*The cause is hidden but the result is known*

Ovidius (43 BC-17 or 18 AC)

Dagu workshop at Gondar University May 14-18, 2018

Advanced Epidemiology

Lars Åke Persson

# CASE-REFERENT STUDY

# Design and inferences

Suppose that we want to study
the association between breast-feeding
and diarrhoeal disease

Three alternative approaches:
1) A cross-sectional study
2) A cohort study
3) A case-referent study

IMCH, Lars Åke Persson

# The case-referent study

- A prospective study was not feasible
- We have to use retrospective information about breast feeding
- Cases are defined as 200 children 6-11 mo. With severe diarrhoea diagnosed at the clinic a certain week
- Referents should represent the population that generated the cases (maybe randomly selected from the area)

# The case-referent study

- Odds ratio = (120/80)/(60/140) = 3.5

- It can be shown that under certain (most) circumstances OR ~ RR

- $Chi^2$ ?

- We may calculate test-based confidence interval OR $^{1\pm 1.96 / \sqrt{Chi^2}}$

| Cate-gory | Cases | Refe-rents |
|---|---|---|
| Not BF | 120 | 60 |
| BF | 80 | 140 |
| Total | 200 | 200 |

# What do you want to show?

| Objective | Design |
|---|---|
| Prevalence | Cross-sectional |
| Incidence | Cohort |
| Risk, cause | Cohort; case-referent |
| Prognosis | Cohort |
| Treatment effect | RCT |

# Case-control (referent) study

Exposed

Cases

Non-exposed

Study Population

Exposed

Controls

Non-exposed
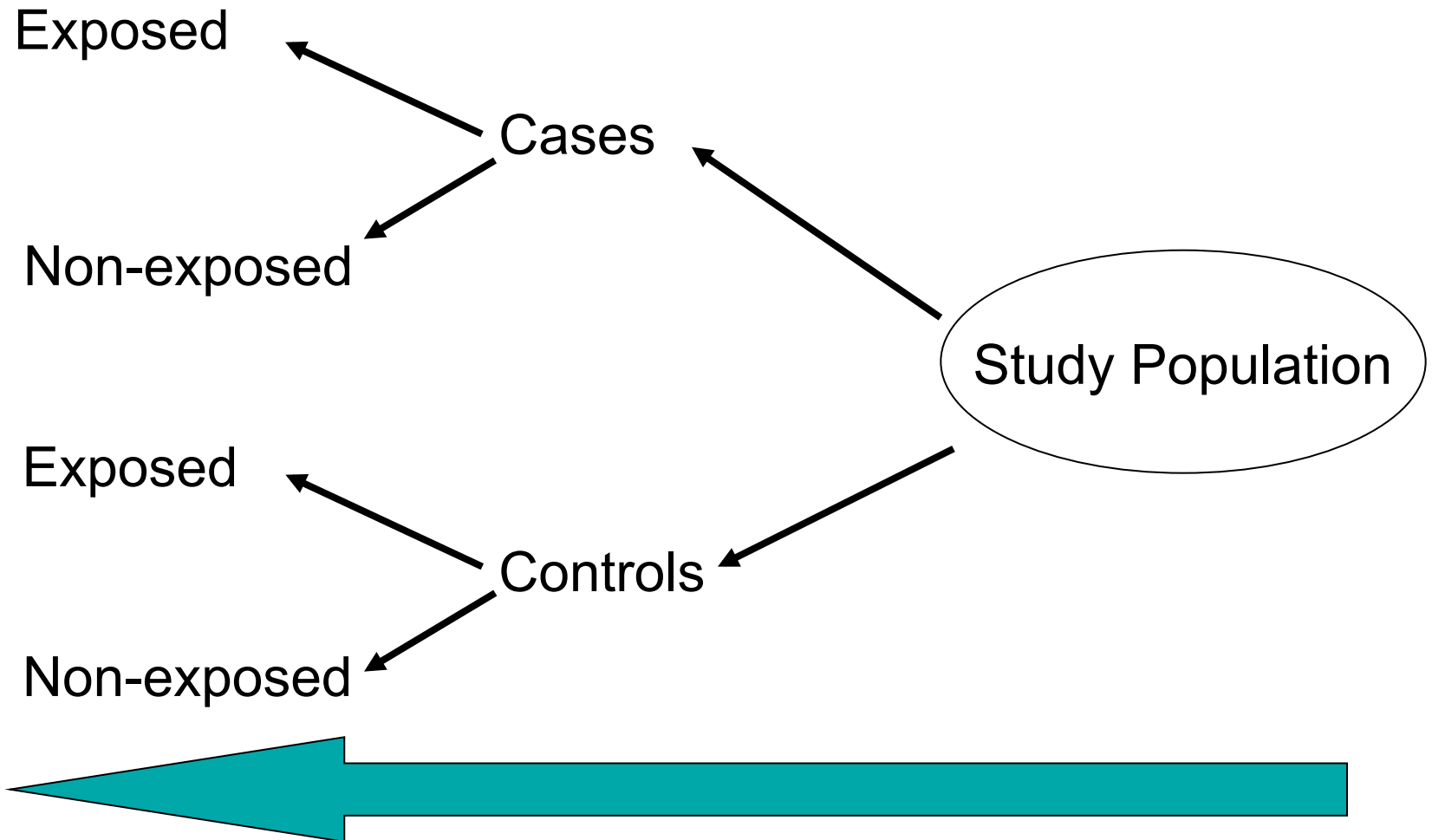
# Case-referent study (case-control)

