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Infectious Disease Modeling and the Dynamics of Transmission

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Abstract The dynamics of any infectious disease are heavily dependent on the rate of transmission from infectious to susceptible hosts. In many disease models, this rate is captured in a single compound parameter, the probability of transmission β. However, closer examination reveals how β can be further decomposed into a number of biologically relevant variables, including contact rates among individuals and the probability that contact events actually result in disease transmission. We start by introducing some of the basic concepts underlying the different approaches to modeling disease transmission and by laying out why a more detailed understanding of the variables involved is usually desirable. We then describe how parameter estimates of these variables can be derived from empirical data, drawing primarily from the existing literature on human diseases. Finally, we discuss how these concepts and approaches may be applied to the study of pathogen transmission in wildlife diseases. In particular, we highlight recent technical innovations that could help to overcome some the logistical challenges commonly associated with empirical disease research in wild populations.

1
Introduction

Many of the chapters in this volume have been explicitly concerned with the current increase in zoonotic disease emergence and have attempted various articulations of the causes and impediments to infectious disease transmission and spread into human populations from wildlife. An essential tool for establishing linkages between population processes of infectious disease and disease emergence is the development of mathematical models of disease processes where critical variables effecting disease dynamics can be identified and assessed. Mathematical models have a long history in infectious disease ecology starting with Bernoulli's modeling of smallpox (Bernoulli 1760) and including Ross's analysis of malaria (Ross 1911), but they have seen an expanded development over the last 25 years (Anderson et al. 1981; Anderson and May 1991). We now have models for many of the most important human emerging infectious diseases or diseases that threaten to emerge, e.g., HIV (Anderson and May 1988, 1991; Nowak and May 2000), malaria (Aron and May 1982; Macdonald 1957), SARS-coronavirus (Anderson et al. 2004; Lipsitch et al. 2003), rabies (Childs et al. 2000; Murray and Seward 1992; Murray et al. 1986; Russell et al. 2005; Smith et al. 2002), and influenza (Ferguson and Anderson 2002; Ferguson et al. 2003; Longini et al. 2005), to name a few. Mathematical models are also being used to explore wildlife disease dynamics (Grenfell and Dobson 1995; Hudson et al. 2002) and possible routes of zoonotic disease emergence. Understanding disease dynamics across hosts is an essential first step in understanding and articulating those conditions under which new diseases can emerge from wildlife reservoirs.

It is easy to recognize that the first obstacle to establishment of any infectious disease is the successful transmission from infected individuals into susceptible hosts. In the absence of sustained transmission, any infectious disease is doomed and will not spread. Most mathematical models coalesce transmission into a single phenomenological transmission rate (β) between infected and susceptible hosts, and this rate masks a great deal of information. In this chapter, we wish to examine how the transmission rate can be parameterized and decomposed into its underlying contributing variables, and how these measures can be applied to zoonotic disease dynamics.

There are three fundamental characteristics which will influence the likelihood of sustained transmission among susceptible and infected hosts: the infectiveness of the pathogen, the transmission probability, and the contact pattern and rate, which together affect the basic reproductive number (R_o) of the pathogen. In this chapter, we review some of these basic concepts with explicit

attention to how these fundamental characteristics can be assessed in specific host–pathogen systems. Throughout the chapter, we will be following formulations from Halloran (1998) who has an excellent introduction to these concepts in the context of human disease dynamics.

2 Basic Concepts

Partitioning and estimating the parameters that enter into a quantitative characterization of the transmission process requires distinctions between the time course of infectiousness (i.e., that time interval over which infected individuals are capable of transmitting the pathogen to new susceptible individuals) versus the time course of disease (the expression of symptoms associated with infection). Imagine a time line beginning with a susceptible host within the population (Fig. 1). At some time point (T) the susceptible individual becomes infected by a pathogen. For the time course of infectiousness, after initial infection, the host may undergo a latent period (τ) where the pathogen can be resident in the host but not be transmitted to other hosts. The latent period is followed by an infectious period (γ) where pathogen can be transmitted. At some final time, the infectious individual loses its infectiousness and moves into a non-infectious class either through recovery or death. The time course for disease differs from infectiousness in that upon the onset of infection (T) the host moves into an incubation period (δ) where disease symptoms are absent. When symptoms appear, the host moves into the symptomatic period (σ) that lasts until the symptoms disappear and the host recovers or dies. The initiation and duration of these periods may not correspond. For example, in some diseases the latent period can be shorter than the incubation period in which case hosts are infectious before symptoms appear, e.g., ungulates infected with rinderpest virus become infectious approximately 24–48 h before the onset of symptoms (Plowright 1968). In other diseases, the latent period can be longer than the incubation period. For example, *Plasmodium falciparum* malaria has an incubation period of approximately 14 days in humans. However, the infective stages of the parasite that are infective to mosquitoes only begin to appear approximately 10 days after the onset of symptoms (Halloran 1998).

