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Analytic epidemiological studies as part of an epidemic investigation

* Víctor M. Cárdenas[1], Dora R. Ramírez[2], Gloria I. Suárez Rangel[3]
Authors' affiliations: [1]Editor in Chief, AJFE, Little Rock, Arkansas, USA., [2]Field Epidemiologist, Paraguarí, Paraguay, [3]Field Epidemiologist and Associate Editor of AJFE Bogotá, Colombia
*Corresponding author: Dr. Victor M. Cardenas Email: cardenasvictor08@gmail.com

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Abstract

In responding to an epidemic, the professional field epidemiologist establishes through descriptive epidemiology facts that suggest one or more hypotheses about risk factors concerning the environment (including institutions, their policies and other social determinants), the host or the agent, which require testing. Hypotheses should be formulated in such a way that the statement spells out the design with a reference to the null hypothesis, i.e., explicitly states how the hypothesis will be tested. The evidence required involves systematically collecting information on the exposures of interest and their health status through analytic epidemiologic studies (e.g., ecological, cohort, or case-control studies). We discuss when it is indicated to choose one type of study over another and the advantages and disadvantages of cohort and case-control studies.

Keywords: epidemics, disease outbreaks, epidemiologic methods, ecologic studies, cohort studies, case-control studies.

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Considering the premise that no two epidemiologists will ever follow exactly the same research path, as mentioned by Michael B. Gregg in his book *Field Epidemiology* [1], the question arises as to when to conduct an epidemiological study, and when to use one design or another, whether case-control or cohort in an epidemic investigation. Before answering the question, it is necessary to review the steps in a field investigation of an epidemic or outbreak. More appropriately, the inquiry or field investigation of an epidemic or outbreak is part of the emergency response to an epidemic outbreak or epidemic. We will begin, following Dr. James S. Koopman presenting this concept during his lecture given in Bogotá in 1994 during a course on intermediate methods, by introducing the concept that there are two stages in the inquiry, a descriptive stage, which for the purpose of this article will be called preliminary, fundamental to the inquiry and which, although preliminary, includes aspects of intervention in the response, and the second stage, which is the analytical stage, which in this article will be called definitive and which may or may not confirm the findings of the preliminary stage. The steps of the inquiry are recapitulated in Table 1.

Table 1. Steps in systematic inquiry as part of the public health response to an outbreak

Preliminary Phase
1. Prepare for the investigation after receiving notification or rumor (Invitation, contacts, paperwork, responsibilities, literature review, previously used questionnaires, computers, sample collection supplies, equipment, transportation, accommodations, per diem)
2. Determine the existence of the outbreak (Past vs. current or expected vs. current notifications, unusual or never seen before features)
3. Establish the diagnosis and a working case definition (Based on clinical data from interviewing and exploring preferably in person, and laboratory tests, if there is no diagnosis *per se*, at least describe a syndrome, e.g., "undifferentiated febrile syndrome" adding epidemiologic criteria -time, place, person variables as needed)
4. Ascertain, list and count cases using passive or active surveillance (Known cases, identify unknown cases, search among contacts, at-risk populations, sentinel sites, or a random sample to estimate the total if there are too many)
5. Develop and maintain an updated list of cases and collect data on exposures and risk factors to guide them in person, place and time and calculate attack rates by relating cases to the population at risk. (Descriptive epidemiology, use denominators to estimate risk, standardize attack and mortality rates)
6. State hypotheses about the agent, host, and environment factors, including those related to institutional arrangement and societal determinants. (State the design in the null statement, e.g., "the attack rates in adults were similar to those in children")
7. Verify if the hypotheses are supported by the facts established by descriptive epidemiology. (An exercise of inference, logic, and interpretation of the results of the descriptive analysis).
8. Establish prevention and control measures (These are generally initiated as soon as a diagnosis has been made or even earlier on the basis of suspicion and are refined as the investigation progresses.)
9. Plan, execute and evaluate a public health communication plan. (Immediate, daily, weekly reports, notification to regional, national or international levels according to agreed upon procedures)

10. Establish surveillance

(To evaluate the effect of control measures and detect secondary or subsequent waves)

Definitive Phase

1. Determine the need for and feasibility of more systematic inquiries.

(Consider what is known and unknown to set up priorities)

2. Determine epidemiological strategies to test the hypotheses in the most efficient way.

(Epidemiological studies -ecological, cohort, case-control, tracing products that could have carried the agent, environmental studies including vectors).

