The probability of severe disease in zoonotic and commensal infections

Steven A. Frank^{1*} and Joan S. Jeffrey²

¹Department of Ecology and Evolutionary Biology, University of California, Irvine, CA 92697-2525, USA

²Veterinary Medicine Teaching and Research Center, School of Veterinary Medicine, University of California at Davis, Tulare, CA 93274, USA

Cross-species transfers of pathogens (zoonoses) cause some of the most virulent diseases, including anthrax, hantavirus and Q fever. Zoonotic infections occur when a pathogen moves from its reservoir host species into a secondary host species. Similarly, commensal infections often have a primary reservoir location within their hosts' bodies from which they rarely cause disease symptoms, but commensals such as *Neisseria meningitidis* cause severe disease when they cross into a different body compartment from their normal location. Both zoonotic and commensal infections cause either mild symptoms or severe disease, but rarely intermediate symptoms. We develop a mathematical model for studying three factors that affect the probability of severe disease: the size of the inoculum, the route of inoculation and the frequency of naturally occurring infections that do not cause symptoms but do induce protective immunity (vaccinating inoculations). With a single route of infection, increasing pathogen density causes inoculations to develop more often into disease rather than asymptomatic vaccinations that provide protective immunity. With two routes of infection, it may happen that a lower density of a pathogen or of a particular antigenic variant leads to a relatively higher frequency of disease-inducing versus vaccinating inoculations. This reversal occurs when one route of infection tends to vaccinate against relatively common pathogens but less often vaccinates against relatively rare pathogens, whereas the other route of infection is susceptible to disease-inducing inoculation even at relatively low pathogen density.

Keywords: antigenic variation; dosage; epidemiology; mathematical model; vaccination

1. INTRODUCTION

Pathogens occasionally infect species that differ from their normal host. Such cross-species transfers, called zoonoses, cause some of the most virulent human diseases (Palmer *et al.* 1998). For example, anthrax infections typically arise from carcasses of diseased mammals, and hantavirus infections come from aerosols of rodent excreta.

Transmission of zoonotic infections flows from reservoir populations into the secondary host. In this regard, zoonoses are similar to commensal infections. A commensal microbe lives in its host, rarely causing noticeable symptoms. But some commensals cause a low frequency of disease when they cross into a different body compartment from their normal location. For example, *Neisseria meningitidis* is a widespread bacterial commensal of humans that typically colonizes the nasopharynx. Nearly all infections cause no symptoms. On rare occasions, the bacteria enter the bloodstream and cross the blood–brain barrier, causing meningitis (Mims *et al.* 1993).

In both zoonotic and commensal pathogens, disease-causing infections form terminal stages that rarely contribute back to the reservoir population. These infection dynamics free the pathogens from the normal balance between transmission and virulence (Anderson & May 1982; Ewald 1983) allowing the pathogens to maintain highly virulent characters in the secondary host or

atypical body compartment (Levin & Bull 1994; Frank 1996; Holt 1996).

Many zoonotic and commensal pathogens cause either mild infections or severe disease, but rarely intermediate symptoms (Palmer *et al.* 1998). We analyse three factors that determine the incidence of severe disease from what are normally very mild infections. First, the frequency of mild infections influences the proportion of hosts that gain immunity against subsequent, more severe inoculations. Second, the size of the inoculum affects the probability that the infection develops into disease or protective immunity without overt symptoms. Third, the route of inoculation also affects the probability that an infection develops into severe disease or asymptomatic, protective immunity—for example, airborne, cutaneous and intestinal inoculations may have different dose–response curves.

We use mathematical models to show that these three attributes have important consequences for the dynamics of zoonotic and commensal infections. With a single route of infection, increasing pathogen density causes inoculations to develop more often into disease rather than asymptomatic infections that provide protective immunity (natural vaccinations). With two routes of infection, it may happen that a lower density of a pathogen or of a particular antigenic variant leads to a relatively higher frequency of disease-inducing versus vaccinating inoculations. This reversal occurs when one route of infection tends to vaccinate against relatively common pathogens but less often vaccinates against relatively rare pathogens, whereas the other route of infection is susceptible to

*Author for correspondence (safrank@uci.edu).

disease-inducing inoculation even at relatively low pathogen density.

2. BACKGROUND

(a) Definitions

Here we define some of the terms that recur throughout the paper. Disease-inducing inoculations lead to symptomatic infections. Vaccinating inoculations lead to asymptomatic infections and protective immunity. In our analysis, vaccinating inoculations are simply small, naturally occurring inoculations that lead to subclinical infection and induce immune memory. Seroprevalence is the frequency of hosts that have antibodies and protective immunity against a particular pathogen strain. Dosage is another term for inoculum size.

