# Study Design and Analytic Epidemiology for Outbreak Investigations

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## Objectives

- Define analytic epidemiology
- Describe types of studies to investigate outbreaks
- Discuss control group selection
- Prepare 2 x 2 table
- Calculate and interpret measures of association



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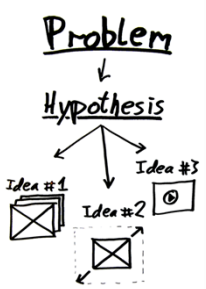
## Analytic Epidemiology

- Differs from descriptive epi (person, place, time)
- Develop then test hypothesis
- Examine **exposures** and **outcomes**
- Use **comparison group** (controls)

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## Exposure and Outcome

- Exposure= potential risk factor
  - Ate specific food item
  - Worked with a chemical
  - Had a certain behavior (e.g., smoking)
- Outcome= Disease
  - Cancer
  - Diarrhea
  - Injury

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## Common Types of Studies

- Cohort
- Case-Control
- Case-case

- These are **observational** studies, as compared with experimental studies



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## Cohort Design

- Start with defined group, classified by exposure status
  - Exposed group
  - Non-exposed group

- Assess who developed disease



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## Cohort Studies examples

- Nurse's Health Study- 1970's
  120,000 female nurses – risk factors for cancer and cardiovascular disease
- Outbreak following a wedding reception
- Illness in a school classroom
- Outbreak after church potluck

www.nhs3.org

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## Why use a cohort?

- Known denominator: # at **risk** of disease
- Compare exposed and unexposed groups
- However, not always possible to define cohort

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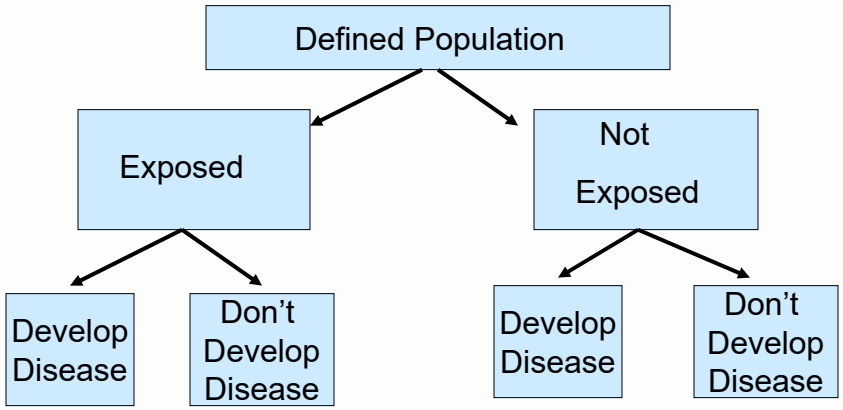
## Cohort Study

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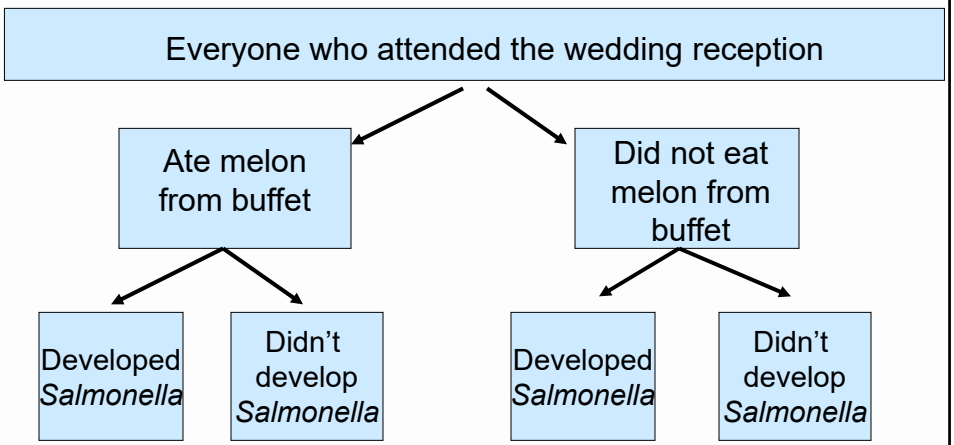
## Cohort Study

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## Case-Control Design

- Classify people by outcome
  - Cases- have disease
  - Controls- do not have disease
- Assess past exposure



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## Case-control study examples

- Smoking and lung cancer, 1950s
- *Salmonella* outbreak associated with nationally distributed product

