Analytic Study Design

DMID/ICSSC
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Cohort Studies
Example of a Prospective Cohort Design: Treatment of Severe Malaria in Children

The Present

Sample

PTX present

PTX absent

The Future

Death

No Death

Death

No Death

Population
In a Cohort Study

- The outcome has not occurred when the study starts... usually

- Are retrospective cohort studies possible?
Bias: Cohort Compared to Case-Control

- Prospective cohort studies do not have two potent causes of bias in the case-control studies
  - Selection bias in the control group
  - Ascertainment bias in measuring exposure
- While biased, tend to be less biased than case-control
Additional Advantages of Cohort Studies

Because potential causative factors are measured before the outcome occurs, a cohort study can establish that they preceded outcome.
Steps in Prospective Cohort Studies

1. Select a sample from the population
2. Measure exposures (predictor variables)
3. Measure confounding factors
4. Follow-up the cohort
5. Measure outcome variables
6. Analyze results
## Simple Cohort Study Analysis

<table>
<thead>
<tr>
<th></th>
<th>Exposed</th>
<th>Unexposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants developing outcome</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>Participants not developing outcome</td>
<td>c</td>
<td>d</td>
</tr>
<tr>
<td>Total number of participants</td>
<td>$N_1$</td>
<td>$N_0$</td>
</tr>
</tbody>
</table>

Relative risk $RR = \frac{\text{incidence of outcome in exposed group}}{\text{incidence of outcome in unexposed group}} = \frac{a/N_1}{b/N_0}$

Attributable risk = \( \frac{\text{incidence of the outcome that can be attributed to the exposure}}{\text{total number of participants}} = \frac{a}{N_1} - \frac{b}{N_0} \)
## Cohort Study Analysis Example

<table>
<thead>
<tr>
<th></th>
<th>Exposed</th>
<th>Unexposed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td><strong>No Outcome</strong></td>
<td>95</td>
<td>195</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>100</td>
<td>200</td>
</tr>
</tbody>
</table>

- $I_E = 5.0\%$
- $I_{E} = 2.5\%$
- $RR = 2.0$
- $AR = 2.5\%$
The Problem of Lost To Follow-up

<table>
<thead>
<tr>
<th>Exposure (PTX)</th>
<th>Outcome (Death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTX</td>
<td>$I_{\text{PTX}}$ 0% Lost to Follow-up</td>
</tr>
<tr>
<td>No PTXs</td>
<td>$I_{\text{No}}$ 30% Lost to Follow-up</td>
</tr>
</tbody>
</table>

(Lost to follow-up have higher incidence of death)

Measured death rate in No PTX group too low

Biases comparison

--- Is the incidence rate in No PTX group lower than in the PTX group?
The Problem of Lost To Follow-up

Exposure (PTX)

- PTX
- No PTXs

Outcome (Death)

- $I_{PTX}$: 20% Lost to Follow-up
- $I_{No}$: 20% Lost to Follow-up

Lost to follow-ups have unknown impact on outcome

Measured death rate in both groups too low or high

Bias?

In reality, LFUs could be different in both groups
Minimize Losses to Follow-up

- *Must* minimize losses

- Address procedures for minimizing losses in greater detail later in the week
  - Retention
  - Cohort and RCTs face similar issues
Since exposure is likely known by both the participants and study investigators, danger of diagnosis of outcome being influenced by exposure class
Minimize Ascertainment Bias in Cohort Studies - Determination of Outcomes

- Consistent
- Equal for all exposure groups
- Establish explicit, objective criteria
- Outcomes should be assessed blindly, if possible
<table>
<thead>
<tr>
<th></th>
<th>PTX</th>
<th>PTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>15</td>
<td>45</td>
</tr>
<tr>
<td>No</td>
<td>85</td>
<td>55</td>
</tr>
</tbody>
</table>

Death

$RR = \frac{15\%}{45\%} = 0.33$
Confounding Bias Occurs

- Not hypothetical
- Occurs in both cohort and case-control
- Confounding is confusing and needs convincing
  - Play with numbers
  - See page 37
In this example you suspect:

**SES** is strongly associated with both **PTX** and death,

i.e., **SES** is a **Confounder**
<table>
<thead>
<tr>
<th></th>
<th>PTX</th>
<th>PTX</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High SES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes Death</td>
<td>9</td>
<td>3</td>
<td>10%</td>
</tr>
<tr>
<td>No Death</td>
<td>81</td>
<td>27</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Low SES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes Death</td>
<td>6</td>
<td>42</td>
<td>60%</td>
</tr>
<tr>
<td>No Death</td>
<td>4</td>
<td>28</td>
<td>60%</td>
</tr>
</tbody>
</table>

RR = \frac{10\%}{10\%} = 1.0

RR = \frac{60\%}{60\%} = 1.0
Example of confounding in a hypothetical cohort study of PTX and death

- When the relative risk is controlled for the confounding effect of SES, the decreased risk (protective effect) disappears.

- Play with the numbers in the salpingitis example on page 37.
Advantages of Cohort Studies

- Efficient with higher incidence (approx. > 20%)
- Excellent for studying rare exposures
- Less opportunity for selection bias and ascertainment bias than case-control studies
- Clear temporal sequence of exposure and outcome
- Obtain incidence rates and relative risk
- Yields more understandable information than case-control studies
Disadvantages of Cohort Studies

- Contains selection bias and probably more ascertainment bias than an RCT
- With rare outcomes, large sample sizes and relatively expensive to conduct
- Long-term follow-up difficult when the latency period for the outcome is long
- Follow-up may be difficult -- losses affect results
- Exposure status may change during study
At a minimum for a cohort study, address in the protocol:

- Entry criteria
- Definitions of the exposure groups (comparison groups) [and implications for selection bias]
- The planned procedures to achieve retention and follow-up of participants
- Selection and measurement of potential confounding factors
- Endpoint: Next sessions (Methods to ascertain outcomes, including blinding procedures, if any)
Case-Control Studies
### Incidence and Relative Risk From a Case-Control study

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>E</td>
<td>90</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>200</td>
</tr>
</tbody>
</table>

**Incidence rate in E?**

**Incidence rate in E?**

**RR?**
Cohort Study

Start with \( a + c \) and \( b + d \); determine OUTCOME

Case-Control Study

Start with \( a + b \) and \( c + d \); then determine EXPOSURE
Example of a Case-Control Design: Use Bednets and Severe Malaria in Children

The Past or Present

- Bednets present
- Bednets absent

The Present

- Severe Malaria
  - Sample of cases
  - Population with disease (cases)

- No Severe Malaria
  - Sample of controls
  - Much larger population without disease (controls)
Case-Control Study

Some Advantages:

- Rare diseases
- Diseases with long latency period
- Fewer subjects
- Less Expensive
- Quicker to complete
Case-Control Study

Some Weaknesses:

- Recall bias
- Difficulty in selecting an appropriate control group
- Does not yield incidence rates in exposed and unexposed groups
Incidence rates cannot be calculated

Hence, a relative risk cannot be calculated

So what do we do?

Approximate the RR with an odds ratio
RR Estimation in a Case-Control Study

<table>
<thead>
<tr>
<th>Exposure (Yes)</th>
<th>Outcome NO (Control)</th>
<th>Yes (Case)</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>A</td>
<td>B</td>
<td>A + B</td>
</tr>
<tr>
<td>No</td>
<td>C</td>
<td>D</td>
<td>C + D</td>
</tr>
</tbody>
</table>

\[
RR = \frac{A}{A + C} \frac{B}{B + D}
\]

If the rates are low (\( \approx < 5\% \))

Then \( A/C \approx A/(A + C) \)

And \( B/D \approx B/(B + D) \)

\[
RR \approx \frac{A/C}{B/D} = \frac{AD}{BC} = \text{odds ratio}
\]
### RR Estimation in a Case-Control Study

