2. THE CASE REPORT AND EVIDENCE BASED MEDICINE

2.1. What is a case report? What is a case series?

Box 2: Case Reports & Case Series

A case report is a detailed description of one or two patients with a special condition and how this condition was diagnosed and treated, including final outcome.

A case series is a collection of (three or more) patients with a common characteristic used to describe some clinical, pathophysiological, or operational aspect of a disease, treatment, exposure, or diagnostic procedure.

The case report/series is almost always the first step of medical investigation and serves to generate hypotheses. Thus, it is the prerequisite for larger, statistical studies that can explore associations at a population level.

Case reports and series are the oldest form of medical research and were used to describe patients and their illness as well as autopsy explorations. The ancient Egyptians are known for their case reports, and Hippocrates and his students wrote entire volumes of them. This continued until the advent of medical statistics/epidemiology which enabled researchers to look at large groups of patients and populations and measure risk.

Some examples of famous case reports/series over the past 150 years are illustrated in the boxes below.

Box 3: Case report & first rabies vaccine

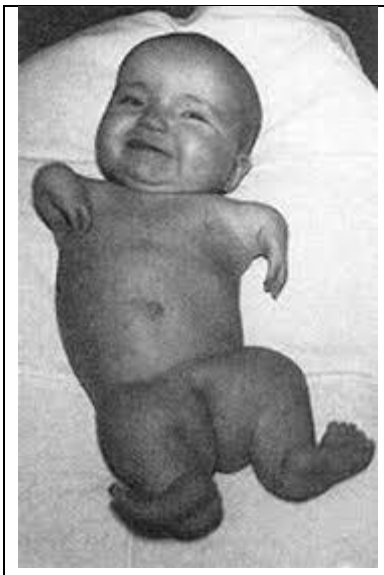
In 1885 whereas the French bacteriologist Louis Pasteur had been working on an anti-rabies vaccine for several years, a young boy bitten by a rabid dog was brought to him by the child's desperate mother. The child received a series of inoculations and never developed the disease. Pasteur published a case report the same year which led the way for anti-rabies vaccines.

Box 4: Case series on hysteria

In 1895, the Austrian physician and psycho-analyst Sigmund Freud, published a series of cases of women suffering from "hysteria" whom he had personally treated.

The theories Freud put forward to explain neuroses had a fundamental influence on Western psychology and psychoanalysis in particular.

Box 5: Case series on unexplained birth defects



The 1960s saw an epidemic of babies born with serious birth defects of unknown origin.

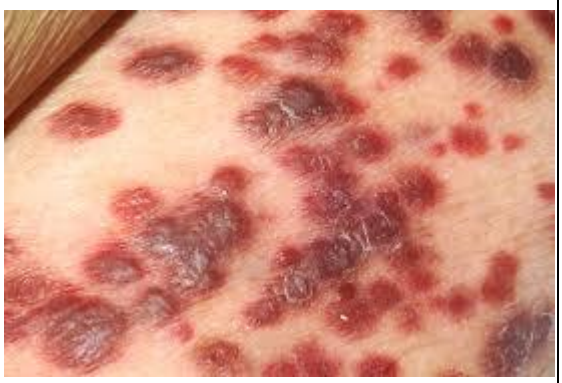
An Australian physician published a case series of babies with birth defects suggesting that the drug (thalidomide) their mothers had taken to fight nausea might have caused the defects.

His hypothesis led to interruption of the drug being given to pregnant women and was later shown to be correct.

Box 6: Case series of Kaposi's Sarcoma and HIV-AIDS

In 1981, a short case series on Kaposi's Sarcoma was published in the form of a letter, remarking on the fact that all the cases had in common homosexual practices, suggesting possible sexual transmission of an unknown infection.

This turned out to be the first report of HIV-AIDS.



2.2. What is Evidence Based Medicine?

With the advent of statistics as a science in the late 19th century and the amazing development of epidemiology in the second half of the 20th century, Evidence Based Medicine marked a departure from expert medical opinion towards statistically based evidence. In the 1990s, the Cochrane Collaboration was created with the specific mandate of reviewing available evidence systematically to produce statistically grounded recommendations for clinical practice.