3. Collect and analyze information preferably in the field.

4. Contrast the study (or studies') results with the facts established by descriptive epidemiology.

5. Reaffirm or adjust or rectify the control and prevention measures and the communication strategy according to the new results.

In public health practice, in the first phase of responding to and studying an epidemic, the epidemiologist will 1) prepare the fieldwork (background, invitations, definition of the roles of team members, documentation, etc.); 2) determine the existence of an epidemic; 3) obtain a diagnosis, even if only syndromic, of the epidemic condition or disease, develops and disease and seek agreement on a working case definition, adding elements of the epidemiologic variables -time, place and person- as appropriate; 4) search for or list all or most cases, or a random sample of cases if there are too many, as is often the case in epidemics of respiratory or enteric diseases, (such as age and sex), by passive or active surveillance, including surveys of homes or workplaces and others, 5) compiles a list of cases with dates and times of onset of symptoms, places of residence and place of work or school or others, occupation and other relevant risk factors for descriptive epidemiology. 6) develops working hypotheses about exposures (agent, host and environmental factors) that could have given rise to the epidemic; 7) considers the support that a given hypothesis might have based on the findings of the descriptive epidemiology; 8) establishes or recommends epidemic control measures as appropriate; 9) establishes, implements and evaluates a communication plan that includes notifications to the different levels of the surveillance system and control programs, as well as with the media; and 10) establishes and evaluates at least extended surveillance which may allow the evaluation of the recommendations implemented and to anticipate the resurgence of the disease in the population. These steps are not necessarily taken in that order. Sometimes, for example, in the case of a potentially fatal condition, such as botulinic food poisoning, with only the suspicion of botulism, the practitioner must find out how to procure the antitoxin, since it takes time to obtain it, and institute measures to prevent the consumption of leftover food that may be contaminated with the toxin. If the clinical diagnosis were wrong, the worst that can happen, in this example, the toxin orders would have to be cancelled as well as releasing the suspect food.

The most complete ascertainment of cases is very important, especially when the relative frequency, as measured by, say, the attack rate is low (<10%), and sometimes requires extending passive surveillance and even establishing active surveillance or making an inquiry in homes or other sites such as schools or workplaces to get a complete picture of what has or is happening in the community. Obtaining an accurate description of what is happening in the community represents the foundation on which the entire scientific exercise of the epidemiological discipline is based. If there is no good epidemiological

characterization, we will be throwing darts in the dark. It is of the utmost importance to have a good description of the occurrence of the disease or condition of interest, by person, place and time variables.

Descriptive data can be analyzed based on absolute frequencies and proportions, but it is better to relate cases to the population at risk, using a frequency measure such as the attack rate

$$(\frac{new\ cases}{At-\quad population} \times k),$$

which is a proportion, *k*, a constant, usually 100, and the attack rate is the cumulative incidence or risk. The population at risk is the population from which the cases originate, without reducing it only to those exposed but also to those potentially exposed. For example, in an outbreak of food poisoning in a school cafeteria, the population at risk is the people who attended the cafeteria during the risk period. If the incubation period is suspected to be, say, 24 hours, the risk period can be inferred using the range and median from the dates and times of onset. As is known, if the incubation period and the signs and symptoms and their duration are known, the agent can be inferred, even before the laboratory results are available. However, diagnostic confirmation, although not essential for control, as we will discuss later, is important. The hypotheses about etiology are postulated based both on clinical data and the epidemiological features of the disease or condition investigated.

The epidemiologist should have detailed description of signs and symptoms of the epidemic event, condition or disease, the etiology if available (e.g., *Salmonella enteritidis* food poisoning), its duration, the severity measured by the case-fatality or other measure, the attack rate and its distribution by person, place and time, its mode of occurrence, including the environmental factors that contributed to the occurrence to complete the epidemic investigation. Following the example of the school cafeteria outbreak, such as the description of the findings of laboratory studies of food samples served, and how the food was prepared describing the critical points where contamination may have occurred are part of this preliminary inquiry.

