Randomized Controlled Trials

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What is a randomized controlled trial?

- Simplest definition: Individuals are allocated at random to receive one of several interventions (at least two total).
- RCT's are human experiments—the intervention is controlled by the investigator: patients & doctors don't get to choose their therapy!
- RCT's are usually comparative studies ("controlled" in the RCT)
  - Uncontrolled trials can be done (e.g. Phase 1 trial)

Courtesy: J Colford

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19

D.R. Boulware, M.F. Pullen, A.S. Bangdiwala, K.A. Pastick, S.M. Lofgren, E.C. Okafor, C.P. Skipper, A.A. Nascene, M.R. Nicol, M. Abassi, N.W. Engen, M.P. Cheng, D. LaBar, S.A. Lother, L.J. MacKenzie, G. Drobot, N. Marten, R. Zarychanski, L.E. Kelly, I.S. Schwartz, E.G. McDonald, R. Rajasingham, T.C. Lee, and K.H. Hullsiek

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 7, 2020 VOL. 382 NO. 19

A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19

B. Cao, Y. Wang, D. Wen, W. Liu, Jingli Wang, G. Fan, L. Ruan, B. Song, Y. Cai, M. Wei, X. Li, J. Xia, N. Chen, J. Xiang, T. Yu, T. Bai, X. Xie, L. Zhang, C. Li, Y. Yuan, H. Chen, Huadong Li, H. Huang, S. Tu, F. Gong, Y. Liu, Y. Wei, C. Dong, F. Zhou, X. Gu, J. Xu, Z. Liu, Y. Zhang, Hui Li, L. Shang, K. Wang, K. Li, X. Zhou, X. Dong, Z. Qu, S. Lu, X. Hu, S. Ruan, S. Luo, J. Wu, L. Peng, F. Cheng, L. Pan, J. Zou, C. Jia, Juan Wang, X. Liu, S. Wang, X. Wu, Q. Ge, J. He, H. Zhan, F. Qiu, L. Guo, C. Huang, T. Jaki, F.G. Hayden, P.W. Horby, D. Zhang, and C. Wang

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Remdesivir for the Treatment of Covid-19 — Preliminary Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

Why do we need RCTs?

- No other design can get us close to the 'counterfactual' comparison we need to see if an intervention is causally linked to a particular outcome

But, many ethical issues

- Importance of protecting individuals over all other considerations
- Importance of informed consent
- Cannot randomize for harmful exposures
- When is it acceptable to randomize?
- When is it OK to use a placebo arm?
- When is it OK to use sham procedures?
- When should trials be stopped early?

What is random allocation?

- Random allocation means that all participants have a defined probability of assignment to a particular intervention
  - Allocation is not determined by the investigator, clinicians, or participants
  - Allocation is not predictable based on a pattern

Courtesy: J Colford

What purpose is served by random allocation?

- Covariates are distributed equally across the groups at baseline
- Affects both measured and, more importantly, unmeasured variables
- Table 1 in most RCTs will provide a comparison of treatment and comparison groups, with p-values
- Random allocation also facilities blinding

Table 1. Demographic and Clinical Characteristics at Baseline.*

Characteristic	All (N = 1063)	Remdesivir (N = 541)	Placebo (N = 522)
Age — yr	58.9±15.0	58.6±14.6	59.2±15.4
Male sex — no. (%)	684 (64.3)	352 (65.1)	332 (63.6)
Race or ethnic group — no. (%)†			
American Indian or Alaska Native	7 (0.7)	4 (0.7)	3 (0.6)
Asian	134 (12.6)	77 (14.2)	57 (10.9)
Black or African American	219 (20.6)	108 (20.0)	111 (21.3)
White	565 (53.2)	279 (51.6)	286 (54.8)
Hispanic or Latino — no. (%)	249 (23.4)	132 (24.4)	117 (22.4)
Median time (IQR) from symptom onset to randomization — days‡	9 (6–12)	9 (6–12)	9 (7–13)
No. of coexisting conditions — no. /total no. (%)‡			
None	193/920 (21.0)	91/467 (19.5)	102/453 (22.5)
One	248/920 (27.0)	131/467 (28.1)	117/453 (25.8)
Two or more	479/920 (52.1)	245/467 (52.5)	234/453 (51.7)
Coexisting conditions — no./total no. (%)			
Hypertension	460/928 (49.6)	231/469 (49.3)	229/459 (49.9)
Obesity	342/925 (37.0)	177/469 (37.7)	165/456 (36.2)
Type 2 diabetes	275/927 (29.7)	144/470 (30.6)	131/457 (28.7)
Score on ordinal scale — no. (%)			
4. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (Covid-19–related or otherwise)	127 (11.9)	67 (12.4)	60 (11.5)
5. Hospitalized, requiring supplemental oxygen	421 (39.6)	222 (41.0)	199 (38.1)
6. Hospitalized, receiving noninvasive ventilation or high-flow oxygen devices	197 (18.5)	98 (18.1)	99 (19.0)
7. Hospitalized, receiving invasive mechanical ventilation or ECMO	272 (25.6)	125 (23.1)	147 (28.2)
Baseline score missing	46 (4.3)	29 (5.4)	17 (3.3)

Table 1 from Remdesivir RCT

We must make sure randomization is not subverted (allocation must be concealed)

- If those making the decision about patient eligibility are aware of the arm of the study to which the patient will be allocated --if randomization is unconcealed-- they may systematically enroll sicker-- or less sick-- patients to either treatment or control groups.
- This will defeat the purpose of randomization and the study will yield a biased result.

- Example: RCT of open vs laparoscopic appendectomy (example from Users' Guides):
  - trial ran smoothly during the day
  - at night, however, the attending surgeon's presence was required for the laparoscopic procedure but not the open one; and the limited operating room availability made the longer laparoscopic procedure an annoyance.
  - reluctant to call in a consultant, and particularly reluctant with specific senior colleagues, the residents sometimes adopted a practical solution.
  - when an eligible patient appeared, the residents checked the attending staff and the lineup for the operating room and, depending on the personality of the attending surgeon and the length of the lineup, held the translucent envelopes containing orders up to the light.
  - as soon as they found one that dictated an open procedure, they opened that envelope. The first eligible patient in the morning would then be allocated to a laparoscopic appendectomy group according to the passed-over envelope
  - If patients who presented at night were sicker than those who presented during the day, the residents' behavior would bias the results against the open procedure.

Deciphering the allocation concealment scheme

Schulz KF, Grimes DA. Allocation concealment in randomised trials: defending against deciphering. Lancet. 2002 Feb 16;359(9306):614-8

Table 2. Examples of inadequate and adequate allocation concealment methods.[4,8]

Inadequate allocation concealment	Adequate allocation concealment
Allocation Posted on bulletin board	SNOSE (sequentially numbered opaque sealed envelopes)
Translucent envelopes	Pharmacy controlled numbered or coded containers
Unsealed assignment envelopes	Central randomisation (via telephone, fax, or web)
Different weight envelopes	Secure computer assisted method
Unnumbered envelopes	
Allocating more than one assignment at a time	
Different labels	

http://knol.google.com/k/w-kent/why-not-just-flip-a-coin-randomisation/1blm6ty1i8a7z/4#

Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial

Wei Tang,[1,2] Zhujun Cao,[3] Mingfeng Han,[4] Zhengyan Wang,[5] Junwen Chen,[6] Wenjin Sun,[7] Yaojie Wu,[8] Wei Xiao,[9] Shengyong Liu,[10] Erzhen Chen,[11] Wei Chen,[1,2] Xiongbiao Wang,[12] Jiuyong Yang,[13] Jun Lin,[14] Qingxia Zhao,[15] Youqin Yan,[16] Zhibin Xie,[17] Dan Li,[18] Yaofeng Yang,[19] Leshan Liu,[20] Jieming Qu,[1,2] Guang Ning,[21] Guochao Shi,[1,2] Qing Xie[3]

Equal numbers of cards with each group assignment number randomly generated by computer were placed in sequentially numbered envelopes that were opened as the patients were enrolled.

Phase I, II, III, IV trials

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

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Developed by the National Library of Medicine

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Study Phase

Most clinical trials are designated as phase I, II, or III, based on the type of questions that study is seeking to answer:

- In Phase I clinical trials, researchers test a new drug or treatment in a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.
- In Phase II clinical trials, the study drug or treatment is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety.
- In Phase III studies, the study drug or treatment is given to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely.
- In Phase IV studies, the post marketing studies delineate additional information including the drug's risks, benefits, and optimal use.

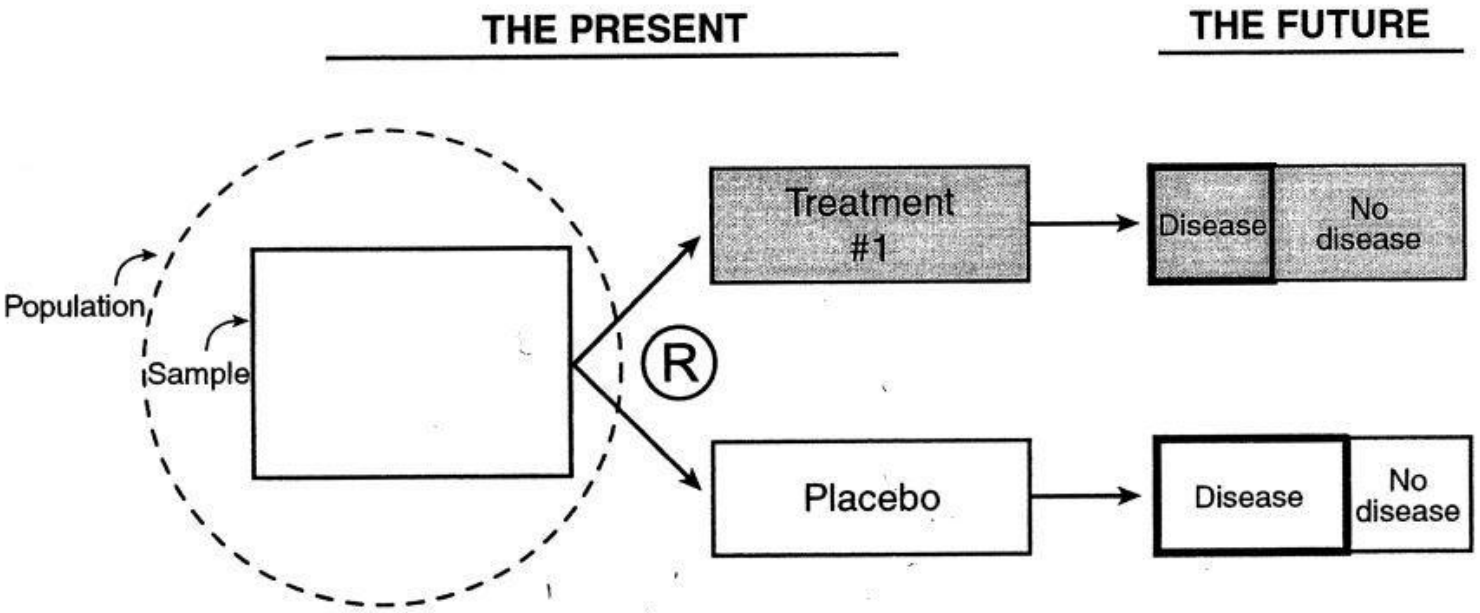
These phases are defined by the Food and Drug Administration in the Code of Federal Regulations.

