Epidemiological study methods

4.Intervention Studies

Similar to cohort studies, intervention studies also follow the population for a certain period of time looking for development of a particular outcome. The major difference in intervention studies is that we expose one group of the population to an exposure which we are interested in (intervention) to find its effect on the outcome. The remainder of the population is just observed without any intervention. One of the best and most widely used types of intervention studies is called a **Randomized Controlled Trial (RCT)** in which participants are allocated randomly to receive or not to receive the intervention.

Example: A randomized controlled trial was undertaken in Australia (Lewis JR 2011) to study the effect of supplementary calcium on atherosclerotic vascular disease in older women. 1460 old women were randomized to receive 1200 mg of calcium carbonate daily or an identical placebo. The women were followed up for 5 years for the development of atherosclerosis or death due to it.

What do we measure in an intervention study?
We measure incidence risk (or rate) of the outcome among the exposed group (the intervention group) and he incidence risk of the outcome in the unexposed group (the control group). Then we compare these two by calculating the risk ratio. If we have the total follow-up time we can calculate rates and rate ratios in the same way.
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Incidence risk = # of new cases/ Total population at risk
Incidence ratio= incidence in intervention group/ incidence in control group

Why we conduct intervention studies?
Randomized controlled trails are the best design to investigate the effectiveness of new interventions whether these are new medications, treatment procedures or more complex treatment health services interventions. RCTs can be used to investigate the effect of the intervention on preventing the outcome, or on modifying the outcome which could be course of a disease or other health-related outcomes. Randomized controlled trials are the best design to investigate the effectiveness and side effects of a new form of intervention

Steps in undertaking intervention studies

1. Defining the study question
The study question in an intervention study is usually about the effectiveness of a certain new exposure e.g. a vaccine, a drug, a clinical procedure which we want to test. For example a company has developed a new vaccine for influenza and we want to see how effective it is on preventing influenza from occurring. The question could be about comparison of a new drug with and old one e.g. "is this new drug better than the old drug?" There are two types of interventions which we may study

1. Interventions which are intended to prevent an outcome occurring. For example, the aim of hepatitis B vaccination is to prevent infection with hepatitis B
2. Interventions intended to modify the course of a disease once it occurs. For example studying the effect of antiretroviral drugs on the course of HIV disease.

***2. Selecting* the study population**
First we have to identify the target population that is the population to whom the intervention is applicable if it is found to be effective. Then we must select the study population, i.e. the individuals who will actually take part in the study. The study population should be a representative sample of the target population so that they are similar to the target population in terms of age, sex, severity of disease and other relevant factors.

3. Allocating the Intervention
The best way to allocate the intervention to the study subjects (i.e. giving them the exposure) is randomization in which we randomly allocate the intervention to some people to let chance decide who is selected for the intervention and who is selected for the control group.

- Randomization means that every participant has a known chance (usually an equal chance) of being allocated to either of the treatment groups, and neither the investigator nor the participant can predict which group the participant will be allocated to. Randomization is usually done by assigning random numbers to the study participants, and using these random numbers to indicate which group the participant is allocated to.

- The major advantage of randomization is that the comparison groups will usually be similar with respect to all exposures except the intervention

- Randomization minimizes the possibility of bias affecting the allocation groups. When randomization is done properly, the investigator has no control over which patient receives which intervention, and so the outcome cannot be influenced by the investigator's preferences.

There are other methods for allocation of the intervention which are not quite random. For example, we might decide to allocate patients born on an even-numbered day of the month to the intervention group, and those born on an odd-numbered day to the control group. Alternatively we might decide to allocate alternate patients to the intervention group, according to the day of the week, or the order in which they were seen by the investigator. These methods are not satisfactory, because if the investigator can predict which group the patient will be assigned to before the patient is recruited to the study, the investigator could potentially manipulate the allocation system.

What should the control group receive?
The control group is not given the same thing as the intervention group. They could be given a placebo or the standard treatment.

1. A placebo is a treatment that resembles as closely as possible the active treatment, but has no active constituent. Placebo controls are appropriate when we are uncertain whether the intervention is better than no treatment at all, and there is no standard treatment in use.

