Cell
PRESS

Directly transmitted viral diseases: modeling the dynamics of transmission

Jennie S. Lavine[1], Mary Poss[1] and Bryan T. Grenfell[1,2]

[1] 208 Mueller Laboratory, Center for Infectious Disease Dynamics, The Pennsylvania State University, University Park, PA 16803, USA
[2] Fogarty International Center, National Institutes of Health, Bethesda, MD 20892, USA

A key hurdle in understanding the spread and control of infectious diseases is to capture appropriately the dynamics of pathogen transmission. As people and goods travel increasingly rapidly around the world, so do pathogens; we must be prepared to understand their spread, in terms of the contact network between hosts, viral life history and within-host dynamics. This will require collaborative work that takes into account viral life history, strategy and evolution, and host genetics, demographics and immunodynamics. Mathematical models are a useful tool for integrating the data and analyses from diverse fields that contribute to our understanding of viral transmission dynamics in heterogeneous host populations.

Decoupling disease from transmission

Microbiological and molecular research has revolutionized our understanding of the causes and mechanisms of infectious disease; however the quantitative dynamics of pathogen transmission, a key process that drives the likelihood and extent of epidemic outbreaks and pathogen evolution, is still not well understood. It is crucial to recognize that severity of disease is not necessarily correlated with transmission. For example, subacute sclerosing panencephalitis, caused by the measles virus years after the original symptoms occur [1], is a severe and often fatal disease, but has little impact on population level dynamics because there is no transmission of the virus. And the converse can be true – someone can be highly infectious yet show few disease symptoms, as in 'superspreading' events during the SARS (severe acute respiratory syndrome) epidemic [2,3]. SARS is a rare example of a pathogen where many of the transmission events in an emergent epidemic were recreated from contact tracing [4]. Molecular techniques are now also used to trace a chain of transmission based on sequence similarities [5]. However, large-scale transmission experiments, such as those carried out with influenza virus in ferrets [6,7], are the ideal way to gain insight into biological processes that drive the transmission process. Unfortunately, for economic and ethical reasons, they are difficult to conduct on a sufficiently large scale to fully quantify transmission for the range of important pathogens.

In most cases, therefore, we need to assess the implications of individual host-level variables for population-level transmission more indirectly. Mathematical models are a powerful tool here, allowing the researcher to integrate the many disciplines, including virology, immunology, viral and host genetics and behavioral sciences, that contribute to our knowledge of viral transmission. Epidemiological modeling and analysis is one way to assess correlation between data from these various fields. For example, the probability and rate ratios of transmission per contact event during different stages of HIV infection were estimated using Poisson regression. Statistical models were then used to identify co-variates that were associated with higher transmission. These included high viral load, genital ulcers and young age [8]. Population-level ecological modeling of disease dynamics has also influenced disease control policy for human and animal infections, such as identifying the proportion of a population that needs to be vaccinated against a diverse range of infections [9,10].

Mathematical models with parameters that account for pathogen characteristics (replication strategy and evolution) and host characteristics (genetics, behavior, duration and strength of immunity, population mixing and variability) are a means to integrate available data to unravel viral transmission dynamics. This review will cover basic tenets of disease ecology and examine recent advances in ecological disease modeling that begin to bring all these parameters together in biologically relevant models of viral spread. The techniques addressed in this review aid in identifying which aspects of virus–host systems determine how a virus spreads in a population and help public health professionals create effective prevention and treatment strategies.