Types of RCT's—classification schemes

- Based on how the participants are exposed to the intervention
  - Parallel trials
  - Crossover trials
  - More complex designs
    - Trials with factorial design
    - Adaptive designs, etc

Courtesy: J Colford

Simple, two-arm (parallel) RCT

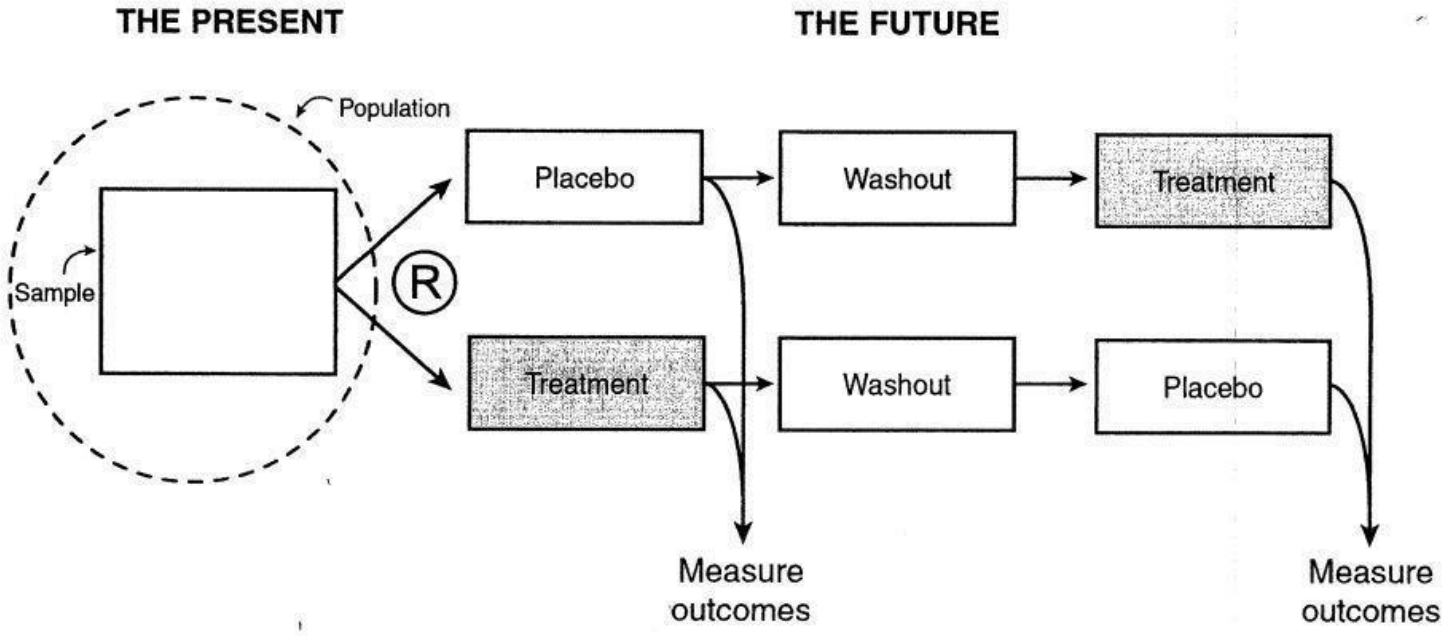


■ **FIGURE 10.1**

In a randomized trial, the investigator (a) selects a sample from the population, (b) measures baseline variables, (c) randomizes the participants, (d) applies interventions (one should be a blinded placebo, if possible), (e) follows up the cohort, (f) measures outcome variables (blindly, if possible) and analyzes the results.

Hulley et al. Designing Clinical Research. 2nd Edition. Lippincott Williams & Wilkins,

Cross-over RCT design



■ **FIGURE 11.4**

In the cross-over randomized trial, the investigator (a) selects a sample from the population, (b) measures baseline variables, (c) randomizes the participants, (d) applies interventions, (e) measures outcome variables, (f) allows washout period to reduce carryover effect, (g) applies intervention to former placebo group, (h) measures outcome variables again.

Hulley et al. Designing Clinical Research. 2nd Edition. Lippincott Williams & Wilkins,

Types of RCT's—classification schemes

- Based on who knows what (about the intervention that is being assessed)
  - Open trials
  - Single blind trials
  - Double blind trials
  - Triple and quadruple-blind trials

Courtesy: J Colford

Blinding

- Relevant groups who may/may not have knowledge of treatment assignments
  - Participants
  - Investigators/clinicians administering intervention
  - Investigators assessing outcomes
  - Data analyst(s)
- Open label trials
  - All participants and investigators know who is getting which intervention
    - E.g. medical vs. surgical treatments

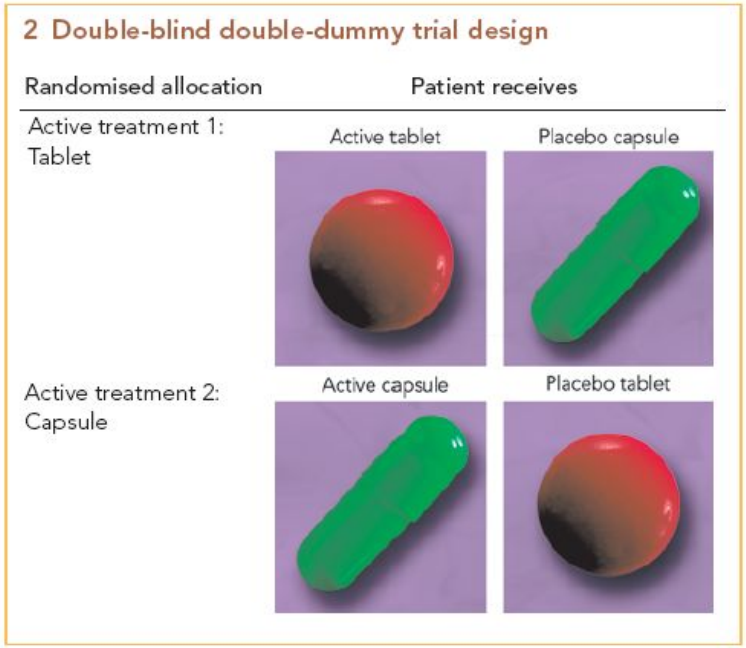
Figure 1: **The authors: double blinded versus single blinded**

Schulz & Grimes. Lancet 2002

Courtesy: J Colford

Single, double, triple, and beyond

- Single-blind
  - The participants (usually) or the investigators assessing outcome (alternately) do not the assignments
- Double-blind
  - Two groups do not know—usually it is the participants and the outcome assessors/investigators
- Triple or quadruple blinding
  - Three or four of the relevant groups (prior slide) are not aware of the treatment assignment



Forder, MJA, 2005

Courtesy: J Colford

Who was blinded?

	Patients	Care providers	Trial investigators	Data analysts (stats)
HCQ (BMJ)				
Remdesivir (NEJM)			?	?
Lopinavir-Ritonavir (NEJM)				

Blinding

Panel 1: **Potential benefits accruing dependent on those individuals successfully blinded**

Individuals blinded	Potential benefits
Participants	Less likely to have biased psychological or physical responses to intervention More likely to comply with trial regimens Less likely to seek additional adjunct interventions Less likely to leave trial without providing outcome data, leading to lost to follow-up
Trial investigators	Less likely to transfer their inclinations or attitudes to participants Less likely to differentially administer co-interventions Less likely to differentially adjust dose Less likely to differentially withdraw participants Less likely to differentially encourage or discourage participants to continue trial
Assessors	Less likely to have biases affect their outcome assessments, especially with subjective outcomes of interest

Schulz KF, Grimes DA. Blinding in randomised trials: hiding who got what. Lancet. 2002 Feb 23;359(9307):696-700

Unblinding can introduce bias

- Aspirin Myocardial Infarction Study (AMIS), 1982
- Aspirin/Placebo → survival for 3-4 years after myocardial infarction
- 95 / 285 (33%) deliberately tested the capsule
  - Taste, smell, acid test or professional analysis
- 67% of testers guessed right (47% of non-testers)

Howard, J *et al.* 1982 Clin Pharmacol Ther 32(5), 543-53

Courtesy: J Colford

Concealment of allocation vs. blinding

- Concealment of allocation:
  - Procedure to protect the randomization process **before** the subject enters the trial
    - Failed concealment from the investigator or clinician
    - Failed concealment from the patient
  - Concealment of allocation is ALWAYS feasible
  - If not done, results in selection bias (randomization benefits are lost, and treatment assignment is no longer truly random)
- Blinding:
  - Masking of the treatments **after** randomization (once trial begins)
    - Failed masking of patients, investigators, outcome assessors, etc
  - Blinding is not always feasible
  - If not done, can result in patients biasing their responses because of their knowledge of treatment; can also lead to biased outcome assessment because investigators have knowledge of treatment

Bias in RCTs

- Can occur at all phases:
  - Planning, selection of participants, administration of interventions, measurement of outcomes, analysis of data, interpretation and reporting of results, publication of reports, and even in the reading of the report!
- Selection bias:
  - E.g. due to lack of concealment of allocation
  - Due to attrition and differential losses
- Information bias:
  - Participant response bias (due to lack of blinding)
  - Outcome ascertainment bias (due to lack of blinding)
- Bias due to competing interests
- Reporting biases
  - Outcome reporting bias, etc

Courtesy: J Colford

Selection bias

- Definition: Selection bias is when there are systematic differences in the way participants are accepted or rejected for a trial, or in how the intervention is assigned to participants once they have been accepted
- Don't get a false sense of security as a result of randomization, easy to introduce selection bias in a RCT!
- Example: bias due to lack of concealment of allocation

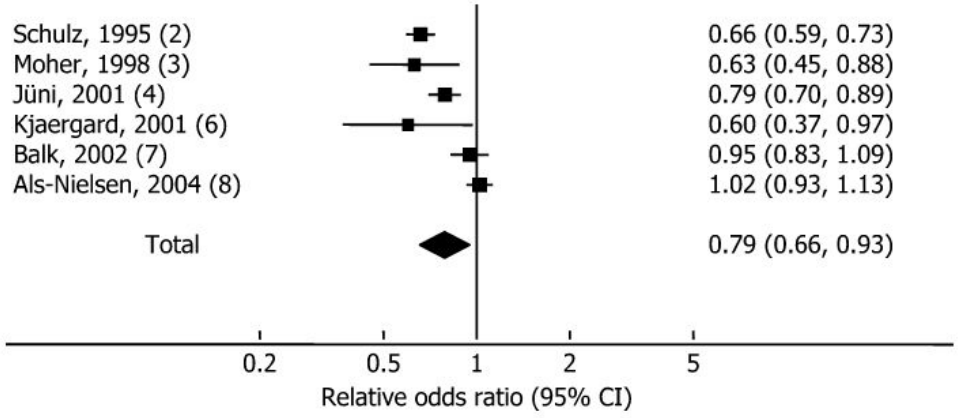


FIGURE 1. Forest plot of a random-effects meta-analysis of methodological studies calculating the relative odds ratio between groups of randomized trials with or without adequate allocation concealment. The squares show the point estimates for individual studies (horizontal bars, 95 percent confidence interval (CI)); the diamond shows the overall relative odds ratio from the meta-analysis.

