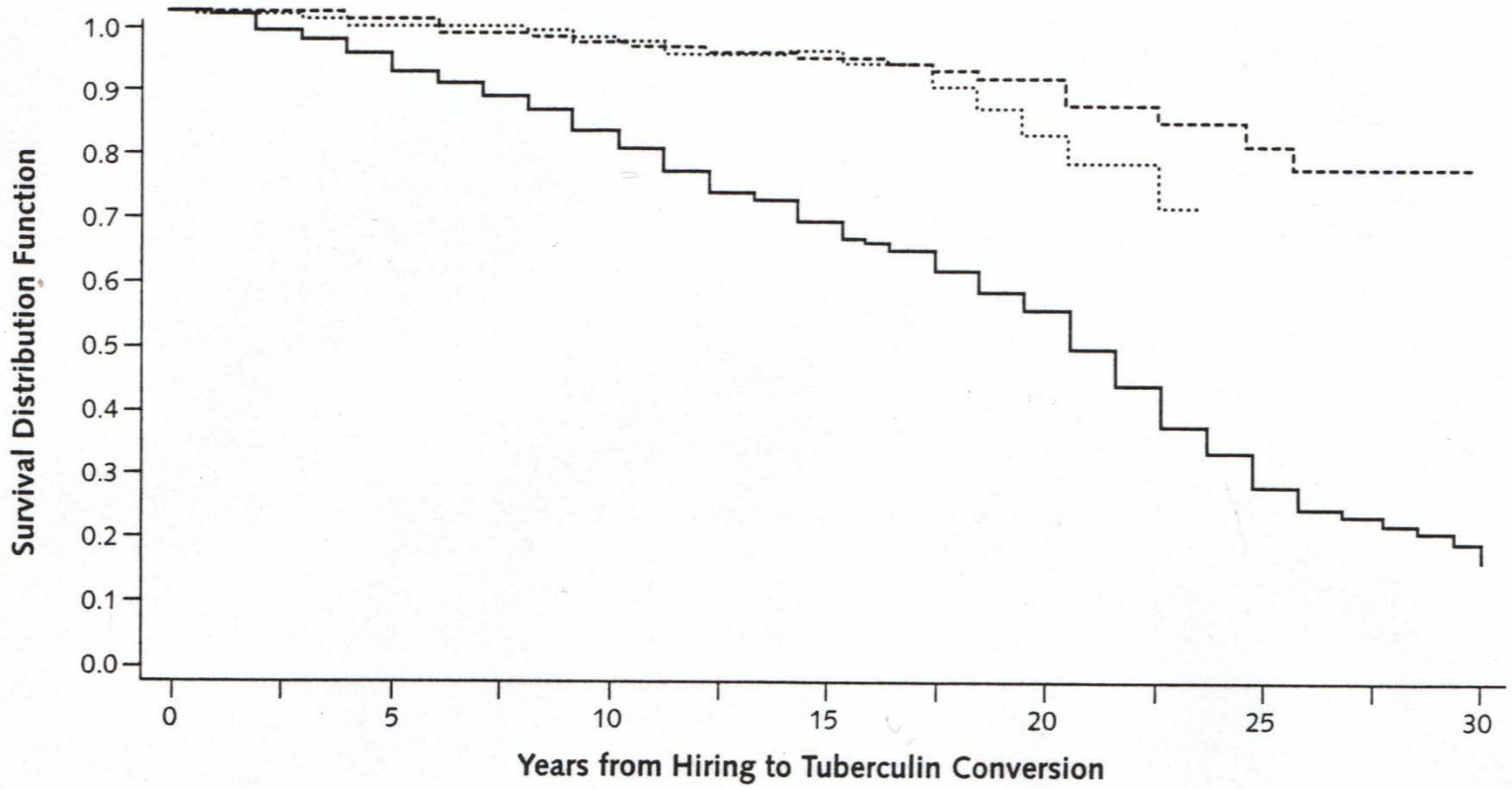


Average ARI: Preclinical 0.2%

Clinical 2.9%

Incidence of TB in Brazil: 75/100 000

Example of Kaplan-Meier analysis: General Hospital Ventilation and time to TST conversion



Personnel, *n*						
< 2 ACPH	471	372	217	139	79	22
≥ 2 ACPH	651	518	237	104	42	20
Low-risk/ nonclinical	150	122	74	38	15	3

Retrospective Analytic Studies: Case Control

General design

- Identify Cases - patients with disease
- Identify Controls - without disease
- Measure exposures in both
- Analysis - is exposure more likely (odds > 1) in cases than controls

Case Control study – example
TB outbreak in Kangiqsualuujuaq

Factors associated with acquisition of TB infection during the outbreak.

