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Design and Analysis of Vaccine Studies

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Dedicated to those lives saved by vaccination.

Preface

Immunization is one of the greatest advances in public health. Figure 0.1 shows a camel with a solar powered refrigerator on his back. Many vaccines contain live viruses that need to be kept cold, or the viruses will die and the vaccines will lose their ability to produce an immune response. The chain of refrigeration is called the cold chain. This camel is carrying vaccines in the solar powered refrigerator across a hot desert to the far reaches of civilization. The inspiration of this image is that it represents the dedication of the world to bring the vaccines to everyone.

The first major success, and the origin of the word vaccination (*vacca* for cow), was Jenner's introducing cowpox-based vaccine against smallpox in the late 18th century. After nearly a century hiatus, at the end of the 19th century, inoculations against cholera, typhoid, plague, (all three caused by bacteria) and rabies caused by a virus, were developed. By the early 20th century, statisticians of the stature of Karl Pearson, Major Greenwood and Udny Yule were heartily involved in discussions of evaluating these vaccines in the field. In the 1920's, new vaccines included Bacille Calmette-Guérin against tuberculosis pertussis, diptheria, and tetanus, and the 1930's yellow fever, influenza and rickettsia. After World War II, the development of new vaccines burgeoned with the development of cell cultures in which viruses could grow, enabling development of oral polio vaccine and vaccines against measles, mumps, rubella, adenovirus, varicella, and adenovirus, among others. Further new technologies have enabled development of new generations of vaccines to replace the old ones and attempts to make new vaccines against malaria, HIV and many others where the infectious agent still outwits the researchers (Plotkin, Orenstein, Offit 2008). Some vaccines are highly efficacious, and protective effects are recognizable even without subtle statistics. Others are less efficacious, so that study design and statistical analysis are more challenging. Other aspects of the biology the infectious agents also pose statistical challenges.

Statistical inference made great advances in the 20th century and the 21st has much more in store (Efron 1998). The development of statistics, clinical trial design, and epidemiologic methods in the 20th century had their coun-

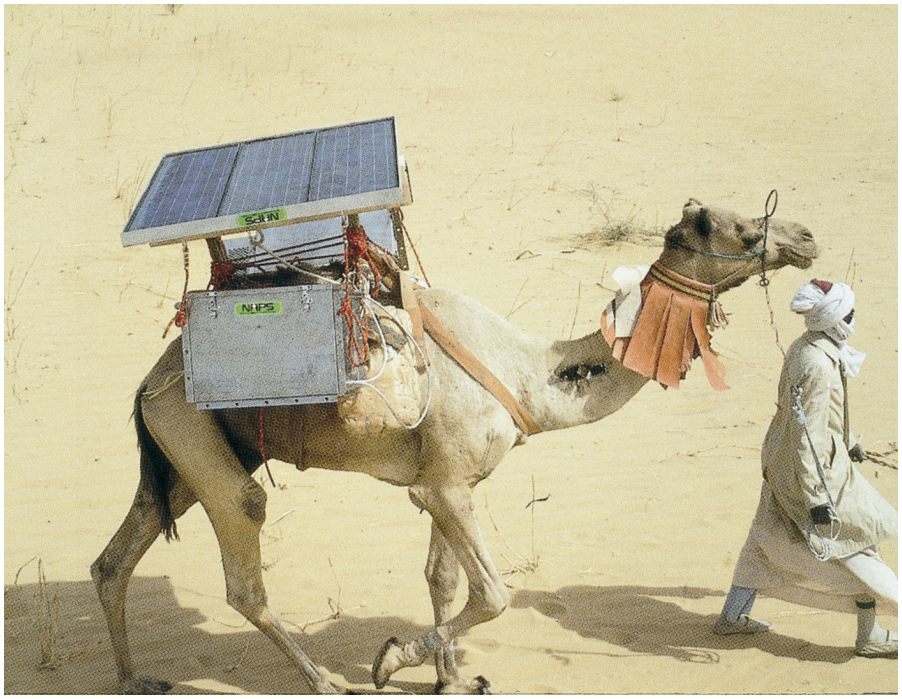

Fig. 0.1. Camel with solar electricity powered refrigerator with vaccines being kept in the cold chain. Image courtesy of Naps Systems Oy, Finland.

terparts in advances in vaccine studies as well. The early vaccine field studies predate randomized trials and contain detailed discussion about confounders. Some of the earliest randomized studies were in infectious diseases and vaccination.

The focus has historically been on evaluating the direct protective effects of immunization in the individuals who are immunized. However, vaccination of certain individuals can affect whether other unvaccinated individuals become infected. Due to the dependent happening nature of infectious diseases (Ross 1916), widespread immunization can have many different kinds of effects in populations. Also, since the effects of vaccination generally need to be evaluated in the field, studies take place in the wild, in a manner of speaking, where the important and dynamic population of the infectious agent of interest is circulating with the humans as hosts. Increasing interest is being given to effects of vaccination in addition to the direct protective effects. This book is about the myriad different effects of vaccination and their evaluation.

Different approaches to vaccine studies have been developed by researchers working on particular infectious diseases. Similarly there are people who specialize in particular musical instruments and are pianists, clarinetists, or violinists. But then there are musicians who can play just about any instrument.

Our focus is on general principles that can be applied to many infectious diseases and many vaccines. Our aim is to present a unified view of vaccine field studies and infectious diseases in general.

