Study Designs for Dependent Happenings

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In 1916, Sir Ronald Ross defined "dependent happenings" as events where the number affected in a unit of time depends on the number already affected. That is, the incidence depends on the prevalence, a characteristic of many infectious diseases. Because of this dependence, interventions against infectious diseases can have not only direct protective effects for the person receiving an intervention, but also indirect effects resulting from changes in the intensity of transmission in the population. This paper develops the conceptual framework for four types of study designs that differentiate and account for direct and indirect effects of intervention programs in dependent happenings. (Epidemiology 1991;2:331–338)

Keywords: epidemiologic methods, study design, vaccine efficacy, vaccines, infectious disease.

In his theory of happenings,[1] Sir Ronald Ross divided events into two classes, "namely (a) those in which the frequency of the happening is *independent* of the number of individuals already affected; and (b) those in which the frequency of the happening *depends* on this quantity."[2] To the first class belong such happenings as noninfectious diseases and accidents. To the second class belong infectious diseases or membership in societies "due to propagation from within, from individual to individual."[2] Happenings appear in contemporary literature as events or occurrences, and dependent happenings are those in which incidence depends on the prevalence.

Because of the dependency of events in infectious disease, two types of effects, direct and indirect, can result from intervention programs. Direct effects of an intervention such as vaccination or chemotherapy are the protective effects in the person receiving the treatment. Indirect effects result from alterations in transmission of an infectious agent in a population consequent to an intervention program. Measures of effect in infectious disease epidemiology need to be defined precisely in terms of whether they measure direct or indirect effects.

This paper develops the conceptual framework for four classes of study designs for dependent happenings characterized by the choice of comparison population and by how they differentiate and account for direct and indirect effects of intervention programs. In the next section, we define dependent happenings in infectious disease. In the third section, we define direct, indirect, total, and overall effects of intervention programs and delineate the four classes of study designs. Next, we present four classes of study designs. Then we consider a few aspects and limitations of each of the types of study designs. In the last section, we consider a few situations that do not fit into any one particular study design.

Dependent Happenings in Infectious Diseases

Sir Ronald Ross developed his theory of happenings,[2] or pathometry (*pathos*, from the Greek, meaning a happening), as a generalization of his quantitative modeling of the transmission dynamics of malaria. His purpose was to develop a general theory describing the number of individuals in a population "affected by *something* (such as a disease)."[2]

Ross considered a population of P individuals to be composed of a number Z of those affected and a number A of those not affected. The happening element h, comparable to the contemporary hazard or incidence, described the rate at which unaffected persons become affected. The happening element h could be either independent of the number already affected in the population or dependent on this number. In the first case, he spoke of independent happenings, and in the second case, dependent happenings. He formulated his general theory of happenings by embedding the happening element in differential equations describing a dynamic population with birth, death, immigration, and emigration rates. In dependent happenings, the happening

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element h depends on the prevalence,

$$h = c\frac{Z}{P},$$

where c is some constant, and Z/P is the proportion affected, or prevalence.

Ross considered the theory generally applicable to phenomena other than disease, including commerce, political parties, trade unions, accidents, and standard of wealth. Miettinen[3] also pointed out that the epidemiologic principles of occurrence research in medicine can be extended to the study of occurrence in general. He confined his methods, however, to independent occurrences. In these situations, direct effects of an intervention in an individual are not assumed to affect the outcome for others. An epidemiology of infectious diseases, on the other hand, needs to take account of the dependence in happenings.

The definition of dependent happenings need not be confined to the transition from one state to another. Ross pointed out that happenings can occur in people who were already affected, although this would not be registered as a change from unaffected to affected state. An example of such a phenomenon is superinfection in malaria, in which a person who is already infected can be inoculated with another brood of parasites from an infective mosquito bite.[4] In some infections, such as helminths, the burden of disease is related to the density of parasites in the body.[5,6] The density of parasites in the host is dependent on the amount of exposure, thus these density effects also need to be included in a dependent-happening epidemiology.