2. The standard treatment is appropriate when an existing treatment is available in use for the condition and we cannot deprive the patient from this treatment. We compare the new treatment with the standard one. Even in this case it is better to mask which treatment the participants receive to minimize the possibility of reporting bias by the participants, and observer bias by the investigators.

4. Follow-up and Ascertainment of outcomes
The outcome of interest must be clearly defined, preferably using a case definition. We follow both groups and keep record of all outcomes that develop in each group. It is very important to maximize completeness of follow-up in intervention studies and ascertain occurrence of as many outcomes as possible. This means that we have to try our best to follow up as completely as possible all patients and record all outcomes if possible. Incomplete follow up means we have missed a lot of outcomes. If there is incomplete follow-up, and the completeness of follow-up differs between the intervention and the control groups, bias may be introduced. We should also try to ensure that the person who assigns outcome diagnoses does not know which treatment group the subject was allocated to, because if he knows this he may introduce bias.

5. Analysis of data
We measure incidence risk (and incidence rate) as in a cohort study, for both the intervention group and the control group. Incidence risk is the proportion of individuals developing the outcome. We then compare the risk among the intervention group with that in the control groups (risk ratio).

For example suppose in a study on the effectiveness of an influenza vaccine, 20,000 people were studied: 10,000 were given the vaccine and 10,000 were not give the vaccine. The two groups were followed up for one year.

Intervention group	Total sample	People with the outcome (influenza)
Vaccine	10,000	10
No vaccine (or placebo)	10,000	20

Risk of influenza in the intervention (vaccinated) group=number of cases of influenza among the vaccinated group/ total of the people in the vaccinated group

Risk of influenza in the control group= number of cases of influenza among the control group/ total of the control group

Risk ratio is the comparison of the above two risks.

Incidence of influenza in the intervention group=10/10,000=1 per 1000 per year

Incidence of influenza in the control group=20/10,000=2 per 1000 per year

Risk ratio= incidence in intervention group/ incidence in control group=
1 per 1000 per year/2 per 1000 per year= 0.5=50%

This means that incidence of influenza in the vaccinated group was half of incidence of influenza in the control group i.e. the vaccine was effective in reducing number of case by half in people who got the vaccine.

6.Interpretation of results

Before making conclusion from an intervention study we have to consider sources of error. Both selection bias and information bias can happen in intervention studies. Blinding is a useful strategy to minimize information bias. **Blinding** is the process of making subjects unaware of the intervention being given. Blinding can be done for the patients and observers. Usually we blind the subjects i.e. they don't know whether they are receiving the new treatment or the old one (or the placebo). In **double blinding,** in addition to the patients, the observers are also unaware of the type of intervention given to the subjects. Double blinding is very important in reducing reporting and observer bias. Example: If the patient knows that she is receiving the new drug for her migraine she may feel better and report her headache as less. If the observer knows that this subject has received the new drugs he may press the patient to report improvement.

Another important strategy to reduce bias is **completeness of follow-up.** Loss to follow up and poor ascertainment of the outcome is a problem. Therefore, we have to follow up all study groups completely. If we fail to follow up all individuals in both intervention and control groups completely and in the same way to ascertain development of the outcome then our results will be biased. For example, if follow-up is not complete, we may miss more migraine patients with improvement in their headache and thus the results will not be true.

Ethical Issues in Intervention Studies

Intervention studies include subjecting some patients to a new intervention, drug or clinical procedure. This raises ethical issues. Firstly the intervention should be safe. Secondly there should be no proven better intervention to deprive the patient from. Thirdly randomization should be ethical. This is true when there is no evidence that one treatment is better than the other. In any case, informed consent should be taken and the patient should be free to withdraw from the study any time he/she wants to..

Strengths and Weaknesses

Strengths

- Randomization minimizes the risk of bias in treatment allocation, and of confounding due to both known and unknown confounders
- Because of less bias, RCT can provide strong evidence on causal relationship between the exposure and the outcome
- Multiple outcomes can be studied, and the incidence of disease can be measured

Weaknesses

- Often difficult, expensive and may be complex, may need large study teams and long follow-up periods
- Some research questions cannot be addressed using intervention studies for ethical reasons