The basic model

The most basic population-level epidemic model for viral infections is the compartmental, ordinary differential equation, the SEIR model, which tracks the proportion of a population in four classes – susceptible, exposed, infected and infectious, and recovered and immune – over time (Figures 1a, 2a; Box 1). The SEIR model captures the epidemic dynamics of measles well [11]. Measles is an acute infection, and virus shedding occurs for a defined and relatively constant period in most infected persons, so
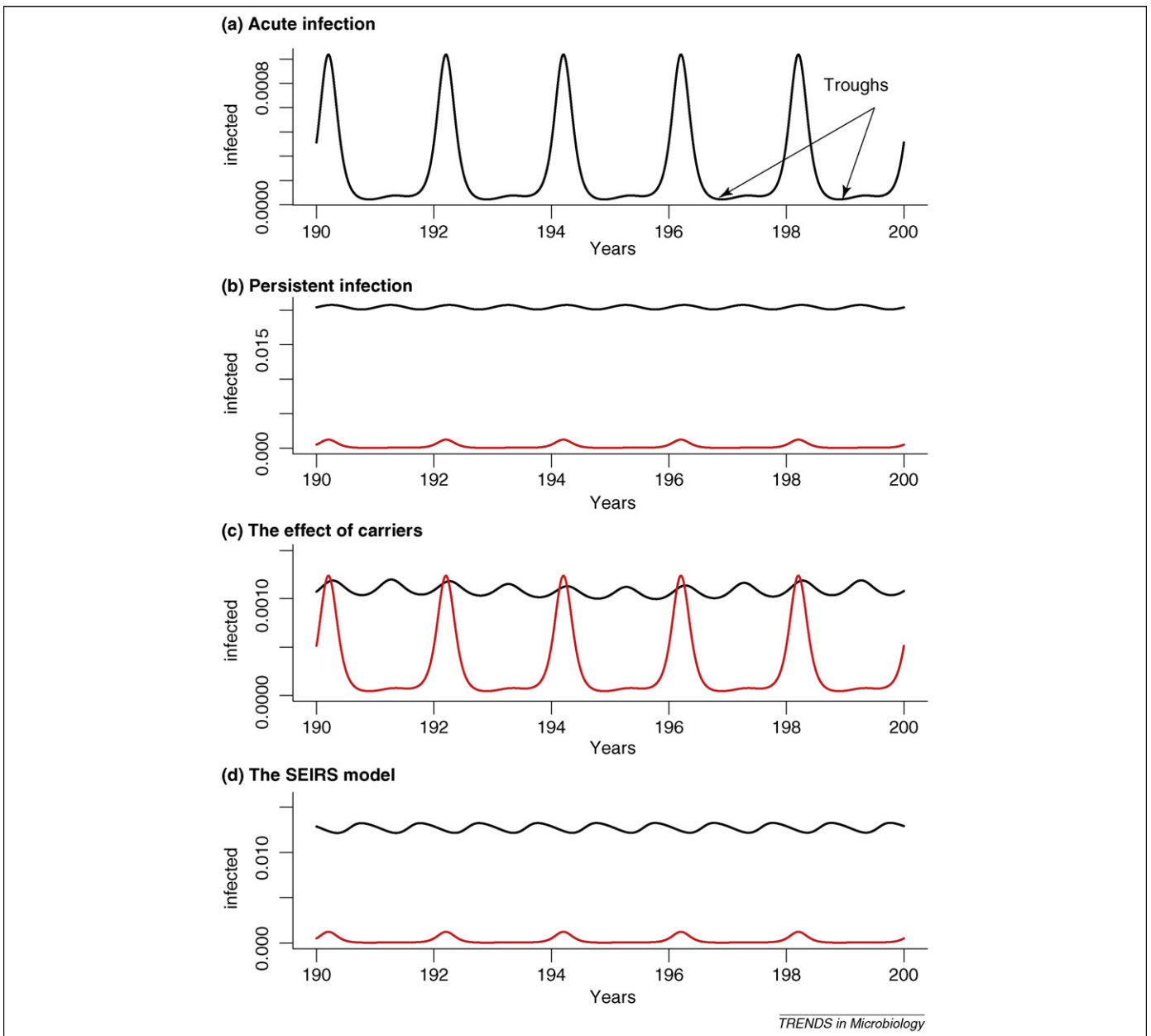
Figure 1. Model simulations of ten years of epidemic with a variety of parameters. Each graph plots the output of a simulated epidemic over ten years. A transient period of 190 years, not plotted here, was run to move the dynamics onto a stable limit cycle. The proportion of the population infected is plotted as a function of time in years. All simulations were run according to variants of the SEIR (susceptible, exposed, infectious, and recovered) model (Box 1). The model was seasonally forced using a sinusoidal function with a period of one year for more realistic dynamics by varying the transmission coefficient according to $\beta(t)$. Seasonal forcing is a common phenomenon in childhood infections for which the dynamics are dependent on annual school term cycles. The transmission coefficient, $\beta0$, and the infectious period, γ^{-1}, were adjusted for each model to maintain approximately constant R_0, as calculated assuming the sinusoidal term in $\beta(t) = 0$. The parameters, unless otherwise specified were: N = 1, γ = 73, σ = 45.625, μ = 1/45, $\beta0$ = 1250, $\beta1$ = 0.1, ρ = 1. See Table 1 for units and biological interpretations of the parameters. (**a**) A standard SEIR model for an acute infection with seasonal forcing. The acute, SEIR epidemic model is shown in red in (b), (c) and (d) to highlight the differences. (**b**) A standard chronic infection with γ = 1, $\beta0$ = 17.12329. (**c**) The carrier model divides the infected class into two groups, those who carry and those who clear the infection. This graph shows the effect of having 1% of the population as carriers, maintaining the infection chronically with $\beta0$ = 150.7841 and $\gamma2$ = 0.1 or an infectious period of ten years. This has two noticeable effects on the epidemic curve. First, the number of infected individuals at any time is increased. Second, the depth of the troughs (difference between the maximum and minimum number of infected individuals) is smaller in the model with carriers than a homogeneously acute infection (trough depth 0.000202 and 0.00119, respectively). The minimum population size to maintain the expected number of infecteds > 1 is 1004 with carriers, versus 22 975 for the homogeneous acute system. (**d**) The SEIRS model incorporates a loss of immunity and return to the susceptible class. Loss of immunity in an acute infection results in no longer having biannual cycles, just seasonally forced yearly fluctuations and an overall increase in disease prevalence compared with the acute infection model.