Variable	Newly Infected, N=88 N(%)	Uninfected, N=67 N(%)	Crude OR (95CI)	Adjusted OR (95CI)
Age 15	24 (27)	34 (51)	ref	ref
Age 15 - 29 y.o.	41 (47)	26 (39)	**3.8 (2.1 - 6.9)**	**4.2 (1.7 - 10.3)**
Age ≥ 30 y.o.	23 (26)	7 (10)	**4.2 (1.5 - 12)**	5.0 (0.8 - 30)
Visited a gathering house	47 (53)	16 (24)	**3.7 (1.6 - 8.1)**	**3.6 (1.3 - 9.9)**
Lived with smear-positive person**	20 (23)	1 (1)	**19 (3.3 - 113)**	**20 (4.0 - 100)**

Case Control Studies

Advantages

- Relatively cheap and quick
- Particularly useful for studying rare conditions
  - Or conditions with long latency

Disadvantages

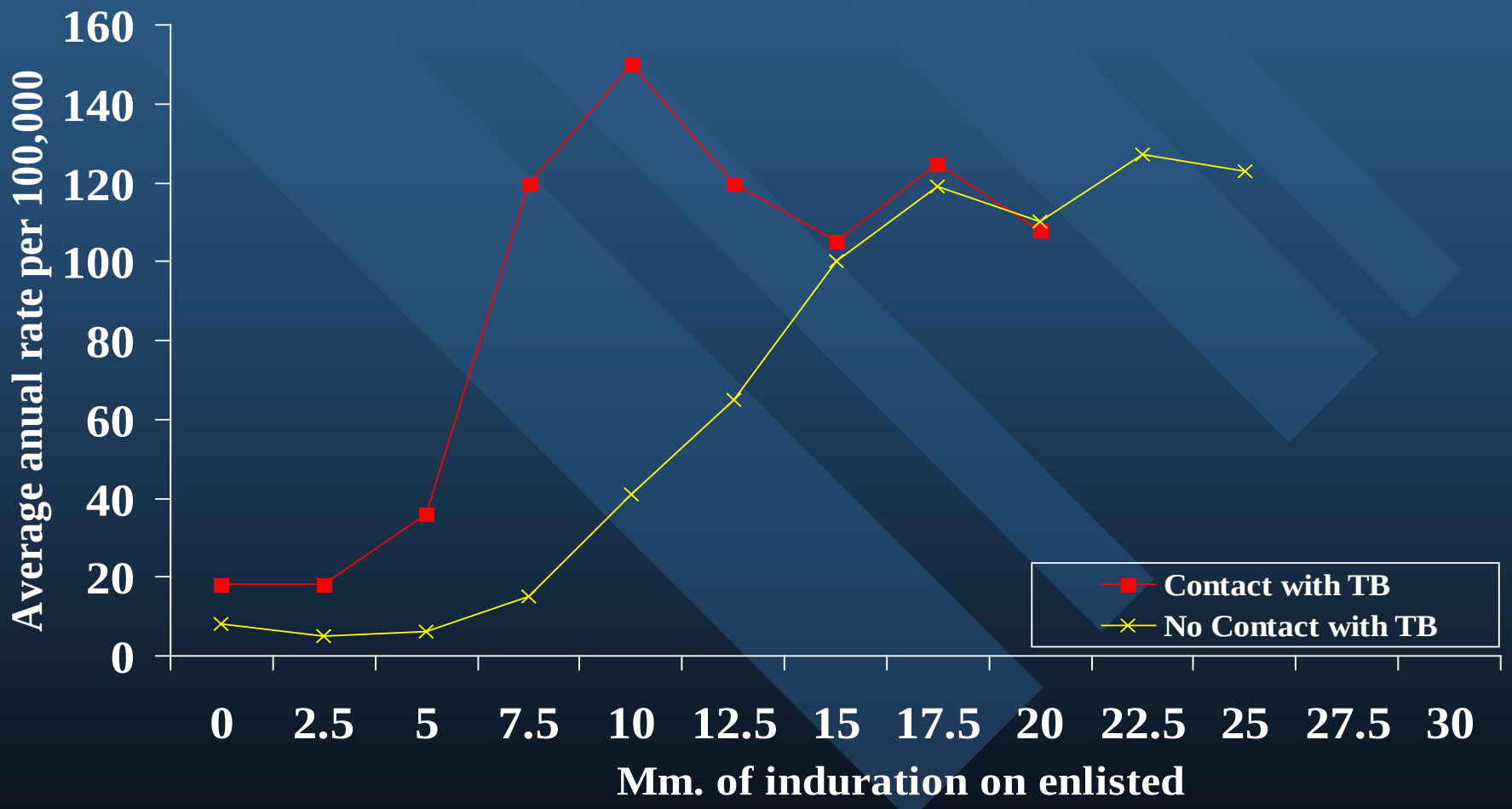
- **Controls, Controls, Controls**
  - Very difficult to select proper controls
  - This is the source of most problems in case control studies
  - And is why they are generally considered weak evidence.
- Difficulties of retrospective exposure assessment
  - particularly if long latency