Box 7: Definition of Evidence Based Medicine

> *The consistent use of knowledge derived from biological, clinical, and epidemiological research in the management of patients, with particular attention to the balance of benefits, risks, and costs of diagnostic tests, screening programs, and treatment regiments, taking account of each patient's circumstances, including baseline risk, comorbid conditions, culture, and personal preferences.*
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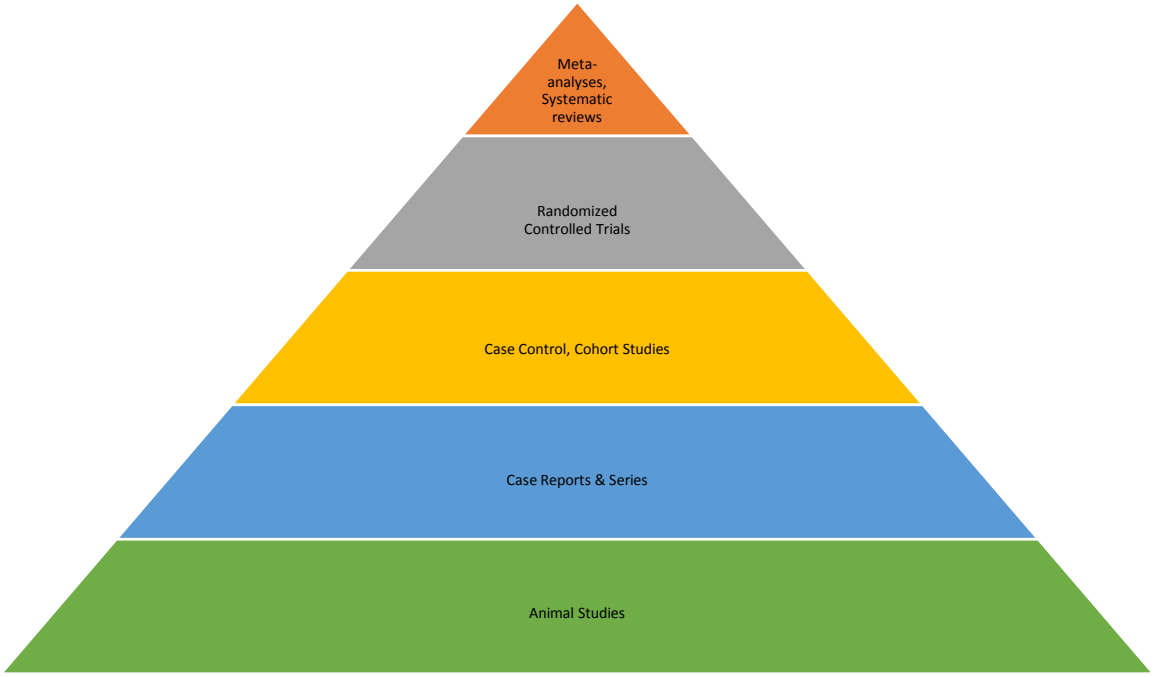
> - A Dictionary of Epidemiology, 2014

Figure 1: Hierarchy of Medical Studies in Evidence Based Medicine



Case reports/series are placed low on the evidence pyramid because they consider individual patients (as versus patient groups) and thus have no statistical power. That being said, case reports/series have always played an essential role of signalling new events and providing the first-line evidence needed to test hypotheses with statistical methods. There is an increasing trend to include case reports/series in systematic reviews and to value case reports when considering evidence of patient-centred care.

2.3. DIFFERENT STUDY TYPES USED IN MEDICAL AND EPIDEMIOLOGICAL RESEARCH

Case Report. The Case Report describes the occurrence of a health condition in one or two patients usually in terms of patient symptoms, clinical manifestations, diagnosis, treatment, and outcome.

E.g. Description of a case of trachoma with unusual manifestations and evolution.

Case Series. The Case Series describes the occurrence of a health condition in three or more patients either concomitantly, retrospectively, or prospectively but remains observational and does not engage in multivariable statistical analysis looking at associations (risk) and causality.

E.g. Description of 12 cases of neonatal tetanus occurring in a given country or area.

Retrospective Analysis. The retrospective analysis, often based on patient files, looks at series of patients on the basis of their diagnosis, treatment, or management, but contrary to the Case Series it engages in multivariable statistical analysis to look at associations and risk factors.

E.g. Examine patient files of children with leukemia to determine which factors might be associated with increased survival.

Outbreak Study. An outbreak study can resemble a Case Series but is specific to communicable diseases and focuses more on tracking the source of infection/index case than particular characteristics of the patients or how they were treated.

