Viral Dynamics and Mathematical Models

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1 Introduction

The application of mathematics to explore the dynamics and control of viral infections has a long history, which predates its application in many other fields of biology, as well as the germ theory itself [1]. A particularly fruitful area for development has been the dynamics of acute immunizing infections, with their relatively simple natural history and rich notification time series [2–4]. The last three decades have seen a considerable upsurge in the use of mathematical and computational models to explore the dynamics and control of a wide range of viral infections. This phase arose initially from developments in ecological population dynamics [4]; it was then greatly accelerated, both by the explosion in computational power and by the emergence of human immunodeficiency virus (HIV) infection, severe acute respiratory syndrome (SARS), and other potential pandemic threats [5].

In this chapter, we review basic concepts in infection dynamics and control, via a synthesis of epidemic models and data. We begin with acute immunizing infections, focusing on measles as a case study of the impact of herd immunity and other determinants of epidemic dynamics. We then extend the discussion to dynamical modeling applications to a range of other acute and chronic viruses, with a variety of more complex life histories. After a brief discussion of models for the within-host dynamics of viruses, we conclude with suggestions for gaps in knowledge and future research needs.

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2 Dynamics of Acute Immunizing Infections

2.1 Observed Epidemic Patterns

Acute immunizing infections typically generate recurrent epidemics in large communities. We illustrate these patterns with the best documented case – the dynamics of measles in large cities in England and Wales [2, 3]. Figure 5.1a shows the time series of raw weekly notifications for measles in London from 1944 (shortly after measles cases became notifiable) to 1994.

These data indicate three fairly distinctive dynamical eras:

- 1944–1950: Principally annual epidemics.
- 1950s–1960s: Regular, mainly biennial epidemic cycles, with intervening small annual peaks – incidence rates are markedly *seasonal* (Sect. 2.4).
- 1970s onwards: The vaccine era brought declining incidence, with increasing irregular, lower-amplitude epidemic cycles. By the end of the series shown in this figure, cases became very sporadic, with increasing levels of mis-notification of clinically identified cases [7].

As well as these fluctuations in individual large cities, there are also rich dynamical patterns in the *spatial spread* of epidemics among large and small communities (Sect. 4). Regional and temporal demographic variations, especially in *birth rate*, can also markedly influence dynamics (Sect. 2.4).

2.2 Epidemic Dynamics: The SEIR Model

The striking epidemic patterns of acute immunizing infections are particularly well documented for widely notifiable infections such as measles. The process of explaining these

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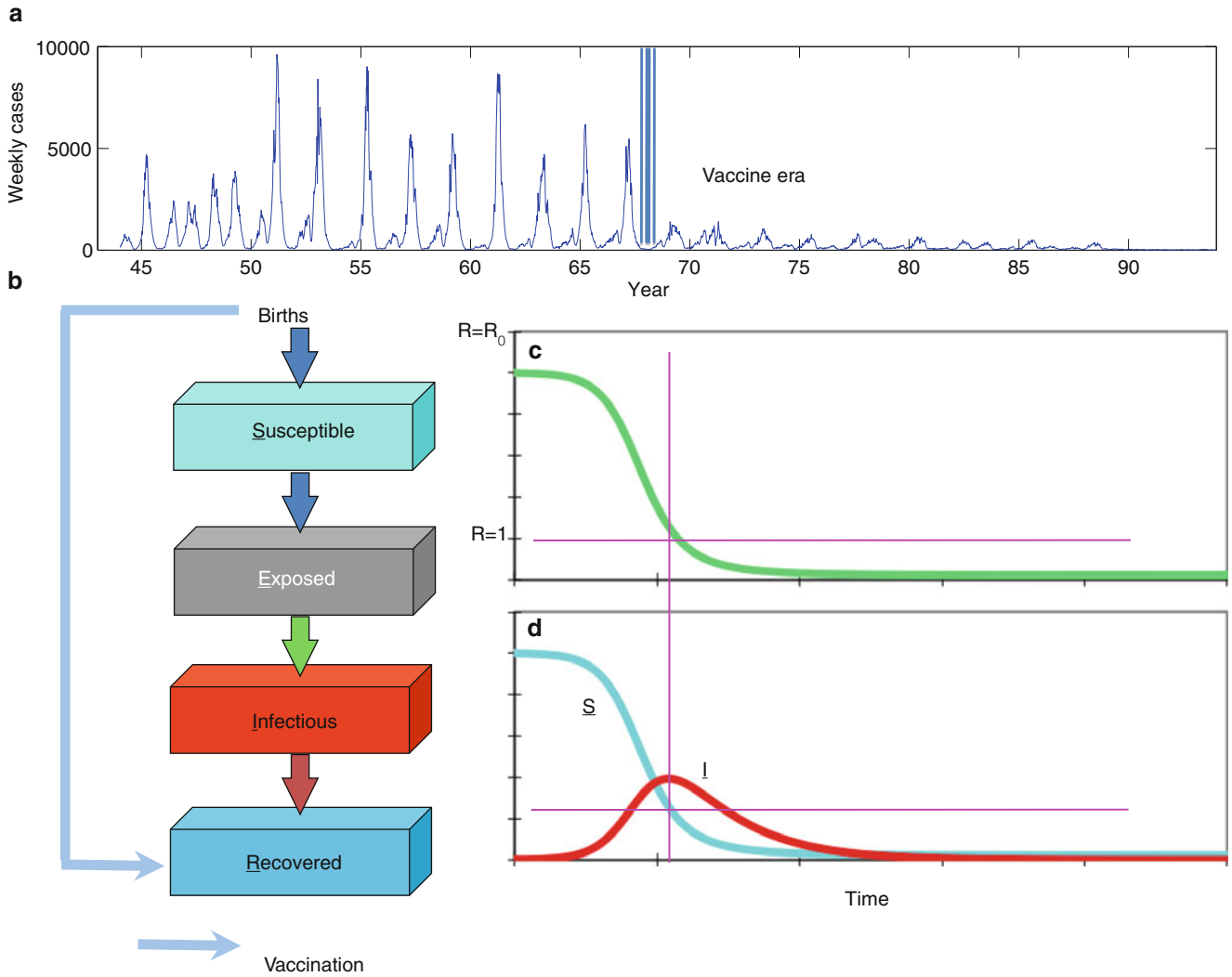