  Restaurant outbreak of norovirus




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## Selecting Controls

- Do not have the disease, but at risk of disease
- Must have had potential for exposure
- Should be representative of cases

- Key: **If they developed the disease, could they be identified as case?**



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## Potential control groups

- Others who ate at same restaurant
- Neighborhood residents
- Family members
- Friends
- Coworkers
- Random digit dialing
- Classmates
- Medical clinic patients



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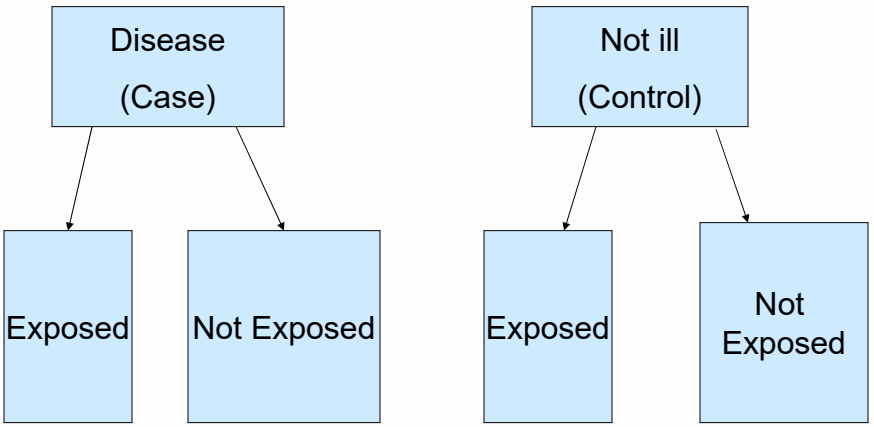
## Case-control Study

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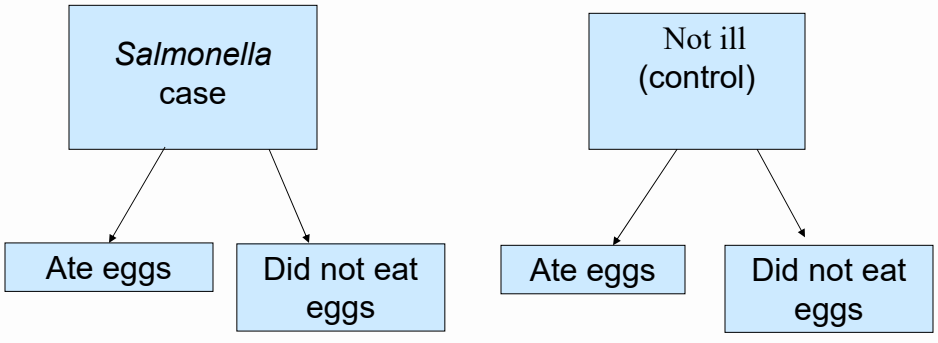
## Case-control Study Example

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# Advantages & Disadvantages

| | Cohort | Case-control |
|---|---|---|
| Advantages | Can evaluate rare exposures<br>Can calculate risk | Quick<br>Smaller size<br>Cost effective<br>Can evaluate rare disease |
| Disadvantages | Inefficient if incubation is long<br>Potential expense<br>Loss to follow up | Recall bias<br>Selection bias |





# Measures of Association

- Quantifies magnitude of association between exposure and disease
  - Cohort study: relative risk (RR)
  - Case-control study: odds ratio (OR)

## 2 X 2 table

| | Diseased | Not diseased | Row total |
|---|---|---|---|
| Exposed | a | b | a+b |
| Not exposed | c | d | c+d |
| Column total | a+c | b+d | a+b+c+d= Grand total |



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## Cohort Study: Relative Risk (RR)

- Risk of disease in exposed ÷ risk of disease in unexposed
- RR= a/(a+b) ÷ c/(c+d)

| | | Disease: Yes | Disease: No |
|---|---|---|---|
| Exposure | Yes | a | b |
| | No | c | d |

**How to interpret If RR = 1?**



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## Calculate RR for Cohort Study

- *Salmonella* Enteritidis outbreak among group of coworkers that had catered lunch with taco bar
- 40 workers ate fresh salsa; 30 developed *Salmonella* Enteritidis and 10 did not
- Another 40 workers did not eat fresh salsa; 2 developed *Salmonella* Enteritidis and 38 did not

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## Relative Risk 2 X 2 table

| | *Salmonella* Enteritidis | No *Salmonella* Enteritidis | Total |
|---|---|---|---|
| Salsa | a | b | a+b |
| No salsa | c | d | c+d |

Please raise hand when you (your group) has completed.