(b) Zoonotic diseases

Our model depends on three attributes: seroprevalence, dosage and route of inoculation. For each attribute, we list a few examples from zoonotic diseases to illustrate the assumptions of our model. All of our examples come from Palmer *et al.*'s (1998) collection of articles on zoonoses.

(i) Seroprevalence

Many zoonotic inoculations cause subclinical infections. These non-symptomatic cases can be inferred by study of host antibody titre against the zoonotic parasite's antigens. Infection rates are of course much higher in particular human populations or worker groups that live in close association with the reservoir population.

Relatively high seroprevalence and low rates of clinical disease have been reported for the following pathogens in particular subpopulations: *Chlamydia psittaci* (Caul & Sillis 1998), *Burkholderia pseudomallei* (Blue *et al.* 1998), *Leptospira* (Ellis 1998), Lassa virus (Howard 1998), vesicular stomatitis virus (Morgan-Capner & Bryden 1998), hantavirus (Clement *et al.* 1998), Rift Valley fever virus (Swanepoel 1998), yellow fever virus (Monath 1998), *Trypanosoma cruzi* (Marsden 1998), *Leishmania* (Ashford 1998), *Cryptosporidium parvum* (Coop *et al.* 1998) and *Toxoplasma gondii* (Dubey 1998).

(ii) Dosage

It is well known that increasing numbers of pathogens in an inoculation often cause increasingly severe disease symptoms. For potentially lethal diseases, studies usually provide the number of pathogens required to induce death in 50% of hosts (LD_{50}). Palmer *et al.*'s (1998) compilation reports many LD_{50} -values for different diseases. Those values vary widely among pathogens and sometimes among different strains of the same pathogen.

There is less information about the dosage needed to produce asymptomatic infection with subsequent protective immunity. Sjögren & Sutherland (1975) showed that milk from infected cattle provided a low dose of *Mycobacterium tuberculosis* sufficient to induce protective immunity but not disease in most human hosts.

Traditional prevention of *Leishmania* symptoms in West Asia was by intentional inoculation of virulent organisms into a small cut (Ashford 1998). This natural vaccination prevents disease symptoms in subsequent infections.

Experimental inoculations of *Leishmania major* into mice showed dose dependency: low dosage resolved without symptoms and provided future protection, whereas high dosage caused disease (Menon & Bretscher 1998).

Our models assume these sorts of dual thresholds, in which low doses provide asymptomatic infection with subsequent protective immunity and high doses lead to disease symptoms. Such dual thresholds for disease are probably widespread, although not universal.

(iii) Route of inoculation

Many zoonoses cause different symptoms or have different dose-response patterns depending on route of inoculation. For example, anthrax produces different symptoms for cutaneous, pulmonary and intestinal inoculation and different LD_{50} -values have been reported for cutaneous and pulmonary inoculations (Turnbull 1998). Repeat symptomatic infections in the same individual are rare, suggesting that recovery can provide protective immunity.

Pasteurella is a widespread commensal of animals, frequently an asymptomatic component of the oral and pharyngeal flora. Disease apparently occurs most often by invasion of a wound or following infection by another pathogen (Barrett 1998).

Coxiella burnetii causes Q fever. Aerosol and cutaneous inoculation frequently leads to disease. Ingestion of contaminated milk does not cause disease and sometimes causes seroconversion (Marrie 1998).

(c) Commensal infections: poultry cellulitis

In poultry cellulitis (Messier *et al.* 1993; Barnes & Gross 1997) relatively rare pathogen strains apparently cause most of the disease. Singer *et al.* (2000) performed the following experiment. Forty two-week-old chickens were put onto a rice hull litter. The litter was inoculated with four strains of *Escherichia coli* isolated from cellulitis lesions. The birds also inoculated the litter with *E. coli* in their faeces. The distribution of *E. coli* strains in the litter was measured by DNA fingerprinting of 96 litter isolates over the following four weeks. The birds were artificially scratched in week 4 and the scratches were inoculated with swabs that had been dragged through the litter. The *E. coli* in the 21 cellulitis lesions that developed were cultured in week 5 and the strain distribution measured.

Rare *E. coli* strains in the litter caused the majority of the cellulitis lesions. Given the limited data available, there are many possible explanations. For example, the rare strains in the litter may have virulence factors that enhance success in skin lesions. Alternatively, the dynamics of immunity may favour rare strains in large, disease-producing scratches.