This book is intended to serve three audiences: researchers specializing in vaccine and infectious disease studies; scientists interested in understanding vaccine and infectious disease studies; and students in statistics, biostatistics, epidemiology or infectious diseases. The prerequisites for understanding much of the material in the book are minimal. In many sections of the book, we have emphasized the conceptual development. We have not assumed a knowledge of concepts of infectious disease epidemiology or dynamic models, and include considerable material on these subjects, since they are integral to our approach. We also do not assume a knowledge of vaccines or the immune response to infection and vaccination, and include a brief chapter covering these topics. The models and analytic methods require some comfort with equations. We do not explain statistical methods, such as likelihood and Bayesian based inference. However, it is not necessary to understand how inference is conducted to understand the general ideas of the book. We have marked a few sections as being highly technical that can be skipped.

Many thanks to John Kimmel, whose patience and support saw us through. Several colleagues have contributed to this book. (names) Several former graduate students, now colleagues – (names) –have contributed in many ways to the development of this book. Much of the research represented in this book was supported by the National Institute of Allergy and Infectious Disease grants R01-AI32042, R29-AI31057, and R01-40846, and the Brazilian Reseach Council (CNPq).

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Introduction and Examples

1.1 The Need of Vaccine Studies Framework

1.1.1 A few historical examples

Vaccine efficacy and vaccine effectiveness, VE, are generally estimated as one minus some measure of relative risk, RR, in the vaccinated group compared to the unvaccinated group:

$$VE = 1 - RR\ . \tag{1.1}$$

The groups being compared could be composed of individuals or of populations or communities.

Historically, interest has been on evaluating protective effects of vaccination. Study designs and statistical analysis have played a role since early on. In the November 5, 1904, issue of the *British Medical Journal*, Karl Pearson published a criticism of the Antityphoid Committee's report on the antityphoid inoculation statistics from the South African War and from India that had recommended continued use of antityphoid inoculation. Armed with the correlation coefficient, he re-analyzed the data and claimed that the correlations between protection against disease and inoculation ranged from 0.021 and 0.445, mostly around 0.1, with the correlations against mortality in a similar range. He compared these values with his analysis of the relation of recovery from smallpox with smallpox vaccination, which were in the range 0.578 and 0.769. Although he demurred somewhat due to his lack of knowledge about typhoid, he wrote "that the results are such as would justify suspension of antityphoid inoculation as a routine method." The immunologist A.E. Wright countered the following week, saying that although he did not understand the correlation coefficient, the mortality was reduced four- to six-fold, so that Pearson's conclusion must be wrong and that the Medical Advisory Board, who had heeded the criticism "could not hide behind Professor Pearson's petticoats." The argument continued in the *British Medical Journal* weekly for

a full nine weeks until December 31, 1904, when Pearson finally gave up continuing the controversy after Wright refused to deal with what he had called "statistical minutiae" and the "mathematical expression".

In 1915, the statisticians Major Greenwood and Udny Yule published a treatise on "The Statistics of Anti-typhoid and Anti-cholera Inoculations, and the Interpretation of such Statistics in general" in the *Proceedings of the Royal Society of Medicine*. The 85-page paper begins "Hardly any subjects within the range of preventive medicine is of more immediate importance than the methods of prophylaxis which ought to be adopted with respect to typhoid fever and cholera" (page 113). As well as presenting much of the data available at that time, the paper develops a general approach to analyzing and interpreting such data. They lay out the conditions for valid inference and use the Pearson chi-square to calculate significance of inoculation's effect against disease and mortality. They discuss the heterogeneity in susceptibility and protection, and the role of a possible threshold of protection. Person-time analysis was not invented yet, so they discussed the problem of people being inoculated during the course of the epidemic, thus changing their status. Figure 1.1 shows two tables with data on anti-typhoid inoculation from the original Greenwood and Yule (1915) paper. The problem was whether to "class as inoculated those who were so at the date of the last return made or only those actually inoculated at the time of arrival on the foreign station." In the former case, shown in Table I of Figure 1.1, there may be an exaggeration of the "number of men who were inoculated during the whole exposure to infection", and in the latter case, shown in Table II, one would underestimate it "because many inoculations were done shortly after arrival."

In 1939, Kendrick and Eldering reported on a large pertussis vaccine field trial in Michigan. Figure 1.2 shows data from the Kendrick and Eldering (1939) paper on number of cases and person-time at risk in the pertussis trials. Figure 1.3 shows data from the Kendrick and Eldering (1939) paper on number of cases and number of exposures to pertussis in the trial. It is not unusual for vaccine studies to present two such analyses. We show the relation of these analyses to one another. Both the Greenwood and Yule (1915) and the Kendrick and Eldering (1939) papers pre-date formal randomized studies and discuss in detail potential sources of bias.

In 1954, an enormous field study of the Salk killed poliomyelitis vaccine was undertaken with great publicity in the United States. A total of 1,829,916 children participated in the nationwide study. The Summary Report by Thomas Francis, Jr. et al. of the trial was published early in 1955 in the *American Journal of Public Health*. In December 1955, K.A. Brownlee wrote an invited, highly critical review article for the *Journal of the American Statistical Association* on the statistics of the 1954 polio vaccine trials. The original design plan, called the Observed Control Study, was "to administer vaccine to children in the second grade of school; the corresponding first and third graders would not be inoculated, but would be kept under observation for the occurrence of poliomyelitis in comparison with the inoculated second graders."

TABLE I.—ANTI-TYPHOID COMMITTEE'S DATA.

First arrangement.

	Not attacked	Attacked	Total
Inoculated	10,322	56	10,378
Not inoculated	8,664	272	8,936
Total	18,986	328	19,314

$\chi^2 = 180{\cdot}98$, P = less than 0·0001.

TABLE II.—ANTI-TYPHOID COMMITTEE'S DATA.

Second arrangement.

	Not attacked	Attacked	Total
Inoculated	6,759	56	6,815
Not inoculated	11,396	272	11,668
Total	18,155	328	18,483

$\chi^2 = 56{\cdot}23$. P = less than 0·0001.