Gluud, AJE 2006

Information (reporting, ascertainment or detection) bias

- Definition: Ascertainment bias occurs when the results are systematically distorted by knowledge of which intervention each participant is receiving
- Can be introduced by the person administering the intervention, the participants, the investigator, the data analyst, or even the manuscript authors
- Result: Can exaggerate the effect (away from the null)

Courtesy: J Colford

How can ascertainment bias be minimized?

During….

- Randomization
- Delivery of intervention
- Assessment of outcomes
- Data analysis/manuscript

- Blind the participant as to which intervention receiving
- Blind the individuals who administer the interventions
- Blind the individuals who record the outcomes
- Blind the statisticians

Courtesy: J Colford

Power & sample size in RCTs

- Power is ability of a trial to pick up a real effect, if it actually exists
- E.g. Lopinavir-Ritonavir trial:
  - Sample size was set at 160, since it would provide the trial with 80% power to detect a difference, at a two-sided significance level of $\alpha = 0.05$
  - Difference expected between two arms: 8 days in the median time to clinical improvement between the two groups

How to critically assess an RCT?

Users' Guides for an Article About Therapy

Are the results valid?

Did experimental and control groups begin the study with a similar prognosis?

- Were patients randomized?
- Was randomization concealed (blinded or masked)?
- Were patients analyzed in the groups to which they were randomized?
- Were patients in the treatment and control groups similar with respect to known prognostic factors?

Did experimental and control groups retain a similar prognosis after the study started?

- Were patients aware of group allocation?
- Were clinicians aware of group allocation?
- Were outcome assessors aware of group allocation?
- Was follow-up complete?

What are the results?

- How large was the treatment effect?
- How precise was the estimate of the treatment effect?

How can I apply the results to patient care?

- Were the study patients similar to my patient?
- Were all clinically important outcomes considered?
- Are the likely treatment benefits worth the potential harm and costs?

USERS' GUIDES TO THE MEDICAL LITERATURE
A Manual for Evidence-Based Clinical Practice

Cohort Studies

Figure 1: **An early cohort in search of favourable outcomes**

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Cohort studies

1. Start with a population at risk
2. Measure exposures and covariates at baseline
3. Follow-up the cohort over time with
   a) Surveillance for events
   b) re-examination
4. Keep track of attrition, withdrawals, drop-outs and competing risks
5. Compare event rates in people with and without exposures of interest
   - Incidence rate is the most appropriate measure of effect
   - Adjust for confounders and compute adjusted rate ratio

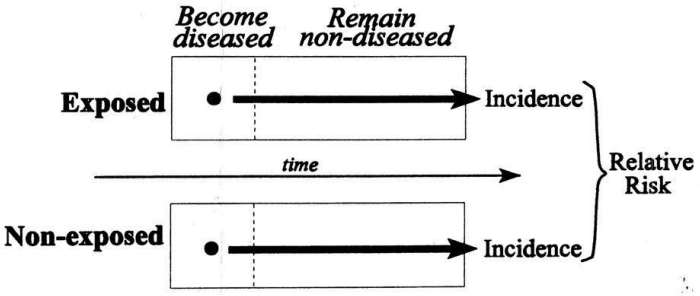

Figure 1–14 Basic analytical approach in a cohort study.

Cohort study

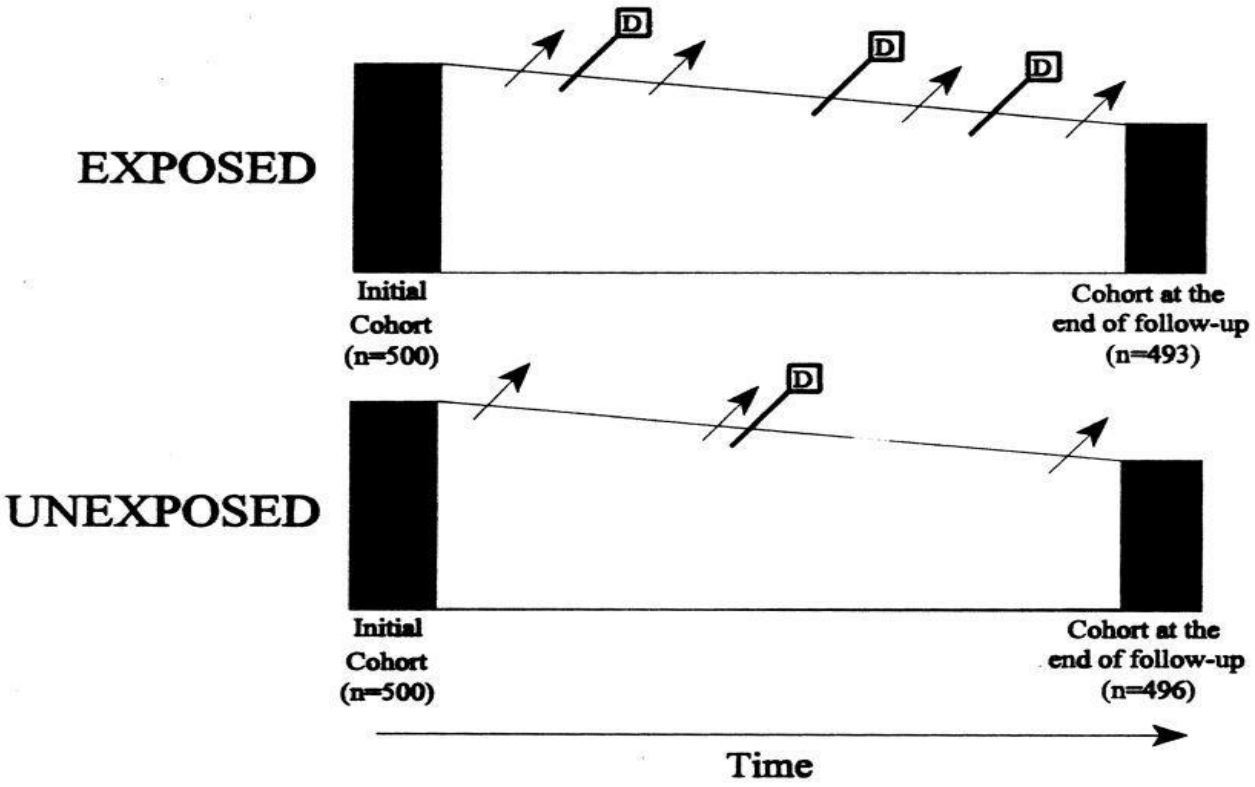

Figure 1–15 Same cohort study as in Figure 1–13, but the ascertainment of events and losses to follow-up is done separately among those exposed and unexposed.

Cohort studies

- Can be large or small
- Can be long or short duration
- Can be simple or elaborate
- Can look at multiple exposures and multiple outcomes
- Can look at changes in exposures over time
- For rare outcomes need many people and/or lengthy follow-up
- Are usually expensive because of the numbers and follow-up requirements
- But once a cohort is established, it can be productive for a long, long time!

FRAMINGHAM HEART STUDY

A Project of the National Heart, Lung and Blood Institute and Boston University

Three generations of participants.

The dedication of our thousands of participants has made, and continues to make, our rigorous epidemiologic research possible.

National **Heart Lung and Blood** Institute
Boston University

Welcome to the Framingham Heart Study

In 1948, the Framingham Heart Study embarked on an ambitious project in health research to identify the common factors that contribute to cardiovascular disease by following its development over a long period of time in a large group of participants. >>

Phillip Wolf, MD, Principal Investigator, and Dan Levy, MD, Director, with the staff of the Framingham Heart Study.

Genomic Research at the Framingham Heart Study (SHARe Study)

VIEW SHARe WEBSITE >>

Recently the Honorable Michael O. Leavitt, United States Secretary of Health and Human Services, expressed the nation's appreciation to participants of the Framaingham Heart Study. Their many years of dedication has made possible the SHARe (SNP Health Association Research) project, the new state of the art phase of scientific discovery previously announced in the Winter 2007 newsletter. The SHARe project was officially launched with a nationwide presentation in Washington on October 1, 2007.

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RCCS Overview

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RCCS Background

Initiation

Initiated in 1994, the Rakai Community Cohort Study (RCCS) is an open population-based cohort which enrolls all consenting adult residents aged 15-49 in ~50 communities distributed throughout the district.

What Data is Collected

Participants respond to a detailed sociodemographic, behavioral, sexual network, mobility, health and service utilization interview, and provide a blood sample for HIV testing

Conducting Census

Prior to each survey visit, a household census is performed in the study communities, it describes household membership, births, death since the last visit, duration of stay per member, household possession, dwelling characteristics and mobility data is captured first at this level

Approximately 18,000 individuals participate in the RCCS

Through over 150 peer reviewed Journal articles, data from RCCS has been central in contributing towards HIV prevention, care and treatment discourse locally and internationally.

https://www.rhsp.org/research/rccs/rccs-overview

How are cohorts assembled or identified?

- By geographical region
  - E.g. Framingham heart study
- By occupational group
  - Nurses Health Study
  - British Doctor's health study
- By disease
  - Rakai Community Cohort Study on HIV
- By risk groups
  - San Francisco Men's Health Study (gay men)
  - IV Drug Users cohort (ALIVE Study in Baltimore - AIDS Linked to the Intravenous Experience)
- By exposure event
  - Japanese Atomic Bomb Survivors
  - 9/11 FDNY workers cohort

How are cohorts assembled or identified?

- Often, researchers begin with a large cross-sectional study (e.g. survey)
- They then go back and re-survey the same population after a time period
- This converts a cross-sectional into a cohort design

Mycobacterium tuberculosis Infection in Health Care Workers in Rural India

Comparison of a Whole-Blood Interferon γ Assay With Tuberculin Skin Testing

Madhukar Pai, MD, PhD
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Sandeep Dogra, MD
Shriprakash Kalantri, MD, MPH
Deepak K. Mendiratta, MD
Pratibha Narang, MD
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Reuben M. Granich, MD, MPH
Gerald H. Mazurek, MD
Arthur L. Reingold, MD
Lee W. Riley, MD
John M. Colford, Jr, MD, PhD

Context *Mycobacterium tuberculosis* infection in health care workers has not been adequately studied in developing countries using newer diagnostic tests.

Objectives To estimate latent tuberculosis infection prevalence in health care workers using the tuberculin skin test (TST) and a whole-blood interferon γ (IFN-γ) assay; to determine agreement between the tests; and to compare their correlation with risk factors.

Design, Setting, and Participants A cross-sectional comparison study of 726 health care workers aged 18 to 61 years (median age, 22 years) with no history of active tuberculosis conducted from January to May 2004, at a rural medical school in India. A total of 493 (68%) of the health care workers had direct contact with patients with tuberculosis and 514 (71%) had BCG vaccine scars.

Interventions Tuberculin skin testing was performed using 1-TU dose of purified protein derivative RT23, and the IFN-γ assay was performed by measuring IFN-γ response to early secreted antigenic target 6, culture filtrate protein 10, and a portion of tuberculosis antigen TB7.7.

Main Outcome Measures Agreement between TST and the IFN-γ assay, and comparison of the tests with respect to their association with risk factors.

Results A large proportion of the health care workers were latently infected; 360 (50%) were positive by either TST or IFN-γ assay, and 226 (31%) were positive by both tests. The prevalence estimates of TST and IFN-γ assay positivity were comparable (41%; 95% confidence interval [CI], 38%-45% and 40%; 95% CI, 37%-43%, respectively). Agreement between the tests was high (81.4%; κ=0.61; 95% CI, 0.56-0.67). Increasing age and years in the health profession were significant risk factors for both IFN-γ assay and TST positivity. BCG vaccination had little impact on TST and IFN-γ assay results.