Artificial vaccination provides strain-specific protective immunity (Panigrahy *et al.* 1984; Gyimah & Panigrahy 1985; Sandhu & Layton 1985). Thus, the birds may have developed protective immunity against the common strains by inoculations through small skin pricks or scratches, but were less likely to acquire naturally vaccinating inoculations against relatively rare strains. Our model provides a quantitative framework to develop this hypothesis for cellulitis and other commensal infections.

Table 1. *Parameters of the model*

parameter	description
A	age of host
τ	delay between disease-inducing inoculation and appearance of disease symptoms
s	delay between vaccinating inoculation and appearance of protective immunity
ν	rate of vaccinating inoculations; see equation (10)
δ	rate of disease-inducing inoculations; see equation (9)
R_L	rate of inoculation by the typically disease- or lesion-inducing pathway L
R_V	rate of inoculation by the typically vaccinating pathway V
D_L	threshold inoculum size to produce disease by the L pathway
D_V	threshold inoculum size to produce disease by the V pathway
P_L	threshold inoculum size for protective immunity (vaccination) by the L pathway
P_V	threshold inoculum size for protective immunity (vaccination) by the V pathway
q	controls variation in mean inoculation size or in the frequency of antigenic variants

3. THE MODEL

(a) *Disease-inducing versus vaccinating infections*

The goal is to calculate the probability that, in an individual, a disease-producing inoculation occurs before protective immunity develops and disease symptoms appear before age A . Two parameters and two random variables aid in expressing this probability. Let the parameter τ be the time required for disease symptoms to appear after a disease-producing inoculation and the parameter s be the time required for protective immunity to develop after an inoculation that leads to asymptomatic infection. Let the random variable X be the waiting time until the first inoculation that can lead to asymptomatic infection and protective immunity and let the random variable Y be the waiting time until the first inoculation capable of causing disease. Table 1 gives brief definitions for the main parameters of the model.

If the times and sizes of inoculations occur independently, then exponential distributions provide reasonable models for the waiting time distributions for X and Y . In particular, let ν be the rate of vaccinating inoculations and δ be the rate of disease-producing inoculations. The per-capita rate of inoculation above a threshold inoculum size is often referred to as ‘the force of infection’ (Anderson & May 1991). Thus, ν is the vaccinating force of infection and δ is the disease-producing force of infection.

The vaccinating force of infection ν corresponds to the probability density of an inoculation being of sufficient size to cause the first vaccinating infection in an individual at a particular point in time x according to the standard exponential density function

$$f(x) = \nu e^{-\nu x}, \quad (1)$$

as shown, for example, in Anderson & May (1991). Similarly, the disease-producing force of infection δ

corresponds to the probability density of an inoculation being of sufficient size to cause the first disease-producing infection in an individual at a particular point in time y according to the standard exponential density function

$$g(y) = \delta e^{-\delta y}. \quad (2)$$

The standard forms for the cumulative density functions are

$$\Pr(X < x) = F(x) = 1 - e^{-\nu x}, \quad (3)$$

$$\Pr(Y < y) = G(y) = 1 - e^{-\delta y}. \quad (4)$$

The key probability is that a disease-producing inoculation occurs before protective immunity develops and that disease symptoms appear before age A . This probability can be expressed in symbols as

$$\Phi = \Pr(Y < s + X \text{ and } Y < A - \tau). \quad (5)$$

If $A - \tau < s$, there is no time for protective immunity to develop. Thus, the probability of observing disease symptoms before age A is simply that a disease-producing inoculation occurs before $A - \tau$, allowing τ time-units for the symptoms to emerge after inoculation. This probability is $G(A - \tau) = 1 - e^{-\delta(A - \tau)}$.

If $A - \tau > s$, the probability in equation (5) is

$$\Phi = G(A - \tau)[1 - F(A - \tau - s)] + \int_0^{A - \tau - s} G(s + x)f(x)dx. \quad (6)$$

On the right-hand side, the first part of the sum is the probability that inoculation leading to symptomatic infection occurs in time to lead to observed disease, that is $\Pr(Y < A - \tau) = G(A - \tau)$ and the first inoculation that would lead to asymptomatic infection and protective immunity occurs too late to prevent a symptomatic infection, that is $\Pr(X > A - \tau - s) = 1 - F(A - \tau - s)$. The second part of the sum on the right-hand side is the probability that, over the time-interval $(0, A - \tau - s)$, an inoculation that could lead to protective immunity occurs, but an inoculation that leads to symptomatic infection occurs before protective immunity can develop.

