Observational Studies

Design of Epidemiologic Studies

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

To finish the teaser from the last lecture…..

Different Variables May Be

Effect Modifier(s)

Potential Confounder(s)

Other things

If measured these are usually “covariates” in the statistical model

Effect Modification

Interaction

Synergy

Could be larger or smaller

Association between outcome and another variable (e.g. intervention) is modified by different levels of a third variable

Smoking, Asbestos, and
Lung Cancer

Smoking (alone) ↑ risk of lung cancer by A

Asbestos exposure (alone) ↑ risk of lung cancer by B

Smoking AND having asbestos exposure ↑ risk of lung cancer by MORE/LESS than A+B

Effect Modification

A Short Introduction to Epidemiology

Neil Pearce chapter (2005)

The phrase effect modification, defined for different professions

Biostatisticians, public health workers, physicians, lawyers, biologists, epidemiologists,….

Confounding

Two or more variables

Known or unknown to the researchers

Confounded when their effects on a common response variable or outcome are mixed together

Association between an exposure and outcome is misestimated due to the failure to account for a third factor (the confounder)

Consider

Association observed between carrying matches in your pocket and lung cancer

Carrying matches causes lung cancer

OR

Association between carrying matches and lung cancer is result of confounding by another unmeasured variable associated with both

(Pam Shaw, CTR Course 2013)

Coffee and Pancreatic Cancer

Coffee and Smoking

Confounding Example

Relationship between coffee and pancreatic cancer, BUT

Smoking is a known risk factor for pancreatic cancer

Smoking is associated with coffee drinking

Coffee drinking is associated with smoking

Smoking is not a result of coffee drinking

Coffee and Pancreatic Cancer

What is Confounding

If an association is observed between coffee drinking and pancreatic cancer

Coffee actually causes pancreatic cancer, or

Coffee Causes Pancreatic Cancer

What is Confounding

If an association is observed between coffee drinking and pancreatic cancer

Coffee actually causes pancreatic cancer, or

The coffee drinking and pancreatic cancer association is the result of confounding by cigarette smoking

Smoking is a Confounder: Coffee does NOT cause Pancreatic CA

How to Handle Confounding

Identify potential confounders

MEASURE THEM!

In the data analysis use

Stratification, or

Adjustment (add the variable to the model)

Fear the unknown!

More to Confounding? Yes!

Residual confounding

Poor measure of the confounder

Physical activity

Even when we put the confounder as measured in the model, not really explaining the effect of real physical activity in the model

Example

Ever Smoked yes/no; pack years

Randomization =
No Confounders! Wrong!

Side note

Randomization helps protect against confounding

Does not prevent confounding

Non-random drop-out or attrition

Patients testing substance

And then dropping out, or taking more of item

Confounding and Effect Modification

Objectives

Define epidemiology

Identify common observational study designs and understand why they may or may not be used to answer a research question

Chapter 18, 3rd Edition

Thanks to Jerry Menikoff, OHRP, for rearranging, editing and providing comment on these slides

Outline

Definitions

A few study designs

Bias

Conclusions

What is Epidemiology?

Study of the distribution and determinants of disease and injury in human, animal, plant, or other populations

[Human] disease does not occur at random

[Human] disease has causal and preventive factors that can be identified through systematic investigation of different populations or subgroups of individuals within a population

Hennekens and Buring, 1987

Think Outbreak
Epi - Epidemic

What is Epidemiology?

Studying epidemics

EIS (Epidemic Intelligence Service) at CDC

Big cohort studies

Nurses Health Study

Many things in between

Considered (by some) cornerstone of Public Health Research

Are all big epi studies refuted?

All the epidemiologic studies prior to Women's Health Initiative (WHI)

They did not agree, really

Now with new statistical methods, well, hindsight was 20/20

Or adjust for socioeconomic status...

Prevention hard to study except by epidemiology

New York Times Magazine, 16 September 2007: http://tinyurl.com/5jjhkh

Epidemiology is Hard

Measure many things

Measure each thing many different ways

Measure each of those VERY accurately

Often

Do not lose any data

Same way every time

You cannot know what you do not measure

Epidemiology and Hypotheses

Epidemiology is hypothesis generating evidence

Like circumstantial evidence in court?