AN ESTIMATED ONE THIRD OF the world's population is infected with *Mycobacterium tuberculosis*,[1] presenting a major impediment to tuberculosis control. Despite the importance of latent tuberculosis infection (LTBI), the tubercu-

Serial Testing of Health Care Workers for Tuberculosis Using Interferon-γ Assay

Madhukar Pai, Rajnish Joshi, Sandeep Dogra, Deepak K. Mendiratta, Pratibha Narang, Shriprakash Kalantri, Arthur L. Reingold, John M. Colford, Jr., Lee W. Riley, and Dick Menzies

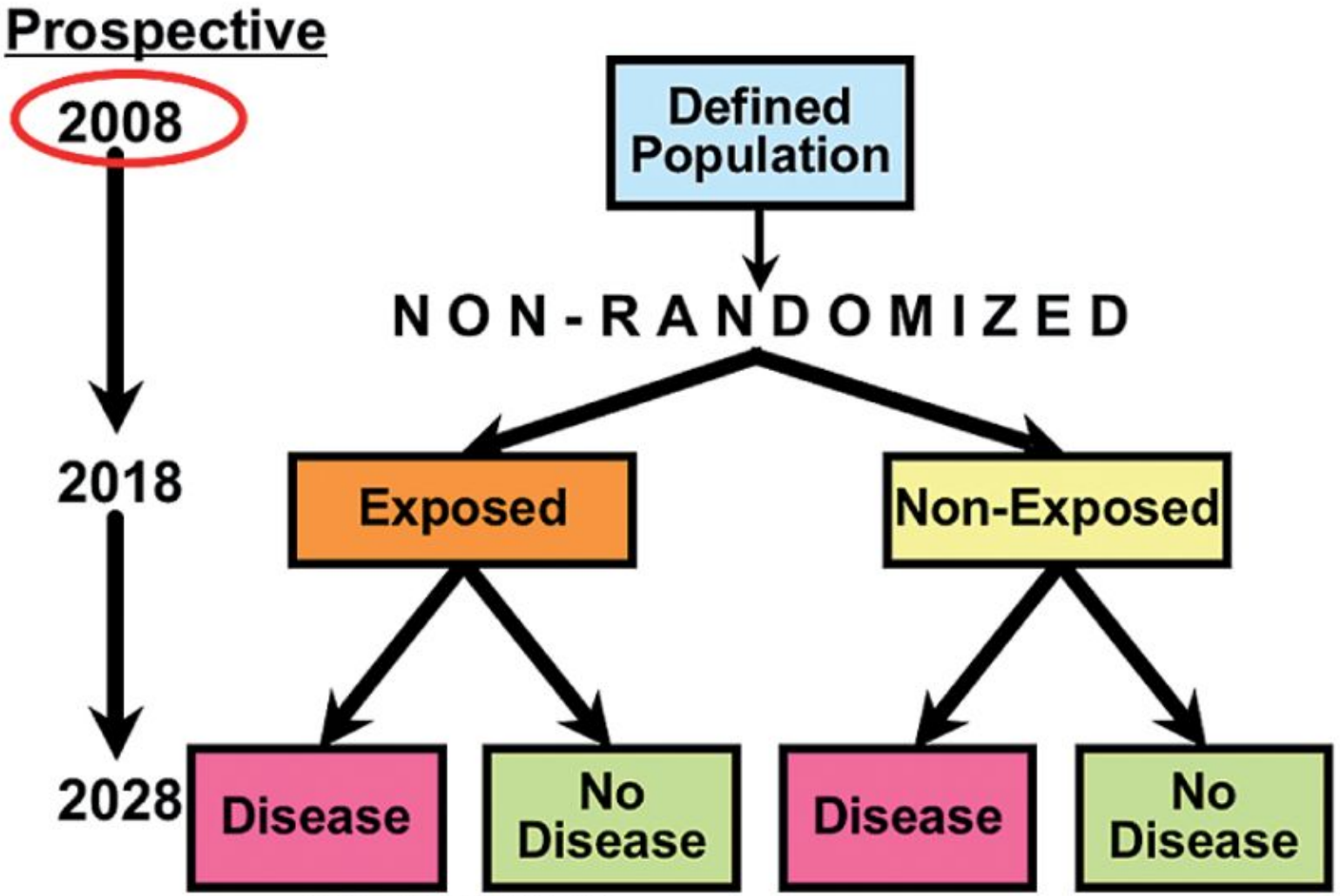
Divisions of Epidemiology and Infectious Diseases, School of Public Health, University of California, Berkeley; Division of Pulmonary and Critical Care Medicine, San Francisco General Hospital, University of California, San Francisco, California; Departments of Medicine and Microbiology, Mahatma Gandhi Institute of Medical Sciences, Sevagram, India; and the Montreal Chest Institute, McGill University, Montreal, Quebec, Canada

Predictive value of latent tuberculosis tests in Indian healthcare workers: a cohort study

Methods to define exposure and outcome status

- Existing records
  - Occupational (e.g. employee health records)
  - Medical/pharmacy records
  - Vital registration records (births, deaths)
  - Census records
  - Medicare database and the like
- Interviews/questionnaires
- Direct measurements on participants (e.g. periodic health exams and tests)

Prospective cohort design



Time frame for a hypothetical prospective cohort study begun in 2008.

COVID-19 & Pregnancy

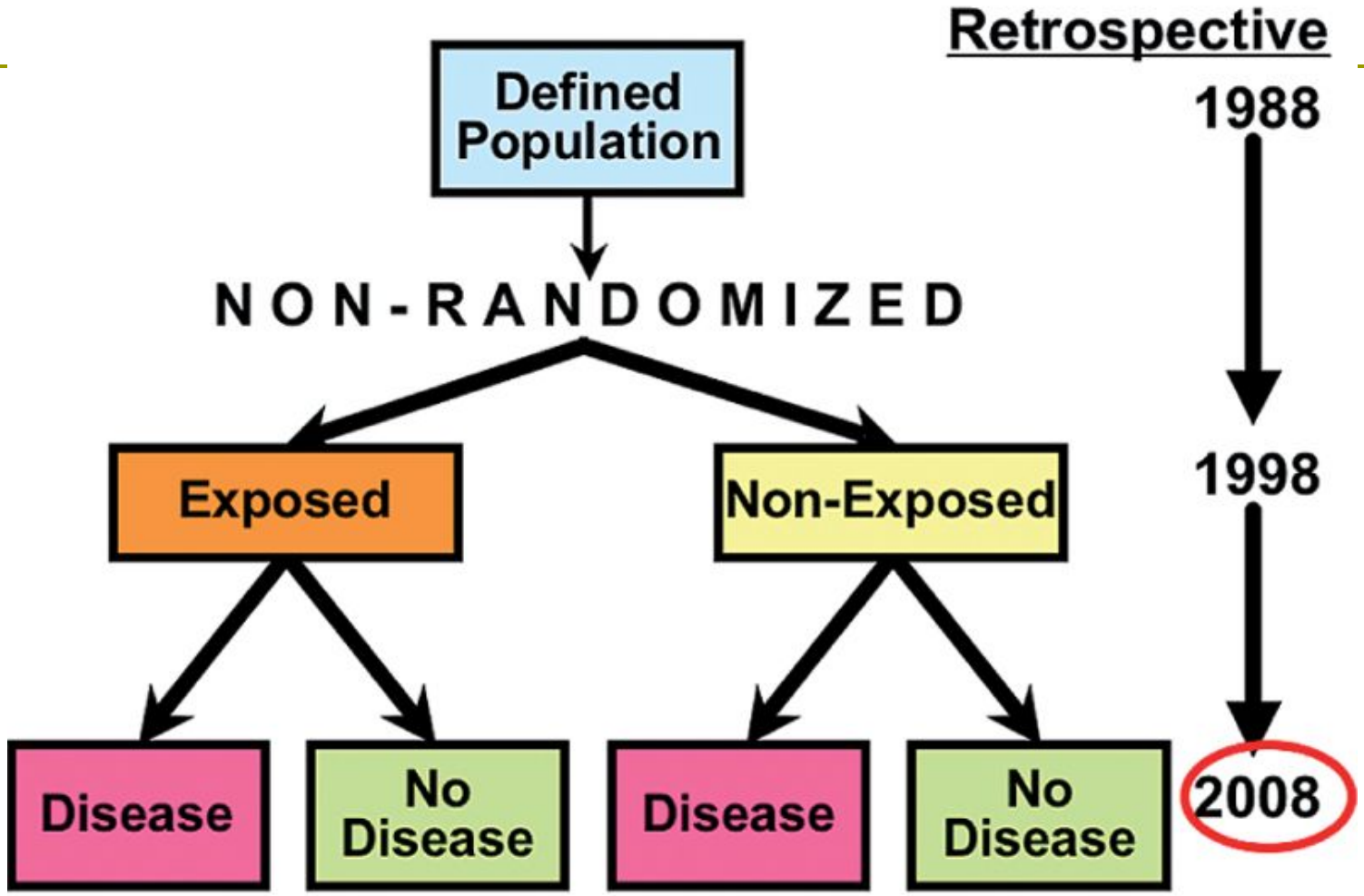
INTERCOVID: A prospective cohort study of the effects of COVID-19 in pregnancy and the neonatal period

Coordinated by the INTERGROWTH-21st Team at the University of Oxford

INTERCOVID is a large, multi-national, prospective cohort study with the aim of assessing the effect of COVID-19 in pregnancy on maternal, fetal and neonatal outcomes worldwide.

- 'Exposed' cases are pregnant women with: a) laboratory confirmed COVID-19; b) radiological pulmonary findings suggestive of COVID-19; c) maternal symptoms compatible with COVID-19, or d) absence of symptoms, whilst in close interaction with a person(s) with confirmed COVID-19.
- Each 'exposed' case is compared with two 'non-exposed' pregnant women, considered as representative of the pregnant population at each study site.
- Both 'exposed' and 'non-exposed' women will be recruited at any stage of pregnancy; women and their babies will be followed up until hospital discharge post-delivery.
- Assuming that COVID-19 in pregnancy increases the risk of a common outcome, such as preterm birth, from 10% to 15%, it is possible to have 80% power with 500 'exposed' women and 1000 'non-exposed' women

Retrospective cohort design



Gordis: Epidemiology, 4th Edition.

Time frame for a hypothetical retrospective cohort study begun in 2008.

Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State

Eli S. Rosenberg, PhD[1]; Elizabeth M. Dufort, MD[2]; Tomoko Udo, PhD[1]; et al

- **Design, Setting, and Participants** Retrospective multicenter cohort study of patients from a random sample of all admitted patients with laboratory-confirmed COVID-19 in 25 hospitals in New York
- **Exposures** Receipt of both hydroxychloroquine and azithromycin, hydroxychloroquine alone, azithromycin alone, or neither.
- **Main Outcomes and Measures** Primary outcome was in-hospital mortality.