Fig. 5.1 (**a**) Observed spatiotemporal dynamics of measles in England and Wales, showing weekly aggregate time series of notifications for London. (**b**) Basic flows of individuals captured by the SEIR model. (**c**) Schematic time series of numbers of susceptible individuals, arising from flows in panel **b**, and in particular following the introduction of one infectious individual into a wholly susceptible population; the effect of birth rate on susceptibility is ignored. (**d**) Corresponding dynamics for the proportion of the population susceptible (line marked "*S*") and the proportion infected (line marked "*I*") (**b**, **d**: Taken from Fig. 2, Grenfell [6]. Figure found on p. 38)

cycles, as well as that of addressing associated public health issues, has spawned an extensive analytical literature, spanning public health epidemiology, theoretical biology, and population dynamics [4, 5, 8–10]. The key conceptual tool has been a family of compartmental dynamical models, based on the SIR (susceptible-infected-recovered) paradigm [2–5, 11, 12]. As described below, the SIR family successfully captures many key features of the epidemiological dynamics and control of viral infections.

The basic SIR formulation embodies the dynamics of immunizing infections. Because viruses reproduce rapidly in the host, we ignore within-host kinetics in the simplest SIR models (but see Sect. 8); depending on model details, this leads to a compartmentalization of the host population between (as yet uninfected) susceptible individuals, infected, recovered, and other classes. An initial taxonomic split here is between the SIR model (which crudely assumes that all infected individuals can pass on infection) and the SEIR (susceptible, exposed, infected, recovered) model, which adds an "exposed" (infected but not yet infectious) class [4]. SIR and SEIR models have qualitatively very similar dynamics [13]; however, we describe the latter with its more realistic depiction of viral incubation. The basic SEIR model, illustrated in Fig. 5.1b, reflects the following set of biological assumptions; we use measles as the classic acute exemplar here [14]. After a few months of maternally derived passive immunity, infants enter the virus-naïve "susceptible" (S) class; susceptibles can then become infected by close contact with infectious individuals (generally via

respiratory aerosol for measles). Infection moves individuals into the "exposed" (E) class, where they incubate but do not transmit the infection for around a week; this leads to the infectious (I) class, where virus is shed, again for approximately a week, after which individuals enter the recovered state (R). In the basic SEIR model, recovered individuals are assumed to be immune for life, both to clinical disease and to retransmitting the infection. However, subclinical infection (and hence boosting of immunity [15, 16]) is in principle possible. The lifelong sterilizing immunity induced by such an infection also makes this an excellent potential vaccine candidate [4]. For the SEIR model, vaccination is at its simplest assumed to be delivered to a proportion p of infants at the end of the maternal immunity period (i.e., near the effective "birth" of susceptibles). For individuals who seroconvert, immunity is then often assumed to be lifelong, moving susceptibles into the recovered class (Fig. 5.1c). There is also a considerable literature exploring more operationally realistic age distributions and immunogenic characteristics of vaccines in specific cases [5, 17].