E.g. An outbreak of Yellow Fever vaccine following the contamination of an index case in Nigeria presumably infected by monkeys in the game reserve where he worked.

Case Control Study. The Case Control Study looks at two groups of people. One group consists of persons with disease X. The other group consists of persons without disease X, but who are in all other ways similar to the persons in the first group (sex, age, socio-economic status…). It then documents differences between the two groups and uses statistical analysis to determine if these differences could be actual risk factors for disease X.

E.g. Compare a group of women aged 45-55 years with severe hypertension to a group of women of the same age frequenting the same PHC center, but who are not hypertensive. What are the differences between the two groups? Maybe in the first group there are more women who smoke, who do not engage in regular exercise, who have stressful jobs… etc.

Randomized Controlled Trial. The Randomized Controlled Trial is meant to compare (usually) two interventions (drugs, vaccines, therapeutic protocols…). Patients are randomly assigned to receive treatment A or treatment B. When the trail is "blinded" neither they nor their physicians know which treatment they are receiving. They are followed over time for outcome. Then the results are compared using complex statistical methods to determine which treatment is more effective. The RCT is often called the "gold standard" trial, because it avoids many types of potential errors inherent to other study designs.

E.g. A new anti-psychotic is developed to treat severe symptoms of patients with schizophrenia. It is unclear whether this drug is better than the standard drug prescribed to these specific patients. After randomization, half the schizophrenic patients on an out-patient psychiatric ward receive the same drug they have been taking, and half take the new drug. Neither the patients nor their psychiatrists know which drug they are taking until the end of the trial. Then patient symptoms are compared to determine which drug is more effective.

Cohort Study. The Cohort Study generally looks at large population groups over a long period of time. Its purpose is to observe a group of healthy people to begin with and then see which people in the group develop illness; or to look at a large group of people with the same diagnosis and follow disease evolution. Then it looks back in time to see if there are differences between those who developed disease and those who remained healthy. A Cohort Study can be done prospectively or retrospectively.

E.g. A famous example of a cohort study is the Framington Study which began in 1948 in the American town of Framington and is on-going. It follows a cohort of several hundred persons to look at risk factors cardiovascular disease as well as factors which protect against disease. The Framington Study is looking already at the third generation.

Cross-Sectional Study. A Cross-Sectional Study looks at disease prevalence at one point in time. It is usually used to look at prevalence on a large scale.

E.g. the prevalence of HIV in the adult population of Swaziland in 2018.

Ecological Study. An Ecological Study looks at aggregate data mostly to generate hypotheses on the basis of striking differences between populations.

E.g.: an ecological study might look at the number of hip fractures in the senior population in a northern European country (with little sunshine) compared to a southern European country (with lots of sunshine) and hypothesize that exposure to sun, and thus absorption of vitamin D, is protective factor against bone fracture.

Box 7: Distinguishing between a Case Series and a Cohort Study

The main difference between a large Case Series and a Cohort Study is that the first provides descriptive data only, while the second engages in multivariable analysis to look a statistical risk.

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Clinical trials refer to research on specific treatments (drugs, vaccines) and usually include one or more Randomized Controlled Trial. All clinical trials are, by definition, experimental. Clinical trials are referred to in terms of *phases.*

Box 8: The phases of clinical trials

Phase I. It is the first test of a drug (or candidate vaccine) in a small group of humans to determine its safety and mode of action. It usually involves a relatively small number of healthy volunteers. The focus is on safety and pharmacological profiles; it may also assess dose and route of administration. *Phase II.* Pilot efficacy studies. Initial trail to examine efficacy, usually in volunteers; with vaccines, the focus is on immunogenicity, and with drugs, on demonstration of safety and efficacy in

comparison to existing regimens. Usually but not always, subjects are randomly allocated to the study and control groups.

Phase III. Extensive clinical trial. This phase is intended for complete assessment of safety and efficacy. It commonly involves large numbers of patients with the disease or condition of interest, sometimes thousands; it uses random allocation to study and control groups.

Phase IV. Post-marketing clinical trial. Conducted after the regulatory authority has approved registration and marketing begins. The common aim is to estimate the incidence of rare adverse reactions and other potential effects of long-term use in real life; it may also uncover potentially new uses and indications.

- Source: Porta M, Ed. A Dictionary of Epidemiology, 6th ed, Oxford University Press 2014.