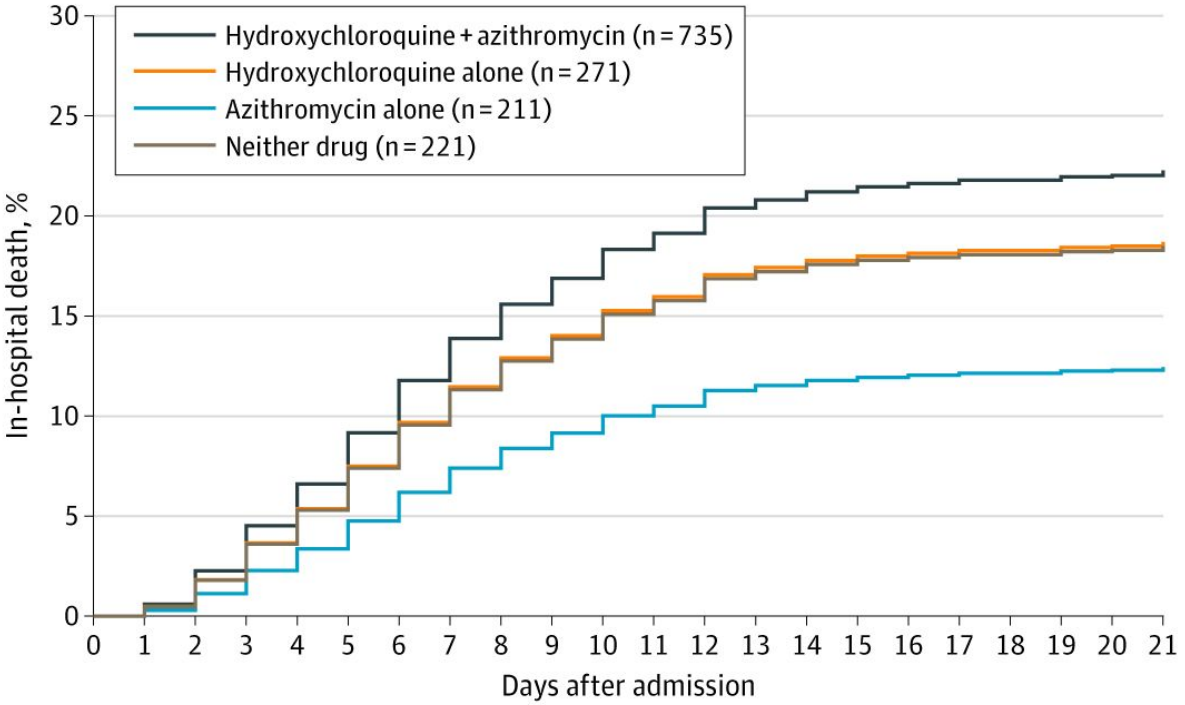
Table 3. Model-Adjusted Risk of In-Hospital Death, Cardiac Arrest, Arrhythmia

Outcome	Model type[a]	Estimate (95% CI)			
		Hydroxychloroquine + azithromycin vs neither drug	Hydroxychloroquine alone vs neither drug	Azithromycin alone vs neither drug	Hydroxychloroquine alone vs azithromycin alone
In-hospital death (hazard ratio)	Cox proportional hazards	1.35 (0.76-2.40)	1.08 (0.63-1.85)	0.56 (0.26-1.21)	1.92 (0.99-3.74)
Cardiac arrest (odds ratio)	GEE logistic regression	2.13 (1.12-4.05)	1.91 (0.96-3.81)	0.64 (0.27-1.56)	2.97 (1.56-5.64)
Abnormal ECG findings (odds ratio)[b]	GEE logistic regression	1.55 (0.89-2.67)	1.50 (0.88-2.58)	0.95 (0.47-1.94)	1.58 (0.77-3.24)

Abbreviations: ECG, electrocardiogram; GEE, generalized estimating equation.

[a] Models adjusted for sex, age category (<65 vs ≥65 years), diabetes, any chronic lung disease, cardiovascular disease, abnormal chest imaging, respiration rate >22/min, O_2 saturation <90%, elevated creatinine, and AST >40 U/L as fixed effects and repeated measures for hospital.

[b] Abnormal ECG included prolonged QT and arrhythmia.



No. at risk (in hospital)

	Admission	Day 7	Day 14	Day 21
Hydroxychloroquine + azithromycin	735	653 (384)	568 (106)	557 (47)
Hydroxychloroquine alone	271	245 (136)	226 (59)	220 (28)
Azithromycin alone	211	191 (33)	190 (4)	190 (2)
Neither drug	221	206 (63)	197 (19)	195 (13)

Bias in cohort studies

- Selection bias
- Information bias
- Confounding

POTENTIAL BIASES IN COHORT STUDIES

A number of potential biases must be either avoided or taken into account in conducting cohort studies. The major biases include the following:

1. *Bias in assessment of the outcome:* If the person who decides whether disease has developed in each subject also knows whether that subject was exposed, and if that person is aware of the hypothesis being tested, that person's judgment as to whether the disease developed may be biased by that knowledge. This problem can be addressed by masking the person who is making the disease assessment and also by determining whether this person was, in fact, aware of each subject's exposure status.
2. *Information bias:* If the quality and extent of information obtained is different for exposed persons than for nonexposed persons, a significant bias can be introduced. This is particularly likely to occur in historical cohort studies, in which information is obtained from past records. As we discussed with regard to randomized trials, in any cohort study, it is essential that the quality of the information obtained be comparable in both exposed and nonexposed individuals.
3. *Biases from nonresponse and losses to follow-up:* As was discussed in connection with randomized trials, nonparticipation and nonresponse can introduce major biases that can complicate the interpretation of the study findings. Similarly, loss to follow-up can be a serious problem: If people with the disease are selectively lost to follow-up, the incidence rates calculated in the exposed and nonexposed groups will clearly be difficult to interpret.
4. *Analytic bias:* As in any study, if the epidemiologists and statisticians who are analyzing the data have strong preconceptions, they may unintentionally introduce their biases into their data analyses and into their interpretation of the study findings.

Confounding: a key concern with cohort studies

Table 1 Comparison of cohort studies and randomised controlled trials

Item	Cohort studies	Randomised controlled trials
Populations studied	Diverse populations of patients who are observed in a range of settings	Highly selected populations recruited on the basis of detailed criteria and treated at selected sites
Allocation to the intervention	Based on decisions made by providers or patients	Based on chance and controlled by investigators
Outcomes	Can be defined after the intervention and can include rare or unexpected events	Primary outcomes are determined before patients are entered into study and are focused on predicted benefits and risks
Follow-up	Many cohort studies rely on existing experience (retrospective studies) and can provide an opportunity for long follow-up	Prospective studies; often have short follow-up because of costs and pressure to produce timely evidence
Analysis	Sophisticated multivariate techniques may be required to deal with confounding	Analysis is straightforward

Cohort study on HRT and cardiovascular disease

POSTMENOPAUSAL ESTROGEN THERAPY AND CARDIOVASCULAR DISEASE

Ten-Year Follow-up from the Nurses' Health Study

MEIR J. STAMPFER, M.D., GRAHAM A. COLDITZ, M.B., B.S., WALTER C. WILLETT, M.D., JOANN E. MANSON, M.D., BERNARD ROSNER, PH.D., FRANK E. SPEIZER, M.D., AND CHARLES H. HENNEKENS, M.D.

Abstract *Background.* The effect of postmenopausal estrogen therapy on the risk of cardiovascular disease remains controversial. Our 1985 report in the *Journal*, based on four years of follow-up, suggested that estrogen therapy reduced the risk of coronary heart disease, but a report published simultaneously from the Framingham Study suggested that the risk was increased. In addition, studies of the effect of estrogens on stroke have yielded conflicting results.

Methods. We followed 48,470 postmenopausal women, 30 to 63 years old, who were participants in the Nurses' Health Study and who did not have a history of cancer or cardiovascular disease at base line. During up to 10 years of follow-up (337,854 person-years), we documented 224 strokes, 405 cases of major coronary disease (nonfatal myocardial infarctions or deaths from coronary causes), and 1263 deaths from all causes.

Results. After adjustment for age and other risk factors, the overall relative risk of major coronary disease in women currently taking estrogen was 0.56 (95 percent confidence interval, 0.40 to 0.80); the risk was significantly reduced among women with either natural or surgical menopause. We observed no effect of the duration of estrogen use independent of age. The findings were similar in analyses limited to women who had recently visited their physicians (relative risk, 0.45; 95 percent confidence interval, 0.31 to 0.66) and in a low-risk group that excluded women reporting current cigarette smoking, diabetes, hypertension, hypercholesterolemia, or a Quetelet index above the 90th percentile (relative risk, 0.53; 95 percent confidence interval, 0.31 to 0.91). The relative risk for current and former users of estrogen as compared with those who had never used it was 0.89 (95 percent confidence interval, 0.78 to 1.00) for total mortality and 0.72 (95 percent confidence interval, 0.55 to 0.95) for mortality from cardiovascular disease. The relative risk of stroke when current users were compared with those who had never used estrogen was 0.97 (95 percent confidence interval, 0.65 to 1.45), with no marked differences according to type of stroke.

Conclusions. Current estrogen use is associated with a reduction in the incidence of coronary heart disease as well as in mortality from cardiovascular disease, but it is not associated with any change in the risk of stroke.
(N Engl J Med 1991; 325:756-62.)

Confounding was adjusted using multivariate analysis

Table 2. Relative Risk of Cardiovascular Disease among Current and Former Postmenopausal Hormone Users, as Compared with Those Who Never Used Postmenopausal Hormones, after Adjustment for Age and Multiple Risk Factors.*

Group†	No. of Person-Years	Major Coronary Disease		Fatal Cardiovascular Disease		Total Stroke		Ischemic Stroke		Subarachnoid Hemorrhage	
		No. of Cases	RR (95% CI)	No. of Cases	RR (95% CI)	No. of Cases	RR (95% CI)	No. of Cases	RR (95% CI)	No. of Cases	RR (95% CI)
No hormone use	179,194	250	1.0	129	1.0	123	1.0	56	1.0	19	1.0
Current hormone use	73,532										
Adjusted for age	—	45	0.51 (0.37–0.70)	21	0.48 (0.31–0.74)	39	0.96 (0.67–1.37)	23	1.26 (0.78–2.02)	5	0.80 (0.30–2.10)
Adjusted for age and risk factors	—		0.56 (0.40–0.80)		0.61 (0.37–1.00)		0.97 (0.65–1.45)		1.46 (0.85–2.51)		0.53 (0.18–1.57)
Former hormone use	85,128										
Adjusted for age	—	110	0.91 (0.73–1.14)	55	0.84 (0.61–1.15)	62	1.00 (0.74–1.36)	34	1.14 (0.75–1.74)	12	1.42 (0.70–2.90)
Adjusted for age and risk factors	—		0.83 (0.65–1.05)		0.79 (0.56–1.10)		0.99 (0.72–1.36)		1.19 (0.77–1.86)		1.03 (0.47–2.25)

*RR denotes relative risk, and CI confidence interval.

†Women with no hormone use served as the reference category in this analysis. The risk factors included in the multivariate models were age (in five-year categories), cigarette smoking (none, former, current [1 to 14, 15 to 24, and ≥25 cigarettes per day]), hypertension (yes, no), diabetes (yes, no), high serum cholesterol level (yes, no), parental myocardial infarction before the age of 60 (yes, no), Quetelet index (in five categories), past use of oral contraceptives (yes, no), and time period (in five two-year periods).

