RESEARCH STRATEGIES FOR THE CLINICIAN

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Every clinician through the years developes a rich fund of experience. He sees variety in disease occurrence, presentation, natural history, outcome and response to treatment. As he goes along he automatically learns from this experience and applies it to sharpen his clinical sense and skills. When asked to reason why he follows a certain practice, however, he often resorts to anecdotes or stories about some of his patients. In the last 25 years, determined efforts have been made to use scientific techniques to evaluate methods of treatment, diagnosis or etiology. Applications of these methods will help the practising clinician to self audit and report his data according to the rules of modern clinical research. This will increase manyfold the value of his past clinical experience and translate his clinical impressions into hard evidence. Moreover, clinicians may make observations in their practice which may prompt them to ask questions, the answers to which may again be obtained by applying appropriate research strategies. The proper use of research strategies will thus help to improve professional understanding of clinicians and in a wider sense, help in the advancement of science.

Laboratory science is often called 'real' or 'hard' science since by using animals, cells or cultures, the scientist can control many factors that may interface with the interpretation. Studies of humans are not so easy. Firstly, they are not passive laboratory animals and extraneous factors cannot be controlled. Secondly, many problems may take many years to develop or improve and it is not always feasible to study human subjects over the full course of the disease. Finally, the ethics of research on human subjects also places restrictions on what can be done. Nevertheless questions concerning human health can only ultimately be answered by research on human beings.

Conducting a research study involves the following steps:

1. The research question should be identified after appraisal of current literature. A refutable or testable hypothesis should be evolved.
2. The objectives of the study should be outlined.
3. An appropriate study design should be identified which would answer the research question/test the hypothesis.
4. A target population to whom the results would apply should be identified.
5. A suitable sampling frame should be arrived at. Inclusion and exclusion criteria should be identified. This will decide the final study population which should be representative of the target population.
6. A protocol should be formalized. A pilot study or 'test run' may be done to

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advantage before finalizing the final protocol. This will often help in estimation of sample size.

7. Making the necessary measurements of disease, parameter, exposure, outcome, *etc*. Follow up with or without intervention may be necessary depending on the study design.
8. Analysis and interpretation of results.

Research Questions and Hypotheses

Research questions may pertain to disease etiology, distribution, presentation, diagnosis, prognosis or treatment. Formulation of a research question means organizing one's thoughts into a succinct statement of what one intends to do and why. Research questions and hypotheses are closely related but are not quite the same, both in form and in purpose. A hypothesis is a statement of belief that can be refuted or confirmed by one's observations. It is made at a much higher and more abstract level, and an attempt is made to generalize about the inferences to be made from the data. Hypotheses are often stated in the null form so that they become refutable. This is because scientific generalizations while rarely verifiable are generally falsifiable. For example, it is possible to refute the statement 'not all swans are white' by observation of a single black swan. It is not as easy to refute the positive form – 'all swans are white' as all swans would have to be observed. A hypothesis should contain the statement which is capable of being refuted and also the framework in which the hypothesis is expected to hold(1,2).

Objectives

Once the research question has been formulated, the researcher, in order to proceed with its testing, needs to set out a number of objectives whose successful achievement will enable that question to be answered.

Types of Study Design

The design of any research study must be appropriate for the research question being asked. There are 2 broad groups of research studies – observational and experimental. Observational studies may be descriptive or analytical. Descriptive studies may be cross-sectional surveys, case series or case reports, while analytical studies may either be longitudinal (cohort) or case control in type(1-4). Experimental studies may be clinical trials, field trials or community intervention trials.