estimating the rate at which individuals leave the infected and infectious class is possible. Further, the characteristic clinical manifestations of measles also make historical epidemic patterns based on disease notification relatively reliable. Measles also induces lifetime immunity, consistent with the assumption that once individuals recover, they never return to the susceptible class. Furthermore,

the measles virus does not evolve quickly to escape immunity in previously infected hosts [12]. Thus, there is no return of individuals from the recovered class to the susceptible pool. The basic SEIR model goes a long way in explaining measles and other childhood disease dynamics [13–15]. The SEIR assumptions do not fit most other viral infections, however. Different viral strategies
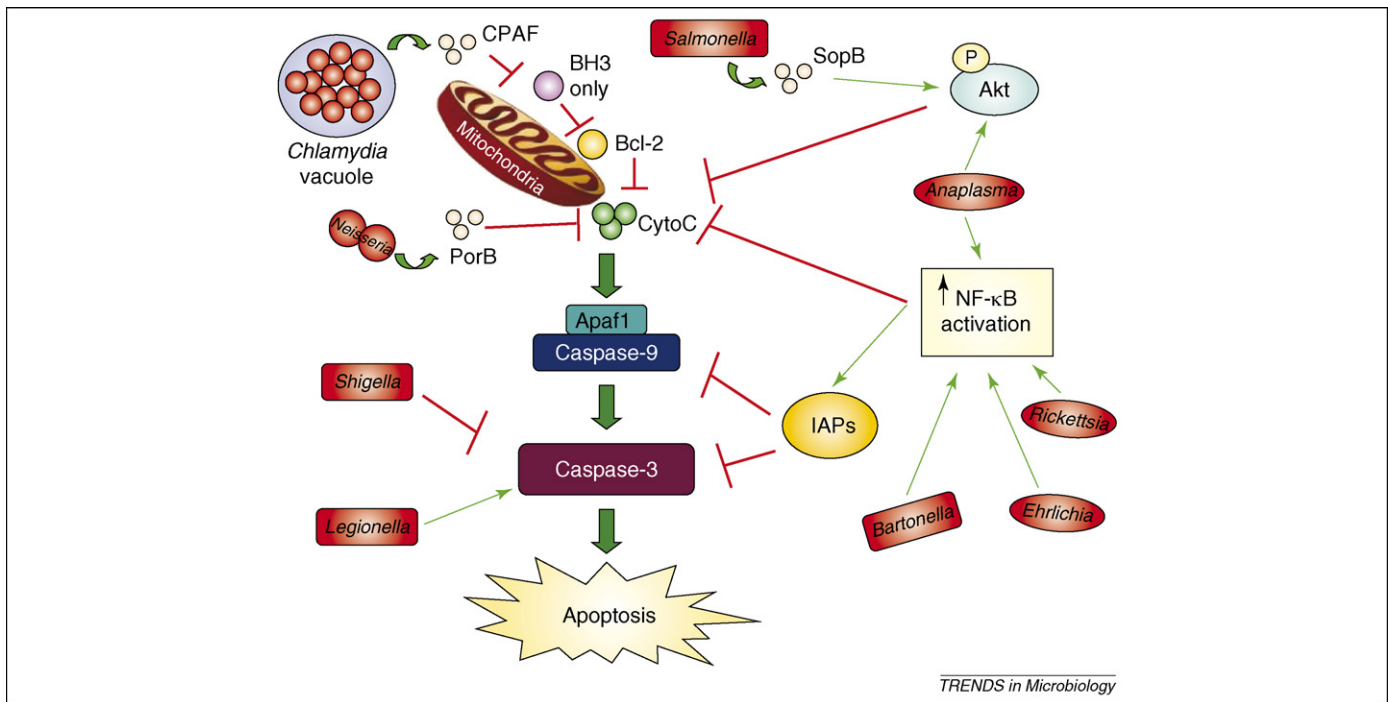
Figure 2. Flow diagrams of viral transmission mathematical models. Each parameter, shown as a Greek letter next to an arrow, defines the rate of movement from one class to the next. μ, birth and death rates; β, transmission coefficient; σ, rate at which infected individuals become infectious; γ, rate at which infectious individuals lose their ability to transmit; ρ, rate of loss of immunity. (**a**) A schematic of the SEIR model for acute (see Figure 1a) and chronic infections (see Figure 1b) in a homogeneous population with no loss of immunity. (**b**) The carrier model with a variable infectious period (see Figure 1c). One percent of the population leaves the infectious class at rate γ2, and the other 99% leave at rate γ1. (**c**) A diagram of the SEIRS model (see Figure 1d). The long arrow from the recovered class to the susceptible class indicates individuals who have recovered from an infection and lose their acquired immunity at rate ρ.

interact with behavioral and genetic heterogeneities in host populations to create transmission dynamics that are not as well explained with a simple SEIR model. Before exploring important features of hosts and pathogen biology that drive epidemic dynamics, we review the biological underpinnings of key parameters of the basic model.

The central parameters: transmission coefficient and infectious period

The transmission coefficient (β) is a measure of transmission that allows for contact frequency and probability of infection given a close contact. It can be converted to a point estimate for the probability that a susceptible individual becomes infected after risky contact with an infectious individual. This parameter is defined by a combination of viral and host characteristics. For example, a large value of β could come from a highly susceptible naïve host, a highly infectious host, or a highly infectious virus. It is dependent on viral strain, amount of virus being released from the infected host, and the susceptible host's tissue of entry and genotype.

In the basic SEIR model, the infectious period, (γ^{-1}), determines how long an individual spends in the infectious class before moving into the recovered class. The recovered class comprises individuals who can no longer transmit the pathogen, although they might still have disease symptoms. It is also possible to model death caused by disease by incorporating a case fatality rate, usually denoted α; however, we do not include this in the models in Figure 1. Not all infected individuals are in the infectious class. People who have been infected but cannot yet transmit are in the 'exposed' class. The rate of movement out of that class

defines the latent period, (σ^{-1}). The SEIR model accounts for this latent period, whereas the simpler SIR (susceptible, infectious and recovered) version does not. Viral replication rate, tissue tropism, host behavior, genetics and immune response all affect the potential to transmit. The transmission coefficient and the infectious period in combination with demographic parameters, such as birth and death rates, help capture the dynamic patterns of an epidemic. See Table 1 for a summary of model parameters.