RCT on HRT and cardiovascular disease

Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women

Stephen Hulley, MD; Deborah Grady, MD; Trudy Bush, PhD; Curt Furberg, MD, PhD; David Herrington, MD; Betty Riggs, MD; Eric Vittinghoff, PhD; for the Heart and Estrogen/progestin Replacement Study (HERS) Research Group

Context.—Observational studies have found lower rates of coronary heart disease (CHD) in postmenopausal women who take estrogen than in women who do not, but this potential benefit has not been confirmed in clinical trials.

Objective.—To determine if estrogen plus progestin therapy alters the risk for CHD events in postmenopausal women with established coronary disease.

Design.—Randomized, blinded, placebo-controlled secondary prevention trial.

Setting.—Outpatient and community settings at 20 US clinical centers.

Participants.—A total of 2763 women with coronary disease, younger than 80 years, and postmenopausal with an intact uterus. Mean age was 66.7 years.

Intervention.—Either 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate in 1 tablet daily (n = 1380) or a placebo of identical appearance (n = 1383). Follow-up averaged 4.1 years; 82% of those assigned to hormone treatment were taking it at the end of 1 year, and 75% at the end of 3 years.

Main Outcome Measures.—The primary outcome was the occurrence of nonfatal myocardial infarction (MI) or CHD death. Secondary cardiovascular outcomes included coronary revascularization, unstable angina, congestive heart failure, resuscitated cardiac arrest, stroke or transient ischemic attack, and peripheral arterial disease. All-cause mortality was also considered.

Results.—Overall, there were no significant differences between groups in the primary outcome or in any of the secondary cardiovascular outcomes: 172 women in the hormone group and 176 women in the placebo group had MI or CHD death (relative hazard [RH], 0.99; 95% confidence interval [CI], 0.80-1.22). The lack of an overall effect occurred despite a net 11% lower low-density lipoprotein cholesterol level and 10% higher high-density lipoprotein cholesterol level in the hormone group compared with the placebo group (each $P<.001$). Within the overall null effect, there was a statistically significant time trend, with more CHD events in the hormone group than in the placebo group in year 1 and fewer in years 4 and 5. More women in the hormone group than in the placebo group experienced venous thromboembolic events (34 vs 12; RH, 2.89; 95% CI, 1.50-5.58) and gallbladder disease (84 vs 62; RH, 1.38; 95% CI, 1.00-1.92). There were no significant differences in several other end points for which power was limited, including fracture, cancer, and total mortality (131 vs 123 deaths; RH, 1.08; 95% CI, 0.84-1.38).

Conclusions.—During an average follow-up of 4.1 years, treatment with oral conjugated equine estrogen plus medroxyprogesterone acetate did not reduce the overall rate of CHD events in postmenopausal women with established coronary

MANY OBSERVATIONAL studies have found lower rates of coronary heart disease (CHD) in women who take postmenopausal estrogen than in women not receiving this therapy.[1-5] This association has been reported to be especially strong for secondary prevention in women with CHD, with hormone users having 35% to 80% fewer recurrent events than nonusers.[6-12] If this association is causal, estrogen therapy could be an important method for preventing CHD in postmenopausal women. However, the observed association between estrogen therapy and reduced CHD risk might be attributable to selection bias if women who choose to take hormones are healthier and have a more favorable CHD profile than those who do not.[13-15] Observational studies cannot resolve this uncertainty.

For editorial comment see p 650.

Only a randomized trial can establish the efficacy and safety of postmenopausal hormone therapy for preventing CHD.

From the University of California, San Francisco (Drs Hulley, Grady, and Vittinghoff); The Johns Hopkins University, Baltimore, Md (Dr Bush); Wake Forest University School of Medicine, Winston-Salem, NC (Drs Furberg and Herrington); and Wyeth-Ayerst Research, Radnor, Pa (Dr Riggs).

A complete list of the HERS Research Group participants appears at the end of this article.

HERS was funded by Wyeth-Ayerst Research. Dr Grady has been a consultant to Eli Lilly, and she and Dr Hulley receive research support from that company. Dr

Confounding was not an issue because of randomization

Table 1.—Baseline Characteristics of HERS Participants (n=2763) by Treatment Group*

Characteristic	Treatment Group: Estrogen-Progestin (n=1380)	Treatment Group: Placebo (n=1383)	*P* Value
Demographics			
Age, mean±SD, y	67±7	67±7	.32
White, %	88	90	.14
Education, mean±SD, y	13±3	13±3	.84
CHD risk factors			
Current smoker, %	13	13	.84
Diabetes on oral medication or insulin, %	19	18	.44
Systolic blood pressure, mean±SD, mm Hg	135±19	135±19	.88
Diastolic blood pressure, mean±SD, mm Hg	73±10	73±10	.89
LDL cholesterol, mean±SD, mmol/L (mg/dL)	3.75±0.96 (145±37)	3.75±0.98 (145±38)	.83
HDL cholesterol, mean±SD, mmol/L (mg/dL)	1.29±0.34 (50±13)	1.29±0.34 (50±13)	.41
Triglyceride, mean±SD, mmol/L (mg/dL)	1.90±0.72 (168±64)	1.86±0.72 (165±64)	.25
Time since last menstrual period, mean ± SD, y	18±8	18±8	.31
Body mass index >27 kg/m^2, %	57	55	.44
Exercise >3 times weekly, %	39	38	.72
No. of drinks per week, mean±SD	1.4±4	1.3±4	.83
General health poor or fair, %	24	24	.94
Postmenopausal estrogen use, %†	24	23	.43
CHD manifestations			
Signs of congestive heart failure, %‡	10	9	.38
Q-wave myocardial infarction, %	17	17	.94
Percutaneous coronary revascularization, %	45	45	.96
Coronary artery bypass graft surgery, %	42	41	.64
Medication use			
Aspirin, %	78	78	.73
β-Blockers, %	33	32	.72
Lipid-lowering medications, %	45	47	.26
Calcium channel blockers, %	55	55	.83
Angiotensin-converting enzyme inhibitors, %	17	18	.57
Diuretics, %	28	28	.79
Multivitamins, %	29	30	.45

How to critically read cohort studies?

- **Selection**
  - 1) Representativeness of the exposed cohort
  - 2) Selection of the non exposed cohort
  - 3) Ascertainment of exposure
  - 4) Demonstration that outcome of interest was not present at start of study
- **Comparability**
  - 1) Comparability of cohorts on the basis of the design or analysis
- **Outcome**
  - 1) Assessment of outcome
  - 2) Was follow-up long enough for outcomes to occur
  - 3) Adequacy of follow up of cohorts

Case-control studies

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Acute-onset smell and taste disorders in the context of COVID-19: a pilot multicentre polymerase chain reaction based case–control study

Á. Beltrán-Corbellini[a], J. L. Chico-García[a], J. Martínez-Poles[b,c], F. Rodríguez-Jorge[a], E. Natera-Villalba[a], J. Gómez-Corral[a], A. Gómez-López[a], E. Monreal[a], P. Parra-Díaz[a], J. L. Cortés-Cuevas[d], J. C. Galán[d], C. Fragola-Arnau[e], J. Porta-Etessam[c,f], J. Masjuan[a] and A. Alonso-Cánovas[a]

[a]*Department of Neurology, University Hospital Ramón y Cajal, Madrid;* [b]*Department of Neurology, Hospital La Luz, Madrid;* [c]*Neurological Disorders Study Group, Institute for Sanitary and Biomedical Research Clínico San Carlos (IdISSC), University Hospital Clínico San Carlos, Madrid;* [d]*Department of Clinical Microbiology, University Hospital Ramón y Cajal, Madrid;* [e]*Department of Otorhinolaryngology, University Hospital Ramón y Cajal, Madrid; and* [f]*Department of Neurology, University Hospital Clínico San Carlos, Madrid, Spain*

- Aim: to determine whether new-onset STDs are more frequent amongst COVID-19 patients than influenza patients.
- This was a case–control study including hospitalized patients of two tertiary care centres.
- Cases: 79 consecutive patients positive for COVID-19 PCR
- Controls: 40 patients positive for influenza PCR
- Exposure: A self-reported smell and taste disorders questionnaire.

Results

	Case	Control
STD	31	5
No STD	48	35

OR= (31/48) / (5/35) = 4.5

$$\text{OR} = \frac{\text{Odds of STD among cases}}{\text{Odds of STD among controls}}$$

Case-control study on HCQ for prevention

Indian J Med Res, Epub ahead of print
DOI: 10.4103/ijmr.IJMR_2234_20

Quick Response Code:

Healthcare workers & SARS-CoV-2 infection in India: A case-control investigation in the time of COVID-19

Pranab Chatterjee[1,#], Tanu Anand[7,#], Kh. Jitenkumar Singh[2], Reeta Rasaily[3], Ravinder Singh[4], Santasabuj Das[8], Harpreet Singh[5], Ira Praharaj[6], Raman R. Gangakhedkar[6], Balram Bhargava[†] & Samiran Panda[9]

Table III. Patterns of hydroxychloroquine (HCQ) prophylaxis in healthcare workers