Descriptive Studies

Cross-sectional Studies: These are also known as surveys or prevalence studies. A cross-sectional study is one in which subjects of interest in a population are investigated for outcome and/or exposure (*Fig. 1*). It may be a simple description of the prevalence of characteristics such as height, diabetes, blood pressure, *etc.* (survey). Distribution of disease or characteristics are studied according to time, place and person. The important aspect of a cross-sectional study is that data from subjects are only obtained once. The study may go on for years with continuous enrolment but will still be cross-sectional if data are obtained on only one occasion from each subject. Sometimes a whole population is surveyed. More usually, a sample in a random manner and inferences drawn from the sample are extrapolated

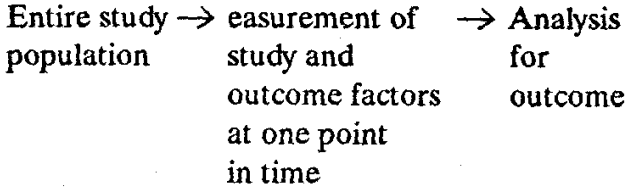


Fig. 1. Design of cross-sectional studies.

to the population. For the extrapolation to be 'valid' the sample should be representative of the larger population and to have been done in an unbiased manner. There are no controls in a descriptive study.

Cross-sectional studies are generally hypothesis generating studies. The large majority of clinical studies published in Indian medical journals are cross-sectional. Such studies are at their best when used to estimate a current reality, *e.g.,* immunoglobulin levels in preterm and small for date newborns(5); nutritional health and psychosocial profile of institutionalized children(6) or 'Parental attitudes towards epilepsy'(7). By studying the distribution of exposure and disease in a population it is often possible to formulate hypotheses relating to disease etiology. For example, it may be found that immunoglobulin levels are higher in small for date babies than in preterms. However, since there is no time component to these studies, incidence measures become impossible and disentangling of cause effect relationships can be difficult.

Strengths of Cross-sectional Studies

Cross-sectional studies allow several outcomes to be studied. One can control the selection of subjects and measurements. They are of relatively short duration and yield prevalence and relative prevalence. Cross-sectional studies are also a good first step for a cohort/case control study.

Weaknesses

Cross sectional studies do not establish sequence of events and do not yield incidence or true relative risk. They have potential for bias due to self selection of subjects, survivor bias, *etc.* They are also not feasible for rare conditions.