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## 2X2 table results

| | *Salmonella* Enteritidis | No *Salmonella* Enteritidis | Total |
|---|---|---|---|
| Salsa | 30 | 10 | 40 |
| No salsa | 2 | 38 | 40 |

RR = a/(a+b) ÷ c/(c+d)

30/(30+10) ÷ 2/(2+38)

RR= 15

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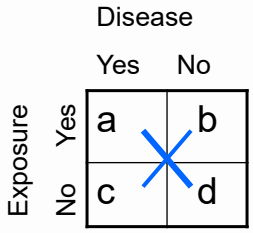
## Relative Risk conclusion:

Those who ate salsa had higher risk (15X) of developing *Salmonella* Enteritidis than those who didn't eat salsa

## Case-Control Study: Odds Ratio (OR)

- Compare odds of exposure for cases and controls
- **Odds Ratio (OR) =**
  - a/c ÷ b/d
  - **ad/bc**




Cross product



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## Case-Control Study: Calculate OR

- Cases: 40 restaurant patrons with *Salmonella* Enteritidis; 30 ate eggs and 10 did not
- Controls: 40 restaurant patrons without *Salmonella* Enteritidis; 2 ate eggs and 38 did not

**Why might a case-control study be good option for restaurant outbreak?**



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## Odds Ratio 2 X 2 Table

| | *Salmonella* Enteritidis | No *Salmonella* Enteritidis |
|---|---|---|
| Eggs | a | b |
| No eggs | c | d |
| Total | a+c | b+d |

Take a moment to enter numbers into 2X2 table.



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## Odds Ratio 2 X 2 Table

| | *Salmonella* Enteritidis | No *Salmonella* Enteritidis |
|---|---|---|
| Eggs | 30 | 2 |
| No eggs | 10 | 38 |
| Total | 40 | 40 |



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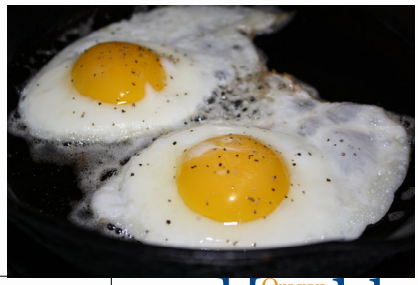
## Odds ratio 2X2 table results

- **Odds Ratio (OR) = (a*d)/(b*c)**
- **OR=**
- Conclusion:
  Cases were ___ times more likely than controls to have eaten eggs



Please indicate when you (your group) has completed.

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## Odds ratio 2X2 table results

- **Odds Ratio (OR) = (a*d)/(b*c)**
- 30x38 ÷ 10x2
- **OR= 57**
- Conclusion:
  Cases were 57 times more likely than controls to have eaten eggs

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# Case-case study example: Shotgun

- Compare exposures between 2 groups of cases
- Cluster of STEC 4 cases: compare exposure frequencies with background exposure frequencies in Shotgun database
- Shotgun database provides background exposure frequencies from previously interviewed cases (Salmonella and STEC)

| Exposure | Code | YES | % | Backgrnd | Binomial |
|---|---|---|---|---|---|
| 331 | CarrotsLoose | 2 / 4 | 50 | 18% | 0.1547 |
| 336 | PepperBell | 2 / 4 | 50 | 26% | 0.2813 |
| 338 | PepperRed | 2 / 4 | 50 | 16% | 0.1180 |
| 339 | PepperYellow | 2 / 4 | 50 | 9% | 0.0456 |

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# Is this a true association?

- P-value <0.05)

  https://tidsskriftet.no/en/2015/09/why-p-value-significant

- Case control study example

  OR=57 (95% CI, 12–280) P<0.0001

  https://www.medcalc.org/calc/index.php


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## Study Design and Analytic Epidemiology

# Questions?


**Stand up and stretch break**



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## Study Design and Analytic Epidemiology

### Exercise

- Handout: CD 303 Exercises (pages 8-10)
- Work in group to complete questions
- Complete each question before proceeding to next question
- Will review questions together at end



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## Study Design and Analytic Epidemiology

### Review of Opening Scenario

On **August 10,** the Oregon County Health Department received a report of a child with *E. coli* O157 (O157) diarrhea. This was their first O157 report in over a year. Within 24 hours Oregon County had received 3 more reports of O157 infection in children.