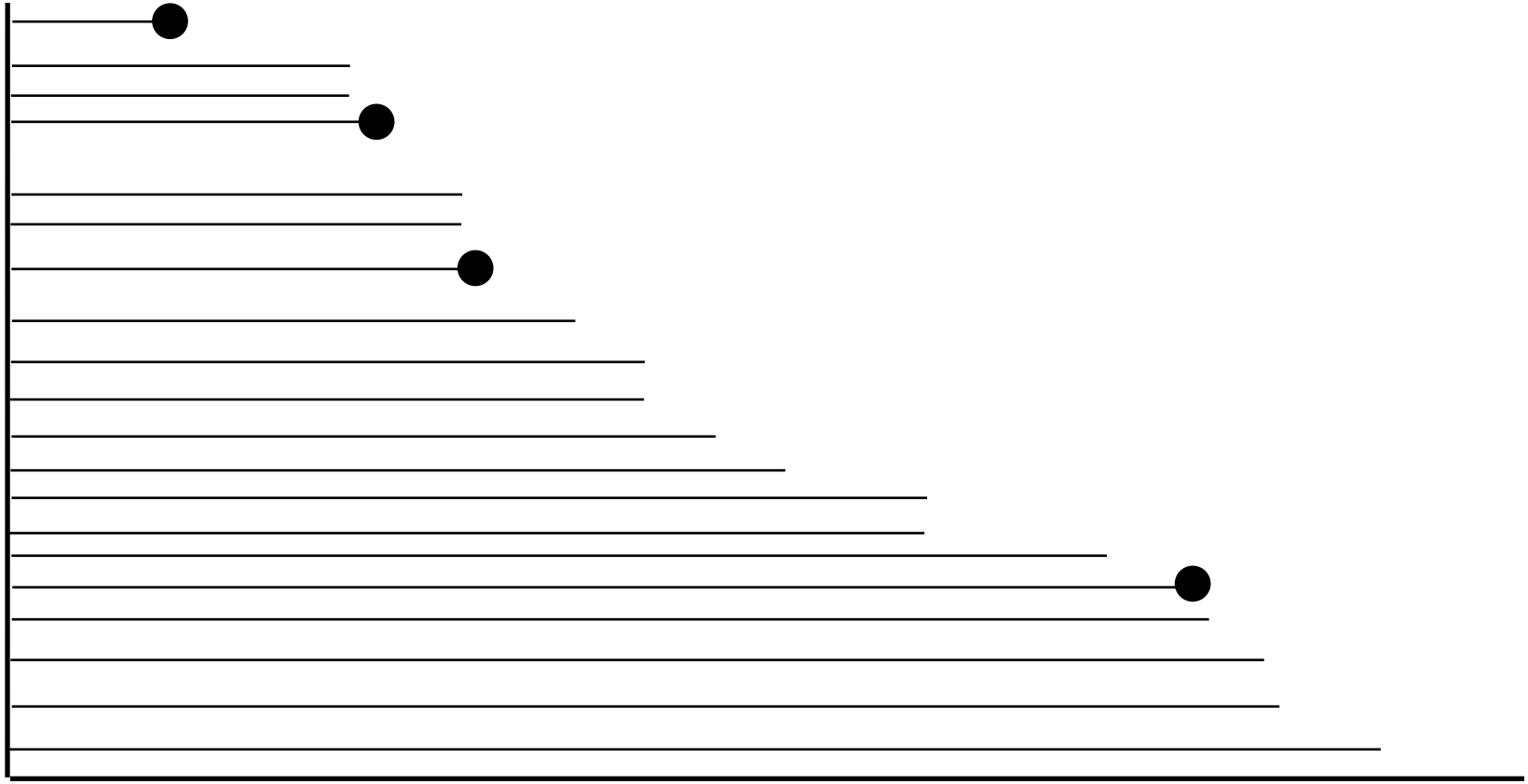
Parameters	Cases (n_1=378) (%)	Controls (n_2=373) (%)	OR	95% CI of OR	*P*
HCQ prophylaxis					
No	206 (54.5)	180 (48.26)	1.28	0.96-1.71	0.087
Yes	172 (45.50)	193 (51.74)	Ref		
Number of maintenance doses of HCQ prophylaxis taken					
>6	12 (3.17)	56 (15.01)	0.19	0.1-0.36	<0.001
4-5	42 (11.11)	67 (17.96)	0.55	0.35-0.84	
2-3	70 (18.52)	37 (9.92)	1.65	1.06-2.58	
HCQ loading dose and irregular recall of maintenance	48 (12.7)	33 (8.85)	1.27	0.78-2.07	
None	206 (54.5)	180 (48.26)	Ref		
Combination prophylaxis					
HCQ only	130 (34.39)	133 (35.66)	0.85	0.62-1.17	0.002
HCQ+azithromycin+vitamins	25 (6.61)	16 (4.29)	1.36	0.71-2.64	
HCQ+vitamins	6 (1.59)	25 (6.70)	0.21	0.08-0.52	
HCQ+non-allopathic systems of medicines or others	11 (2.91)	19 (5.09)	0.51	0.23-1.09	
No HCQ	206 (54.5)	180 (48.26)	Ref		

Introduction to case control designs

- The case control design is really an efficient sampling technique for measuring exposure-disease associations in a cohort that is being followed up or "study base"
- All case-control studies are done within some cohort (defined or not)