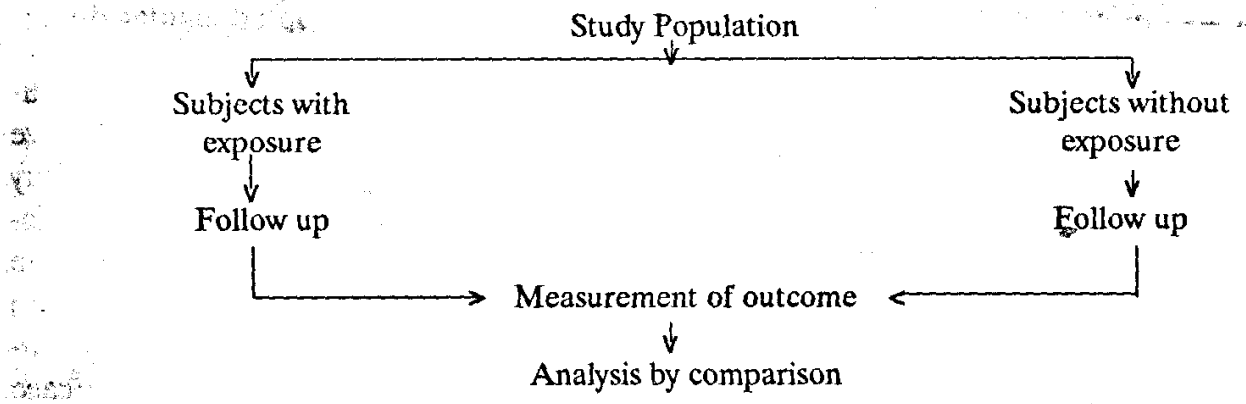
Case Series and Reports

Case series often describe the distribution of symptoms and signs or investigative findings in a particular disease, which may be generalized to all patients with the disease. Such studies are especially valuable for rare or newly described illnesses. The link between rubella in pregnancy and congenital anomalies is an example of a case series which helped to unearth an important association. Similarly, consumption of milk kept in copper vessels was found to be associated with Indian Childhood Cirrhosis. Examples of case series in recent issues of Indian Pediatrics are those on congenital syphilitic hepatitis(8); blood pressure in children(9), *etc.* In the study on syphilitic hepatitis, it was observed that 8 out of 10 patients developed hepatitis after initiating penicillin therapy, thus raising the question of it being an autoimmune reaction or secondary to the products of treponemal lysis. In the study on symptomatic hypertension it was found that tubulointerstitial pathology was the commonest cause in chronic persistent hypertension and glomerular causes were the commonest cause in acute hypertension. Case reports and series can only be used to generate hypotheses, not to test them.

Analytical Studies

Longitudinal Studies

In this type of study people who are free of the disease of interest but differ in a certain exposure are followed and the incidence of disease measured (*Fig. 2*). Such studies are also known as cohort or follow up studies. The starting point in a longitudinal study would be a population characterized according to exposure, *e.g.,* developmental outcome of infants with birth asphyxia or long term effects of lead intoxication.



	Disease	
	Yes	No
Exposed to hypothesized etiologic factor	a	b
Not exposed to etiologic factor	c	d

direction of study

From the Table above,

$$\text{Relative Risk} = \frac{\text{disease in exposed}}{\text{disease in non-exposed}} = \frac{a/a+b}{c/c+d}$$

Fig. 2. Steps of a cohort study.

Thus, there are 2 groups-those exposed and non exposed. At the end of the follow up period the incidence rate of the disease in both the groups is determined. The ratio of incidence in exposed over incidence in non exposed represents Relative Risk (RR) which is a direct measure of association between suspected cause and effect. An example of a recent cohort study that appeared in Indian Pediatrics is on the effect of maternal labetolol on the newborn infant(10). Here, 48 neonates born to mothers who had received labetolol for pregnancy induced hypertension were compared with 81 neonates whose mothers were treated with drugs other than labetolol. Both the groups were monitored for neonatal hypoglycemia. It was found that infants in the first group had a significantly higher incidence of hypoglycemia and it was concluded that maternal labetolol therapy was associated with increased risk of neonatal hypoglycemia.

In assembling cohorts the following general considerations are taken into account;

(*a*) The diagnostic and eligibility criteria of the disease must be defined beforehand; (*b*) The cohorts must be free from the disease under study at the time of enrolment. Therefore, members who already have evidence of the disease under study should be excluded; and (*c*) Both the groups, *i.e.*, exposed and not exposed should be comparable in respect of all other possible variables which may influence the frequency of the disease, (*i.e.*, known confounders).

Strengths of Cohort Study

Cohort studies allow the incidence of the disease in question to be calculated and they provide a direct estimate of Relative Risk. Several possible outcomes related to a single exposure can be calculated. Dose response ratios can be calculated.

Weaknesses

Cohort studies are generally unsuitable for investigating uncommon diseases or diseases with low incidence. They generally take a long time to complete and may be plagued by administrative problems such as loss of patients, exprienced staff, *etc.* Also, selection of comparison groups which are representative of the exposed and unexposed segments of the population may be a limiting factor.

Case Control Studies

Such studies have 3 distinctive features: (*a*) Both exposure and outcome have occurred before the start of the study; (*b*) The study proceeds backwards from effect to cause (*Fig. 3*); (*c*) It uses a control or comparison group to support or refute a hypothesis. Controls should be carefully chosen and should be as similar as possible to the cases under study except for absence of the disease under study (*e.g.,* they may have undergone the same diagnostic work up but found negative).