Standard calculations yield the total probability of interest as

$$\Phi = 1 - \frac{e^{-\delta s}(\nu + \delta e^{-(\nu + \delta)(A - \tau - s)})}{\nu + \delta}. \quad (7)$$

Throughout the derivation, the parameter for age (A) and the parameter for time to develop disease symptoms after a disease-producing inoculation (τ) always occur in combination as $A - \tau$. Thus, without loss of generality, we can drop the parameter τ and interpret A as current age minus time to develop disease symptoms.

An increase in the parameter s , the time to develop protective immunity after a vaccinating inoculation, causes an increase in Φ , the probability of developing symptomatic disease. In this article we emphasize the qualitative effects of various processes on Φ . Because s has only a quantitative effect, we will set $s = 0$ to simplify the following analysis. The simplified form of Φ from equation (7) with $\tau = s = 0$ can be written as

$$\Phi = (1 - e^{-(\nu+\delta)A}) \frac{\delta}{\nu + \delta}, \quad (8)$$

where $1 - e^{-(\nu+\delta)A}$ is the probability that any inoculation occurs before age A and $\delta/(\nu + \delta)$ is the probability that a disease-inducing inoculation occurs before a vaccinating inoculation. For large values of A , the probability Φ approaches $\delta/(\nu + \delta)$.

(b) Rates of inoculation

In this model, pathogens can enter hosts by two different routes. The first pathway often leads to disease, but a low infecting dose causes asymptomatic infection that provides immune protection against later inoculations. The second route of inoculation typically develops into an asymptomatic infection and subsequent immune protection, but a high infecting dose causes disease. We use the subscript L for the pathway of inoculation that typically produces a lesion or disease, and the subscript V for the pathway of inoculation that typically vaccinates or is asymptomatic.

We assume that the number of pathogens (dosage) in each inoculation follows an exponential distribution. If the mean number of pathogens entering the host for a particular pathway of inoculation is $q\mu$, then the probability that the number of pathogens is greater than a threshold k is $e^{-k/q\mu}$. We have split the mean into two parts: μ is the base-level mean and $0 < q \leq 1$ is a parameter that controls inoculation density. The parameter q can represent either variation in total inoculation density or the frequency of different antigenic variants. Note that the exponential distribution allows one to express the probability of being above a threshold in a scale-free way with respect to the mean, that is k/μ is the value of the threshold relative to the maximum value of the mean.

The course of an individual's lifetime with regard to asymptomatic or disease-causing inoculations depends on the rates at which such inoculations occur. For a given inoculation in the typically disease- or lesion-producing pathway (L) the threshold number of pathogens required to cause disease is β_L and the expected (mean) number of pathogens per inoculation is E_L . For this pathway of inoculation, we can express the threshold for disease relative to the mean as $D_L = \beta_L/E_L$. Likewise, for the L pathway the threshold number of pathogens required to cause asymptomatic infection and subsequent immune protection is α_L and the expected (mean) number of pathogens per inoculation is E_L . Thus, the threshold for immune protection relative to the mean is $P_L = \alpha_L/E_L$. (See table 1 for brief definitions of the key threshold parameters.)

The typically vaccinating route of infection (V) has analogous thresholds for disease-causing inoculations or protective inoculations. The expected number of pathogens entering by this route is E_V . The disease threshold relative to the mean is $D_V = \beta_V/E_V$, where β_V is the threshold number of pathogens for causing disease by the typically vaccinating route. The protective threshold relative to the mean is $P_V = \alpha_V/E_V$, where α_V is the threshold number of pathogens for causing asymptomatic infection and subsequent protection by the typically vaccinating route. For both pathways $\alpha < \beta$ and inoculations less than α do not cause disease or protective immunity.

These definitions lead to four important probabilities: $e^{-D_L/q}$, the probability of being above the disease

threshold in the L pathway; $e^{-P_L/q}$, the probability of being above the threshold for asymptomatic infection and immune protection for the L pathway; $e^{-D_V/q}$, the probability of being above the disease threshold in the V pathway; and $e^{-P_V/q}$, the probability of being above the threshold for asymptomatic infection and immune protection for the V pathway. The parameter q controls the total pathogen density or the relative density of a particular antigenic variant.

The rates of inoculation by the L and V pathways are R_L and R_V . Thus, the total rate of disease-inducing inoculations by both pathways is

$$\delta = R_L e^{-D_L/q} + R_V e^{-D_V/q}. \quad (9)$$

The total rate of effectively vaccinating inoculations that lead to asymptomatic infection and subsequent immune protection is

$$\nu = R_L (e^{-P_L/q} - e^{-D_L/q}) + R_V (e^{-P_V/q} - e^{-D_V/q}), \quad (10)$$

where the subtracted probabilities remove cases in which inoculations are above the disease-inducing thresholds.