The rate of conversion of susceptible hosts into infected hosts is governed by two factors: the number of susceptibles in the host population and what has been conventionally referred to as the force of infection (Anderson and May 1991; Begon et al. 2002). The force of infection is the product of (1) the rate of contact, c, between individuals in the host population, (2) the probability, m,

that an individual contact is between a susceptible individual and an infected individual that is also infectious, and (3) the transmission probability, ρ, that a contact between an infectious host and a susceptible host leads to a successful transmission event (Begon et al. 2002). Most often the infectiveness, *m*, is assumed to be proportional to the fraction of infectious individuals in the total population, i.e., the prevalence, *P*, of the disease.

3 Basic Reproductive Number

With the concepts introduced so far, it would seem that any effort to model disease transmission would require knowledge of many parameters. Often we cannot ascertain these component parts since they are exceedingly difficult to estimate. As a consequence, many disease ecologists have focused on a single index, the basic reproductive number (R_0), which captures many of the most important features of disease dynamics, especially where one is concerned with conditions leading to epidemic emergence.

R_0 is defined as the "average number of secondary infections produced when one infected individual is introduced into a host population in which every host is susceptible" (Anderson and May 1991). R_0 is defined by the following:

$$R_0 = \begin{bmatrix}\text{number of contacts}\\ \text{per unit time } (c)\end{bmatrix} \times \begin{bmatrix}\text{transmission}\\ \text{probability per contact } (\rho)\end{bmatrix} \times \begin{bmatrix}\text{duration of}\\ \text{infectiousness } (\gamma)\end{bmatrix},$$

i.e. $R_0 = c\rho\gamma$

However, there are also alternative means to estimate R_0 without knowing these components, which is certainly one reason for its popularity. For example, R_0 can be assessed phenomenologically (given its definition) as the average per capita rate of increase in infectious individuals when a pathogen emerges into a new previously unexposed population since all the individuals resident in this new population are presumed susceptible. This was the technique used by Lipsitch et al. (2003) to calculate R_0 for SARS coronavirus during its rapid emergence in 2003. Consequently, we can directly measure R_0 without necessarily knowing the details of the transmission process that generates that overall number of secondary infections in the population. The R_0 for a variety of wildlife diseases is given in Table 1. Anderson and May (1991) provide a comparable table for human infectious diseases and Dietz (1993) provides an overview of methods used to estimate R_0 from population data. Ferrari et al. (2005) have recently derived a maximum likelihood estimator

for R_0 using chain binomial models as a refinement to calculating R_0 using discrete time-series data.

The capability to directly quantify R_0 can be a useful first step in predicting disease emergence. For a disease to increase in the host population, an infectious individual must at least replace itself with more than one infectious secondary case, i.e., the disease will increase if $R_0 > 1$. If $R_0 < 1$, then the disease will fade from the host population and go extinct. If $R_0 = 1$, then every infectious individual replaces itself with one and only one new infectious individual and the disease prevalence in the population will be stable, i.e., the disease will be "endemic."

However, the basic reproductive number, R_0, does have some significant limitations with regard to predicting newly emerging pathogens. R_0 is *not* a fixed property of a pathogen. Rather (as is apparent from its definition) it is only defined within a certain population of hosts governed by a specific contact pattern, duration of infectiousness, and transmission probability. One could have very different underlying biological transmission processes that generate identical basic reproductive numbers. For example, the R_0 for measles is approximately 9, which also happens to be the R_0 for HIV among intravenous drug users (Halloran 1998). However, measles has a high transmission and short duration of infection, while HIV has a low transmission and long duration of infection. This feature can make comparisons of R_0 across diseases very difficult since R_0 is a compound expression of three variables. What R_0 captures is the capacity to generate an epidemic given some (unfortunately often unknown or not assessed) transmission process. Both measles and HIV have a high capacity to generate an epidemic assuming a given transmission process, but at very different time scales and governed by very different underlying transmission components.