May be the only information outside of the laboratory

Fundamental limitation of observational studies

Distinguish associations

CANNOT inherently determine causation

Generating Hypotheses

Epidemiology

Clinician experience/observation

Out of thin air

Causal Inference in Observational Studies: Epidemiologic Criteria

Statistical significance

Strength of association (odds ratio, relative risk)

Dose-response relationships

Temporal sequence

Consistency of the association (internal "validity")

Replication of results (external validity)

Biological plausibility

Experimental evidence

Experimental or Observational

Epidemiologists used several different types of studies

Interventional or experimental

Researcher influences what happens to subjects (e.g., clinical trial)

Different concept for human subject protections

Observational

Descriptive (who, what, where, when)

Analytical (how, why)

Outline

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Observational Studies

Case Reports

Case Series

Cross-sectional Surveys

Case-Control Study

Cohort Study

Case Reports and Series

Observations of patients with defined clinical characteristics

Certain disease

Cluster of symptoms

Description of data without comparison groups

Data from well defined group of people

Case Reports and Series

Clear definitions of phenomenon

Same definitions for all individuals in series

Observations reliable and reproducible

GOOD observational studies very useful

Descriptive Statistics

Mean; median

Standard deviation/error

Proportions

Confidence limits or intervals

Separate data for subgroups

By sex, age, etc

Case Reports and Series

Hypothesis formation

Natural history

Clinical experience

Biased patient selection?

Generalizability of results?

Chance or characteristic?

Example

Initial report of five cases of pneumocystis pneumonia in previously healthy, homosexual men

US Centers for Disease Control and Prevention. Pneumocystis pneumonia-- Los Angeles. MMWR 1981; 30:250-2.

Observational Studies

Case Reports

Case Series

Cross-sectional Surveys

Case-Control Study

Cohort Study

Cross-sectional or Prevalence Surveys

Observe prevalence and characteristics of disease

Participant characteristics in a well defined population

Cross-sectional or Prevalence Surveys

Define population

Derive a sample of the population

Define the characteristics being studied

Standardized observations

Clearly defined

Methods of data collection applied equally to all study participants

Prevalence & Incidence
Defined

Prevalence

with disease / # at risk

If you take a snap shot

How many diabetics in Brazil right now

Prevalence = Incidence * Duration

Incidence

NEW cases of disease (over a period of time) / # at risk during that period

How many new (incident) cases of diabetes diagnosed in 2007 / # who could develop disease in 2007

What is Described in Tables

Descriptive

How common is the factor?

Characteristics of a group

Distribution of factors of interest (e.g. age)

Associative

Relationships between factors

How do those with one factor differ from those without?

Cross-sectional or Prevalence Surveys

Descriptive

Prevalence (% or cases per 105, etc)

Mean or median levels of relevant factors

Subset by important subgroups

Analyses

Categorical

Chi-square test, Fisher's Exact test, logistic or ordinal regression

Continuous

t-Test, regression or other analyses

Cross-Sectional Observational Studies

Collect a representative sample

Simultaneously classify by outcome and risk factor

Positive Attributes

Inexpensive for common diseases

More representative cases (vs. case series)

Tend to be short (duration)

Specific population

Simultaneous wide variety of measurements

Negative Attributes

Unsuitable for rare diseases

Unsuitable for disease of short duration

High refusal rate → inaccurate prevalence estimates

More expensive/time consuming than case control studies

Time is the best/worst confounder of all

Examples

Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999-2002. JAMA 2004;291:2847-50.

Measure height and weight in National Health and Nutrition Examination Survey (NHANES)

Flegal KM, Graubard BI, Williamson DF, Gail MH. Cause-specific excess deaths associated with underweight, overweight, and obesity. JAMA 2007;298:2028-37.

Observational Studies

Case Reports

Case Series

Cross-sectional Surveys

Case-Control Study

Cohort Study

Case Control Studies

Observations regarding possible associations between a single outcome (usually a disease) and one or more hypothesized risk factors or exposures

Well suited for studying

Rare diseases

Diseases with long latency periods

Generally quicker and less expensive than cohort studies

Case Control Studies

Compare the prevalence or level of the possible risk factor between

Representative group of disease subjects

CASES

Representative group of disease-free

CONTROLS

Same population

Case Control Studies

Cases and Controls

Cases represent all patients who develop disease

Controls represent general ‘healthy’ population not developing the disease

Information collected from cases and controls in the same way

Cases

Well defined population

Standardized selection criteria

Sometimes NESTED case control study (both groups nested in a large cohort study)

Where?