Selection of proper cases and controls is crucial to this kind of study. For example, a case control study design was used to study the association between Reye's syndrome and medications(11). Thirty patients of Reye's syndrome whose diagnosis was confirmed by an expert panel were enrolled. A total of 145 controls of 4 types were selected. Controls were matched for age, race, antecedant illness and selected from the same hospital and emergency room, school, neighbourhood and by random digit dialling (community controls). Results showed that significantly more cases than controls had received salicylates during matched antecedant illness.

Similarly, a case control design was used to study the prognostic factors in childhood pneumonia. Cases were children with pneumonia who died. Matched controls were selected from children with pneumonia who survived(12). Associated illnesses, age under 6 months, marasmic state, and congeni-

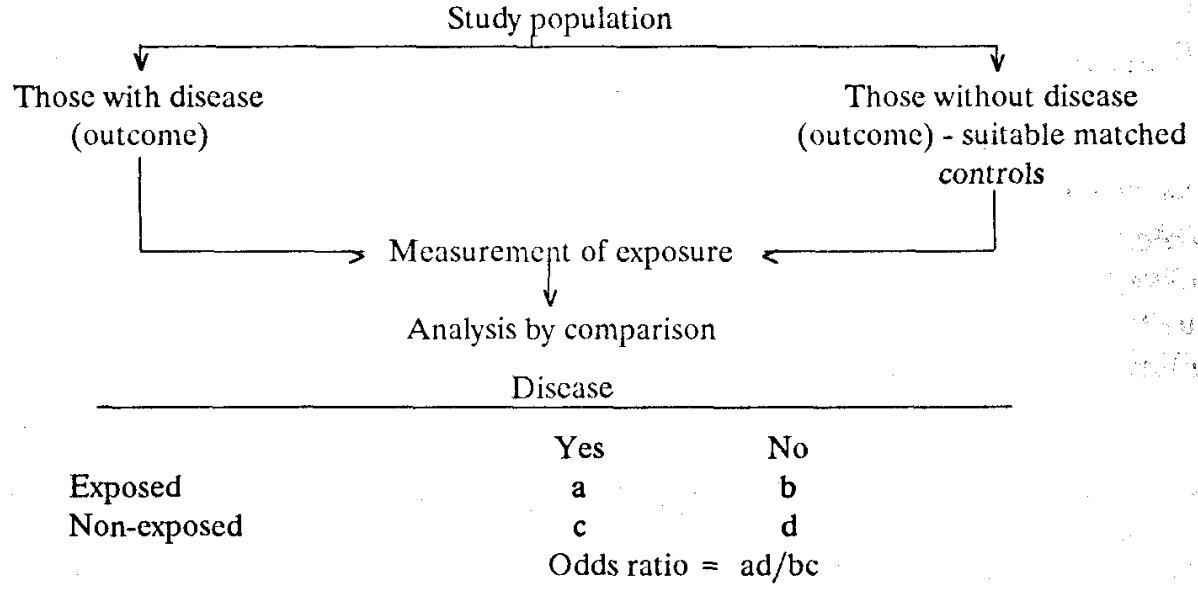


Fig. 3. Steps in a case control study.

tal anomalies were significant risk factors for higher mortality.

The measure of association derived from case control studies is known as the Odd's Ratio. Odds ratio closely approximates relative risk provided the incidence of the disease in the free living population is relatively low.

Strengths of Case Control Studies

The major advantage with case control studies is that they are relatively easy to carry out, rapid and inexpensive and require fewer subjects. They are particularly suitable for investigation of rare diseases. They involve no risk to subjects, so ethical problems are minimized. Several different etiological factors can be studied together. They also do not have any attrition problems as follow up is not required.