Ideally, for the purposes of predicting disease emergence, we would like to know the values of the underlying components of transmission that produce the overall pattern of R_0 and, ideally, how these components might change under alterations in environmental condition effecting the likelihood of disease emergence. For example, habitat fragmentation without loss of local habitat quality may generate new contact rates, c, while deterioration of habitat without changing patterns of connectivity may affect the transmission probability, ρ. Both changes might generate the same overall alteration in R_0. Yet the biological measures needed to respond to these different changes might be quite different since the pattern of emergence is driven by entirely different changes in transmission mechanism. Consequently, we should be attending to the development of methods for the direct assessment of the components of R_0 as a goal toward increasing our capacity to predict disease emergence.

4
Estimating the Transmission Probability

There are two common techniques used to estimate the likelihood that an encounter between an infected individual host and a susceptible individual will result in successful transmission of the pathogen leading to new infections. The first method, the secondary attack rate (SAR), focuses on the fate of a single infected index case (host) that comes into contact with many susceptible host individuals in the population. The second method, the binomial model of transmission probability, tracks one uninfected but susceptible host as it comes into contact with many infectious hosts. Both methods have been commonly used in human disease epidemiology but have not been used in assessing wildlife disease dynamics. Consequently, our examples will be draw from the human disease literature, but the methods should be extendable to wildlife disease dynamics.

The secondary attack rate is simply defined as the ratio of the number of hosts exposed that develop disease relative to the total number of susceptible exposed hosts, i.e.,

$$SAR = \frac{\text{total secondary cases}}{\text{total susceptible exposed}}$$

Before we can use this method, however, we must understand how one defines an exposed host and a secondary infected host. Let us observe one susceptible individual in the population. This individual host becomes infected at time T and will be designated the primary infected host. Primary hosts can, in general, be characterized as having (1) a maximum infectious period (I), i.e., the maximum time that individuals within the host population remain infectious, (2) a minimum incubation period (E1), i.e., the minimum time required before symptoms appear, and (3) a maximum incubation period (E2), i.e., the maximum time period before which symptoms will appear. We can arrange these time intervals along a time axis (Fig. 2) that can then be used to define secondary infections. Imagine four hosts that become symptomatic after contact with the primary infected host at time intervals specified in Fig. 2, line B. Which of these are likely to be the consequence of transmission from the primary infected host? Alternatively, which of these cases are clearly not the consequences of transmission from the primary?

Host 2 becomes symptomatic within the minimum incubation period (E1) so it could not have received its infection from the primary host. Similarly, host 5 becomes symptomatic after contact at a time greater than the sum of the maximum infectious period (I) and the maximum incubation period (E2). Consequently, it could not have been the recipient of pathogen from the

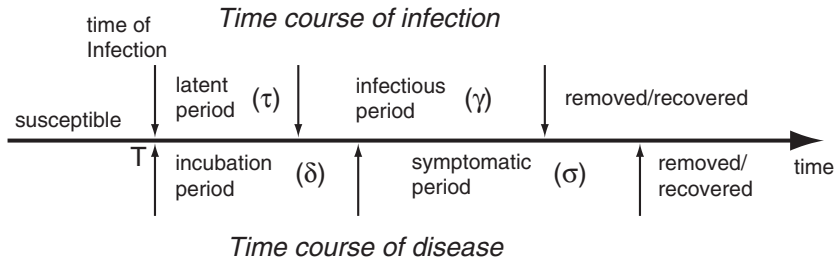

Fig. 1 Representative time intervals for the course of infection and disease used in the calculation of transmission rate