Most of the time, the epidemiological investigation ends there, for several reasons. The first reason is undoubtedly that, in the context of public health practice, there are other demands that make it impertinent to emphasize research at the expense of resource use, the most important of which is the time that the epidemiologist and team can devote to research. Drs. Richard Goodman, Jay Buehler and Jeff Koplan of the Centers for Disease Control and Prevention in 1990 summarized this situation in the following tetrachoric or 2x2 table (Table 2) [2].

Table 2. Relative Priority of Investigative and Control Efforts During an Outbreak, Based on Knowledge of the Source, Mode of Transmission, and Causative Agent

Causative agent	Source/Mode of Transmission or Occurrence	
	Known	Unknown
Known	+++ Control +Investigation	+Control +++Investigation
Unknown	+++Control +++Investigation	+Control +++Investigation

+++ Highest priority + Lowest priority
Source: Reference 2.

As part of an outbreak or epidemic investigation, whether the emphasis is on investigation or not, it is considered important to include the collection of environmental and other data that give context to the findings of the descriptive epidemiology and the clinical and laboratory data. Some level of surveillance should also be established, since the epidemiologist may often be surprised by the fact that the epidemic transitions from a period of low transmission or occurrence to secondary or further waves, sometimes even larger than the initial one.

As part of the descriptive phase, one compares attack rates by characteristics using the best available denominators. Such a comparison necessarily involves an underlying hypothesis, namely that there are differences in rates by characteristics of place, person, and time. The test of these hypotheses, sometimes disdainfully said to be "too descriptive" for not including the designs one is more familiar, and talked about in most epidemiology texts, one compares the experiences of groups of people, or looks into the occurrence of the epidemic over time. Both approaches are ecological studies, which were described by Dr. Hal Morgenstern in 1982 [3] as the comparison of disease occurrence among characteristics related to exposures of interest that are measured at the level of groups of individuals to make inferences about the relationship between exposures and disease occurrence.

For example, the comparison of COVID-19 rates among Hispanics or Latinos in El Paso, Texas with corresponding rates in non-Hispanics or Latinos in that community, with morbidity and mortality rate ratios of 1.6 and 2.0, respectively are an example of such a group experience analysis. In the same epidemic study, the authors did an ecological time series study, which Morgenstern said are those in which "a change in exposure, such as the initiation of an intervention program, compares the slope in the disease trend before and after the intervention" [3]. The authors determined the apparent effect of school and business closure orders on the subsequent occurrence of reported COVID-19 cases per day in El Paso County, Texas, finding a reduction of 3.8% per day after the intervention [4]. The authors acknowledged among the limitations of both findings that other variables underlying the difference in ethnicity or epidemic dynamics may have played a role. For example, Hispanics may have been more exposed for reasons related to their lower income and socioeconomic status, or because of higher-risk occupations or having more households with women as the only gainfully employed persons in the household. In the second finding on the effect of the lockdown orders on the daily reported number of cases, the authors acknowledged that at the same time those orders were in place, there was greater use of facemasks, hand hygiene, and avoidance of gatherings.

The study of the epidemic sometimes continues in what is considered the definitive phase of the inquiry, for example to verify findings such as those noted above. This phase revolves around working hypotheses, which may relate to, say, the etiology of the outbreak, or the mechanism of transmission or more generally of its occurrence, or to preventable host or environmental factors, including health policies, and other determinants of the health status of populations. If there are reasons to evaluate working hypotheses, these often arise from the qualitative phase of the epidemiological inquiry. These are often based on clues generated from the stories told by the cases, or from patterns of exposures that the cases have as seen in the case listing. A finding from the experience of groups can generate hypotheses to be tested at the individual level. The authors of the El Paso study had the opportunity to test whether Hispanic/Latino ethnicity or socioeconomic status or occupation were factors related to the observed excess rates. Using data from a sample of individuals they found that ethnicity independent of socioeconomic status as measured by schooling and occupation, and adjusted for age and sex, increased the risk of SARS-CoV-2 infection (odds ratio [OR] of 6.6) [4].