The rates δ and ν can be used in equations (7) and (8) in order to calculate the probability that an individual receives a disease-inducing or vaccinating inoculation by a particular age A . Table 1 lists the parameters of the model.

4. DOSAGE AND A SINGLE ROUTE OF INFECTION

When there is only a single route of infection, increasing the average dosage increases the probability of developing symptomatic infection. We show this by reducing the result in equation (7) for two routes of infection to a special case in which there is only one route. To accomplish this reduction, we set the rates and thresholds for each pathway to be the same. This makes the pathways equivalent, in effect producing a total infection process with a twofold increase in rate relative to infection by each pathway.

The processes for the two pathways L and V can be made equivalent by setting $R_L = R_V = R$, $D_L = D_V = D$ and $P_L = P_V = P$. With these assumptions $\delta = 2Re^{-D/q}$ and $\nu + \delta = 2Re^{-P/q}$, where variations in q control the average dosage per inoculation. Substituting into equation (8) shows that the probability of symptomatic disease Φ increases with average dosage per inoculation q . As age A increases to large values, Φ approaches $\delta/(\nu + \delta) = e^{-(D-P)/q}$.

5. INTERACTION OF DOSAGE AND ROUTE OF INFECTION

Different routes of infection can reverse the typically increasing relationship between pathogen density and disease. With two routes of infection, it may happen that a lower density of a pathogen or of a particular antigenic variant leads to a relatively higher frequency of disease-inducing versus vaccinating inoculations. This reversal occurs when one route of infection tends to vaccinate against relatively common pathogens but less often vaccinates against relatively rare pathogens, whereas the other route of infection is susceptible to disease-inducing inoculation even at relatively low pathogen density.

Figure 1. Rates of vaccinating and disease-causing inoculations and consequences for disease. The top panels show the rates of vaccinating (ν) and disease-causing (δ) inoculations as functions of the density of pathogens q . All quantities are on a $\log_{10}$ scale. The rates are calculated from equations (9) and (10) with $s = \tau = 0$, $D_V = \infty$, $R_L = 1$, $R_V = 10^4$, $D_L = 0.02$, $P_V - D_L = 0.1$ and $D_L - P_L$ given above each panel. The bottom panels plot $\delta/(\nu + \delta)$, the relative frequency of first inoculations that lead to disease symptoms rather than non-symptomatic, protective immunity.

Many of the parameters in table 1 influence the frequency of disease-inducing versus vaccinating inoculations. This large parameter space requires a step-by-step approach to building a picture of the interactions between various processes. We begin with the relative frequencies of individuals that have experienced either a vaccinating or disease-inducing inoculation. This relative frequency is independent of age, depending only on the rates at which vaccinating or disease-inducing inoculations occur.

The relative frequencies of vaccinating or disease-inducing inoculations provide important information, but do not tell the whole story. For example, vaccinating inoculations may be relatively more common early in life, but the total frequency of inoculations may be low. As age increases, the relative frequency of first inoculations that induce disease may increase as the probability of any inoculation rises.

(a) Relative frequencies of symptomatic and vaccinating inoculations

Recall that, over all routes of infection, δ is the total rate of disease-inducing inoculations and ν is the total rate of vaccinating inoculations. At any age, the relative frequency of first inoculations that lead to disease is $\delta/(\nu + \delta)$, assuming, as discussed above, that $s = 0$. With the definitions in equations (9) and (10), this relative frequency is

$$\frac{\delta}{\nu + \delta} = \frac{R_L e^{-D_L/q} + R_V e^{-D_V/q}}{R_L e^{-P_L/q} + R_V e^{-P_V/q}}. \quad (11)$$

This value depends on seven parameters, which makes study difficult.

The interesting qualitative features of the model can be made clearer by reducing the parameters with a

simplifying assumption. Assume that most disease-inducing inoculations occur by the typically lesion- or disease-inducing route of infection, that is $R_L e^{-D_L/q} \gg R_V e^{-D_V/q}$. This allows us, as an approximation, to drop the right term of the sum in the numerator, giving the relative frequency of disease-inducing inoculations as

$$\frac{\delta}{\nu + \delta} = \frac{1}{e^{(D_L - P_L)/q} + (R_V/R_L) e^{-(P_V - D_L)/q}}, \quad (12)$$

with the four parameters $D_L - P_L$, $P_V - D_L$, R_V/R_L and q .