Fig. 1.1. Two tables from the original Greenwood and Yule (1915) paper containing data on anti-typhoid inoculations and attack rates in the military. The two tables represent two differing arrangements of the data.

(Report, page 1). Someone noticed the problem that this was not a blinded study, plus other factors such as differences in age that might lead to bias. So, to "have data which could provide an accurate gauge of the effect, free of possible bias in diagnosis and reporting," (Report, p.1), the plan was changed in mid-stream. In the second plan, called the Placebo Control Study, "children of the first, second, and third grades would be combined. One half would receive vaccine; the other matching half, serving as strict controls, would receive a solution of similar appearance...." (Report, p. 1) Fewer than half of the children were in the second part of the study. Brownlee's colorful judgment was that "It is a pity that explicit credit is not given to whomever was responsible for this change. However, only 41 percent of the trial was rescued and the remaining 59 percent blundered along its stupid and futile path." (Brownlee, 1955, page 1007). Despite possible design flaws, the vaccine was determined to have a 72 percent efficacy (lower 5% confidence limit 61) against paralytic polio in the Placebo Study Areas and 62 percent efficacy (lower 5% confidence limit 51) in the Observed Study Areas. The Salk killed injected polio vaccine and Sabin live oral polio vaccines transformed the epidemiology of the disease. Transmission of the three polio virus strains has been eliminatd in most countries of the world.

In 1916, Sir Ronald Ross published his treatise on The Theory of Happenings in the *Proceedings of the Royal Society of London*. Ross had already

TABLE 9

Incidence of pertussis in test and control groups based on period at risk

Time at risk and subsequent attack	Groups in study		
	Both groups	Injected	Control
Number of children	4212	1815	2397
Person-years	4575	2268	2307
Number of attacks	400	52	348
Annual pertussis attack rate per 100	8.7	2.3	15.1

PEARL KENDRICK AND GRACE ELDERING

Fig. 1.2. Results of a pertussis vaccine trial in Michigan, USA, in the 1930's (from Kendrick and Eldering 1939).

been awarded the second Nobel prize in medicine for elucidating that malaria was transmitted by mosquitoes. He was also an amateur mathematician who developed the early mathematical models of malaria and interventions. In his more general 1916 treatise, Ross wrote that " Different kinds of happenings may be separated 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*...to class (b) belong infectious diseases, membership of societies and sects with propagandas, trade-unions, political parties, etc., due to propagation from within, that is, individual to individual" (page 211). Due to the dependent happenings in infectious diseases, vaccination can produce several different kinds of effects at both the individual and the population level. In an individual, vaccination can induce a biologically protective response against infection and/or disease, and/or reduce the degree or duration of infectiousness for other individuals. Widespread vaccination in a population can reduce transmission and produce indirect effects, even in individuals who were not vaccinated.

During the 20th century, two for the most part distinct mathematical areas developed. One are was in the arena of statistics and inference, including

TABLE 12

Persons in the study series exposed to pertussis according to "type" of exposure and proportions of those exposed who were attacked

	Classification according to history of exposure				No history of exposure
	Definite in own household	Definite in other household	Indefinite	Total	
Both groups					
No. of exposures...	243	161	166	570	3642
Attacks.....	172	39	14	225	175
Per cent.....	70.8	24.2	8.4	39.5	4.8
Vaccine group					
No. of exposures...	83	100	114	297	1518
Attacks.....	29	5	4	38	14
Per cent.....	34.9	5.0	3.5	12.8	0.9
Control group					
No. of exposures...	160	61	52	273	2124
Attacks.....	143	34	10	187	161
Per cent.....	89.4	55.7	19.2	68.5	7.6

PEARL KENDRICK AND GRACE ELDERING

Fig. 1.3. Results of a pertussis vaccine trial in Michigan, USA, in the 1930's (from Kendrick and Eldering 1939)

the development of the randomized trial, and further developments of clinical trials and epidemiological study design. The primary focus of vaccine studies was on evaluating direct protection in vaccinated compared with unvaccinated people. The underlying dynamics of transmission of the infectious agent did not play an important role. Epidemic theory made great advances in the 20th century as well. Both deterministic and stochastic models of infectious disease dynamics and interventions were developed. Especially with the advent of computers, models could become more complex. Epidemic theory and computer models could be used to study potential indirect effects of widespread vaccination or other interventions. However, the relation to the field studies, prospective data collection, and statistical analysis remained tenuous.

1.1.2 Growth of interest in population effects

In the latter decades of the 20th century, interest began to grow in evaluating more than just the direct protective effects of vaccination. During the 1980's there was great hope that effective malaria vaccines were imminent. The malaria parasite has three main stages of its life cycle in humans, one for infection, one for disease, and one for transmission to the mosquitoes. Naturally, the problem of designing studies to evaluate a transmission-blocking vaccine, which would not protect the immunized individual at all, led to the

idea of using community randomized designs to evaluate the reduction in overall incidence due to use of such a vaccine.

In the early 1990's the *Hemophilus influenzae* (Hib) vaccine was introduced. Young children were vaccinated with the result that incidence in young infants nearly disappeared. This effect was apparently due to a large reduction in carriage of the infectious agent in the nasal passages. The indirect effects of vaccinating was astonishing, and interest grew on how to measure the effect accurately with good study designs and statistical analysis. More recently, similar phenomena are being observed with meningococcal vaccination (Ramsay et al 2003)and pneumococcal vaccination (Hennessy et al 2005). With these conjugate vaccines, evidence is mounting that a stronger immune response is required to reduce carriage than to prevent invasive disease. Very young children are not able to mount such a good immune response. So that if reduction in carriage is the goal to reduce the overall transmission in a population, then it might require a change in the world–wide immunization schedule of infants and young children, which cannot be undertaken lightly. Thus, interest is keen in accurate evaluation of the changes in transmission and incidence of invasive disease by reducing carriage in contrast to direct protection against invasive disease.