<table>
<thead>
<tr>
<th></th>
<th>Cases control</th>
<th>Cases cases</th>
<th>Control control</th>
<th>Control cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>A: 100</td>
<td>B: 30</td>
<td>C: 2000</td>
<td>D: 2000</td>
</tr>
<tr>
<td>Control</td>
<td>E: 130</td>
<td>E: 4000</td>
<td>2100</td>
<td>2030</td>
</tr>
</tbody>
</table>

#### Incidence rates

- **RR**: \( \frac{4.8\%}{1.5\%} = 3.2 \)
- **OR**: \( \frac{100 \times 2000}{30 \times 2000} = 3.3 \)
- **S_1**: .5
- **S_0**: .05
- **OR**: \( \frac{50 \times 100}{15 \times 100} = 3.3 \)

**Incidence rates?**

**RR?**
# Why Is A Case-Control Study Efficient?

## Cohort Study

<table>
<thead>
<tr>
<th></th>
<th>E</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>No Disease</td>
<td>1000</td>
<td>2000</td>
</tr>
<tr>
<td></td>
<td>1015</td>
<td>2010</td>
</tr>
<tr>
<td></td>
<td>3025</td>
<td></td>
</tr>
</tbody>
</table>

## Analogous Case Control Study

<table>
<thead>
<tr>
<th></th>
<th>E</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases (Disease)</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Controls (No Disease)</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>55</td>
<td></td>
</tr>
</tbody>
</table>
Why Is A Case-Control Study Efficient?

Cohort Study

Study Size = 3025

RR = 3.0  95% CI (1.4 - 6.3)  p = .005

Analogous Case-Control Study

Study Size = 55

OR = 3.0  95% CI (1.0 - 9.0)  p = .05
**Cohort Study**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Exposed</th>
<th>Unexposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Outcome</td>
<td>4,990</td>
<td>19,990</td>
</tr>
<tr>
<td>Outcome</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

Total Study Size 25,000

RR = 4.0
95% CI [1.7 – 9.6],
p = .001

**Case-Control Study**

<table>
<thead>
<tr>
<th></th>
<th>Exposed</th>
<th>Unexposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Controls</td>
<td>10</td>
<td>40</td>
</tr>
</tbody>
</table>

Total Study Size 70

OR = 4.0
95% CI [ 1.2 – 14.3],
p = .01
### Case-Control Examples

<table>
<thead>
<tr>
<th># Controls</th>
<th>OR</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>3.0</td>
<td>.87 – 10.6</td>
</tr>
<tr>
<td>60</td>
<td>3.0</td>
<td>1.04 – 8.8</td>
</tr>
<tr>
<td>90</td>
<td>3.0</td>
<td>1.10 – 8.3</td>
</tr>
<tr>
<td>120</td>
<td>3.0</td>
<td>1.14 – 8.0</td>
</tr>
</tbody>
</table>
Is a case-control study always efficient?

Can a cohort study be more efficient?
### Case-Control Study

<table>
<thead>
<tr>
<th></th>
<th>Exposed</th>
<th>Unexposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Incidence</td>
<td>10</td>
<td>10,000</td>
</tr>
<tr>
<td>Low Incidence</td>
<td>20</td>
<td>100,000</td>
</tr>
<tr>
<td>Total</td>
<td>10,100</td>
<td>100,200</td>
</tr>
</tbody>
</table>

### Cohort Study

<table>
<thead>
<tr>
<th></th>
<th>Exposed</th>
<th>Unexposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Incidence</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>High Incidence</td>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>110</td>
</tr>
</tbody>
</table>
Greater Chance of Bias in Case-Control Studies

- All of the relevant events, disease and exposure, have already occurred when the study begins

- Two potent sources of bias
  - Bias in ascertaining exposure
  - Selection of a control group
Bias in Case-Control Studies

Information Bias
- Information is gathered differently from cases and controls
- Difference related to risk factor
- Recall bias is most common

Selection Bias
- Cases and controls are selected differently
- Difference in selection is related to risk factor
Ascertainment Bias in Case-Control Studies

- Data collectors and participants can be prejudiced by knowledge of outcome
  - Especially if associations are alleged