What conditions must be met for the relative frequency of disease-inducing inoculations to increase as the total density of the pathogen q decreases? We can examine this question by studying the two terms in the denominator of equation (12).

For the first term $e^{(D_L - P_L)/q}$, note that $D_L - P_L \geq 0$ because the threshold for a disease-inducing inoculation by the L pathway D_L must be greater than or equal to the threshold for a protective or vaccinating inoculation by the L pathway P_L . Thus, a decline in q means that $e^{(D_L - P_L)/q}$ increases and $\delta/(\nu + \delta)$ declines. This term cannot explain how declining q increases the relative frequency of disease-producing inoculations.

The second term can counteract the effects of the first only if $e^{-(P_V - D_L)/q}$ declines with decreasing q . This requires $P_V > D_L$, that is P_V , the threshold number of pathogens to induce vaccinating protection relative to the average number of pathogens inoculated by the V pathway, must be greater than D_L , the threshold number of pathogens to cause disease relative to the average number of pathogens inoculated by the L pathway. If $D_L = P_L$, then $P_V > D_L$ is a necessary and sufficient condition for $\delta/(\nu + \delta)$ to increase with declining q in equation (12). If $D_L > P_L$, then $P_V > D_L$ is a necessary

Figure 2. The relative frequency of disease-inducing inoculations for various parameter combinations. Plots are based on equation (12). A decrease in $D_L - P_L$ lowers the dominant value of pathogen density q . An increase in $P_V - D_L$ raises the frequency of disease-inducing inoculations. In all plots $s = \tau = 0$ and $D_V = \infty$. For the top row, $P_V - D_L = 0.02$; for the bottom row, $P_V - D_L = 0.1$.

Figure 3. Accumulation of symptomatic infections with increasing age A . The probability of symptomatic infection at a particular age is given by Φ in equation (7) using δ and ν from equations (9) and (10). In all plots $s = \tau = 0$ and $D_V = \infty$. Age A can be measured on any time-scale, with the average number of inoculations at age A given by $R_L A = 0.002A$ and $R_V A = 2A$ for the L and V routes of infection. The ratio of inoculation rates by different routes is $\log(R_V/R_L) = 3$. The parameter S provides a scaling factor for the remaining parameters with $P_L = 0.01S$, $P_V = 0.08S$ and $D_L = 0.02S$.

condition, but the net outcome depends on the balance between the processes given by the two terms in the denominator of equation (12).

Figure 1 illustrates how different routes of infection can cause relatively rare pathogens to inflict more disease than relatively common pathogens. In figure 1a, at low pathogen density the rate of disease-causing inoculations δ is higher than the rate of vaccinating inoculations ν . As pathogen densities increase, ν rises above δ . The relative changes of ν and δ cause the frequency of disease-causing inoculations $\delta/(\nu + \delta)$ to decrease as pathogen density rises (figure 1b). In figure 1a,b, the L route of infection has the same threshold for disease as for vaccination, $D_L - P_L = 0$. When $D_L > P_L$, a more complex pattern arises (figure 1c), leading in that example to a maximum relative frequency of disease-causing inoculations at a pathogen density of approximately $\log(-2) = 0.01$.

If there exists a pathogen density that causes a local maximum in the relative frequency of disease-causing inoculations, as in figure 1d, that pathogen density is given by

$$q^* = \frac{P_V - P_L}{\ln(R_V/R_L) + \ln(P_V - D_L) - \ln(D_L - P_L)}. \quad (13)$$

This equation shows the qualitative effects of various parameters on q^* . For example, q^* declines with a decrease in $P_V - P_L$ or $D_L - P_L$. A rise in either R_V/R_L or $P_V - D_L$ also causes a decline in q^* . Figure 2 illustrates these trends for a few parameter combinations.

(b) Total frequencies at various ages

The relative rates of vaccinating and disease-inducing inoculations provide only partial information about

disease incidence. Consider, for example, the lower-left panel of figure 2 with a high $R_V:R_L$ ratio. A low pathogen density q causes a high relative frequency of disease-inducing inoculations, whereas a high pathogen density causes a low relative frequency of disease-inducing inoculations. However, the total rate of inoculations declines as pathogen density decreases. The way in which disease-inducing inoculations arise over an individual's lifetime depends on both the relative frequency of disease-inducing inoculations and the total rate of inoculations.