During a primary pneumococcal vaccine trial conducted in the 1990's, some concern developed about whether the number of events being observed in the study would be sufficient to support licensure of the vaccine. A community-randomized study was designed and implemented to evaluate the reduction in incidence of widespread vaccination, especially the reduction in the vaccinated children in the communities where vaccination was offered compared to the unvaccinated in the control communities (Moulton et al 2001). The idea of the study was that it would lend support to the primary study. However, the vaccine was licensed before completion of the community-randomized study, so that the latter trial was interrupted.

Ali et al (2005) reanalyzed a large-scale trial of killed cholera vaccine in Bangladesh, relating the level of vaccine coverage in the different geographic areas with the reduction in incidence. In general, interest in evaluating possible indirect effects of widespread vaccination either before or after licensure is growing. The idea is gaining attention in the HIV vaccine world where currently few people believe that a vaccine will block infection, but could help control the initial growth of virus in the blood, thus reducing infectiousness for others. This could have potentially important public health benefits which would be good to evaluate prospectively.

Influenza researchers have believed for decades that children are responsible for most of the transmission of influenza in the community. They have promoted vaccination of children as an important public health measure to reduce transmission in adults and high-risk groups who might themselves not respond well to immunization. A community-based study in Texas to evaluate the effects of vaccinating schoolchildren against infuenza on adults has been ongoing in Texas, USA, since 1998 (Piedra et al 2007). The Texas study as

well as many other influenza vaccine studies do not use biologically confirmed influenza illness as the outcome. Instead a case definition is used based on symptoms only without biological confirmation, including many illnesses that would not be affected by an influenza vaccine. Thus the estimates of the effect of the vaccine is much lower than if only biologically confirmed influenza illnesses were used. We consider approaches to improving such estimates in this book.

Pertussis vaccines have been in widespread use since the 1930's. Vaccination is very effective against overt pertussis disease. However, considerable controversy raged over whether pertussis vaccination had any effect on the circulation of the bacteria on the population. Indirect evidence based on population-dynamic arguments suggested that the circulation of the bacteria was not reduced, just serious disease. However, the evidence was considered inconclusive. A study in Niakhar, Senegal, was conducted in the early 1990's of pertussis vaccination, in which the primary interest was in the protective effects of vaccination. Because the study took place within a larger population-based study, the data also allowed estimation of the effect of the vaccine on reducing transmission from vaccinated breakthrough cases compared with transmission from unvaccinated cases (Préziosi and Halloran 2003a). Furthermore, the study data were appropriate to estimate the effect of vaccination on the severity of disease in those who did develop pertussis (Préziosi and Halloran 2003b).

These are only a few recent examples of growing interest in evaluating more complex effects of vaccination in populations. Our goal in this book is to provide a systematic framework for understanding the different effects of vaccination and how they relate to one another, principles of study design and statistical analysis, and the underlying transmission dynamics.

1.2 Scope and Outline of the Book

Different types of studies are required for different phases of vaccine development. The statistical problems in vaccine studies range from small sample exact analysis for sample sizes of 2 to 8 animals or people, to randomized field trials with hundreds to several thousands of people, to community trials with hundreds of thousands of participants, and finally to surveillance in populations with hundreds of millions of inhabitants. The early phase of vaccine development involves searching for candidate vaccine antigens. These include *in vitro* studies as well as testing in animals. More recently, designer approaches to vaccine discovery using computer models of various parts of the infectious agent and the immune system have been developed. Once a candidate antigen is found, then a vaccine is formulated. If appropriate animals are available for that particular infectious agent, then the vaccine candidate will be tested for safety, immunogenicity, and possibly efficacy against experimental challenge with the infectious agent.

Then the vaccine goes into humans for various phases of clinical testing. Phase I is primarily safety and possibly immunogenicity. Phase II studies are further safety and immunogenicity testing in humans. Phase III studies are generally field evaluation of direct protective efficacy, with further accumulation of safety data. Recently, there has been some discussion of integrating evaluation of indirect effects for some vaccines into Phase III studies. The Phase III studies are the field studies that are generally used to apply for licensure of a vaccine. Once a vaccine is licensed, then the efficacy and safety of the vaccine in regular usage is often monitored and evaluated using a variety of studies. The post-licensure studies are somewhat generically referred to as Phase IV studies. Phase II studies are generally not designed to be large enough to evaluate the protective efficacy of the vaccine. Phase IIb studies have been proposed that are something like proof-of-concept studies. They are powered possibly to estimate an effect with moderate significance. The idea is that the trial might be expanded to be larger if there is some evidence of an effect.

The Phases III and IV studies are the main focus of our book, in that we focus on field studies. In defining the various effects of vaccination and their relation to one another, we implicitly assume a randomized study, with observational studies being departures from the randomized study (Rosenbaum 1995). Departures from the randomized study can result in confounding and types of biases. Our general paradigm is that of causal inference. Aspects of our book are largely conceptual, showing the interface between study design, statistical analysis, and epidemic theory. After giving an overview of the book, the remaining part of this chapter introduces some key definitions in infectious disease research and causal inference.