The basic reproductive number (R_0)

A key concept for understanding disease transmission is R_0, the basic reproductive number. R_0 is the expected number of secondary infections resulting from the introduction of one infected individual into a completely susceptible population during the lifetime of the primary infection. A pathogen with an $R_0 > 1$ is expected to spread throughout a population; with $R_0 < 1$, it is expected to become extinct. At its simplest, R_0 can be characterized as β/γ [16–18].

R_0 has been used to predict and compare the expected performance of epidemic control strategies such as vaccination [9]. It can also be useful for thinking about different evolutionary strategies of viral fitness. For example, two viruses could have the same R_0, but one has a low value of β and long infectious period, whereas the other has the opposite. Although the viruses exhibit different dynamics and 'strategies' for establishment and persistence, they are equally fit when at equilibrium in the host population [19–21]. We maintain the same estimate for R_0 in all of the models in Figure 1. Although R_0 can be useful for designing control strategies and assessing viral fitness, recent stu-

Box 1. The equations behind the SEIR model

The basic SEIR model is a deterministic, ordinary differential equation model that tracks the progression of individuals through four classes – susceptible, exposed, infected and recovered – over time. The rates of change in the sizes of each class are functions of rate parameters (μ, β, σ and γ) (see Table 1 in main text) and the current sizes of each class, as expressed by the following system of equations:

$$dS/dt = \mu(N\text{-}S) - \beta(t)SI/N \tag{1}$$

$$dE/dt = \beta(t)SI/N - (\mu + \sigma)E \tag{2}$$

$$dI/dt = \sigma E - (\mu + \gamma)I \tag{3}$$

$$dR/dt = \gamma I - \mu I \tag{4}$$

$$\beta(t) = \beta0(1 + \beta1\cos(2\pi t)) \tag{5}$$

The model can be expressed in absolute numbers of individuals in each class, in which case N is the population size. Alternatively, it can be expressed as proportions of the total population in each class, in which case N is 1. When N = 1, as was used in the simulated epidemics shown in Figure 1 (of main text), the mixing term $\beta(t)SI$ represents pseudo-mass action. The minimum population size necessary to maintain the expected number of infections >1 is equal to the inverse of the infected proportion at the bottom of a trough. R_0 was kept approximately constant by maintaining $\beta0/\gamma = 17.123$, a value that illustrates epidemic cycles well and is realistic for some infections. The basic equations can be changed to emphasize other aspects of disease transmission. Two modifications shown in Figure 1 (of main text) are the carrier and SEIRS models. The carrier model allows for two infectious classes that have different infectious periods, γ and $\gamma2$. The $\beta0$ for this model is chosen such that $0.99(\beta0/\gamma) + 0.01(\beta0/\gamma2) = 17.123$. Mathematically, dI/dt is replaced by the following two equations:

$$dI1/dt = 0.99\sigma E - (\mu + \gamma)I \tag{6}$$

$$dI2/dt = 0.01\sigma E - (\mu + \gamma2)I.\ \beta0 = 150.7841 \tag{7}$$

In the SEIRS model, individuals can lose immunity and return to the susceptible class at rate ρ. The modifications to the basic model involve replacing dS/dt and dR/dt with the following:

$$dS/dt = \mu(N\text{-}S) - \beta(t)SI/N + \rho R \tag{8}$$

$$dR/dt = \gamma I - (\mu + \rho)I \tag{9}$$

dies indicate the pitfalls of using R_0 as a predictive statistic for pathogen emergence or extinction owing to viral and host heterogeneities [2]. These heterogeneities will be explored later in this review.

SEIR parameters reflect host and viral characteristics

Each of the parameters in the basic SEIR model reflects both viral and host characteristics that affect transmission. For the rest of the paper, we will divide our discussion into host and viral characteristics that affect spread in a population by tuning the transmission coefficient, β, and/or the infectious period. We will explore how host genetic and viral characteristics sometimes necessitate other epidemiologically significant modifications to the basic SEIR model. These modifications will incorporate loss of immune memory or immune escape, the presence of a varied host population in which there are carriers who transmit a virus for longer than the usual range and spread on a social contact network (Figures 1, 2; Table 2).

Viral effects

Viral life strategy significantly affects the infectious period, thereby altering the course of infection in an individual and spread in a population. Viruses that elicit a productive host immune response and are cleared quickly occur as, sometimes dramatic, epidemic cycles in a population (Figure 1a). These viruses include measles, influenza and rhinoviruses [22], among others. Many viruses are not cleared by the host immune system, however, and can persist in the host for an indeterminate amount of time, often leading to endemic population dynamics.