- Simpler to organise
- Referents represent population that generated the cases
- Retrospectively comparing exposure between cases and referents
- Estimate relative risk by calculate exposure odds ratio
- Hypothesis generation
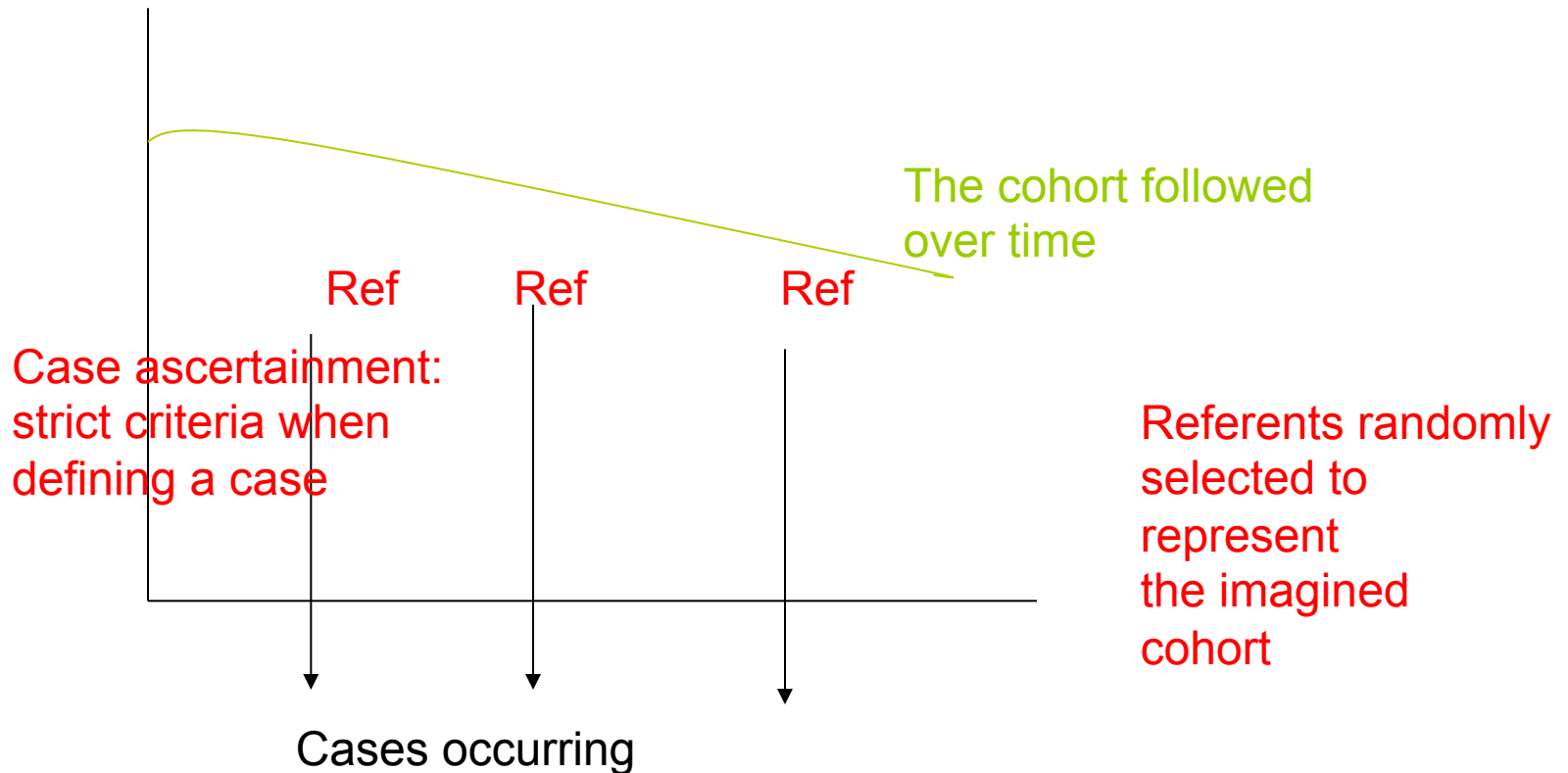- One outcome
- Bias major problem