- Try to ascertain exposure in an unbiased manner
  - Blinding
  - Visual aids to stimulate memory
Case-Control Study

Case Definition:

- Define objective criteria for reliable diagnosis of disease
- Know what population you are selecting cases from
  - Clinic, hospital, etc.
  - Population based
Control Selection:

- Controls should represent the population from which cases were selected
- Free of disease being studied
- Selection must be independent of exposure being studied
- Matching is not what it seems! Generally it is better not to match
Case-Control Study of Risk Factors for AIDS

Case Selection:
- MSM AIDS cases diagnosed in San Francisco during 1983-1984

2 Control Groups:
- MSM STD clinic patients
- MSM from same neighborhood as cases
AIDS by Number of Partners

<table>
<thead>
<tr>
<th>AIDS Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 100 Partners Per Year</td>
<td>0 – 5 Partners Per Year</td>
</tr>
</tbody>
</table>

STD Clinic Controls (HIV-) \( \text{OR} = 2.9 \)

Neighborhood Controls (HIV-) \( \text{OR} = 52.0 \)

STD Patients

AIDS

<table>
<thead>
<tr>
<th>100+</th>
<th>0 - 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>10</td>
</tr>
</tbody>
</table>

Controls

<table>
<thead>
<tr>
<th>100+</th>
<th>0 - 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>25</td>
</tr>
</tbody>
</table>

OR = \frac{90 \times 25}{10 \times 75} = 3.0

Neighborhood

AIDS

<table>
<thead>
<tr>
<th>100+</th>
<th>0 - 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>10</td>
</tr>
</tbody>
</table>

Controls

<table>
<thead>
<tr>
<th>100+</th>
<th>0 - 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>85</td>
</tr>
</tbody>
</table>

OR = \frac{90 \times 85}{10 \times 15} = 51.0
## NSAIDs → Colorectal Cancer

### Cases – Colorectal Cancer Patients

<table>
<thead>
<tr>
<th>Hospital Controls</th>
<th>Exposure to NSAIDS</th>
<th>Impact on Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis</td>
<td>Reduce</td>
<td></td>
</tr>
<tr>
<td>Peptic Ulcers</td>
<td>Increase</td>
<td></td>
</tr>
</tbody>
</table>
Advantages of Case-Control Studies

- Case-control studies are useful and efficient for studying low frequency outcomes (i.e. approx. <5%)
- Case-control studies are useful for studying health problems with a long latent interval
- With rare outcomes, case-control studies are less time consuming and less expensive than cohort studies
Disadvantages of Case-Control Studies

- Easier to Do . . . . . . . Wrong

- Prone to more selection bias than cohort studies: control group selection difficult

- Prone to more ascertainment bias than cohort: incomplete records or recall bias

- Cannot determine incidence rates

- By definition, pertinent to one outcome

- Cannot observe temporality of association
At a Minimum, for a Case-Control Study, in the Protocol Include:

- Definition of cases
- Selection of the control group(s) [implications for selection bias]
- Selection and measurement of potential confounding factors
- Analogous endpoint: The ascertainment of exposure and the related procedures to minimize ascertainment bias (including whether any blinding would be attempted)
Randomized Controlled Trials

The methodologic standard of excellence for scientific experiments
Epidemiologic Study Designs

- **Cohort**
  - Exposure → Outcome

- **Case-Control**
  - Outcome → Exposure

- **Randomized Controlled (Clinical) Trials (RCT)**
RCT PARADIGM

Population of Interest

Child <5 year presenting at hospital with severe malaria

Randomize

PTX

Placebo

Outcome Assessment
Death within 7 days
In observational studies, statistical methods allow investigators to control for confounding factors.

- Must be measured (ABLE)
No statistical method can achieve comparability on unknown or unmeasured factors in analysis phase.

Random allocation is the only known method to assure comparability.
Comparison of Results from Cohort Study and RCT

Intervention: Exercise in men after M.I.

Outcome: Recurrent M.I.