There are a variety of viral strategies for establishing persistent infection in the host. The papillomaviruses, which can cause warts, have evolved a unique ability to replicate in squamous epithelial cells, which are not under

Table 1. Definition of model parameters

Parameter	Units	Biological significance
t		Time in years
N		Total population size, set to 1 in these models
S		Proportion of the population that has no immunity to the virus
E		Proportion of the population that have been exposed to the virus, but are not yet infectious
I		Infectious proportion of the population
R		Recovered and immune proportion of the population
$\beta0$		Base transmission coefficient reflecting viral, immunological and social factors
$\beta1$		Additional seasonally dependent transmission coefficient
μ	yr^{-1}	Life expectancy (inverse), birth and death rate
σ	yr^{-1}	Latent period (inverse), rate of movement from 'exposed' to 'infectious'
γ	yr^{-1}	Infectious period (inverse), rate of movement from 'infectious' to 'recovered'
ρ	yr^{-1}	Length of immunity (inverse), rate of movement from 'recovered' to 'susceptible'

Table 2. Effects of molecules and mechanisms on model parameters and technique

Molecule or mechanism	Example of virus it impacts	Affect on model	Refs
IL-10	Lymphocytic Choriomeningitis Virus	γ^{-1} (infectious period)	[22]
IFN-γ		γ^{-1} (infectious period)	[23]
Population level immune escape	Influenza Virus	Incorporate phylodynamics	[38–41]
Loss of immunity	Respiratory Syncytial Virus	SIRS (susceptible, infected, recovered, susceptible)	[36,37]
Within host immune escape	Hepatitis C Virus	γ^{-1} (infectious period)	[21]
Carriers	Nucleopolyhedroviruses, Varicella–Zoster Virus	Division into two infectious classes	[32,33]
Host heterogeneity	All	Network models, heterogeneous compartmental models	[2,8,43,45]

active immune surveillance [23]. Virus production is minimized until cells differentiate, at which time transmission is achieved. Retroviruses use a different strategy to achieve a persistent infection; they integrate into the host genome. These RNA viruses are maintained as replication-competent DNA proviruses for the lifetime of the cell. Both strategies for persistence have similar population level dynamic consequences. They produce a long infectious period, which in turn results in an infected population at close to dynamic equilibrium, although seasonal or stochastic effects might drive fluctuations around this steady state in practice (Figure 1b).

Phenotypic and genotypic viral heterogeneity can affect virus transmission as well. Many viruses can cause either acute or persistent infections. For example, some individuals infected with hepatitis C virus (HCV) clear the virus, or rapidly succumb to the infection, resulting in an acute infection [24]. However, HCV is an RNA virus with a high error rate and is capable of generating extensive genetic diversity. This can lead to immune escape within a host and, consequently, a potential carrier, exhibiting a persistent infection with a long infectious period [25] (Figures 1c, 2b).

The knowledge gained from virological studies can help disease ecologists choose appropriate models for the host–pathogen system they are studying. The resulting mechanistic epidemiological models can also be used to estimate viral infection parameters such as infectious period. These population level estimates from natural settings can support *in vitro* and *in vivo* laboratory work that estimates the same quantities.

Host effects
At the population level, rapid and effective host-mediated clearance results in a short infectious period and epidemic dynamics (Figure 1a). In a host population in which all hosts allow the virus to persist, however, there will be a long infectious period and endemic dynamics will occur, resembling those caused by viruses that avoid clearance. Recent immunological studies elucidate specific mechanisms by which a host determines whether a virus is cleared or persists.

Although cellular and humoral components of the host adaptive immune system are key effectors of virus clearance, cytokines produced soon after exposure also determine the duration of infection. For example, mice with low levels of interleukin 10 (IL-10) or those treated with antibody to the IL-10 receptor cleared lymphocytic choriomeningitis virus (LCMV), whereas those with high levels of IL-10 sustained persistent infections [26]. The type I and type II interferons (IFN), which derive their names from the ability to protect against virus infection, promote both early virus containment and effective viral clearance by adaptive immunity. For example, LCMV can persist in the presence of antigen-specific CD8 (cluster of differentiation 8) T cells, which control viral infection, in IFN-deficient mice [27]. Not surprisingly, viruses have evolved a variety of mechanisms to block IFN [28].

Host populations are not homogeneous with regard to their susceptibility to, and ability to clear, viral infection. Individuals in a population differ owing to nutrition,

genetics and the presence of concomitant infections. These heterogeneities affect the dynamics in complex ways that will be explored in the last section of this review. Population genetic studies have identified polymorphisms in the human population in both regulatory and coding regions for many of the genes associated with viral clearance, including IL-10, IL-2, IL-6, TNF-α (tumor necrosis factor α) and TNF-β [29,30]. Individual hosts are not static in their susceptibility to infection over time. Malnutrition has long been linked to susceptibility to infectious disease. There is an association between decreases in solar radiation or nutritional intake of vitamin D through cod liver oil and higher incidence of respiratory infections, in particular influenza [31]. Moreover, an intriguing study on selenium suggests that its deficiency allows coxsackievirus and influenza to evolve a higher level of virulence in malnourished hosts [32]. Polymicrobial infections are the rule, not the exception [33], and it is possible that they affect susceptibility to a secondary infection and the ability to clear either infection.

The host's immune status affects both the infectious period and the probability of acquiring an infection given contact, so knowledge of the host populations' average immune status can help in calibrating models. In practice, however, host populations will characteristically be heterogeneously immune. Basic SEIR models do not take these individual and temporal heterogeneities into account and thereby could miss important consequences for public health measures. Here, we review how these host heterogeneities, and complexities in viral life history, have prompted refinements of the basic SEIR framework.