The term "happening" raises a few post-1960s eyebrows, and one might prefer "event" or "occurrence" in its place. Its use seems desirable because of its historical roots in Ross's original formulation. The word "dependent" is the most obvious choice to describe phenomena that are the opposite of independent, where independence is the underlying assumption in most epidemiologic and statistical theory. Methods for dependent happenings will constitute only one part of infectious disease epidemiology, however, since not all infectious diseases exhibit dependent happening behavior. This behavior depends to some extent on how one defines population. Some infections, including zoonoses such as Lyme disease, rabies, sylvan yellow fever, and toxoplasmosis, and environmental hazards such as tetanus, are not dependent on how many other humans have the infection. Interventions in humans against these infections would commonly not have indirect effects.

Effects of Interventions in Infectious Diseases

The dependent happening structure of events in infectious diseases results in there being direct, indirect, total, and overall effects of interventions. In this section, we define and present examples of these different kinds of effects.

First, we need to differentiate between interventions in individuals and intervention programs in populations. Individuals may receive the intervention directly. This includes vaccination, chemotherapy, behavioral education, or the use of bed nets to prevent mosquito vectors of malaria from biting susceptible persons at night. If many individuals in a population receive an intervention, then we can view the population as having received an intervention program. In some cases, the interventions are in the environment and are not received directly by individuals. In this case, we also consider that the population has received the intervention program. Examples would include mosquito control programs to reduce malaria transmission or the installation of wells to prevent transmission of guineau worm.

Direct Effects

The *direct effect* of an intervention received by an individual is the difference between the outcome in the individual with the intervention and what the outcome would have been without the intervention, all other things being equal. This definition of a direct effect corresponds to Rubin's notion of causation in that it is defined for the unobservable difference between the response in the observed person receiving the intervention and what it would have been in the same person without the intervention.[7]

An example of a direct effect is the reduction in the probability of becoming infected that results from immunization with a vaccine, given exposure to infection. Another instance would be lengthening of the interval between infection and death in an individual due to chemotherapy. The latter is an example of a postinfection intervention. Its direct effect is studied conditionally on having already been infected.

Indirect, Total, and Overall Effects

The *indirect effect* of an intervention program in an individual is the difference between what the outcome is in an individual *not* receiving the intervention in a population with an intervention program and what the outcome would have been in the individual, again not receiving the intervention, but in a comparable population with no intervention program. It is, then, the effect of the intervention program on an individual who did not personally receive the intervention.

The combined *total effect* in an individual of an

intervention and an intervention program is the difference between the outcome in the individual receiving the intervention in a population that has an intervention program and what the outcome would have been in the individual had he or she not received the intervention in a comparable population that has no intervention program. The total effect, then, is the effect of the intervention program combined with the effect of the intervention that the individual personally receives.

The *overall effect* of an intervention and an intervention program is the difference in the outcome in an average individual in a population with an intervention program compared with the outcome of an individual in a comparable population without an intervention program.

A simple indirect effect is the reduction in the probability per unit time of becoming infected that results from reduced exposure to infection consequent to a mass immunization program. Thus, an unvaccinated person in a population with an immunization program experiences a changed hazard or incidence compared with what it would have been if the population had had no vaccination program. The analogous total effect would be the effect experienced by a vaccinated person, who has both the benefits of the vaccine and the indirect effects of the reduced transmission. The overall effect would be the weighted average of the reduction in incidence in the vaccinated and unvaccinated.

An early description of indirect and overall effects of immunization was given in 1792 by William Buchan. This was half a century after the introduction into Europe from Turkey of inoculation against smallpox using live smallpox virus.[8]

> We have been the more full upon this subject [of the importance of smallpox inoculation] because the benefits of inoculation cannot be extended to society by any other means than making the practice general. While it is confined to a few, it must prove hurtful to the whole. By means of it the contagion is spread, and is communicated to many who otherwise never would have had the disease. Accordingly it is found that more die of the smallpox now than before inoculation was introduced; and this important discovery, by which alone more lives might be saved than by all the endeavors of the Faculty [of Medicine], is in a great measure lost by its benefits not being extended to the whole community. (p 218)

This historical example makes clear that not all indirect effects of intervention programs are beneficial.