Figure 3 illustrates the accumulation of disease-inducing inoculations over the lifetimes of individuals. The height of each plot is the probability Φ that an individual will have symptomatic disease before age A . We describe the details of the parameters in the figure legend. Four conclusions follow.

First, advancing age causes a decline in the pathogen density that causes the peak probability of disease. This decline occurs because a lower pathogen density causes a lower total rate of inoculation.

Second, the surfaces in figure 3 are insensitive to the parameter P_L , given that $D_L \geq P_L$. This insensitivity occurs because most protective immunity arises from the typically vaccinating route of infection V.

Third, the scaling of D_L and P_V by S determines the pathogen density that yields the maximum probability of disease. This scaling occurs because the rates of disease-inducing and vaccinating inoculations are dominated by the values of D_L/q and P_V/q . Thus, multiplying both D_L and P_V by a factor S requires rescaling pathogen density to Sq to obtain an invariant effect.

Fourth, the difference $S(P_V - D_L)$ affects the height but not the location of the surfaces in figure 3 when holding S constant. This pattern, which is not shown in figure 3, is similar to the change between the rows of plots in figure 2.

6. CONCLUSIONS

We analysed three factors that influence the probability of severe disease in zoonotic and commensal infections: the size of the inoculum, the route of inoculation and the frequency of naturally occurring vaccinating inoculations. With a single route of infection, rising pathogen density increases the cases of disease. Two routes of infection can reverse this trend. Reversal occurs when one route of infection tends to vaccinate against relatively common pathogens but less often vaccinates against relatively rare pathogens, whereas the second route of infection causes disease-inducing inoculations even at relatively low pathogen density (figure 1).

We designed the models to highlight pathogen density q as a key parameter in the analysis of infection and disease. We have interpreted q as the maximum pathogen density that can occur, with variations in q over the interval $[0,1]$. Given this set-up, we can also interpret q as the frequency of antigenically distinct strains of the pathogen, that is, strains that do not provide cross-reactive immune protection. Thus, from figure 3, an antigenic variant at low frequency (low q) may be responsible for the majority of disease symptoms.

National Science Foundation grant DEB-9627259 supports S.A.F.'s research.

REFERENCES

- Anderson, R. M. & May, R. M. 1982 Coevolution of hosts and parasites. *Parasitology* **85**, 411–426.
- Anderson, R. M. & May, R. M. 1991 *Infectious diseases of humans: dynamics and control*. Oxford University Press.
- Ashford, R. W. 1998 The leishmaniasis. In *Zoonoses* (ed. S. R. Palmer, E. J. L. Soulsby & D. I. H. Simpson), pp. 527–543. Oxford Medical Publications.
- Barnes, H. J. & Gross, W. B. 1997 Colibacillosis. In *Diseases of poultry* (ed. B. W. Calnek, H. J. Barnes, C. W. Beard & Y. M. Saif), pp. 136–137. Iowa State University Press.
- Barrett, N. J. 1998 Pasteurellosis. In *Zoonoses* (ed. S. R. Palmer, E. J. L. Soulsby & D. I. H. Simpson), pp. 165–169. Oxford Medical Publications.
- Blue, S. R., Pombo, D. J. & Woods II, M. L. 1998 Glanders and melioidosis. In *Zoonoses* (ed. S. R. Palmer, E. J. L. Soulsby & D. I. H. Simpson), pp. 105–113. Oxford Medical Publications.
- Caul, E. O. & Sillis, M. 1998 Chlamydiosis. In *Zoonoses* (ed. S. R. Palmer, E. J. L. Soulsby & D. I. H. Simpson), pp. 67–73. Oxford Medical Publications.
- Clement, J., McKenna, P., Van der Groen, G., Vaheri, A. & Peters, C. J. 1998 Hantaviruses. In *Zoonoses* (ed. S. R. Palmer, E. J. L. Soulsby & D. I. H. Simpson), pp. 331–351. Oxford Medical Publications.
- Coop, R. L., Wright, S. E. & Casemore, D. P. 1998 Cryptosporidiosis. In *Zoonoses* (ed. S. R. Palmer, E. J. L. Soulsby & D. I. H. Simpson), pp. 563–578. Oxford Medical Publications.
- Dubey, J. P. 1998 Toxoplasmosis, sarcocystosis, isosporosis, and cyclosporiasis. In *Zoonoses* (ed. S. R. Palmer, E. J. L. Soulsby & D. I. H. Simpson), pp. 579–597. Oxford Medical Publications.
- Ellis, W. A. 1998 Leptospirosis. In *Zoonoses* (ed. S. R. Palmer, E. J. L. Soulsby & D. I. H. Simpson), pp. 115–126. Oxford Medical Publications.
- Ewald, P. W. 1983 Host–parasite relations, vectors, and the evolution of disease severity. *A. Rev. Ecol. Syst.* **14**, 465–485.
- Frank, S. A. 1996 Models of parasite virulence. *Q. Rev. Biol.* **71**, 37–78.
- Gyimah, J. E. & Panigrahy, B. 1985 Immunogenicity of an oil-emulsified *Escherichia coli* (serotype O1) vaccine in chickens. *Avian Dis.* **29**, 1078–1083.
- Holt, R. D. 1996 Demographic constraints in evolution: towards unifying the evolutionary theories of senescence and niche conservatism. *Evol. Ecol.* **10**, 1–11.
- Howard, C. R. 1998 Arenaviruses. In *Zoonoses* (ed. S. R. Palmer, E. J. L. Soulsby & D. I. H. Simpson), pp. 297–310. Oxford Medical Publications.
- Levin, B. R. & Bull, J. J. 1994 Short-sighted evolution and the virulence of pathogenic microorganisms. *Trends Microbiol.* **2**, 76–81.
- Marrie, T. J. 1998 Q fever. In *Zoonoses* (ed. S. R. Palmer, E. J. L. Soulsby & D. I. H. Simpson), pp. 171–185. Oxford Medical Publications.
- Marsden, P. D. 1998 American trypanosomiasis. In *Zoonoses* (ed. S. R. Palmer, E. J. L. Soulsby & D. I. H. Simpson), pp. 513–525. Oxford Medical Publications.
- Menon, J. N. & Bretscher, P. A. 1998 Parasite dose determines the Th1/Th2 nature of the response to *Leishmania major* independently of infection route and strain of host or parasite. *Eur. J. Immunol.* **28**, 4020–4028.
- Messier, S., Quessy, S., Robinson, Y., Devriese, L. A., Hommez, J. & Fairbrother, J. M. 1993 Focal dermatitis and cellulitis in broiler chickens: bacteriological and pathological findings. *Avian Dis.* **37**, 839–844.
- Mims, C. A., Playfair, J. H. L., Roitt, I. M., Wakelin, D. & Williams, R. 1993 *Medical microbiology*. St Louis, MO: Mosby.