Chapter 2 presents a systematic framework for thinking about many of the different types of vaccination effects and the parameters and study designs used to estimate them. This chapter is based on a paper by Halloran, Struchiner, and Longini (1997) that we call the Table Paper because it lays out a 2-dimensional table (Table 2.2) showing several of the main vaccine efficacy and effectiveness parameters. Struchiner et al (1990) and Halloran and Struchiner (1991) introduced four basic study designs for differentiating and evaluating direct and population level effects of vaccination. Struchiner, Halloran and colleagues were particularly motivated by the malaria vaccination discussion of the 1980's and proposed to differentiate vaccines against infection, disease, and transmission (Struchiner et al 1989; Halloran et al 1989). Longini and colleagues were interested in estimating the effects of covariates from household studies in which information on contacts between infectives and susceptibles to allow the estimation of the effect of covariates on the transmission probabilities and the secondary attack rates (Longini and Koopman 1982). In 1996, Rhodes, Halloran and Longini showed formally the relation among the parameters of protective effects using counting process models. The Table Paper is the unification of these various ideas. Further details were published in Halloran et al (1999).

Chapter 3 gives an overview of the immune response to infection, the basis for the idea of prophylatic immunization. The chapter gives a brief history of the development of vaccines. Vaccine safety is of key importance in vaccine studies. Preclinical animal studies and Phase I and II clinical trials are designed to evaluate immunogenicity and safety, thus are also included in Chapter 3. The idea of herd immunity, the level of immunity to an infectious agent in a population, in contrast to the immune response within an individual, is presented.

Chapters 4 and 5 introduce dynamic models. Chapter 4 focuses on the Reed-Frost and Greenwood models, and stochastic, discrete-time methods. Chapter 5 focuses on deterministic, differential equation models. In both chapters, the material presented is motivated by its relation to statistical models for estimation of important parameters, including vaccine effects, and for understanding transmission dynamics in field studies. These two chapters can be read on their own by someone interested in an introduction to dynamic infectious disease models.

Chapter 6 focuses on studies for evaluating the direct protective effects of vaccination. This chapter presents the estimands and estimators for the measures of protective efficacy that do not condition on exposure to infection. Specifically, these include the most common estimators of vaccine efficacy based on the incidence rate, the hazard rate, or cumulative incidence, called the attack rate in infectious diseases. Several examples of field studies are presented. The chapter covers general considerations of designing a study, including choice of populations and comparison populations, choice of outcomes, sample size determination, and randomized versus observational studies. Chapter 7 discusses different distributions of protection in a population and the implications for study design and population dynamics. The problems of measuring vaccine efficacy in the presence of heterogeneity in protection or exposure to infection and of evaluating waning of vaccine efficacy are considered. Chapter 8 considers case-control studies in vaccine evaluation. The choice of outcome measures and the use of validation sets for nonspecific outcomes is presented Chapter 9 presents the evalution of the effects of vaccination on post-infection outcomes and related issues such as selection bias.

Chapters 10 through 12 present household-based studies and related studies, such as the augmented study design, and studies in other transmission units. Chapter 10 presents several examples of studies in households and other small transmission units and discusses some considerations of study design. Chapter 11 gives an overview of the difference in the statistical models of the assumptions of independence among transmission units or that transmissions units are considered within a community. Several approaches to analyzing data assuming that people can become infected within the transmission unit as well as from the community at large are presented. Chapter 12 presents methods of analysis assuming that the transmission units are separate, including the conventional secondary attack rate analysis.

Chapter 13 goes into detail how to estimate indirect, total, and overall effects of widespread vaccination. The first part of the chapter presents approaches comparing incidence before and after implementing a vaccination strategy in a population. The second part of the chapter presents aspect of group-randomized designs in which several communities are compared.

Chapter 14 discusses issues related to the use of exposure to infection to help with the interpretation of vaccine studies and how to compare studies of the same vaccine in different populations.

Chapter 15 focuses on determining immune correlates of protective immunty. Although we touch on the new developments made possible by advances in biological specimen collection, immunology, genome scans, and sequencing of agents, the next generation book on vaccine studies will be the one to cover these in more detail.

Chapter 16 discusses some practical important issues related to vaccine studies, such as the Data and Safety Monitoring Board (DSMB), not covered elsewhere. We do not cover in detail how to conduct a vaccine study.

1.3 Concepts in Infectious Disease Research

1.3.1 Transmission

Transmission from one host to another is fundamental to the survival strategy of most infectious agents. Each infectious agent has its own life cycle, modes of transmission, population dynamics, evolutionary pressures, and molecular and immunologic interaction with its host. The transmission cycle may involve a particular insect or other vector, and consequently its ecology. Studies and interventions need to take the particular transmission, dynamics, and biology of each infectious agent into account.

However, some underlying principles of transmission and dynamics are common to many infectious diseases. These principles are captured in a wide variety of mathematical and statistical models. Since for the infectious agent, the human host population is its ecological niche, some of the principles come from general theories of populations, evolution, and ecology. (see Burnet and White, 1972; McNeill,1976). Some of the principles have their origins in infectious disease epidemiology. When the appropriate data are available, the models can be used to estimate quantities of interest.

One measure of the success of an infectious agent is how effectively it is transmitted. The *transmission probability* p is the probability that, given a contact between an infective source and a susceptible host, successful transfer of the infectious agent will occur so that the susceptible host becomes infected. The transmission probability depends on the type and definition of a contact, the infectious agent of interest, characteristics of the infectious host, and characteristics of the susceptible host (Figure 1.4).