There are often several hypotheses, sometimes competing with each other, that emerge in the preliminary stage of the epidemiological inquiry as part of the outbreak or epidemic response. The best hypotheses should focus on preventable environmental, host, or agent factors, e.g., a vehicle, if any is suspected to be present based on the findings of the descriptive epidemiology. A point-source epidemic usually has a single peak from which the point of exposure can be inferred by subtracting the median value of the incubation period from the peak date/time of symptom onset.

A working hypothesis should state how it will be tested. A hypothesis is a statement or declaration of the relation between an exposure of interest and the occurrence of the disease, while a research question is a statement of such relation in question form. Keep in mind that the statistical testing will be done on null or null hypotheses, i.e., that there are no differences in the occurrence according to the measure of association that we are going to use. Measures of association such as the ratio or difference of rates or risks, or the odds ratio or odds ratio, have null or null values (e.g., risk ratio =1).

Suppose that, in the school epidemic described above, the epidemiologist found in stool samples and leftover food served S. enteritidis, a pathogen often found in eggs and chicken meat. Let us say that, the qualitative part of the inquiry - obtained by interviews with several affected workers and the factory management, it was assumed that, among the different foods and dishes served for lunch at the school, there was a homemade mayonnaise which could have served as the vehicle. The descriptive part added that the attack rate was 32%. Since there is a population at risk that is numerable and experienced a high risk (i.e., >10%) [5], the epidemiologist thinks of a cohort study and writes in his/her notes the alternative hypothesis: school cafeteria attendees who consumed homemade mayonnaise had a higher gastroenteritis attack rate than those who did not consume homemade mayonnaise (i.e., the risk ratio (RR) and was statistically different from 1, the null value (H_0: RR =1). The hypothesis spells out a cohort study as part of an outbreak investigation. In the example, the ratio of the attack rates of

salmonellosis between those who consumed mayonnaise and those who did not was 31.8.

The case-control study is appropriate in situations where the occurrence is less than 10% and there is no easily numerable population at-risk. A circumstance in which a case-control study worked well, using another example of an outbreak of salmonellosis, to stay on topic, was a study of salmonellosis with a certain molecular pattern that were discovered in a laboratory serving say several public health jurisdictions. For example, during the study of an outbreak of Salmonella enteritidis typhimurium that occurred in 2004 in nine U.S. states, the case history suggested that ground beef of a particular brand might be implicated. To test this hypothesis, the investigators assembled a series of 31 patients from which such S. typhimurium strains were isolated and were indistinguishable from each other by pulsed-field gel electrophoresis, and controls were selected from a telephone random digit dialing sample, and were frequency matched by age to the cases. To be considered controls, such person they must not have become ill within the past seven days [6]. The hypothesis was that the paired odds ratio by the consumption of the suspect brand of ground beef was greater than 1. From such finding it can be inferred that the risk of contracting S. typhimurium among those who consumed ground beef of that particular brand was greater than among those who did not if this ratio was statistically different from the null value (H0: OR =1). The paired analysis of ground beef consumption of that brand yielded an OR estimate of 12.7.

To report another case-control study as part of an epidemic investigation, in 1986 we studied the last epidemic outbreak of poliomyelitis in Mexico. Descriptive epidemiology including vaccination history data of the cases, distinguishing the number of doses received before becoming ill from doses received after becoming ill, showed that 79.7% of the cases had received less than three doses and that cases were clustered in rural communities. Analysis of a survey of vaccination coverage by clusters showed high coverage in the state, but in localities with low vaccination coverage according to pediatric age was correlated with the level of coverage achieved in the new strategy called National Immunization Days (NIDs). We decided to conduct an individual-level study of polio cases and randomly selected controls among children listed as eligible to attend the NIDs (2 per case) and among neighbors of the cases (2 per case). Results were compared between the two groups to assess whether there were differences in the estimate of the OR by case type, i.e. find evidence of selection bias. Controls were matched for age (± 3 months in children under 3 years and ± 6 months in children aged 3-5 years). The results of the paired analysis are shown in Table 3, where there were 5 matched sets, where controls were unvaccinated and cases were, while in 27 instances cases were unvaccinated while controls were. The ratio of these sets with discordant status, the matched OR was 5/27 or 0.19, from which the vaccine efficacy (1 – OR) or (1-0.19=0.81) of 81% was estimated [7]. There were no differences in the estimates of the OR by type of control.