# The case-referent study

- Odds ratio =(a/c)/(b/d)= =ad/bc (120/80)/(60/140) = =120*140/60*80=3.5

| Category | Cases | Referents |
|---|---|---|
| Not BF | 120 (a) | 60 (b) |
| BF | 80 (c) | 140 (d) |
| Total | 200 | 200 |

# Incident case-referent study



The cohort followed over time

Ref    Ref    Ref

Case ascertainment: strict criteria when defining a case

Referents randomly selected to represent the imagined cohort

Cases occurring

# RR and OR

|              | Exposed          | Non-exposed      |
|--------------|------------------|------------------|
| *Denominator* | $R_1$ person time | $R_0$ person time |
| *Numerator*  | $A_1$ cases      | $A_0$ cases      |
| *Incidence rate* | $I_1 = A_1/R_1$ | $I_0 = A_0/R_0$ |

Incidence rate ratio, $RR = I_1/I_0 = (A_1/R_1)/(A_0/R_0) = (A_1/A_0)/(R_1/R_0)$

*Compare with the case-referent format!*

$A_1/A_0$ is estimated by a/c

If referents are selected to estimate the exposure distribution in the entire population (the study base) then $R_1/R_0$ of the cohort study is estimated by b/d in the case-referent situation

Thus, $RR = I_1/I_0 = (A_1/A_0)/(R_1/R_0) = (a/c)/(b/d) = ad/bc = OR$

# Bias

- Bias is a systematic error
- Bias can create spurious association (bias away from the null)
- Bias can mask an association (bias towards the null)
- Bias is introduced by the investigator or by the study participants
- Bias can arise in all study types

# Bias

- Bias can be evaluated but not fixed in the analysis
- Two main types of bias: selection or observation bias
- Selection bias most likely to occur in case-referent or retrospective cohort studies
- Selection bias in case-referent study may occur when inclusion in study is not independent of exposure
- Selection bias in cohort study occurs when selection is not independent of outcome
- Little or nothing can be done to fix the bias once it has occurred

# Bias

- Observation bias – systematic error in collection of exposure information, results in misclassification

- Recall bias, interviewer bias, loss to follow up

- Differential and non-differential misclassification

# When interpreting results, ask:

- Given conditions of the study could bias have occurred?
- Is bias actually present?
- Large enough to distort results?
- In which direction? Towards the null or from the null?

# Exposure misclassification

Truth

| Exposure | Cases of diarrhea | Referents |
|---|---|---|
| Poor hygiene | 60 | 40 |
| Good hygiene | 40 | 60 |

OR=

Study 1

| Exposure | Cases of diarrhea | Referents |
|---|---|---|
| Poor hygiene | 48 | 32 |
| Good hygiene | 52 | 68 |

OR=

Study 2

| Exposure | Cases of diarrhea | Referents |
|---|---|---|
| Poor hygiene | 60 | 32 |
| Good hygiene | 40 | 68 |

OR=

## Case-referent study for critical reading

**Protective Effect of BCG Among Children Vaccinated Under Universal Immunization Programme**

V.K. Chadha, L. Suryanarayana, H.V. Suryanarayan, N. Srikantaramu and P. Kumar

*Nationational Tuberculosis Institute, Bangalore, India.*

**Abstract.** A case-control study was conducted to estimate the protective effect of BCG vaccination against tuberculosis among children. The children with suspicion of tuberculosis (TB) attending two hospitals in Bangalore city were registered into the study and subjected to detailed clinical examination and investigations. The presence of BCG scar was taken as evidence of vaccination. Modified Stegen-Jones scoring method was adopted for diagnosing TB. The hospital children with score of ≥ 7 were considered as TB cases. Children residing in the neighbourhood of cases were similarly investigated and those scoring ≤ 4 were labeled as controls. A total of 118 age-sex matched case-control pairs were identified and final analysis was confined to 113 cases and 109 controls after excluding children with doubtful BCG scar. A low protective effect of BCG vaccination at 31% (not significant, statistically) was observed against TB - all forms combined, among children vaccinated as under Universal Immunization Programme. Though the protective efficacy against extra-pulmonary TB was observed to be higher than for pulmonary TB, it was also not significant, statistically. It will be appropriate to conduct further studies on protection rendered by BCG vaccination against tuberculous meningitis and other severe forms of TB. Besides, the quality of vaccination programme including cold chain maintenance also needs to be evaluated. **[Indian J Pediatr 2004; 71 (12) : 1069-1074]**
*E-mail : ntiindia@blr.net.in, vin_chadha@yahoo.com*

**Key words:** *Tuberculosis; BCG; Protective effect.*

1 Why did they do this study?

2 Case ascertainment?

3 Selection of controls/ referents?

4 Size of study?

5 Exposure classification?

6 Managing of confounding?

7 Valid conclusions?