Weaknesses

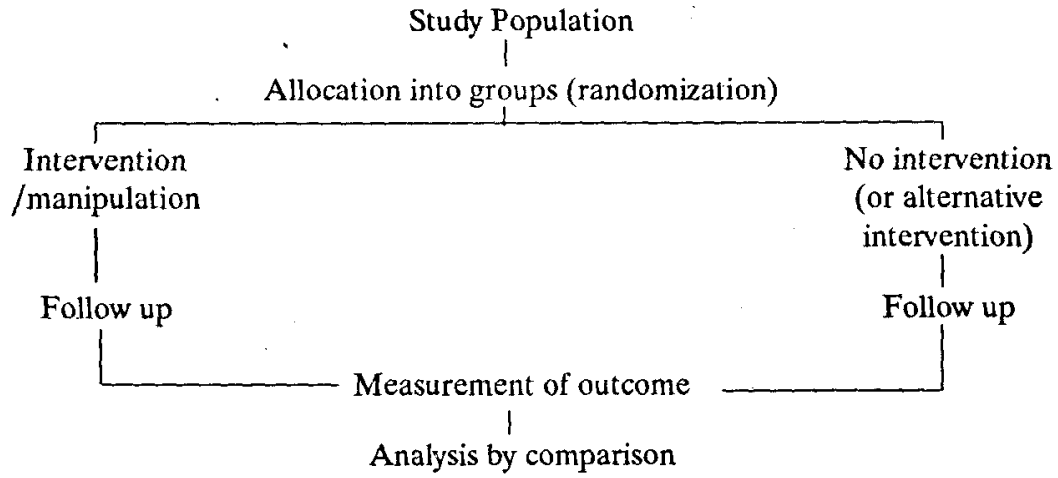
Bias is a major problem with case control studies and needs to be carefully eliminated. They often rely on memory and past records, the accuracy of which may be uncertain. This is the major criticism of case control studies. Selection of appropriate control group may be difficult. Case control studies do not allow incidence to be estimated and do not distinguish between causes and associated factors.

Experimental Studies

The hallmark of an experimental study is that the goal of the research study is paramount and all other factors except the intervention such as drug or health education package are similar in the 2 groups.

Randomized Controlled Trials (RCT)

This is an investigation in which similar groups of individuals are allocated at random by the investigator, to receive or not to receive a therapeutic or preventive intervention (*Fig. 4*). The groups should be drawn from the same source population. Participants are observed for the outcome of



		Outcome	
		Present	Absent
Exposure to manoeuvre or hypothesized causative agent	Yes	a	b
	No	c	d

Fig. 4. Steps of a randomized controlled trial.

interest. The control group receives no intervention, a noneffective intervention (placebo) or the currently accepted intervention which is different from the intervention to be tested. To illustrate this, let us take the example of use of steroids in bacterial meningitis. A pediatric grand round is held and 3 senior pediatricians present their results. Dr. A has carefully tabulated results from 120 patients. He has treated 85 without steroids and 35 with steroids. However, due to hospital policy, the steroids were not used in hospitalized patients, only in private. Dr. B has a similar set of cases but she selects her patients at the bedside by taking 'everything into consideration'. Dr. C, on the other hand, states quite emphatically that using steroids is beneficial and he proves it by presenting results from 1980-85 when he used only antibiotics and from 1985-90 when he used both. Do you think that the results presented by these doctors can be used to decide if steroids are indeed beneficial in bacterial meningitis? Indeed it is obvious that none of these doctors had a true scientific basis to prove or disprove the beneficial effect of steroids. The bias in patient selection precludes any scientific conclusion. Allocation by randomization is necessary to avoid selection bias.

Blinding

In order to reduce bias due to human element, *e.g.,* subject bias, observer bias, *etc.* a good randomized trial is one in which the participant does not know whether he belongs to the study or control group. A double blind trial is one in which neither the investigator nor the participant is aware of the group allocation or treatment received.

An example of a randomized controlled trial that recently appeared in Indian Pediatrics was on the use of vegetale oil fortified feeds in very low birth weight babies(13) and carnitine supplementation in diptheria(14). In the former study, 75 very low birth babies were randomly allocated to one of 23 groups. One group received supplements with predominantly long chain polyunsaturated fatty acids, the second group received MCT abundant, predominantly saturated coconut oil and the third group received no supplement. It was observed that second group who received MCT supplements had a significantly higher rate of weight gain than those who did not receive any supplement or received polyunsaturated fatty acids. In the latter study, 625 patients of diptheria were assigned randomly into 2 groups. One group received carnitine and the other did not. Patients receiving carnitine showed a significant reduction in incidence of myocarditis.