Table 3. Matched comparison of the anti-polio vaccination history of 18 cases of paralytic poliomyelitis and its 63 controls, Sinaloa, México, 1984-1986

Vaccine Status of Cases	Vaccine Status of Controls		Total
	Vaccinated (3+ doses)	Unvaccinated	
Vaccinated (3+ doses)	15	5	20
Unvaccinated	27	16	43
Total	42	21	63

Source: Reference 7

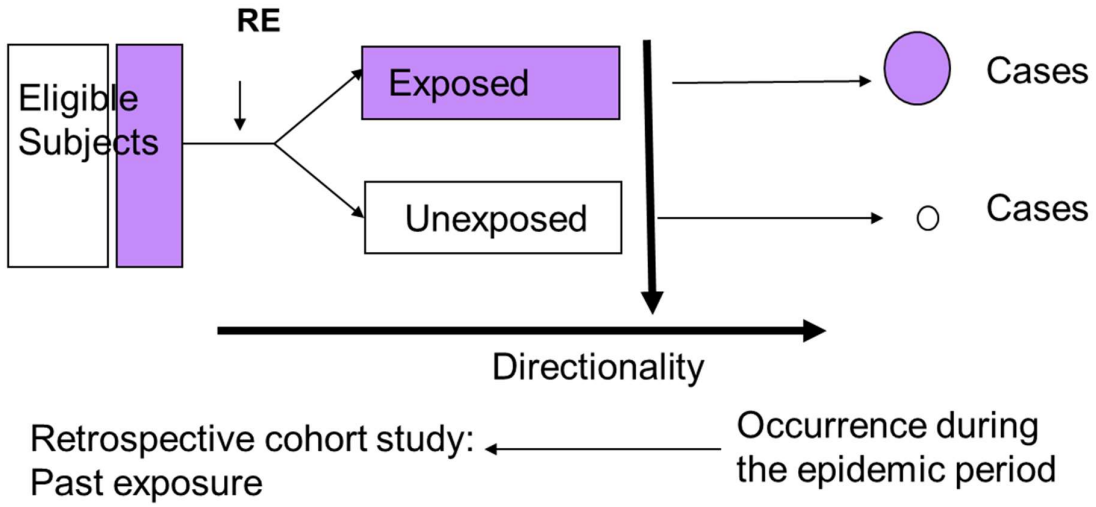
The results of the analyses of the cohort and case-control studies described above should be contrasted with the findings of descriptive epidemiology. They should be consistent in explaining the majority of cases if it is a common source

outbreak. In addition, the findings can refine the search for details in food preparation, or in general the chain of events that led to the exposure. For example, in the case of foodborne outbreaks, weak associations may be found with other foods, suggesting that there was cross-contamination from, say, the use of the same utensils. Also, the finding of exposures that appear to be "protective" (i.e., having a RR or CS <1) could be explained by the fact that those who ate those "protective" foods avoided the foods involved, which can be seen in the available data.

The reader may wonder if there is any equivalence between these studies, the case-control study, and the cohort study, since they might appear to be similar. Although the results should be equivalent, nothing could be further from the truth. The cohort study is for many reasons more informative than the case-control study. One can understand a cohort as a population that shares a common experience. In fact, the name is taken from the Latin word cohors, meaning a unit of soldiers, since in the Roman army a cohort was 600-800 soldiers, i.e., six centurions (100-160 soldiers or centurions or more per centuria) ordered in years of service or seniority, with the first cohort being the most experienced. The modern equivalent of Roman cohorts in modern armies is a battalion. Roman cohorts often had an identifying banner. Therefore, it is correct to define a cohort in terms of demography and epidemiology as a population sharing a common characteristic or exposure. In a study of chronic diseases, for example, exposures of interest such as smoking allow one to define cohorts of smokers and non-smokers, or one can think of a cohort of workers exposed to asbestos fibers. In a retrospective cohort study of an outbreak, say of foodborne disease, there are cohorts of people who consumed and those who did not consume the foods being investigated. For each of these exposures, measures of exposure are developed based on questionnaires generally, and the occurrence of the disease or other event is tracked over time. One can also think of following the mortality experience over time of cohorts of people born in 1900, 1910, 1910, 1920, ...and so on up to the year 2000, say, to look into their experience, for example, as victims of homicide in an ecological study. The cohort study is central to the epidemiological inquiry. What is distinctive about the epidemiological cohort study is that people are selected into a study on the basis of their exposure, not on the basis of whether they have the disease (case) or not (control). The informativeness of the cohort study lies in the fact that one can directly measure the occurrence of disease across exposures.