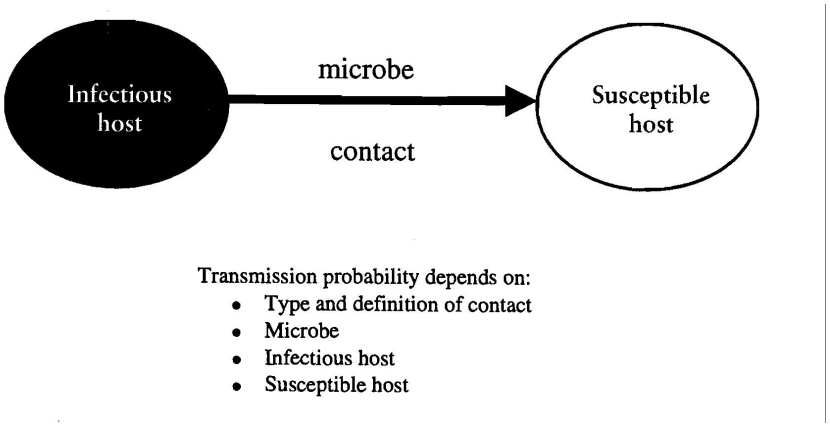

Fig. 1.4. Transmission

1.3.2 Time line of infection

The natural history of infection within a host can be described with reference to either infectiousness or disease (Figure 1.5). Both time lines begin with the successful infection of the susceptible host by the infectious agent. The natural history of infectiousness includes the *latent period*, the time interval from infection to becoming infectious, and the *infectious period*, during which time the host could infect another host or vector. Eventually the host becomes noninfectious, either by clearing the infection, possibly developing immunity, or by death. The host can also become noninfectious while still harboring the infectious agent. The host may also become an infectious *carrier* if he recovers from disease (i.e. asymptomatic), but continues to carry the infection, often remaining infectious.

The natural history of disease in the infected host includes the *incubation period*, the time from infection to symptomatic disease, and the *symptomatic period*. The probability of developing symptomatic disease after becoming infected is the *pathogenicity* of the interaction of the infectious agent with the host. Eventually the host leaves the symptomatic state, either by recovering from the symptoms or by death. If the infectious agent has provoked an autoimmune response in the host, symptoms can continue even after the infectious agent is cleared. An *inapparent case* or *silent infection* is a successful infection that does not produce symptoms in the host. Inapparent cases can be infectious.

While the disease process and its associated time line are important to the infected person and to a physician, the dynamics of infectiousness are important for propagation of the infectious agent and for public health. The relation of the two time lines to one another is specific to each infectious agent and can have important implications for study design, modeling, and public health.

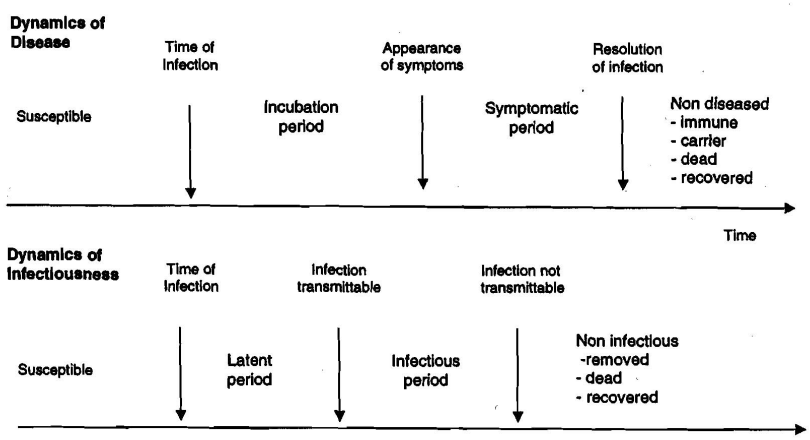

Fig. 1.5. General Timeline of Infection and Disease

HIV poses a particular problem for public health because the virus has a short latent period and a long incubation period. A person infected with HIV could infect many people before symptoms develop. *Plasmodium falciparum*, one of the parasites that causes human malaria, has an incubation period of about 14 days, but the infective stages of the parasite do not appear until about 10 days after the first symptoms. Thus, early treatment of symptoms with a drug that also kills or prevents infective stages could have an important effect on transmission.

The role of changes in behavior relative to the development of infectiousness and symptoms is also important. It is possible to add a third timeline related to behavioral aspects, such as withdrawal to the home with symptoms, going to the hospital, or other aspects that influence how infectives expose other susceptibles, or how susceptibles alter their exposure. Figure 1.6 shows the consensus timeline of infection, disease, and behavior of smallpox infection and disease for an unmodified smallpox, that is, the course in an infected individual who was not previously vaccinated (Longini et al 2007) . Once again the relation between the onset of infectiousness and symptoms is key because the symptoms then influence the behavior.

Figure 1.7 shows a timeline for influenza. There is considerable uncertainty about how much of the infectiousness occurs before symptoms develop. This is important for choosing among public health interventions and for dynamic modeling.

Elveback et al (1976) developed an influenza model that distinguished between illness and infection attack rates. The infected people become infectious, but only a fraction of them develop overt disease. In many studies of infectious agents, it is easier to use overt disease as the outcome, rather than infection, since infection may be difficult to ascertain. If many infections are

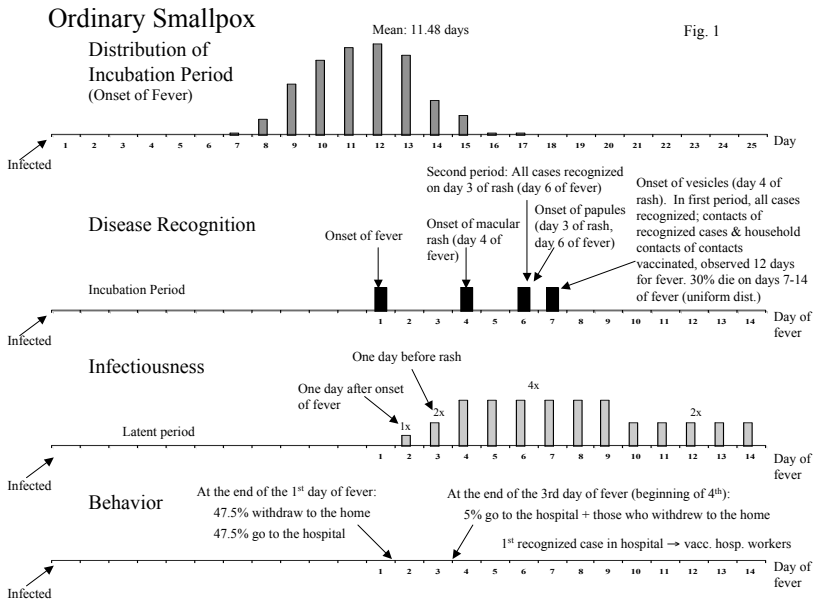

Fig. 1.6. Smallpox Timeline of Infection, Disease, and Behavior (Longini et al 2007)