Analytic Studies – Cohort studies

General design

- Start with population free of disease (of interest)
- Measure of interest
- Follow them for a period of time
- Measure occurrence of disease
- Analysis – occurrence of disease in persons who had/did not have exposure of interest

Average Annual Incidence of Tuberculosis Among Navy Recruits By History of Household Contact



Comstock, Edwards, and Livesay; Am Rev Respir Dis 1974; 110:576

Cohort Studies

Advantages

- Can measure many exposures
- Can measure many diseases
- Temporal relationship clearer (cause before disease)

Disadvantages

- Long and expensive (often very $$$)
- Good for common diseases (some cancers, cardiovascular)
- Inefficient for rare diseases or with long latency
- Also what if you fail to measure key determinants
  - (Solution = freezer)

Experimental Studies:

Uncontrolled

- No control or comparison group
- Phase 1 or Phase 2 drug trials

Experimental Studies:

Controlled Trials

- Non-randomized – allocation to different not done randomly, but rather purposely
- Quasi-randomized – allocation to intervention groups not randomly, but using schemes such as: date of birth, days of week, hospital records
- Randomized – allocation is random so all participants have equal chance of getting each intervention

Experimental Studies – Randomized Trials

General Design

- Pick an intervention – usually a form of treatment
  - You can only pick one
- Find a group of patients that agree to participate
  - Have to be representative of condition
- Give the new treatment to some
  - Some get the old (or no) treatment
  - Do this randomly
- Follow all to see outcomes

Randomized Trials

Intensified regimen containing RIF and Mfx for TB meningitis: an open-label, randomised controlled phase 2 trial

Rovina Ruslami, A Rizal Ganiem*, Sofiati Dian, Lika Apriani, Tri Hanggono Achmad, Andre J van der Ven, George Borm, Rob E Aarnoutse, Reinout van Crevel*

- **Open-label, phase 2 trial. Factorial design**
- **Patients aged >14 with TB meningitis**
  - **All received INH & PZA & Steroids**
- **Randomly assigned for 14 days – by computer-generated schedule:**
  - **RIF: 450 mg vs 600 mg, intravenously, and**
  - **Mfx 400 mg, or Mfx 800 mg, or EMB 750 mg daily.**
- **14 days of treatment all patients, then routine treatment.**
- **Endpoints: PK analyses (blood and CSF) adverse events attributable to tuberculosis treatment, and survival.**

Randomized Trials

Advantages

- Best way to evaluate an intervention
- Best control of bias and confounding

Disadvantages

- Not easy or feasible for all interventions
- Not for studies of risk factors or natural history
- Substantial refusal or drop-out rates can restrict generalizability
- Population selected may not be representative
  - Younger adults with only one condition
  - Often exclude pregnant woman, kids, elderly!

Experimental Community or Field Trials

General Design

- Pick an intervention to be applied at a community level
  - Fluoride in water, public education, vaccination
- Find several communities or population groups
- Apply intervention to some and not others
  - Randomly again
- Measure outcomes at population or group level

Cluster randomized Trials – example

Effect of improved tuberculosis screening and isoniazid preventive therapy on incidence of tuberculosis and death in patients with HIV in clinics in Rio de Janeiro, Brazil: a stepped wedge, cluster-randomised trial

Betina Durovni, Valeria Saraceni, Lawrence H Moulton, Antonio G Pacheco, Solange C Cavalcante, Bonnie S King, Silvia Cohn, Anne Efron, Richard E Chaisson, Jonathan E Golub

- **29 HIV clinics in Rio de Janeiro.**
- **Staff trained in TB screening, TST and INH.**
- **Clinics randomly allocated when began the intervention period. 2 clinics started every 2 months starting from Sept 2005, until Aug 2009**
- **Outcome: TB incidence +/- death**

Community or Field Trials

Advantages

- Only way to study some interventions
- May offer better assessment of likely impact of these interventions

Disadvantages

- All the same problems as ecologic studies
- Also some important ethical issues (eg., fluoride)

Thanks