- Monath, T. P. 1998 Yellow fever. In *Zoonoses* (ed. S. R. Palmer, E. J. L. Soulsby & D. I. H. Simpson), pp. 487–498. Oxford Medical Publications.
- Morgan-Capner, P. & Bryden, A. S. 1998 Foot-and-mouth disease, vesicular stomatitis, Newcastle disease, and swine vesicular disease. In *Zoonoses* (ed. S. R. Palmer, E. J. L. Soulsby & D. I. H. Simpson), pp. 319–329. Oxford Medical Publications.
- Palmer, S. R., Soulsby, E. J. L. & Simpson, D. I. H. 1998 *Zoonoses*. Oxford Medical Publications.
- Panigrahy, B., Gyimah, J. E., Hall, C. F. & Williams, J. D. 1984 Immunogenic potency of an oil-emulsified *Escherichia coli* bacterin. *Avian Dis.* **28**, 475–481.
- Sandhu, T. S. & Layton, H. W. 1985 Laboratory and field trials with formalin-inactivated *Escherichia coli* (O78)–*Pastuerella anatispestifer* bacterin in white Pekin ducks. *Avian Dis.* **29**, 128–135.
- Singer, R. S., Jeffrey, J. S., Carpenter, T. E., Wolfe, S. & Hirsh, D. C. 2000 Competitive pathogenicity of litter *E. coli* to induce cellulitis lesions in a scratch model experiment. In *Proceedings of the 49th Western Poultry Disease Conference*, p. 66. Sacramento, CA: University of California, Cooperative Extension.
- Sjögren, I. & Sutherland, J. 1975 Studies of tuberculosis in man in relation to tuberculosis in cattle. *Tubercle* **56**, 113–127.
- Swanepoel, R. 1998 Rift Valley fever. In *Zoonoses* (ed. S. R. Palmer, E. J. L. Soulsby & D. I. H. Simpson), pp. 459–468. Oxford Medical Publications.
- Turnbull, P. C. B. 1998 Anthrax. In *Zoonoses* (ed. S. R. Palmer, E. J. L. Soulsby & D. I. H. Simpson), pp. 3–16. Oxford Medical Publications.

As this paper exceeds the maximum length normally permitted, the authors have agreed to contribute to production costs.