inapparent, however, using overt disease would result in an underestimate of the level of exposure to infection in the population. Estimation of the incubation and latent periods can be difficult because the time of infection as well as the onset and end of infectiousness are often difficult to observe.

1.3.3 Basic reproductive number, $\mathbf{R_0}$ and generation time, T_g

Another key quantity in infectious diseases is the basic reproductive number, R_0, pronounced "are-zero" or "are-naught". R_0 is defined as the expected number of new infectious hosts that one infectious host will produce during his or her infectious period in a large population that is completely susceptible. This definition applies for small infectious agents, such as viruses and bacteria, also called *microparasites* (Anderson and May 1991) Understanding R_0 is important for public health applications and for describing the population biology of a parasite in a population of hosts. R_0 does not include the new cases produced by the secondary cases, or cases further down the chain. It also does not include secondary cases who do not become infectious. R_0 is a measure of the transmissibility of the strain in the population and largely determines the proportion of the population that will be infected in an epidemic.

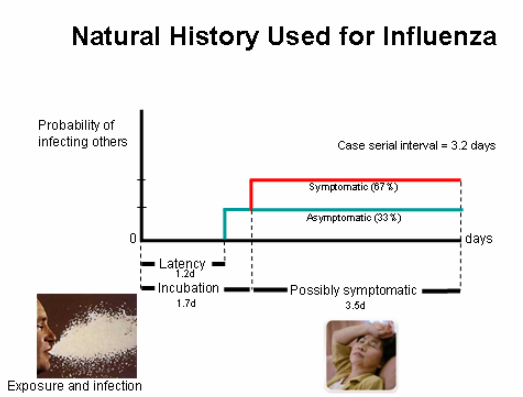

Fig. 1.7. Influenza Timeline of Infection and Disease

The serial interval, also called the generation time, T_g, is the average time between infection of an index case and infection of the secondary cases they produce. It can also be defined as the average time between the onset of symptoms or ascertainment of an index case and the onset of symptoms or ascertainment of the secondary cases they produce, but then additional variability must be taken into account (Svensson 2008). The rate of growth of an epidemic is determined approximately by the ratio R_0/T_g (Fraser et al 2004). Because the generation time of influenza is on the order of 2 to 3 days, and that of smallpox is on the order of 10 to 14 days, influenza epidemics are much more explosive than a smallpox outbreak would be. The goal of intervention is to reduce R_0 so that $R_0 < 1$, which for simple assumptions about population mixing requires transmission rates to be reduced by a fraction $1 - 1/R_0$.

The concept of R_0 comes from general population theory and refers to the expected number of reproducing offspring that one reproducing member of the population will produce in the absence of overcrowding. With larger parasites such as worms, called *macroparasites*, R_0 is the expected number of mature female offspring that one female will produce in her lifetime. In macroparasitic diseases, the parasites are often distributed in a skewed fashion among their hosts which influences the design of intervention programs. We do not consider

macroparasitic diseases in this book. Chapters 4 and 5 have more discussion of R_0.

1.4 Causal Inference and Vaccine Effects

In many parts of this book our approach draws on the potential outcomes approach to causal inference (Rubin 1980, Holland 1986, Robins 1986). Causal inference is a framework for carefully defining causal estimands, that is the quantities that one wants to estimate, and then articulating the conditions and assumptions under which they can be estimated from the observed data. A potential outcome is the outcome that a person would have if a person received a particular treatment. Receiving the treatment does not necessarily occur. Suppose that infection, yes or no, is the outcome of interest. One can imagine that a person would have one potential outcome (not infected) if vaccinated and a possibly, but not necessarily, different (infected) potential outcome if that person were not vaccinated. Generally, in this framework, the potential outcomes are assumed to be determined before a person receives either treatment. That is, the potential outcomes are assumed fixed before any assignment to either vaccine or control. One can define the causal effect at the individual level. The individual causal effect of treatment A compared to treatment B is defined as the difference (or ratio) in the potential outcome under treatment A and the potential outcome under treatment B.

The Fundamental Problem of Causal Inference (Holland 1986) is that generally only one of the potential outcomes of an individual can be observed. That is, generally, if we assign a person to receive either vaccine or control, then we will observe the outcome under that assignment, but not observe the outcome under the other assignment. So, to define an effect that we can observe, we use a population of individuals. The population average causal effect (ACE) is the difference of the expectation of the potential outcomes if everyone received treatment A and the expectation of the potential outcomes if everyone received treatment B. It is still not possible to observe this. However, under two assumptions, we can estimate the population average causal effect from the observed data.