Miettinen OS. Eur J Epidemiol. 2010 Oct;25(10):671-5

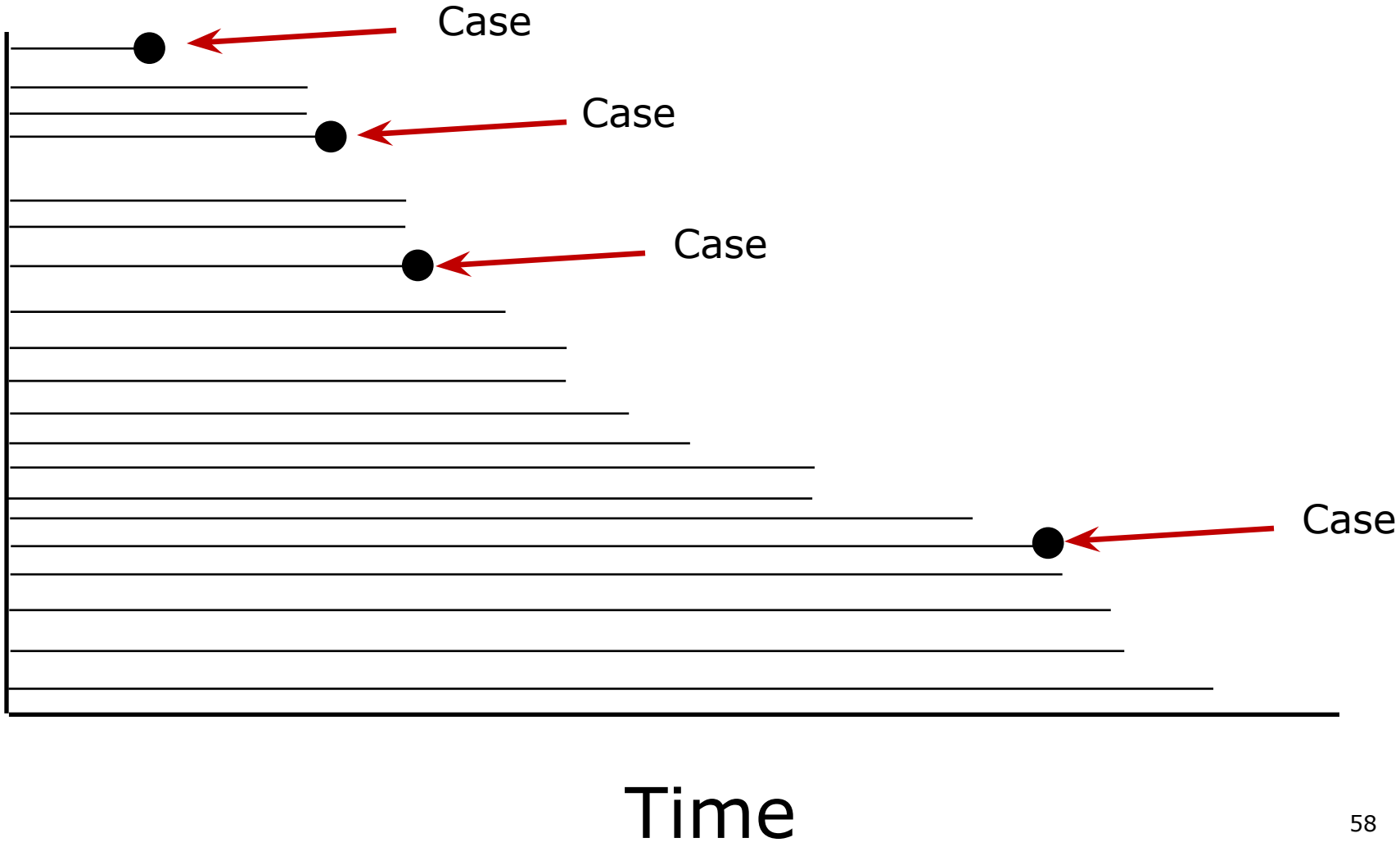
Underlying Hypothetical Cohort



Time

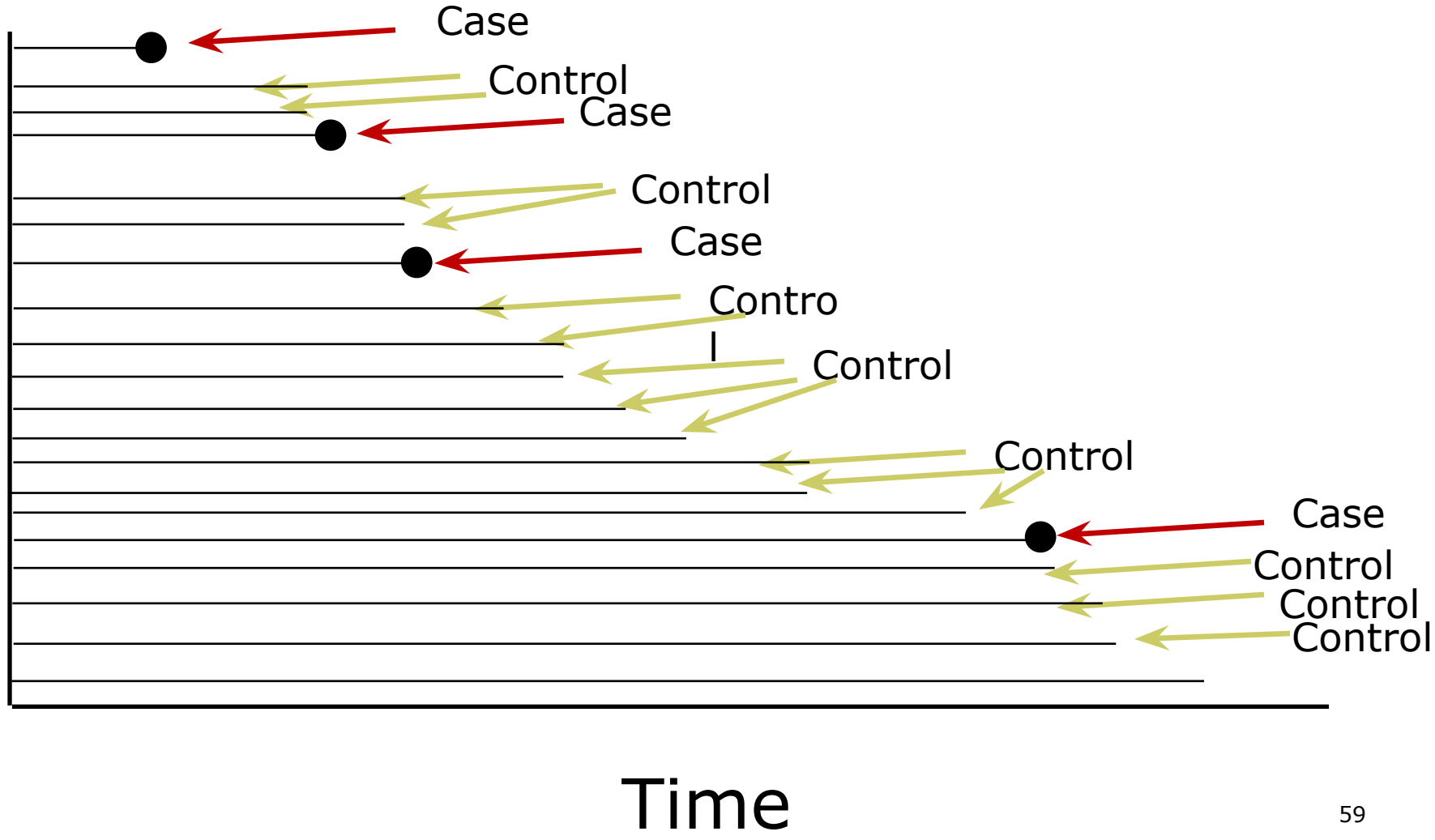
Courtesy: Kris

Cases occur in the cohort



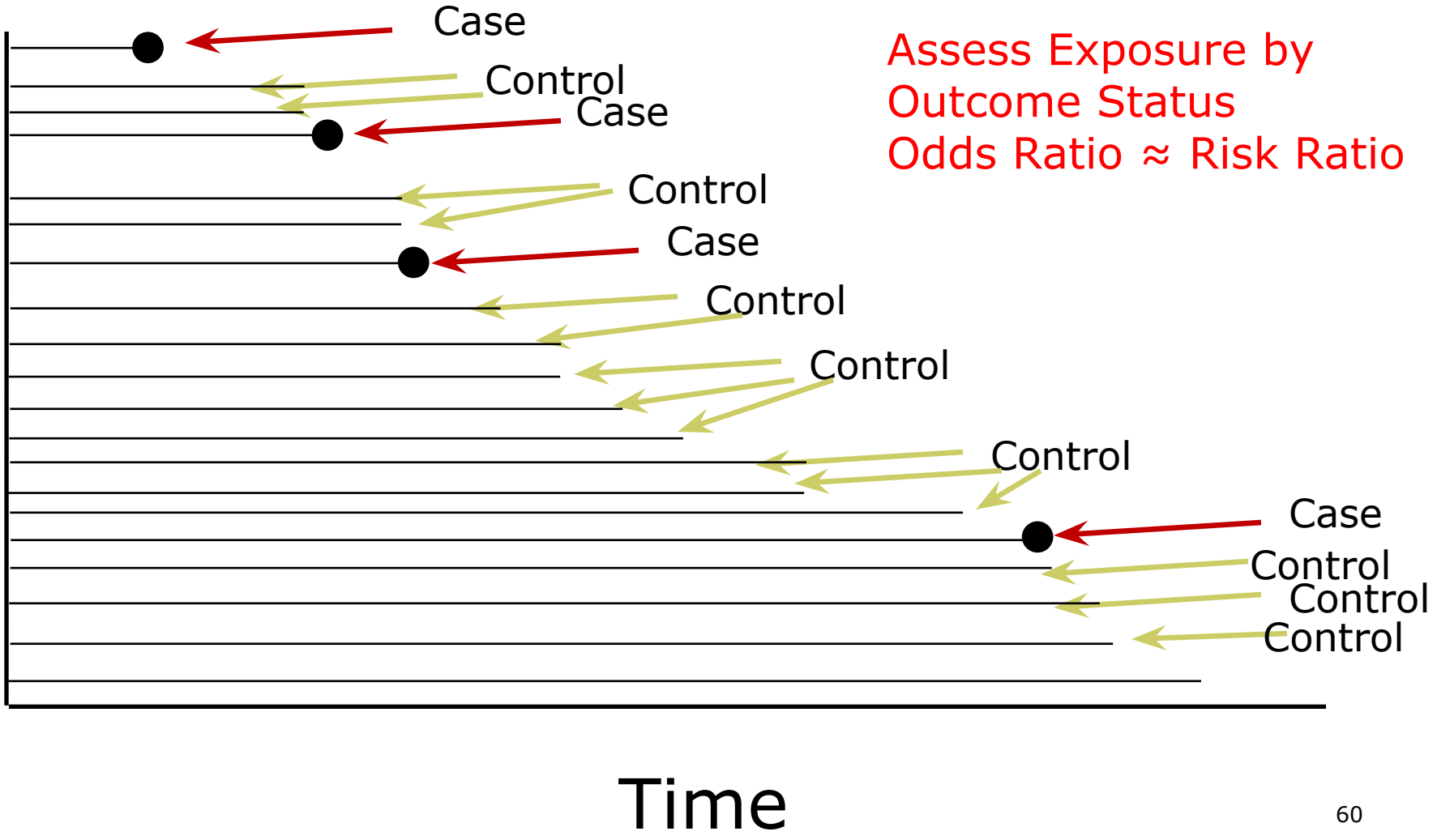
Courtesy: Kris

Controls are those who could have become cases, but did not



Courtesy: Kris

We get odds of exposure in cases vs controls and compute the odds ratio



Courtesy: Kris

TYPES OF CONTROLS

Types of controls in case control studies

- Population controls
- Hospital or disease registry controls
- Friend controls
- Relative controls

Epidemiology 2

Compared to what? Finding controls for case-control studies

David A Grimes, Kenneth F Schulz

Lancet 2005; 365: 1429–33

Family Health International, PO Box 13950, Research Triangle Park, NC 27709, USA (D A Grimes MD, K F Schulz PhD)
Correspondence to: Dr David A Grimes
dgrimes@fhi.org

Use of control (comparison) groups is a powerful research tool. In case-control studies, controls estimate the frequency of an exposure in the population under study. Controls can be taken from known or unknown study populations. A known group consists of a defined population observed over a period, such as passengers on a cruise ship. When the study group is known, a sample of the population can be used as controls. If no population roster exists, then techniques such as random-digit dialling can be used. Sometimes, however, the study group is unknown, for example, motor-vehicle crash victims brought to an emergency department, who may come from far away. In this situation, hospital controls, neighbourhood controls, and friend, associate, or relative controls can be used. In general, one well-selected control group is better than two or more. When the number of cases is small, the ratio of controls to cases can be raised to improve the ability to find important differences. Although no ideal control group exists, readers need to think carefully about how representative the controls are. Poor choice of controls can lead to both wrong results and possible medical harm.

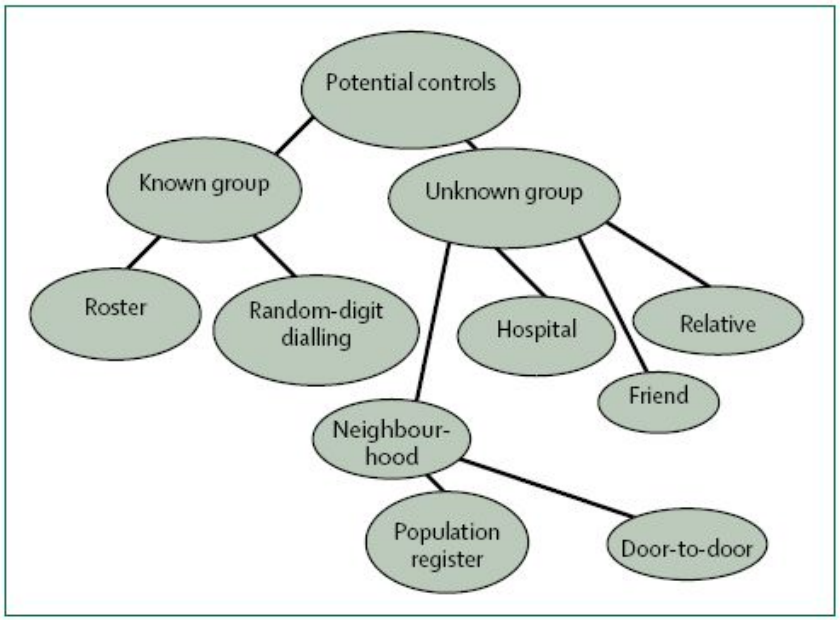


Figure 2: Choosing controls with known and unknown group of study participants

Bias in case-control studies

Selection bias

- Huge concern in case-control studies
  - Which control group is chosen?
  - How are controls actually recruited?
  - Are controls from the same study base that gave rise to the cases?
  - Are controls chosen independent of the exposure?

Selection bias (friend controls)

- **Risk factors for menstrual toxic shock syndrome: results of a multistate case-control study.**

  Reingold AL, Broome CV, Gaventa S, Hightower AW.

- For assessment of current risk factors for developing toxic shock syndrome (TSS) during menstruation, a case-control study was performed
- Cases with onset between 1 January 1986 and 30 June 1987 were ascertained in six study areas with active surveillance for TSS
- Age-matched controls were selected from among each patient's friends and women with the same telephone exchange
- Of 118 eligible patients, 108 were enrolled, as were 185 "friend controls" and 187 telephone exchange-matched controls

Reingold AL et al. Rev Infect Dis. 1989 Jan-Feb;11 Suppl

Selection bias (friend controls)

- Risk factors for menstrual toxic shock syndrome: results of a multistate case-control study

- **Results:**
  - OR when both control groups were combined = 29
  - OR when friend controls were used = 19
  - OR when neighborhood controls were used = 48

- Why did use of friend controls produce a lower OR?
  - Friend controls were more likely to have used tampons than were neighborhood controls (71% vs. 60%)

Reingold AL et al. Rev Infect Dis. 1989 Jan-Feb;11 Suppl 1:S35-41

Direction of bias

		Case		Control
Exposure	Yes	a	⟺	b
	No	c		d

OR = ad / bc

If cases and controls share similar exposures (e.g. friend controls), then a and b will tend to be nearly the same -- this will bias the OR towards 1 (towards null)

Information bias in case-control studies

Sources:

- Poor recall of past exposures (poor memory; can happen with both cases and controls; so, non-differential)
- Differential recall between cases and controls ("recall bias" or "exposure identification bias" or "exposure suspicion bias")
  - Cases have a different recall than controls
- Differential exposure ascertainment (influenced by knowledge of case status)
  - Interviewer/observer bias (cases are probed or interviewed or investigated differently than controls)

Poor recall versus recall bias

Journal of Exposure Science and Environmental Epidemiology (2009) 19, 369–381

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Recall bias in the assessment of exposure to mobile phones

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Most studies of mobile phone use are case–control studies that rely on participants' reports of past phone use for their exposure assessment. Differential errors in recalled phone use are a major concern in such studies. INTERPHONE, a multinational case–control study of brain tumour risk and mobile phone use, included validation studies to quantify such errors and evaluate the potential for recall bias. Mobile phone records of 212 cases and 296 controls were collected from network operators in three INTERPHONE countries over an average of 2 years, and compared with mobile phone use reported at interview. The ratio of reported to recorded phone use was analysed as measure of agreement. Mean ratios were virtually the same for cases and controls: both underestimated number of calls by a factor of 0.81 and overestimated call duration by a factor of 1.4. For cases, but not controls, ratios increased with increasing time before the interview; however, these trends were based on few subjects with long-term data. Ratios increased by level of use. Random recall errors were large. In conclusion, there was little evidence for differential recall errors overall or in recent time periods. However, apparent overestimation by cases in more distant time periods could cause positive bias in estimates of disease risk associated with mobile phone use.
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Information bias: example from case-control study of risk factors for suicide in Pakistan

Table 1 ICD–10 principal diagnosis

Diagnosis	Cases (n=100)	Controls (n=100)
Moderate depressive episode (F32.1)	30	1
Severe depressive episode (F32.2)	43	0
Severe depressive episode with psychotic symptoms (F32.3)	6	2
Schizophrenia (F20)	6	2
Adjustment disorders (F43.2)	3	0
Acute stress reaction (F43.0)	6	0
Alcohol use (F10.0)	0	0
Substance abuse (F11.0)	1	0
Mental retardation (F79)	1	0
Personality disorder (F60)	1	1
No psychiatric diagnosis	4	94

Table 2 Final multivariable conditional logistic regression model

Variable	Adjusted OR (95% CI)
Educational attainment	
No formal education/primary[a]	4.9 (0.8–29.8)
Secondary and above	1.0
Marital status	
Never married	1.0
Ever married	3.6 (0.6–22.3)
Depression	
No	1.0
Yes	208.3 (11.0–3935.2)

a. Adjusted for employment status.

- Close relatives of 100 suicide cases and 100 live controls were interviewed.
- 79/100 suicide cases were found to have had depression.
- Only 3/100 controls were found to have depression (lower than the population average).
- Due to lack of blinding, quality of interviews may have been lower in controls

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Confounding in case-control studies

- Always an issue!
- Can be addressed at the design or analysis stage [usually both]:
  - Design:
    - Matching
    - Restriction
  - Analysis:
    - Multivariable analysis
      - Logistic regression (LR) is the most natural model
      - Results reported as adjusted odds ratios