Cohort: RR = 0.38  95% CI (0.18 - 0.80)  p = 0.006

RCT: RR = 1.3  95% CI (0.73 - 2.2)  p = 0.20
Hormone Replacement and Therapy Coronary Heart Disease (CHD)

- Hormones decrease risk of CHD by 35% to 50%, according to 3 different meta-analysis of numerous observational studies.
- Especially strong for secondary prevention in women with CHD.
Experimentation Trumps Observation

- RCT of hormone-therapy for secondary presentation of CHD
- Relative hazard = 0.99; 95% CI 0.80 - 1.22
- No effect of hormone therapy
- Recent Women’s Health Initiative RCT in healthy women (JAMA 2002; 288: 321-333)
  - CHD: HR=1.29; 95% CI 1.02-1.63)
Chemotherapy for Carcinoma of the Esophagus*

- A meta-analysis of 8 non-randomized studies found a 68% reduction in death (OR=0.32, 95% CI 0.24 - 0.42)

- A meta-analysis of 12 RCTs found a 4% reduction in death

(OR=0.96, 95% CI 0.75 - 1.22)

<table>
<thead>
<tr>
<th></th>
<th>RCTs (57)</th>
<th>Non-Random (43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference in case-fatality rates at ( p &lt; 0.05 )</td>
<td>8.8%</td>
<td>58%</td>
</tr>
<tr>
<td>Results favored treatment over controls (( p &lt; 0.05 ))</td>
<td>60%</td>
<td>93%</td>
</tr>
<tr>
<td>Mean differences in the case-fatality rates ( (p &gt; 0.05) )</td>
<td>( \pm 0.8% )</td>
<td>( \pm 1.7% )</td>
</tr>
</tbody>
</table>
Systematic Review of Randomized vs Non-Randomized Evidence*

- On average, non-randomized studies result in overestimates of effect
- That bias can, however, go in either direction
- That bias can be as large or larger than the effects of worthwhile interventions

EFFECT OF THE ANGIOTENSIN-CONVERTING-ENZYME INHIBITOR BENAZEPRIL ON THE PROGRESSION OF CHRONIC RENAL INSUFFICIENCY

Abstract Background. Drugs that inhibit angiotensin-converting enzyme slow the progression of renal insufficiency in patients with diabetic nephropathy. Whether these drugs have a similar action in patients with other renal diseases is not known. We conducted a study to determine the effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of renal insufficiency in patients with various underlying renal diseases.

The patients in each group were then randomly assigned to receive 10 mg of benazepril or placebo once daily. Randomization was balanced for disease severity at each center.
Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris

Clinical trials have demonstrated a prophylactic role for aspirin in myocardial infarction and in unstable angina pectoris. The Swedish Angina Pectoris Aspirin Trial (SAPAT) is the first prospective study of aspirin in stable angina.

“After showing good tolerance of sotalol for at least three weeks the patients were randomised double blind to aspirin 75 mg daily (n=1009) or placebo (n=1026).”

Lancet
Abstract

Background. In patients with human immunodeficiency virus (HIV) infection, combined treatment with several agents may increase the effectiveness of antiviral therapy. We studied the safety and efficacy of saquinavir, an HIV-protease inhibitor, given with one or two nucleoside antiretroviral agents as compared with the safety and efficacy of a combination of two nucleosides alone.

“The study (AIDS Clinical Trials Group protocol 229) was a randomized, double-blind, phase 2 trial of three treatment regimens”

New England Journal of Medicine
EFFECT OF THE ANGIOTENSIN-CONVERTING-ENZYME INHIBITOR BENAZEPRIL ON THE PROGRESSION OF CHRONIC RENAL INSUFFICIENCY

Abstract  

Background. Drugs that inhibit angiotensin-converting enzyme slow the progression of renal insufficiency in patients with diabetic nephropathy. Whether these drugs have a similar action in patients with other renal diseases is not known. We conducted a study to determine the effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of renal insufficiency in patients with various underlying renal diseases.

Methods. In a three-year trial involving 583 patients with renal insufficiency caused by various underlying disorders, 300 received benazepril and 283 received placebo.