What is an individual causal effect? The individual causal effect is defined as the difference in potential outcomes in individual i under one treatment compared to another treatment. Formally, for $i = 1, \ldots, n$,

$$Z_i = 0, 1 \quad \text{treatment assignment/exposure}$$

$$Y_i(z) \quad \text{outcome under assignment } z = 0, 1$$

$$Y_i(0) - Y_i(1) \quad \text{individual causal effect}$$

Generally in causal inference, the assumption is made that there is no interference between units (Cox 1958). That is, the potential outcomes in an individual are independent of the treatment assignment of others. This is also called the Stable Unit Treatment Value Assumption (Rubin 1980), or SUTVA, where the SUTVA assumption also includes that all treatments and their potential outcomes are represented in the model. In Chapter 13, we discuss how to define causal estimands when using potential outcomes when SUTVA is violated (interference between units) to define direct, indirect, total and overall effects. Here we make the assumption of no interference between units. Then, if there are only two treatments, say, vaccine and control, then the representation with just two potential outcomes is adequate.

The first assumption generally made is that the treatment assignment in one person does not affect the potential outcome in another person. This was called the assumption of no interference by Cox (1958). Rubin (1980) called it the Stable Unit Treatment Assumption (SUTVA). Technically, SUTVA includes as well the assumption that all treatments and their potential outcomes are represented in the model. In this book, we are only concerned with the assumption whether or not there is interference. Clearly, when considering Ross' terms of dependent and independent happenings, the assumption of no interference contradicts the situation in dependent happenings in infectious diseases (Halloran and Struchiner 1995). If the potential outcomes depend on the treatments that other people receive then people have more than just two potential outcomes (Rubin 1978). We return to this in Chapter 13.

The second assumption required is the specification of the mechanism of assignment of the treatments to the individuals. A very useful assignment mechanism is randomization. Under the assumption of no interference between the individuals in the study, and that treatments A and B were assigned randomly, and also perfect compliance with the assignment, then the observed difference in the average outcome in individuals assigned A and the individuals assigned B is equal to the population average causal effect.

To formalize the above ideas, we need at least three elements in the model, a population of units, at least two treatments (the causes), and the response variables, or potential outcomes of interest. Suppose we have a population of individual people, $i = 1, \ldots, n$. For simplicity, assume here just two levels of treatment Z, say, vaccine and control, denoted by $Z = 1$ for vaccine and $Z = 0$ for control. The two potential outcomes Y could be infected and not infected, represented by $Y = 1$ if infected and $Y = 0$ if not infected. Let $Y_i(Z = 1)$ and $Y_i(Z = 0)$ represent the potential outcomes for person i under vaccine and control. Then the *individual causal effect* in person i of vaccine compared with control is $Y_i(0) - Y_i(1)$. For example, if person i would be infected if he received control ($Y_i(0) = 1$) and he would not be infected if he received vaccine ($Y_i(1) = 0$), then the individual causal effect in person i is

$$Y_i(0) - Y_i(1) = 1 - 0 = 1. \tag{1.2}$$

Table 1.1. Four kinds of people and the individual causal effects based on potential outcomes

Stratum	$Y(Z=1)$	$Y(Z=0)$	Causal effect
immune	0	0	0
harmed	1	0	−1
protected	0	1	1
doomed	1	1	0

Since the individual causal effects are not observable, we proceed to the population average causal effect. Assume that we randomly assign $n_0 = n/2$ of the population to vaccine and to control. Under the assumptions of SUTVA and randomization (and compliance), the population average causal effect is

$$\begin{aligned} E\{Y(0) - Y(1)\} &= E\{Y(0)\} - E\{Y(1)\} \\ &= E\{Y(0)|Z=0\} - E\{Y(1)|Z=1\} \\ &= \frac{\sum_{i=0}^{n_0} Y_i(0)|Z=0}{n_0} - \frac{\sum_{i=0}^{n_0} Y_i(1)|Z=1}{n_0}, \end{aligned} \tag{1.3}$$

which is identifiable from the observed data.

Four types of individuals are possible in the population defined by their pairs of potential outcomes under vaccine and control (Table 1.1). First, they could be uninfected whether they receive vaccine or control. These people are called immune (even outside the vaccine literature). They could be infected if they receive vaccine, but remain uninfected if they receive control. These people are considered harmed by the vaccine. They could remain uninfected if they receive vaccine, but become infected if they receive control, called protected by the vaccine. They could become infected under both vaccine and control. These people are called doomed. In some infectious disease papers, the four types of people are sometimes called never infected, harmed, protected, and always infected. The causal inference framework based on potential outcomes induces an inherent heterogeneity in the population.

The latent groups cannot be identified without further assumptions. For example, if a vaccinated person becomes infected, that person could be either a person harmed by vaccination or a person doomed to become infected. If we make the assumption that the vaccine does not harm people, that is, there are no individuals in the harmed stratum, then we know that the infected vaccinated person must be in the doomed stratum. Also, under this assumption, we know that an unvaccinated person who does not get infected must be in the immune stratum. If a vaccinated person does not get infected, however, they could be in the immune or the protected stratum.

The assumption of randomization to specify estimators of the estimands of interest demonstrates how randomization can serve as the point of departure for estimating effects of interest. Observational studies in which the vaccine

assignment is not randomized are subject to biases, but can be viewed as departures from the randomized experiment. By making the assumptions about how an observational study departs from a randomized study explicit, we can understand how our estimates of the estimand of interest differ from what we might have observed in a randomized study.

The flavor of causal inference courses through various aspects of this book. Causal inference methods help in understanding vaccine effects on post-infection outcomes in Chapter 9. Causal inference underlies new approaches to evaluating immunological surrogates of protection in Chapter 15, In Chapter 13 we consider relaxing the assumption of no interference to evaluate indirect, total, and overall effects within the causal inference framework. The potential outcome approach to causal inference is not everyone's cup of tea. Our goal in this book is to present many ideas related to evaluating vaccines. The simple statement of comparing what the outcome would be with vaccine compared to control, the basis of most vaccine studies, has an implicit reference to the framework of causal inference.

Problems

1.1. Problems for Chapter 1 will be added here.

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