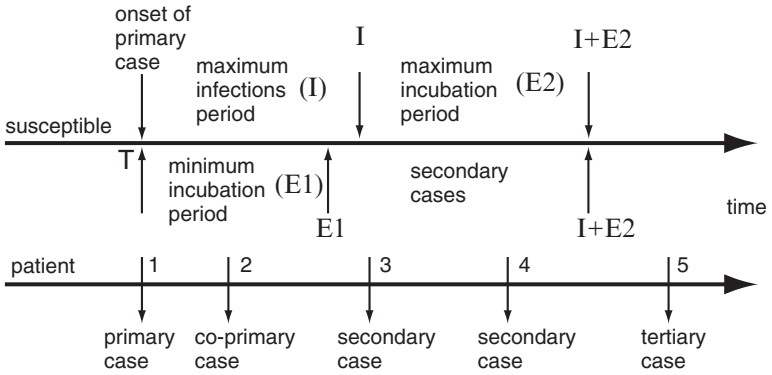

Fig. 2 Representative time intervals used for the determination of secondary cases and the calculation of the secondary attack rate

primary. The only individuals that could have become infected from the primary are those that fall within the time interval defined by E1 as the lower bound and I+E2 as the upper bound. Any individuals appearing symptomatic within this time interval after contact with the primary are considered secondary cases from the primary. Host 3 and host 4 would then be the only secondary cases from the primary.

Kendrick and Eldering (1939) used this method to calculate the SAR for pertussis. Infected individuals show positive throat cultures for 21 days after the onset of symptoms, thus I = 21 days. They ascertained through observation that the minimum incubation period was approximately 10 days and the maximum incubation period was approximately 30 days. Thus, all secondary cases were those cases of exposed individuals to the primary case who developed symptoms during the time interval 10–51 days. Then SAR equals the total

Table 1 Examples for estimation of the basic reproductive rate (R_0) for various pathogens in wildlife species

Pathogen	Host species	Scientific name	R_0	Reference
Rabies virus	Spotted hyena	*Crocuta crocuta*	1.9	East et al. 2001
Phocine distemper virus	Harbor seal	*Phoca vitula*	2.8	Swinton et al. 1998
Mycobacterium bovis	Ferret (feral)	*Mustela furo*	0.18–1.20	Caley and Hone 2005
Mycobacterium bovis	Eurasian badger	*Meles meles*	1.2	Anderson and Trewhella 1985
Classical swine fever virus	Wild boar	*Sus scrofa*	1.1–2.1	Hone et al. 1992
Heterakis gallinarum	Ring-necked pheasant	*Phasianus colchicus*	1.2	Tompkins et al. 2000

number of secondary cases across all households in the population relative to the total number of exposed susceptibles in all households. For the purposes of their study, they defined an exposure as any contact with the primary case for at least 30 min during the infectious period I. For individuals that had not received a test vaccine, the secondary attack rate was substantial, SAR = 0.685. Among individuals that had received the vaccine the secondary attack rate dropped, SAR = 0.128. The vaccine under use at the time appears to have reduced the transmission rate by approximately 82%. Calculations of secondary attack rates with and without vaccination have been traditional methods used to assess the efficacy of a particular vaccination strategy.

Similar techniques have been applied to assess the transmission probability of a variety of human infectious diseases (Table 1). For example, the Centers for Disease Control and Prevention undertook a household case study to calculate the secondary attack rate for SARS-coronavirus during the 2003 outbreak in Singapore (Goh et al. 2004). Examination of households suggests that SARS is not highly contagious among family members (secondary attack rate = 0.062), while the rate of transmission among hospital workers is strikingly higher (secondary attack rate >0.50).

For sexually transmitted disease, the transmission probability is often assessed using the binomial distribution (or its extension the chain binomial) for the following reasons. Assume that the probability of disease transmission during a single contact with an infected host is p. Then the probability of escaping infection following a contact with an infected host is $q = (1 - p)$. Suppose that a susceptible host makes n contacts with an infected host or

with different infected hosts. Then the probability of escaping infection after n contacts is:

$$q^n = (1-p)^n$$

Then the probability of becoming infected after n contacts is:

$$1-q^n = 1-(1-p)^n$$

which is the description for the binomial distribution. The maximum likelihood estimate for p is given by

$$\hat{p} = \frac{\text{number of individuals who become infected}}{\text{total number of contacts with infectives}}$$

The difference between the secondary attack rate (SAR) and $\hat{p}$ is in the denominator. SAR weighs transmission relative to contacts with susceptibles while the binomial distribution weighs transmission relative to contacts with infectious hosts. The two measures are identical, i.e. SAR = $\hat{p}$, when every susceptible has contact with one and only one infectious host.