New England Journal of Medicine
The mortality of critically ill patients with acute renal failure has been halved through intervention by haemodialysis. However, several reports suggest that the course of the disorder may be prolonged by this procedure. Our prospective randomised study was done . . .

Lancet
Randomized Trials Require Methodological Rigor

- Improperly conducted RCTs yield biased results
- Researchers must devote assiduous attention to design and conduct of RCTs
- Only properly conducted RCTs will fulfill their promise of minimizing bias
- Separate presentation later in the week
Advantages of Randomized Trials

- First and foremost, the only effective method known to control selection bias
- Controls confounding bias
- Facilitates effective blinding in some trials
- Theoretically attractive - many statistical methods assume random assignment
- Maintains advantages of cohort studies
Disadvantages of Randomized Trials

- May be complex and expensive
- Difficult and expensive with low incidence outcomes
- May lack representativeness - volunteers may differ from population of interest
- Ethical challenges of experimental research
- Sometimes impossible or impractical
END

Thank You
Case Scenarios

- **Case 1:** Dr. Gates would like to evaluate whether the presence of helminth infection at the time of vaccination with conjugate pneumococcal vaccine impairs antibody responses in children ages 4-8 years in Cameroon. It is postulated that the children with helminth infections will have a Th2 shift in cytokines resulting in impaired antibody responses to conjugate vaccines.

  Previous studies of children in the districts of interest show a 40% prevalence of helminth infections. Participants in prior studies have displayed excellent retention yielding over 95% follow up rates. Dr. Gates estimates that approximately 90% of children in Cameroon without helminth infections would develop adequate antibody titers. She worries that only 70% of children with helminth infections would develop adequate antibody titers.

- **Case 2:** Dr. Michigan working in Malawi would like to determine if adjuvant treatment with 2’ Hydrochalcone in children with cerebral malaria reduces the incidence of death within 14 days of admission to hospital. Chalcones reduce expression of endothelial adhesion molecules which are up regulated in children with severe malaria. In vitro data suggest that 2’-hydrochalcone decreases transcription of ICAM-1, VCAM-1 and E-selectin genes.

  Since all the patients would be hospitalized, the study should realistically yield 100% follow up. Approximately 30% of the children admitted to hospital with cerebral malaria die within 14 days. Dr. Michigan postulates that 2’Hydrochalcone will lead to a 50% reduction in the incidence of death.

- **Case 3:** Drs. Fixit and Royalty would like to determine if positive hepatitis serology, consumption of alcohol, and/or acetaminophen (all with prevalences of 20 to 50% in the population of interest) contribute to the development of portal hypertension in individuals infected with S. japonicum in China. They believe that a long latency interval exists between all the examined exposures and the putative association with the development of portal hypertension.

  They estimate that the incidence of portal HTN in those with S. japonicum is approximately 1-2% in the population of interest. Local health departments have excellent records on the population of interest dating back for 15 years.
• **Case 4:** Investigators in Egypt, Yemen, and Kenya have reviewed the Rift Valley Fever (RVF) literature and believe that antibody inversely correlates with disease outcome. They hypothesize that low antibody production contributes to higher mortality. Further, they hypothesize that IL-12 will increase RVF specific antibody and result in a decreased mortality from RVF compared to a group not receiving IL-12.

They estimate that mortality in those with RVF not receiving IL-12 is approximately 3-4%. In prior studies at their research sites of RVF, investigators have displayed an excellent ability to follow-up participants. They would anticipate being able to achieve about a 98% retention rate in an RVF study.

• **Case 5:** The Malaria Treatment Research Network has decided to evaluate the efficacy of Falgone, a new 8-amino quinolone, in children with moderately severe malaria.

The current standard drug choice in such situations has a treatment failure rate of about 30% at 28 days, based on a few studies in the published literature, with most failures being LTF (late treatment failure). Minimal side effects are associated with the current standard drug of choice.

Based on coverage, Falgone shows great promise. However, some of the untoward effects thought to be related to the drug in the phase II study include neutropenia, transient blurred vision, and proteinuria.