Extending the SEIR model: accounting for key biological complexities

As discussed, the life histories of many viral infections do not fit neatly into the SEIR assumptions and therefore necessitate modifications to this basic framework. Here, we will discuss two such modifications. In the first, there are two compartments for infected individuals: those that maintain the infection and can transmit the infection for a long time (carriers), and those who clear it rapidly. This is denoted by the additional 'infectious' box in Figure 2b and is accounted for mathematically by the incorporation of two different infectious periods [34] (Box 1). In the second case, hosts lose their immunity to all circulating genotypes of a virus. It is then possible for individuals to move from the recovered class back to the susceptible class [35], as denoted by the additional long arrow in Figure 2c [9].

Extending the SEIR model to include carriers
Factors that affect the ability of a host to clear a virus, as mentioned, can result in a few individuals who have a longer than average infectious period (Figure 1c). These heterogeneities are complex and hard to measure at a population level in humans because they arise from interactions of many factors – immunology, genetics, behavior, age, social structure and nutrition, to name a few.

Mathematical models of insect populations infected with nucleopolyhedroviruses demonstrate the important consequences of heterogeneity in the infectious period that are likely to be applicable to human systems as well.

Carriers can allow a virus to persist in a population in which, without carriers, it would run out of susceptible hosts and become extinct. They can also affect the stability of the system, altering the likelihood that small perturbations drastically change the population dynamics [36]. A similar dynamical effect occurs due to the viral life strategy of latency. The occurrence of mildly infectious shingles from Varicella–Zoster virus (VZV) infection years after the initial varicella outbreak could maintain the pathogen in small populations [37].

These findings on the importance of carriers could apply to a wide range of acute infections, which often move rapidly through a population and fade out because of demographic stochasticity, especially in deep interepidemic troughs with at most a few people in a population infected. Host population size is important in maintaining a chain of transmission through these troughs; however, small populations can still allow for disease persistence. One possible explanation for this is immigration: an infected host from outside comes into the population and starts a new round of infections, as seen in measles [11,38]. Another explanation is that a different host species can act as a reservoir for the virus, which could be the case with Ebola virus [39]. A third explanation is the presence of a low proportion of carriers, which can allow persistence even in small populations (Figures 1c, 2b), as might be the case with foot and mouth disease virus (FMDV) [40]. In summary, empirical studies identify the mechanisms and existence of carriers, whereas population dynamic modeling indicates their potential importance for a viral strain avoiding extinction.

Dynamics of immune escape: the SEIRS model
Acute, lifetime immunizing infections such as measles are either cleared by the host's immune system or result in death of the host in a short time period. The recovered individuals never return to the susceptible population because they have generated a protective adaptive immune response. But many viral infections, such as respiratory syncytial virus (RSV), do not provide lifelong immunity, and at some point in the future the host can be re-infected [41]. Evolution of the virus or changes in host immune status can allow for re-infection. The simplest model that reflects loss of immunity is the SEIRS formulation, in which the final 'S' denotes 'susceptible' again. In SEIR terms, this means that individuals in the recovered class become susceptible again (Figures 1d, 2c). The increase in the susceptible class can hinder vaccine development [42].

Rapid virus evolution affects transmission. For example, during an interpandemic influenza outbreak, one strain of influenza travels through a population and most infected people become immune; they enter the 'recovered' class in the SEIR model. The virus in the population continues to evolve, however, and might successfully infect a recovered host after selection for a different antigenic site to which recovered hosts are no longer immune. An assumption of the SEIR model is that anyone who had influenza once would never have it again, whereas a SEIRS model reflects the possibility of re-infection. Similar population-level patterns occur when host immunity wanes to the existing strain [42],

as it can with RSV [43,44]. A fundamental question of some interest is why some agents elicit lifelong immunity and others do not.

In the case of interpandemic influenza, a SEIRS model such as the one in Figure 1d is an overly simplified approach to understanding the dynamics. Interpandemic dynamics are better represented by a compilation of simple SEIRS models, in which each model represents only one antigenic variant. These more complex models combine virological and immunological characterization of antigenic sites with viral sequence and epidemiological data to produce an epidemiological model. These models capture observed viral dynamics better by reflecting differential immunity to different strains [45–47]. They are a prime example of how models can incorporate data and ideas from a variety of disciplines to better reflect and promote understanding of the way a virus moves through a human population.

Extending the SEIR model family: host behavior and heterogeneities
Simple SEIR models can be useful for elucidating the central elements of the transmission process and estimating practically important aspects of viral spread such as transmission probability and infectious period. With these two parameters known, the probability of emergence and relative fitness of different viral strains can be estimated by calculating R_0. As described, however, heterogeneities in the host population can significantly affect these estimates and the resulting dynamic behavior of epidemics and response to control. To incorporate these important heterogeneities, the well-mixed, basic SEIR model family must be extended to include variability in demographics, host age structure, genetics and social behavior. Modeling techniques for incorporating variability are well studied [9]; however, there is little work that empirically relates population heterogeneity to variation in transmission.

The behavior of susceptible and infectious hosts affects both the transmission coefficient and the infectious period. In the basic SEIR model, a contact event is defined as an infected and a susceptible individual randomly bumping into each other. But not all 'bumps' are equal or equally likely. Some contact events are short-lived, whereas some are constant or intimate. Allowing for the focus of transmission to be in schools in the SEIR model created a good fit for the measles data in a variety of settings, indicating that school term forcing is a crucial step in maintaining a measles epidemic [48]. Some aspects of behavior cannot be accounted for in a well-mixed SEIR model, however. Network models that incorporate assortative and disassortative mixing (whether people tend to contact people similar or dissimilar to them more frequently) have shed light on the dynamics of the high prevalence of HIV infection in minority populations in the United States [49] (M. Morris, pers. commun.). Other models involving contact networks have suggested the importance of the structure of a social network for determining the probability of an epidemic or the efficacy of a vaccination strategy [50].