Case registries

Admission records

Pathology logs

High participation rate

Controls

Perfect control group?

Next to never exists

Well defined population

Standardized selection criteria

Sample of

General population (gen pop)

Neighborhood

Families

Hospital

Case Control Studies

Cost to obtain controls

Multiple control groups!

Hospital control

Neighborhood control

‘Adjustment’ of results done during analysis (if subgroups large enough)

Case Control Studies

Again

All observations made using the same methods for cases and controls

Validity of measurement techniques established

Selection, observation, and interviewer bias

Use a 2x2 table

Case Control Studies

Analyses

Chi square or Fisher's exact tests

Proportion of cases exposed (a/a+c) compared to proportion of controls exposed (b/b+d)

Continuous variables

Mean levels of cases compared to controls or non-diseased subjects using Student's t test, non-parametric tests, etc.

Regression methods

Positive Attributes

Study the etiology of rare diseases

Study multiple factors simultaneously

Less time consuming and expensive

‘If assumptions are met’ associations and risk estimates are consistent with other types of studies

Negative Attributes

Do not estimate incidence

Do not estimate prevalence

Relative Risk indirectly measured

Bias is an issue

Hard to study rare exposure

Temporal relationship difficult to document

Example

Case-control design was able to identify relationship of exposure to stilbesterol during mother's pregnancy with occurrence of rare tumor in female offspring many years later

Herbst AL, Ulfelder H, Poskaner DC. Adenocarcinoma of the vagina: Association of maternal stilbesterol therapy with tumor appearance in young women. N Engl J Med 1974;284:878-881.

Example

Case-control design revealed unexpected link between intraocular lens material and risk of serious infection following cataract surgery.

Menikoff JA, Speaker MG, Marmor M, Raskin EM. A Case-control Study of Risk Factors for Postoperative Endophthalmitis. Ophthalmology 1991;98:1761-1768.

Observational Studies

Case Reports

Case Series

Cross-sectional Surveys

Case-Control Study

Cohort Study

Prospective or Longitudinal Cohort Studies

Observations concerning associations between a given exposure (risk factor) and subsequent development of disease

Examine multiple outcomes for a single exposure

Directly calculate incidence of disease for each exposure group

Prospective or Longitudinal Cohort Studies

Concurrent Prospective

Defined population is surveyed

ID group with supposed risk factor

ID similar group without risk factor

Follow them forward in time

Compare incidence rates between groups

Could have a 0 in a cell on the 2x2 table

Non-Concurrent or Retrospective

Non-concurrent prospective study

Defined population with presence/absence of exposure ascertained in accurate, objective fashion in the past

Employment records

Data collected prospectively

Retrospective study

Recall information

Surveyed in present: disease occurrence

Define incidence rates exposed/non-exposed

Define Exposure, Non-Exposure

Exposed and non-exposed are

Representative

Well-defined

Absence of exposure (hard to be sure!)

Well defined

Assumed maintained in non-exposed during the study

Outcomes Definitions

Outcomes (disease outcomes) well defined prior to study

Not changed during course of study

Death – easy to define, ‘hard’ outcome

Subjective symptoms – harder to define

Prospective or Longitudinal Cohort Studies

Standard criteria applied to both exposed and non-exposed groups (again)

Definitions of disease reliable and reproducible (again)

Minimize loss to follow-up

Large non-response rates (>20%) raise questions as to the accuracy of the incidence rates

Prospective or Longitudinal Cohort Studies

Calculate incidence for the study period in exposed, unexposed, and test using Chi square ($\chi 2$) or Fisher's exact test

Measure association with relative risk (or odds ratio)

95% confidence limits

Life-tables (another way to say "survival analysis")

Regression

Positive Attributes

More representative of cases than case-control (incident cases)

More natural history information

Incidence rates available

Relative risk directly estimated

Positive Attributes

‘Less’ bias

Relationship to exposure

Temporal relationship

Rare exposure with frequent cases among exposed

Problematic Attributes

LONG follow-up may be needed

Free-living population follow-up is expensive

Large population usually required

Need baseline data

Rare disease cannot be studied (rare exposures can be studied, though)

Bias (loss to follow-up, assessment, etc)

Prospective or Longitudinal Cohort Study Examples

Prospective cohort study that showed early increase in risk of lung cancer and heart disease mortality and confirmed this over 50 years of follow-up

Doll R, Hill AB. The mortality of doctors in relation to their smoking habits: A preliminary report. Br Med J 1954;228(i):1451-1455.

Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years observations on male British doctors. Br Med J 2004;328:1519-1533.

Prospective or Longitudinal Cohort Study Example

Military medical records used to identify WW II head trauma exposure group and non-trauma comparison group who were traced and evaluated for dementia 50 years later

Plassman BL, Havlik RJ, Steffens DC, et al. Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. Neurology 2000;55:1158-1166.

Is enterovirus (EV) infection associated with increased risk of childhood type 1 diabetes in Taiwan? Identify the study design!

National Health Insurance Research Database includes all claims data 2000-2008 for children 18 or younger; covers 99% of Taiwan residents

Randomly sample with probability 0.5

Identify children with first date of EV infection during 2000-2007 using set of ICD-9-CM codes

Identify children without EV infection, excluding children with EV from 1996-2008 and then frequency match with sex and birth year

Exclude children with prior diagnosis of type 1 diabetes

Article

Enterovirus infection is associated with an increased risk of childhood type 1 diabetes in Taiwan: a nationwide population-based cohort study

http://www.diabetologia-journal.org/files/Lin.pdf

What are your thoughts about the questions raised by our course participant?

Are there internal or external validity issues with this cohort study?

What studies might follow this work?

Longitudinal Study

Robert M. Brackbill, James L. Hadler, Laura DiGrande, Christine C. Ekenga, Mark R. Farfel, Stephen Friedman, Sharon E. Perlman, Steven D. Stellman, Deborah J. Walker, David Wu, Shengchao Yu, and Lorna E. Thorpe

Asthma and Posttraumatic Stress Symptoms 5 to 6 Years Following Exposure to the World Trade Center Terrorist Attack

JAMA 2009;302:502–516

Not All Cohort Studies Are Exposure Based

Vegetarian diets and the incidence of cancer in a low-risk population. Tantamango-Bartley, Yessenia, Jaceldo-Siegl, Karen, Fan, Jing, Fraser, Gary. Cancer Epidemiology, Biomarkers & Prevention (CEBP). 2013 Feb, 22(2):286-94

Pubmed ID: 23169929

DOI: 10.1158/1055-9965.EPI-12-1060

Adventist Health Study-2

69 120 participants

2 939 incident cancer cases

Nested Studies

Case-control

Case-cohort

Nested Case-Control

Select from prospective cohort study

Stored samples

Use baseline and follow up samples and data from newly occurring cases

Compare to matched or unmatched controls

Efficient for expensive/difficult to measure

Helps avoid selection and data collection biases

Need to have enough cases in the cohort and need to store all the samples and data

Nested Case-Cohort

Select from cohort all incident cases and compare to random subset of non-cases

Typically done when

Failure or event of interest is rare

Enormous resources to ascertain covariate values

Very difficult to analyze

Observational Studies

Case Reports/Case Series

Cross-sectional Survey

NHIS (National Health Interview Survey)

Case-Control Study

Groups with or without outcome

Determine who was exposed to risk factor

Cohort Study

Follow a group for a while

Cardiovascular Health Study

Outline

Definitions

A few study designs

Bias

Conclusions

A problem: Bias

Bias – error due to difference between true value and values that are collected for the study

Many types

Selection Bias

Prevalence Incidence bias

Exposed/impacted early? Might miss

Fatal episodes

Transient episodes

Silent cases

Case where evidence of exposure disappears with disease onset

Non-respondent bias

Unwilling or unable to respond

Different exposures/outcomes from respondents?