The cohort study is similar to an experiment, only that the assignment to each exposure is not dependent on the investigator. For most preventable or modifiable exposures, there is rarely an opportunity to do an experiment. Say, for example, in studying the role of usual diet in health, say in diabetes or cancer, there is no realistic or ethical possibility of an investigator assigning people to eat or not to eat a healthy diet for years, so the epidemiological cohort study can be thought of as the closest remedy to the randomized experiment, since in real life, life trajectories lead to lifestyle choices. Similarly, in studies of epidemic outbreaks or epidemics, there is no realistic or ethical way to do such experiments, but they occur in nature. The relation between the design of a retrospective cohort study design that is often done in an epidemic study and a randomized experiment (RE) or randomized clinical trial, which refers to studies of persons affected with a clinical conditions, as in research done in the context of clinical practice is depicted in Figure 1.

Figure 1. Relation between random trials and the epidemiologic retrospective cohort study

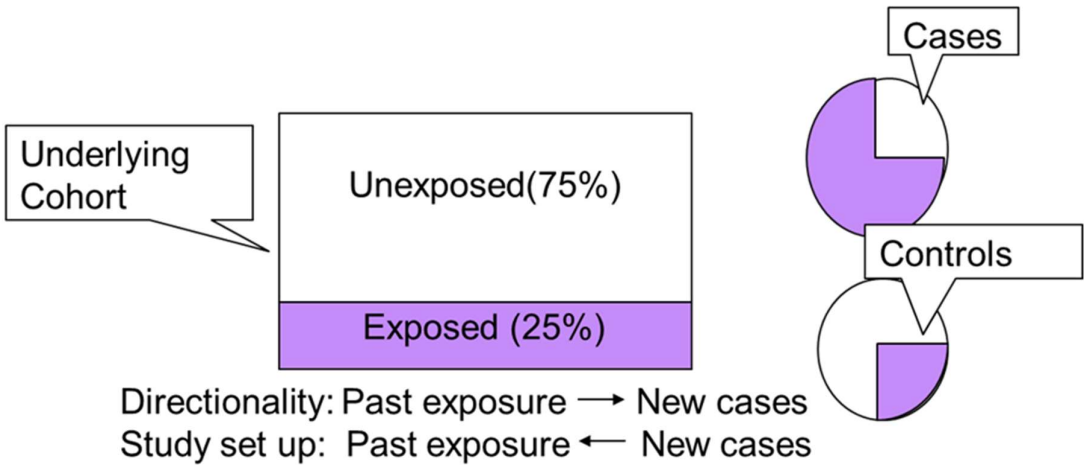


As shown in Figure 1, in the randomized experiment the investigator assigns eligible subjects to have or not to have exposure, and then follows them over time to measure the occurrence of cases in both groups. You have a population base you can directly measure and compare the risk or incidence between the groups according to their exposure. When you do an experiment necessarily the directionality is prospective, the eligible subjects (usually free of the disease) are assigned to the exposure, and the occurrence over time is measured prospectively. The cohort study is also always prospective in nature, because if one looks at it properly, the people who were eligible developed the disease after being exposed. For example, in the school cafeteria outbreak study, all the children and staff who went to lunch had not had salmonellosis before -if there was someone with this condition before they ate in the cafeteria, one can exclude from the denominator as well. The retrospective cohort study is one in which, by the time you start the study, cases and exposure have already occurred. However, you are able to tell what happened first. This is the case of the study of the salmonellosis outbreak in the school cafeteria, cases were reported, some were identified, then it was found that in common they had eaten lunch in the cafeteria, and from there it was decided to survey all those who attended the cafeteria during the at-risk period, to find out what items were eaten and compare the attack rates by food items. The most commonly used epidemiologic design in field epidemiology is the retrospective cohort study.