There is a growing body of theoretical modeling work on the population consequences of individual host variation. These heterogeneities are incorporated into models in a

variety of ways, but usually affect three aspects: the susceptibility, infectiousness or infectious period of a host. The susceptibility and infectiousness of a host have the potential for affecting the probability of a novel pathogen emerging in a population, particularly when in concert with pathogen evolution [2,51]. The presence of a diverse host population can also increase the stability of a system [52]. There is substantial theory, but very little empirical work, on the impacts of host heterogeneities on population processes.

Concluding remarks and future directions

Recent advances in molecular and theoretical studies of host–pathogen interactions have led to a better understanding of transmission dynamics and the importance of heterogeneities (Table 2). There are many exciting questions to explore. How does variability in the host population's genetics, immune response, general health and behavior affect viral spread? What determines variability in the host immune response and length of immune memory? How does a virus' life cycle and evolution impact transmission success?

Virology and immunology research has elucidated mechanisms of viral persistence and clearance, which affect the infectious period and thereby the population dynamics. Population genetics, case histories of concomitant infections, nutritional studies and social science research have provided empirical support for host heterogeneities in susceptibility to and clearance of viral infections. But understanding the population-level effects of these molecular, cellular within-host and between-host properties remains a challenge. Modeling studies that incorporate more of these fields show promise in answering these questions. SEIR models and their variants can reflect loss of immunity and carrier states. Social network models reflect the reality of different levels of contact among members of a population. More collaborative work among virology, immunology, social science, nutritional science and theoretical biology researchers, along with key large-scale transmission experiments will facilitate a better understanding of viral transmission dynamics.

References

1 Hamilton, R. *et al.* (1973) Subacute sclerosing panencephalitis measles virus: study of biological markers. *J. Virol.* 12, 632–642
2 Lloyd-Smith, J.O. *et al.* (2005) Superspreading and the effect of individual variation on disease emergence. *Nature* 438, 355–359
3 Shen, Z. *et al.* (2004) Superspreading SARS events, Beijing, 2003. *Emerg. Infect. Dis.* 10, 256–260
4 Leo, Y.S. *et al.* (2003) Severe acute respiratory syndrome – Singapore, 2003. *M.M.W.R.* 52, 405–411
5 Gagneux, S. *et al.* (2006) Variable host-pathogen compatibility in *mycobacterium tuberculosis*. *Proc. Natl. Acad. Sci. U. S. A.* 103, 2869–2873
6 Herlocher, M.L. *et al.* (2004) Influenza viruses resistant to the antiviral drug oseltamivir: transmission studies in ferrets. *J. Infect. Dis.* 190, 1627–1630
7 Herlocher, M.L. *et al.* (2001) Ferrets as a transmission model for influenza: sequence changes in HA1 of type A (H3N2) virus. *J. Infect. Dis.* 184, 542–546
8 Wawer, M.J. *et al.* (2005) Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai. *Uganda. J. Infect. Dis.* 191, 1403–1409
9 Anderson, R.M. and May, R.M. (1991) *Infectious diseases of humans: dynamics and control,* Oxford University Press
10 Keeling, M.J. *et al.* (2001) Dynamics of the 2001 UK foot and mouth epidemic: stochastic dispersal in a heterogeneous landscape. *Science* 294, 813–817
11 Bjørnstad, O.N. *et al.* (2002) Dynamics of measles epidemics: estimating scaling of transmission rates using a time series SIR model. *Ecol. Monogr.* 72, 169–184
12 Grenfell, B.T. *et al.* (2004) Unifying the epidemiological and evolutionary dynamics of pathogens. *Science* 303, 327–332
13 Finkenstädt, B.F. and Grenfell, B.T. (2000) Time series modelling of childhood diseases: a dynamical systems approach. *J. R. Stat. Soc. Ser. C Appl. Stat.* 49, 187–205
14 Fine, P.E.M. and Clarkson, J.A. (1982) Measles in England and Wales– I: an analysis of factors underlying seasonal patterns. *Int. J. Epidemiol.* 11, 5–14
15 Schenzle, D. (1984) An age-structured model of pre- and post-vaccination measles transmission. *IMA J. Math. Appl. Med. Biol.* 1, 169–191
16 Altizer, S. *et al.* (2006) Seasonality and the dynamics of infectious disease. *Ecol. Lett.* 9, 467–484
17 Dietz, K. (1993) The estimation of the basic reproduction number for infectious diseases. *Stat. Methods Med. Res.* 2, 23–41
18 Diekmann, O. *et al.* (1990) On the definition and the computation of the basic reproduction ratio R0 in models for infectious diseases in heterogeneous populations. *J. Math. Biol.* 28, 365–382
19 Grenfell, B.T. (2001) Dynamics and epidemiological impact of microparasites. In *New Challenges to Health: The Threat of Virus Infection* (Smith, G.l. *et al.*, eds), pp. 33–52, Cambridge University Press
20 Andre, J-B. *et al.* (2003) Within-host parasite dynamics, emerging trade-off, and evolution of virulence with immune system. *Evolution Int. J. Org. Evolution* 57, 1489–1497
21 Ganusov, V.V. *et al.* (2002) Within-host population dynamics and the evolution of microparasites in a heterogeneous host population. *Evolution Int. J. Org. Evolution* 56, 213–223
22 Villarreal, L.P. *et al.* (2000) Acute and persistent viral life strategies and their relationship to emerging disease. *Virology* 272, 1–6
23 O'Brien, P.M. and Saveria Campo, M. (2002) Evasion of host immunity directed by papillomavirus-encoded proteins. *Virus Res.* 88, 103–117
24 Alter, H.J. (2005) HCV natural history: the retrospective and prospective in perspective. *J. Hepatol.* 43, 550–552
25 Chen, S. and Wang, Y-M. (2005) Multigene tracking of quasispecies in viral persistence and clearance of hepatitis C virus. *World J. Gastroenterol.* 11, 2874–2884
26 Brooks, D.G. *et al.* (2006) Interleukin-10 determines viral clearance or persistence *in vivo*. *Nat. Med.* 12, 1301–1309
27 Kolumam, G.A. *et al.* (2005) Type I interferons act directly on CD8 T cells to allow clonal expansion and memory formation in response to viral infection. *J. Exp. Med.* 202, 637–650
28 Hengel, H. *et al.* (2005) Viruses know it all: new insights into IFN networks. *Trends Immunol.* 26, 396–401
29 Moraes, M.O. *et al.* (2003) Interleukin-10 promoter haplotypes are differently distributed in the Brazilian versus the Dutch population. *Immunogenetics* 54, 896–899
30 Meenagh, A. *et al.* (2002) Frequency of cytokine polymorphisms in populations from western Europe, Africa, Asia, the Middle East and South America. *Hum. Immunol.* 63, 1055–1061
31 Cannell, J.J. *et al.* (2006) Epidemic influenza and vitamin D. *Epidemiol. Infect.* 134, 1129–1140
32 Beck, M.A. (2001) Antioxidants and viral infections: host immune response and viral pathogenicity. *J. Am. Coll. Nutr.* 20, 384S–388S
33 Brogden, K.A. *et al.* (2005) Human polymicrobial infections. *Lancet* 365, 253–255
34 Murray, C.J.L. and Salomon, J.A. (1998) Modeling the impact of global tuberculosis control strategies. *Proc. Natl. Acad. Sci. U. S. A.* 95, 13881–13886
35 Hethcote, H.W. (2000) The mathematics of infectious diseases. *SIAM Review* 42, 599–653
36 Boots, M. *et al.* (2003) The population dynamical implications of covert infections in host-microparasite interactions. *J. Anim. Ecol.* 72, 1064–1072
37 Ferguson, N.M. *et al.* (1996) Mass vaccination to control chicken pox: the influence of zoster. *Proc. Natl. Acad. Sci. U. S. A.* 93, 7231–7235
38 Bartlett, M.S. (1960) The critical community size for measles in the United States. *J. Roy. Stat. Soc. A STA* 123, 37–44