The binomial distribution method has been used quite commonly to estimate the transmission probability for HIV given the current concern over this ongoing worldwide epidemic. What is the likelihood of transmission given a sexual encounter? Halloran (1998) presents results of a transmission study in a population of 100 steady sexual couples where one partner was HIV-positive while the other partner was HIV-negative. Over the course of the study period, 25 of the 100 susceptibles became infected. The total number of sexual encounters during the study period was 1,500. From the maximum likelihood estimator then:

$$\hat{p} = {}^{25}\!/_{1500} = 0.017$$

That is, an uninfected person has a little less than a 1:50 chance of contracting HIV following a sexual encounter. The probability of infection after two encounters would be

$$1-\left(1-\hat{p}\right)^2 = 0.034$$

Table 2 provides an overview of the transmission probabilities for a variety of human diseases derived using either SAR or the binomial distribution.

Table 2 Estimates of the transmission probability (ρ) for various human pathogens

Disease	Pathogen	ρ	Method of estimation	Reference
Meningococcal disease	*Neisseria meningitidis*	0.0069	Secondary attack rate	De Wals et al. 1981
Ebola fever	Ebola virus—Sudan	Hospitals = 0.81 Community = 0.12	Secondary attack rate	Francis et al. 1978
Food poisoning	Norwalk-like virus	0.17	Secondary attack rate	Gotz et al. 2001
Cryptosporidiosis	*Cryptosporidium pavum*	0.15	Secondary attack rate	Guerrant 1997
Lower respiratory tract infection	Adenovirus	0.55	Secondary attack rate	Palomino et al. 2000
Whooping cough	*Bordetella pertussis*	Vaccinated = 0.128 Unvaccinated = 0.685	Secondary attack rate	Kendrick and Eldering 1939
AIDS	Human immunodeficiency virus	0.017	Binomial distribution	Halloran 1998
Monkeypox	Monkeypox virus	0.93	Secondary attack rate	Hutin et al. 2001

5
Estimating Transmission in Wildlife and Zoonotic Disease

As outlined above, three factors determine the rate at which new infections occur: (1) the rate of contact (c) between individuals, (2) the probability (m) that any contact is between an infectious and a susceptible individual, and (3) the probability (ρ) that such a contact actually results in a new infection. Despite their indisputable significance for disease dynamics, the estimation of these three parameters is rarely attempted for natural populations. Usually, the necessary temporal and spatial resolution at which epidemiological data have to be collected is simply not obtainable for species in the wild. However, we would argue that this may not always be true and that, especially given recent technological advancements, empirical data for the different components of transmission could be gathered in certain cases. In the following, we will therefore discuss what we feel are promising avenues of current and potential future research in this regard.

Social species probably offer the best opportunities to quantify contact rates, especially if these species are diurnal and can be observed without interfering with natural behavioral patterns. Observational studies have been used very effectively, for example, to obtain detailed information on social interactions in certain primates and ungulates (Berger 1986; Goodall 1986; Mloszewski 1983). In fact, data already collected for these species could conceivably be used to measure rates of contact between individuals. What constitutes a contact event will obviously depend on the specific infectious agent in question and its mode of transmission. Compared to within-group dynamics, determining rates of contact between social groups will usually be more difficult because such events will occur much more rarely and may require monitoring more than one group. For long-term studies, however, data on immigration of new individuals and frequency of encountering other groups may also be available. It is important to keep in mind that in many cases, such as epidemics sweeping through a population, rates of transmission between groups will be of much greater interest. This is simply because rate and course of transmission within a group is unlikely to have much effect on overall disease dynamics compared to the rate at which the disease is introduced to new groups. This is especially true for acute infections, because it is the level of host group contact relative to the length of the infectious period that will ultimately determine the rate of disease spread (Cross et al. 2005).

Contacts are less frequent and thus harder to determine for solitary species, unless opportunity for pathogen transmission is restricted to certain habitat

features that can be monitored closely (e.g., water holes, bird feeders). Where use of such features cannot be determined from direct observation, it may be possible to fit animals with transmitters to record and correlate the time they spend at a common location. For example, Sutherland et al. (2005) used passive integrated transponder (PIT) tags in mice to measure their use of borrows. A hidden antenna connected to a data logger would register each time a marked individual passed the burrow entrance. Use of the same burrow by two individuals within a few minutes of each other was thereby considered an interaction. Although this study did not consider disease transmission, a similar approach could certainly be used to study contact patterns in such a context. Calisher et al. (2000) examined pairs of deer mice captured simultaneously in single-capture traps for antibody to Sin Nombre virus to infer patterns of hantaviral transmission among different demographic classes of mice (see the chapter by Klein and Calisher, this volume).