Another common result of the reduction in transmission consequent to mass immunization is that the average age of first infection will increase.[5,9–13] Some benign childhood diseases, such as rubella and mumps, have higher complication rates when contracted later in life. Thus, indirect effect might include increased morbidity for those not receiving the immunization.

Changes in transmission can produce even more complex dynamic indirect effects. Widespread vaccination can induce a honeymoon period—a period of low incidence during the shift from prevaccination age distribution of susceptibles followed by a rebound in the number of cases.[14] Many diseases, such as rubella and chickenpox, exhibit fairly regular annual, biennial, or triennial fluctuations in the number of cases. The period of these fluctuations may lengthen or their pattern may change after mass immunization.[11,12,15,16]

Some interventions administered to individuals may have only indirect effects. A current example is the gametic vaccine being developed against the sexual stages of the malaria parasite to prevent transmission from the human to the mosquito.[17,18]

Four Study Designs

The different kinds of effects of interventions in infectious disease motivated the definition of broad categories of study designs.[19] These study designs are based on different pairs of comparison populations according to whether the studies measure direct, indirect, total, or overall effects.

The indirect, total, and overall effects are defined *within the context of a particular intervention program.* Common to both indirect and overall effects is the need to imagine a population in which the intervention had not taken place in order to think about how to quantify these effects. Assume, then, that there are two populations, one called population A, the other called population B (Figure 1). Assume further that the two populations are separated in every way that is relevant for transmission of the infection under study. The separation could be geographic, cultural, or temporal. That is, the populations could be located such a distance apart that there is little contact between the two. Or two populations could be separated by some social, class, or cultural behavior patterns so there would be little effective contact between them. Finally, population A could be the preintervention, while population B is the postintervention population. Populations A and B are thus non-cross-reacting.

Now assume that an intervention program is begun in population A so that some, but not necessarily all, of the individuals receive the intervention at random. No intervention is given in population B. In study designs of type I, one group in population A comprises individuals receiving the intervention, and the second group of population A comprises individuals not receiving the intervention (Figure 1). Study designs of type I are

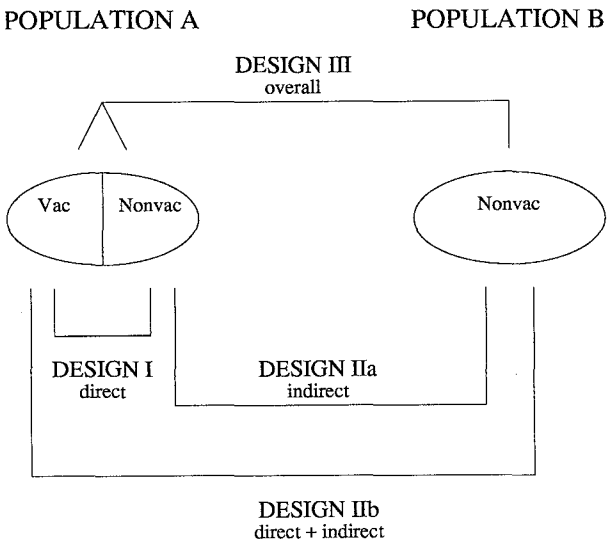

FIGURE 1. Types of effects of interventions against infectious disease, and different study designs based on comparison populations for their evaluation.

supposed to measure direct effects by comparing these two groups that are assumed to be exposed to the same intensity of transmission. The outcome measure in the persons-at-risk receiving the intervention in population A is compared with the outcome measure in the persons-at-risk not receiving the intervention in population A.