Observational or Interviewer Bias

Diagnostic suspicion bias

Exposure suspicion bias

Recall bias

Family information bias

Outline

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Observational Studies are Useful

May be only alternative

Smoking in humans

Long term HAART treatment (antiretroviral therapy for HIV)

What happens in free living people (Cardiovascular Health Study)

May be cheaper and faster than a trial

Do Not Always Agree

Hormone Replacement Therapy

Observational trials

Women's Health Initiative (WHI)

Publication bias?

Incorrect analyses of observational studies?

Different populations?

Observational Studies

Why can observational studies only find a weaker degree of connection?

Subject to confounding

Can correct for what you know, but nothing to be done about the unknown

Sometimes it is unethical to do a randomized trial (e.g. smoking)

Design Issues

Placebo effect

Investigator and participant bias

Unblinded treatment/assessment

Regression to the mean

Natural reduction in disease activity over time

Cheap, fast, get what you pay for

Causation vs. Association

Causation

Established by randomized experimental studies and clinical trials

Association

Observational studies can merely find association between a risk factor and an response

What do I do?

Measure everything you can

Build and investigate models

Test those models on different data

Try propensity scores

Try other methods

Yes there are problems, BUT

One of the biggest mistakes is trying to design a randomized study when we need an observational study

Alternative, predecessor, follow-up studies

Population assessment

It also is a mistake to refuse to do a creative randomized study

Can we randomize in the following cases?

Rapidly fatal disease with no treatment

Never forget, “no treatment” is a treatment alternative and sometimes a superior one

Long latency period

Breastfeeding

For what in whom? (ethics, preference)

Second hand smoke

Birth control

Rare outcome

How to Defend Non-Randomized Studies

Randomization is a research ‘norm’

When a strong rationale is there, one deviates from the norm

Admit limitations to non-randomized study

Explain why randomization is far worse an option to answer the study question

Document how minimizing problems with study approach

Observation: the First Step

Many crucial discoveries in medical history based on observations of a keen individual

Hand washing reduces infection

Sushruta 600 BC, Hippocrates 400 BC

Milk maids did not get small pox, led Edward Jenner to discovery of small pox vaccine 1796

Practice of variolation existed since 1000 BC in India, 10th Century china

Cases of cholera clustered around a water source in 1854 outbreak

John Snow considered father of modern epidemiology

More Information

Publishing guidelines

STROBE (Strengthening the Reporting of Observational Studies in Epidemiology)

MOOSE (Meta-analysis of Observational Studies in Epidemiology)

CDC classroom and self-guided course information

www.cdc.gov/excite/classroom/intro_epi.htm

www.cdc.gov/osels/scientific_edu/ss1978/

Thanks!

Please submit questions and comments electronically so all several thousands of us can share in the dialog

Extra Material:
Introduction to Odds Ratio (OR) and Relative Risk (RR)

Thanks to Steve Simon http://www.pmean.com/01/oddsratio.html

Ratios and Differences

Odds ratios are common

Thanks, Logistic regression

Many better understand risk ratios and risk differences

Feasible for risk ratio and odds ratio to decrease and risk difference to increase

So what do you believe?

2008 Stat Med Brumbeck and Berg

Odds Ratios and
Relative Risk (Risk Ratios)

Both compare the relative likelihood of an even occurring between two distinct groups

Both have limitations

While relative risk (RR) seems more intuitive, sometimes it is unclear which RR we are comparing

Statistics for Binary Data (1)

Let p = probability of an event

30-day survival in a study of septic patients

Proportion of TB cases that are MDR

Relative risk (RR): p1/p2

Good for prospective studies

RR not valid in retrospective case-control studies, biased because probability of being a case is enriched by design

Statistics for Binary Data (2)

Odds = p/1-p

Used in logistic regression, especially in case-control studies when RR cannot be used

Example: for 6-sided die with rolls {1,2,3,4,5,6}

odds of rolling a 3 is 1/5; compare to Prob(3)=1/6.

the odds of rolling an even number is 3/3=1

Odds are different from probability

Comparing odds (odds ratio) different than RR (p1/p2).