Radiotelemetry can also be used to look at simultaneous space use of individuals (see the chapter by Stallknecht, this volume), but the temporal resolution of these data is usually insufficient to infer actual encounters. This can be potentially overcome by the use of radio transmitters that note and record the nearby presence of another transmitter, a technique employed in a current study of rabies virus transmission among raccoons (L. Hungerford, personal communication). A potential problem with all approaches involving electronic tags is that they will underestimate the number of encounters unless all individuals in a population are fitted with a tag. As long as it is known what proportion of the population is tagged though, it may be possible to correct for this bias.

Assuming that contact rates can be determined with sufficient accuracy and precision, we have yet to determine whether a particular contact event involved an infectious individual and whether contact resulted in a new infection. This of course requires detailed knowledge on disease status of all individuals in a population through time. In specific cases, disease status may be inferred retrospectively. For example, mortality following rabies infection in carnivores is close to 100%, and with the help of radio transmitters, carcasses can usually be recovered quickly enough to confirm rabies as the cause of mortality, as has been demonstrated with striped skunks (Greenwood et al. 1997). Furthermore, it is known from experimental studies that animals are only infectious for a few days prior to death. With the previously mentioned technology of cross-talking radio transmitters, the number of other marked raccoons encountered during this time period can be determined along with the proportion of these individuals that subsequently develop disease.

Rabies is somewhat unusual because every infection can be considered to result in disease and ultimately death. For most pathogens, infection status

and periods of infectiousness have to be established based on regular screening. Capturing and sampling individuals on a regular basis may accomplish this. The appropriate length of the interval between samples would thereby depend on the biology and epidemiology of the infectious agent. Because the humoral immune response takes several weeks to develop, individuals may be infectious even if no antibodies can be detected. Thus, screening would ideally involve serological tests as well as efforts to directly detect the infectious pathogen. Problems again arise if not all individuals can be resampled regularly, as will often be the case in wildlife populations. Furthermore, capturing and collecting blood samples may be considered too traumatic to be carried out frequently. Fortunately, considerable progress has been made in recent years regarding the use of noninvasive sampling of wildlife species, including techniques for disease screening. For example, Santiago et al. (2003a, 2003b) were able to determine infection with simian immunodeficiency virus (SIV) in wild chimpanzees using fresh fecal and urine samples that yielded both antibodies and virus RNA. Similarly successful results were obtained for simian foamy virus (SFV; B. Hahn, personal communication), suggesting that these techniques are more widely applicable. A very promising research study would therefore be to combine behavioral data on contact rates within a group with the collection of fecal samples to monitor the infection status of individuals.

The use of modern molecular techniques may even allow us to go one step further and not only determine infection status of an individual but to document the source of that infection. In rapidly evolving RNA viruses, for example, spatial spread among different host populations or geographic areas can frequently be discerned from genetic sequence data (Real et al. 2005; Walsh et al. 2005). By extension, similar methods could be used to identify the most probable donor individual for a new infection using genetic evidence. Probably the most famous application of forensic phylogenetics to date has been that of a doctor who allegedly had used blood from an HIV-infected patient to infect his ex-girlfriend. Phylogenetic analysis showed that the victim's virus sequences were nested within those of the suspected donor but were clearly distinct from other viruses circulating in the larger geographic area. This result was consistent with the proposed direction of transmission from the donor patient to the victim and held up as evidence in court (Metzker et al. 2002). Especially in situations where all possible donors are known (such as in animal social groups) and for pathogens with high standing genetic diversity (increasing the chances of pathogens in different individuals being distinct), molecular epidemiology could become a powerful tool for elucidating actual transmission histories in wildlife populations.

6
Conclusions

In this chapter, we have been concerned with the models and parameters used to describe the process of pathogen transmission. Although most of our case studies came from human diseases, the day when similar studies are being conducted in wild animal species may not be too far off. New and more sophisticated methods for tracing contact patterns and pathogen surveillance are constantly being developed, and we would expect that many of these methods will eventually also find use in the study of wildlife diseases. Better empirical data at hand will undoubtedly facilitate the development of more powerful models, improving our ability to predict, prevent, and control the future emergence and spread of zoonotic diseases.

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