Strengths of Randomized Controlled Trials

With randomization, comparability of groups is very likely for both known and unknown confounders since the groups are derived from the same source population and should only differ by chance. Experiments provide the best chance of obtaining strong evidence of cause and effect. RCTs allow standardization of eligibility criteria, the manoeuvre and outcome assessments. They also allow use of statistical methods which have few inbuilt assumptions.

Weaknesses

Such studies may be expensive to conduct in terms of time, money, and personnel. Many research questions are not suitable due to ethical issues, like cooperation of the patient, other colleagues or rarity of outcome. To some extent, RCTs tend to be an artificial situation, *i.e.,* patients who volunteer for RCT may differ from those to whom the results will be applied and standardized intervention may be different from the common practice.

Community Intervention trials

Here the same principles of RCTs' can be applied to groups or communities, *e.g.,* administration of vitamin A every 6 months to preschool children in a village and comparison of morbidiy and mortality with other villages(15).

REFERENCES

1. Christie D, Gordon I, Heller R. Epidemiology–An Introductory Course for Medical and Other Health Science Students. Newcastle, New South Wales University Press, 1987, pp 45-87.
2. Park JE, Park K. Textbook of Preventive and Social Medicine, Jabalpur, Banarasidas Bhanot Publishers, 1986, pp 66-86.
3. Rothman KJ. Modern Epidemiology. Boston, Little Brown, 1986, pp 51-77.
4. Last JM. A Dictionary of Epidemiology, 2nd edn. Oxford, Oxford University Press, 1988, pp 23-44.
5. Sharma S, Lal Harbans, Saigal RK. Immunoglobulin IgG, IgM and IgA levels in preterm and small for date newborns. Indan Pediatr 1991, 28: 741-744.
6. Sharma KVR, Vazir S, Rao DH, Sastry JG, Rao NP. Nutrition, health and psychosocial profile of institutionalized children. Indian Pediatr 1991, 28: 767-778.
7. Bains HS, Raizada N. Parental attitudes towards epilepsy. Indian Pediatr 1992, 29: 1487-1490.
8. Anand NK, Chellani HK, Wadhwa A, Prasanna SB, Manmohan. Congenital syphilitic hepatitis. Indian Pediatr 1991, 28: 157-160.
9. Khalil A, Singh TP, Arora R, Puri RK. Pediatric hypertension: Clinical profile and etiology. Indian Pediatr 1991, 28: 141-146.
10. Munshi UK, Deorari AK, Paul VK, Singh M. Effects of maternal labetolol on the newborn infant. Indan Pediatr 1992, 29: 1507-1512.
11. Hurwitz ES, Barrett MD, Bregman MS, *et al.* Public Health Service study on Reye's syndrome and medications. NEJM 1985, 313: 849-857.
12. Deivanayagam N, Nedunchelian K, Ramasamy S, Sudhandrakannan, Ratnam SR. Risk factors for fatal pneumonia – A case control study. Indian Pediatr 1992, 29: 1529-1532.
13. Vaidya UV, Hedge VM, Bhave SA, Pandit AN. Vegetable oil fortified feeds in the nutrition of very low birth weight babies. Indian Pediatr 1992, 29: 1519-1528.
14. Ramos ACMF, Barracand L, Elias PRP, Pimental AM, Pires VRS. Carnitine supplementation in diptheria. Indian Pediatr 1992, 29: 1501-1506.
15. Vijayaraghavan K, Radhiah G, Suryaprakasam B, Rameshwar Sarma KV, Reddy V. Effect of massive dose of vitamin A on morbidity and mortality of Indian children. Lancet 1990, 336: 1342-1345.