Odds Ratio (OR)

Odds are related to probability

Odds = p/(1-p)

Probability of horse winning race is 50%, odds are 1/1

Probability of horse winning race is 25%, odds are 1/3 for win or 3 to 1 against win

Case Control Studies

Odds

If probability of diseased person being exposed is a/(a+c), odds are:

Odds and Odds Ratio

Odds of exposure in cases: A/C

Odds of exposure in controls: B/D

Odds Ratio (OR) = [A/C] / [B/D] = [AD] / [BC]

Relative Risk (RR)

Risk in exposed [A/(A+B)] divided by risk in unexposed [C/(C+D)]

Simple comparison between two groups

RR = 1 no difference in risk between the groups

But not used in case-control studies unless…..

Rare Disease, OR, RR

A is small compared to B

All with exposure, # with disease vs. # without

C is small compared to D

All without exposure, # w/ dx vs. # w/o dx

Odds ratio estimates the relative risk well

OR is always further from unity

OR overestimates the magnitude of protective or harmful association

Why we debate the interpretation

Group A has 25% chance of death

Group B has 50% chance of death

Group B has it twice as bad! (Relative Risk)

Nobody says they have an odds ratio of 3; that seems weird (true though)

Actually, sadly, someone will see the odds ratio and say that you are 3 times more likely to die in Group B. Which is False. They might say the odds are 3 times higher, which will be misinterpreted.

More Interpretation

25% mortality from current weird flu

New mutation

75% mortality

Relative risk of 3, odds ratio of 9

Risk difference has an even different interpretation.

Use OR When

Case Control Designs (except maybe rare events)

Need covariate adjustment for confounders, etc

It is feasible to adjust a relative risk but tricky

But be careful when prevalence is not rare

OR can get extreme values

Relative Risk

For every problem Relative Risk can be computed two possible ways

Risk of death, Risk of survival

Does an intervention increase the probability of breast feeding success, or decrease the probability of breast feeding failure

Small relative change in the probability of one event's occurrence is usually associated with a large relative change in the even not occurring

Risk: Difference vs. Ratio

Difference in the absolute risks

Attributable risk

Excess risk attributable to exposure

Relative Risk (RR)

Ratio of two absolute risks

Hazard Ratio (HR)

Ratio between predicted risk of an event for member of A and that of a member of B, holding everything else constant

Is ratio the best to talk to people?

Difference vs. Ratio

Invasive breast cancer WHI (JAMA 288[3]:321-33)

Increase observed estrogen+progestin group

Difference in risk

38 vs 30 per 10 000 person years

Hazard Ratio (HR)

26%

Is your personal risk 26%? No

8 more invasive breast cancers per 10 000 person years? Yes

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2 Examples (KC Mercy)

Physician cardiac catheterization recommendations for patients with chest pain (watched videos)

OR is 0.57 or 1.74

Authors report (Schulman et al 1999) physicians make different recommendations for male patients than for female patients

Data

Schwartz critique said OR overstated the effect

Relative Risk only 0.93 (reciprocal 1.07)

But is it appropriate to look at 90.6% vs 84.7%?

Comparing rates for recommending a less aggressive intervention (9.4% vs 15.3%)

Relative Risk 1.63, reciprocal 0.61

Example

Look at 3mo, did breastfeeding (BF) continue with intervention? Or Stopped?

‘Failure’ RR=0.69 (recip 1.45)

OR=0.16 (recip 6.2)

‘Successful’ breastfeeding leads to different #s

(do Survival analysis)

Odds Ratio have this issue?

OR is not dependent on focusing on one event's occurrence or the failure to occur, one is the reciprocal of the other

But they have other issues

What is Important

Which event matters? Likely they both do

Some say absolute changes in risk matter more

Who cares if you triple your risk of a rare outcome [well….] 3*0.00000001 is basically 0

10% change in a common outcome is HUGE

No wonder they say we lie with statistics

Changes

10 fold increase in lung cancer death

2 fold increase in risk of death from heart disease

But heart disease kills a lot more people in general

This is why some people discuss number needed to treat (NNT) and number needed to harm (NNH)

NNT (from pmean)

Daily low dose aspirin for a year (genpop): NNT=102

One fewer stroke on average for what?

Rates may not be homogenous over time, so careful with the person years

Giving prophylaxis antibiotic after a dog bite: NNT=16

For every 16 dog bites treated with antibiotics we see one fewer infection on average

For Vaccines

See lots of NNT, NNH and the balance between

Numbers make ‘sense’ to people but they have strong assumptions