Study designs of category IIa evaluate the indirect effects of an intervention program. This evaluation is achieved by comparing the outcome measure in the persons-at-risk that did not receive the intervention in population A with the outcome measure in persons-at-risk in the separate population B in which no intervention program took place. The persons in population A that did not receive the intervention experience, only the indirect effects of the intervention.

Study designs of class IIb evaluate the combined direct effects of the intervention and the indirect effects of the intervention program. The outcome measure in the persons-at-risk in population A who received the intervention is compared with the outcome in persons-at-risk in the separate population B in which no intervention program took place.

The class of type III study designs yields a measure of overall public health benefits of an intervention program. The weighted average of the outcomes of the persons-at-risk who received the intervention and those who did not in population A is compared with the outcome in persons-at-risk in population B.

General Remarks

First of all, these study designs are completely general. They do not specify the outcome measure, the parameter of effect, temporal aspects, or sampling methods.

Second, each of these designs includes two *comparable* populations in that, in the absence of an effect, the outcomes of the compared populations could be expected to be identical.[3] Since we are concerned with infectious diseases here, we need to emphasize the comparability of exposure to infection. That is, if there were no intervention program, the individuals in the comparison populations would be exposed comparably to infection.

Third, the emphasis has been on interventions given to individuals, but the program could be applied to the environment, such as vector control or ecological intervention. In this case, no person receives the intervention. Only study designs IIa and III are applicable. These may be considered equivalent since no individuals receive the intervention.

Fourth, these types of study designs are not new. The paradigms they represent have been used implicitly in many different variants over the years. As mentioned above, design I studies that try to ensure equality of exposure to infection are typical of vaccine efficacy studies.[20–22] Designs of type IIa, IIb, and III that compare epidemiologic measures in the population experiencing the intervention with estimates from the preintervention baseline or with estimates from geographically isolated populations with differing interventions are commonly used in infectious diseases.[23–25] What is new is the attempt to develop the study designs systematically. They provide the conceptual framework to clarify old and to develop new parameters of effect in infectious diseases.

Specific parameters will be meaningful only within the context of a particular choice of comparison populations. For example, equality of exposure to infection in the comparison groups was given by Greenwood and Yule in 1915 as one of three conditions for a valid vaccine efficacy study. "The effective exposure to the disease must be identical in the case of the inoculated and uninoculated persons."[20] After intervention, design I is the only design with comparable exposure to infection in the comparison groups. Greenland and Frerichs[26] discuss vaccine efficacy and effectiveness comparing two separate populations, one with a vaccination program and one without. In the context of the classification of the study designs, they are clearly working with a type II or III study. From the Greenwood and Yule criteria, we know that these types of study should not be used to discuss efficacy or direct effectiveness parameters. In designs IIa, IIb, and III, the potential difference in exposure to

infection is an integral part of the conceptual framework. Other parameters are needed to express the effects of interest. Haber et al.,[27] for example, developed parameters for vaccine efficacy and effectiveness in an outbreak of an acute infectious disease corresponding to each of the types of study designs.

Comments on the Study Designs

Design I

The leading characteristic of type I study designs is the need for equal exposure to infection in the comparison groups. Variants of study design I are generally one of two types. Either assumptions are made about equal exposure to infection without identification of the source of infection, or an index case and the person or persons defined as exposed to infection from the index case are identified and studied. The population can either be thought of as randomly mixing or as being composed of smaller transmission units.

The criteria of equal exposure to infection is actually often insufficient for the estimation of direct effects because the parameters of interest and their estimators can also depend on the degree of exposure to infection.[26–30] The amount of exposure to infection must be specified in a good definition of direct effects. Thus, a measure that assumes equal exposure to infection may be sensitive to indirect effects since the program of intervention changes the intensity of transmission. The direct effects of an intervention in dependent happenings are, therefore, more difficult to define and estimate than in independent happenings. The condition "all other things being equal" in the definition of direct effects may not be fulfilled. The measure for direct effects may need to take into account the effect of the intervention program on the transmission system.