39 Groseth, A. *et al.* (2007) The ecology of Ebola virus. *Trends Microbiol.* 15, 408–416

40 Alexandersen, S. *et al.* (2002) Aspects of the persistence of foot-and-mouth disease virus in animals – the carrier problem. *Microbes Infect.* 4, 1099–1110

41 Boukhvalova, M.S. *et al.* (2007) Respiratory syncytial virus infects and abortively replicates in the lungs in spite of preexisting immunity. *J. Virol.* 81, 9443–9450

42 Gomes, M.G.M. *et al.* (2004) Infection, reinfection, and vaccination under suboptimal immune protection: epidemiological perspectives. *J. Theor. Biol.* 228, 539–549

43 Prince, G.A. *et al.* (1983) Mechanisms of immunity to respiratory syncytial virus in cotton rats. *Infect. Immun.* 42, 81–87

44 Ogra, P.L. (2004) Respiratory syncytial virus: the virus, the disease and the immune response. *Paediatr. Respir. Rev.* 5 (Suppl A), S119–S126

45 Smith, D.J. *et al.* (2004) Mapping the antigenic and genetic evolution of influenza virus. *Science* 305, 371–376

46 Ferguson, N.M. *et al.* (2003) Ecological and immunological determinants of influenza evolution. *Nature* 422, 428–433

47 Recker, M. *et al.* (2007) The generation of influenza outbreaks by a network of host immune responses against a limited set of antigenic types. *Proc. Natl. Acad. Sci. U. S. A.* 104, 7711–7716

48 Earn, D.J. *et al.* (2000) A simple model for complex dynamical transitions in epidemics. *Science* 287, 667–670

49 Morris, M. *et al.* (2006) Prevalence of HIV infection among young adults in the United States: results from the add health study. *Am. J. Public Health* 96, 1091–1097

50 Ferrari, M.J. *et al.* (2006) Network frailty and the geometry of herd immunity. *Proc. Biol. Sci.* 273, 2743–2748

51 Yates, A. *et al.* (2006) How do pathogen evolution and host heterogeneity interact in disease emergence? *Proc. Biol. Sci.* 273, 3075–3083

52 Bjornstad, O.N. and Hansen, T.F. (1994) Individual variation and population dynamics. *Oikos* 69, 167–171