All 4 ill children that were reported to Oregon County Health Department over 24-hour period had attended the Oregon County Fair and had bloody diarrhea. The fair had been held **August 1 – 6**. Over ~120,000 people had attended this fair. However, the fair ended 3 days earlier. The fairground facilities are used for activities throughout the year.

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## Study Design and Analytic Epidemiology

### Additional Information:

The Oregon County Fair is a major annual event in Oregon each August. It is a large agricultural fair with hundreds of animal exhibits, food vendors, and amusement rides. More than 170,000 visits were recorded this year.

The fairgrounds are supplied by shallow wells approximately 20-feet deep. Since the fairgrounds are only in operation 42 days of year, the fairground water supply is not considered a community water system but is considered an alternative water source and is regulated under the food code. This type of well must be tested within 60 days of an event. Testing for coliforms was performed on June 20th and was negative.

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## Study Design and Analytic Epidemiology

Question 1: What hypotheses do you want to evaluate?

- *E. coli* was obtained at the fair but exactly where is unknown.
- The usual suspects would be food, water and animals. More specifically, unpasteurized milk, cheese, juice, alfalfa sprouts, uncooked beef and farm animals, (cow, sheep, goats).
- Need to further investigate the water source (wells) as possible source.

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## Study Design and Analytic Epidemiology

Additional information

An environmental investigation of the fairground revealed that much of the fair was supplied by chlorinated water. However, in one area of the fairground, a shallow well (well #6) provided unchlorinated water to several vendors who used the water to make beverages and ice. This area was close to the large animal barn.

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## Study Design and Analytic Epidemiology

Question 2: Do we need a study, if so what type of study?

- Oregon County health department Investigators decided to conduct a case-control study.
- Initial evidence is usually not enough to conclude a point source and investigators look at several possible hypotheses.

Why might case control study be used in this investigation?

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## Study Design and Analytic Epidemiology

Additional information

Cases eligible for inclusion in case control study were people who had attended the Fair and who had stool culture positive for *E. coli* O157 and were the first case in a household (primary cases).

Why limit to first case in household?

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## Study Design and Analytic Epidemiology

Question 3: Whom might you get for controls? How do you find them?

- Family members
- Friends of cases
- Neighbors of case household
- Random digit telephone dialing



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## Study Design and Analytic Epidemiology

### Additional information

For the Oregon County Fair, controls were obtained from credit card receipts of attendees and from persons entered in photography exhibit and children's art exhibit. Controls were selected who had a similar age distribution as the cases.



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## Study Design and Analytic Epidemiology

### Results

Investigators identified 46 primary cases and 84 controls. All primary cases had attended the fair during the last 4 days. Analysis included only controls who attended the fair at least once during the final 4 days and cases and controls with available exposure data (32 cases and 57 controls).

Hypothesis 1: Water from well #6

Among cases, 26 were exposed to well #6 and 6 were not exposed. Among controls, 9 were exposed to well #6 and 48 were not exposed.

Hypothesis 2: Vendor A chicken

Among cases, 14 were exposed to Vendor A chicken and 18 were not exposed. Among controls, 5 were exposed to Vendor A chicken and 52 were not exposed.

Complete 2X2 tables for each exposure.

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## Table 1: exposure to water from well #6

| | Cases (ill) | Controls (not ill) |
|---|---|---|
| Yes, exposed | 26 (a) | 9 (b) |
| No, not exposed | 6 (c) | 48 (d) |
| Total | 32 | 57 |

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## Table 2: exposure to Vendor A chicken

| | Cases (ill) | Controls (not ill) |
|---|---|---|
| Yes, exposed | 14 (a) | 5 (b) |
| No, not exposed | 18 (c) | 52 (d) |
| total | 32 | 57 |

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## Study Design and Analytic Epidemiology

Question 4: What is an appropriate measure of association for a case-control study?

- Odds ratio
- $\frac{a/c}{b/d} = \frac{ad}{bc}$

Complete calculations for each exposure.

- Measure of association for water from well #6? (put in chat)
  - OR=?
- Measure of association for Vendor A chicken? (put in chat)
  - OR=?

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# Calculating odds ratios (a*d)/(b*c)

Exposure to water from well #6

$$\frac{26 \times 48}{9 \times 6} = \frac{1248}{54} = 23.1$$

Exposure to Vendor A chicken

$$\frac{14 \times 52}{5 \times 18} = \frac{728}{90} = 8.1$$

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