The same principles of equal and specified exposure to infection apply to studies of risk factors for infection. Risk of infection is determined by the amount and frequency of exposure to infection, the probability of infection from a specific type of exposure, and possible differences in susceptibilities. Studies of risk factors for infection need to be explicit about whether the risk factor is for frequency of exposure to infection, the type of exposure to infection, or the probability of transmission conditional on a specific exposure to infection.[28,31]

A limitation of type I study designs is that comparison of two groups equally exposed to infection yields no estimate of either the indirect or the overall effects. For this, we need the population with no intervention program.

Designs IIa, IIb, and III

There are several practical and statistical issues raised by study designs IIa, IIb, and III. First, there are practical problems in assembling a comparison population. It is difficult to guarantee that two separated populations have the same transmission conditions. Even if two populations were similar at the outset, either one of them might change over time owing to factors not related to the intervention. Two villages may initially have similar malaria transmission conditions, but a construction project in one might increase pool-size mosquito breeding sites, increasing transmission.

Secondly, changes in transmission may produce different indirect effects in individuals receiving an intervention than in those not receiving the intervention.[9,13,32,33] Taking vaccination as an example, it may be that

$$\text{Indirect effects in the vaccinated} \neq \text{Indirect effects in the nonvaccinated.}$$

Expressed in terms of the study designs, the total effect in the vaccinated estimated from design IIb, which is the combined direct and indirect effects in the vaccinated, minus the direct effects in the vaccinated for design I, might not be equal to the indirect effects in the unvaccinated in study design IIa:

$$\text{Total effects (IIb)} - \text{Direct effects (I)} \neq \text{Indirect effects (IIa).}$$

For example, the vaccinated may have a different average age of infection than the unvaccinated,[13] depending on the mechanism of the vaccine. This inequality might also occur if naturally acquired immunity to malaria and eventual malaria vaccines are both dependent on boosting by natural infection to lengthen their duration of effectiveness.[9] If natural immunity wears off more quickly than the vaccine-induced protection, then the unvaccinated portion of the population become susceptible before those who are vaccinated. They will be more prone to disease and transmit infection more effectively to mosquitoes, providing a source of natural boosting to prolong the effectiveness of the vaccine in the vaccinated. Thus, not only are the indirect effects in the two groups different, but the vaccinated benefit from the unvaccinated.

In Designs II and III, definition of the baseline hazard is also problematic. An unvaccinated person in population A is subjected to a different rate of infection than an unvaccinated person in population B. Thus, comparison of vaccinated persons in population A to unvaccinated persons in population B does not correspond to many of the conventional epidemiologic analyses that assume that

the exposed and control populations are subjected to the same baseline hazard. This comparison is more complicated than a mere nonproportional hazards situation.

Finally, issues of inference are raised by these types of study designs because the unit of observation will often be the entire population;[25] thus, many populations are needed for comparison. Exposure is the intervention program as a whole. This setting raises issues common to ecologic studies[34] and meta-analysis.

Gray Areas

Boosting

Not all situations fit neatly into any one particular study design. One such instance is when immunity induced by a vaccine is sensitive to boosting by natural infection, as discussed above. In this case, exposure to infection could influence either the magnitude of protection conferred by the intervention or the duration of its efficacy. This possibility has been raised with respect to malaria,[9,25,35,36] rubella,[37] pertussis,[38] and measles,[39] among others. The protective effects in the individual would be a composite of the biologic effects of the original intervention in the individual and the transmission intensity, itself a function of the indirect effects. In this case, if two identical persons who receive an intervention are subjected to different transmission conditions and subsequently given a controlled infective challenge, the expected results would be different. Although one might be interested in estimating the direct effects of the vaccine, this would not be possible without taking into account the transmission and the indirect effects.