Now let's think about the case-control study in this same context. The case-control study is an original contribution of epidemiology to research methods and let's see why it is so valuable: it is that epidemiological study in which we start by selecting individuals affected by an event or condition or disease of interest, who form a series (called case series) and are compared using the odds ratio of exposure or so called the odds ratio with individuals who, belonging to the underlying cohort from which the cases come from, are free of the event, condition or disease of interest. Controls are a sample of those members of the underlying cohort who are free of the disease, I who, had they had the event, condition, or disease, would be part of the case series. They form a control series.

Figure 2 shows the relation between the cohort study and the case-control study. Notice that 25% of the entire cohort is exposed. If the controls if they are a representative sample of the underlying cohort from which the cases come, the frequency of exposure among them should reflect the frequency in the cohort, that is 25%. The cases are the affected individuals from the cohort and the frequency of exposure among this series will depend on the relation that exist in nature between the exposure and the risk of the disease, event or condition studied. Note that, in the example, 75% of the cases were exposed. The measure of association used in case-control studies uses the comparison of exposure prevalence between the two series to derive the probability of having developed the disease given exposure and the probability of having developed the disease given no exposure, i.e. the risk ratio or rates, and not simply the comparison of exposure prevalence. In our example it is not 75%/25% or 3, but (0.75/0.25), or the odds of exposure among cases divided by (0.25/0.75), or the odds of exposure among controls, or 3/0.33 or 9.1 the odds ratio, which approximates the risk ratio.

Figure 2. Relation between the cohort study and the case-control study



Note that in both cohort and case-control studies, the directionality or temporality, that is, whether or not the exposure precedes the occurrence of the event, condition, or disease, is well established by a correct inquiry that specifies the timeline in which the onset of exposure occurrence of the event, condition or disease of interest is determined. The genius of the case-control study design is that starts by assembling a series of cases and their controls to then investigate the past exposure, which saves time in chronic diseases with a long latency or incubation. When studying epidemic outbreaks, however, since the cohort study is generally retrospective, there is no such advantage, in terms of waiting for the occurrence of cases, only in terms of the costs of collecting information among tens or hundreds of exposed and unexposed persons. However, the savings of doing a case-control study in such circumstances comes at the cost of not being able to directly calculate the risk or other measures of occurrence.

Nonetheless, it is clear that one advantage of the case-control study over the cohort study is that it does not require an enumeration of all or a sample of exposed and unexposed individuals. However, the case-control study does not allow the study of more than one disease, condition, or event at a time, whereas the cohort study allows the study of different diseases, conditions, or events. In turn, in general, the case-control study allows more exposures to be explored than the cohort study.

We would like to end this summary with some comments on common misunderstandings that we have observed about these two types of studies.

The first we have observed that often retrospective cohort epidemic outbreak studies are mistakenly labeled "cross-sectional studies" since they appear to be similar. During epidemic investigations, we know when the disease or episodes of disease started among those affected and we also have clarity about the timeline of exposure. In general, in health surveys, an inquiry is made in a sample of the population and the occurrence of disease and exposure are measured simultaneously, through mostly standardized survey questions. In cross-sectional studies, existing cases are identified that are not necessarily new, i.e., they are prevalent, so the measures of association are generally prevalence ratios, not risk or incidence ratios, and there is temporal ambiguity by not knowing whether the exposure precedes the occurrence of the disease or not.

The second is the misinterpretation of case-control studies as fashionable in epidemic research, or that they are particularly suitable for investigating various hypotheses, a fishing expedition of sorts, and to deal with the difficulties encountered in identifying a numerable at-risk population [8]. Often the lack of proper application of epidemiological methods in the description can lead to failure to identify a population at-risk, or even if it is identified, to obviate its enumeration because of the apparent ease of substituting one method for the other. One of the consequences of this confusion is that a case-control study is done, selecting as controls apparently unaffected members of a population experiencing a high level of risk, resulting in an exaggeration of the association as the odds ratios often overestimate the risk or rate ratios when the disease is common (i.e., >10%).

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