Biologically, the phenomenon is more than the common notion of *synergism* defined as "a biological response produced by simultaneous exposure to two or more agents that exceeds the combined actions of the agents when working in an 'independent' manner."[40] The biologic effect is a combined action of the vaccine in the individual and the action of the infective challenge provided by the population. Statistically, modeling the protective effects of a vaccine sensitive to natural boosting as a function of the hazard is more than merely adding an interaction term in a multiple effects model. The phenomenon of boosting requires the inclusion of the population level into the model. Some of the statistical issues raised are similar to those in study designs II and III. The development of methods to evaluate interventions sensitive to natural boosting is a particularly intriguing problem.

Contagious Treatments

A problem of another sort is posed by the possibility of *contagious treatments* or *interventions*. A contagious intervention is one that is administered to an individual, but spreads to other individuals. For purposes of effect and transmission, the others have also received the intervention, but they will generally be evaluated as if they had not received the intervention. With live polio vaccine, this is a biological problem resulting from the infectious and replicative capability of the vaccine virus.[22] This is more than mere misclassification. The number of people actually being exposed to the contagious treatment will depend on many factors, including how many people receive the intervention.

The problem of contagious treatments or methods of prophylaxis is not particular to infectious diseases, or live-virus vaccines. Education programs aimed to change behavior related to the spread of infectious diseases, such as HIV, or risk factor for chronic, noninfectious diseases can also spread beyond the persons being targeted. Thus, evaluation needs to take such possible *contagiousness* into account. A theory of dependent happenings could also be useful for developing a theory of dependent or contagious treatments.

Chaos

Several authors[41–43] have argued that measles exhibits aperiodic, or chaotic, behavior in some populations. Conventional methods of analysis may not be adequate to evaluate intervention programs in chaotic systems,[44] just as different methods are needed to characterize chaotic time series[45–48] than to analyze noisy periodic time series.[49] If the transmission dynamics of a system are radically altered by the intervention, it may be that completely different study designs and methods of analysis are needed pre- and postintervention. A dynamic epidemiology is needed to define direct and indirect effects of intervention programs in such situations.

Discussion

Miettinen wrote that afflictions of a population in the aggregate, such as epidemics and famine, are not of the "form characteristic of modern epidemiologic research,"[3] whereas afflictions of individuals in the population are. This dichotomy between the individuals and the population breaks down, however, in infectious disease where the population biology of the host–parasite interaction responds to and influences the outcome of the intervention.

The classes of study designs I, IIa, IIb, and III were conceived to clarify the discussion of direct, indirect, total, and overall effects of interventions. The direct effects of an intervention such as a vaccine, chemotherapy, or education are important to quantify in order to know if the intervention is useful at all or to find

problems in the manufacture, storage, and delivery system.[22] The direct effect of the intervention needs to be separated from the effect produced by the intervention program in the population in order to have a biologically meaningful parameter. Describing direct effects of an intervention can also be a key to understanding the indirect effects,[9] since the indirect and overall effects in the population are functions of the direct effects in the individuals.

Estimation of indirect and overall effects of an intervention program is also important for several reasons. First, it is essential for the evaluation of the overall public health benefits of the program.[32] Second, indirect effects can affect the estimation of direct effects.[19,21,28,50] Third, indirect effects give information on the underlying transmission system and thus can be helpful in elucidating the biologic and dynamic mechanisms producing observed data. Finally, some intervention programs have only indirect effects.

Many issues remain to be solved. A difficult practical issue is the problem of controlling for the amount of exposure to infection and ensuring comparability of exposure to infection in any of the study designs. Our definitions of direct and indirect effects are framed heuristically as counterfactuals. The methods of causal inference based on counterfactuals[7,51] assume, however, that there is no dependence of the outcome between individuals. The theory of counterfactuals will need to be extended for causal inference in dependent happenings, as well as for application if the population is the unit of inference. The development of methods of analysis that relate occurrences at the level of the individual, and possibly within the individual, to phenomena at the level of the population presents a challenge for the coming decade. The four classes of study designs presented here provide the conceptual framework for future methodologic development of a dynamic epidemiology for dependent happenings.

Acknowledgments

The authors thank Sander Greenland, Michael J. Haber, and Ira M. Longini for helpful discussions.

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