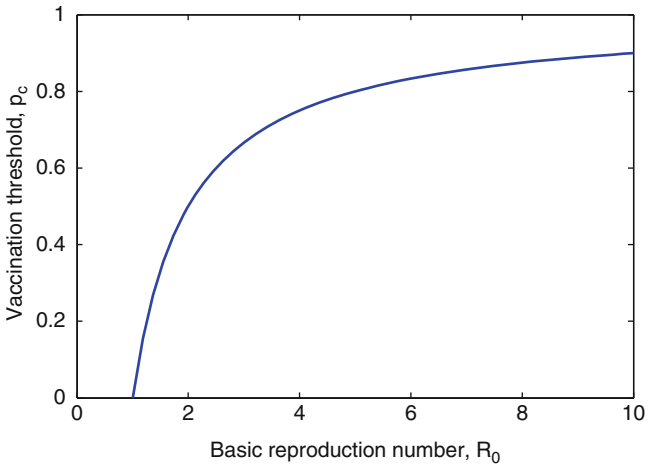

Fig. 5.2 The critical vaccination threshold (p_c) and its dependence on the basic reproduction number, R_0. In the region above the *blue line*, vaccination succeeds in local elimination of infection. Even in the region below the line, however, vaccination can substantially reduce overall transmission

2.3 Herd Immunity and the Impact of Vaccination

We can lay bare much of the dynamical behavior of immunizing epidemics by considering the case of the "simple" epidemic (Fig. 5.1c, d), in which the outbreak occurs sufficiently rapidly to ignore processes of host birth and death. The talismanic quantity here is the basic reproduction number (or ratio) of infection, R_0 [4, 5]. At its simplest, R_0 is defined as the total number of secondary cases caused by an infectious individual when introduced into a well-mixed fully susceptible population. To illustrate the ensuing dynamics, consider an epidemic of infection with $R_0>0$. Since each case initially causes R_0 secondary infections, the epidemic increases more or less exponentially over the first few infectious generations (Fig. 5.1c). However, these dynamics rapidly deplete the susceptible pool. This brings us to the other key parameter of epidemic spread: the *effective* reproduction number, defined as $R=[S/N]R_0$. Here, S/N is the proportion of susceptibles in the population and R is the realized value of R_0 as the epidemic develops [4]. Since S declines over the course of the epidemic (Fig. 5.1c), so does R (Fig. 5.1d).

This progressive decline in secondary infection rates through the epidemic is a manifestation of the key epidemiological process of *herd immunity* [18] – increasing natural immunity of the population that indirectly protects the remaining susceptibles from infection. Eventually, the effective reproduction ratio declines through unity (Fig. 5.1c) as population immunity increases; this corresponds to the herd immunity threshold, above which the epidemic will always decline, even if reintroduced to a closed population. This threshold is thus also a key aim of vaccination campaigns [4, 5]. Remembering that $R=[S/N]R_0$, the associated susceptible proportion at the herd immunity threshold ($R=1$) becomes $s_c=1/R_0$ (Fig. 5.1c); thus, immunizing at a level above $p_c=1-s_c=1-1/R_0$ will eliminate local transmission. As described below, these calculations have been refined considerably to allow for heterogeneities in transmission with age, space, and other characteristics (Sects. 3, 4, and 5). Nonetheless, our simple expression for p_c is an extremely useful metaphor for epidemic control: (1) because of indirect protection, not everyone needs to be vaccinated to eliminate transmission (corresponding to $p_c<1$) and (2) the effort required to increase this level of immunization increases with transmission rates. The latter point is made clear by a simple plot of p_c against R_0 (Fig. 5.2); more transmissible immunizing infections such as measles are harder to control than less transmissible agents such as smallpox. However, this refers to "random" mass vaccination; more targeted strategies such as ring vaccination coupled to active surveillance can promote elimination even below p_c, given (as with smallpox elimination [19]) the right biological characteristics and logistics. Partial immunity and other characteristics of the population can complicate the picture still further (see Sect. 5.2 below). Nonetheless, the metaphor that more transmissibility necessitates a stronger vaccination effort remains.

2.4 Seasonal Transmission and Recurrent Epidemic Dynamics

2.4.1 Observed Epidemic Patterns in Developed Countries

In the simplest analysis of an immunizing infection (Sect. 2.2), sustained cycles of infection will disappear, and the infected proportion in the population will settle to a constant level

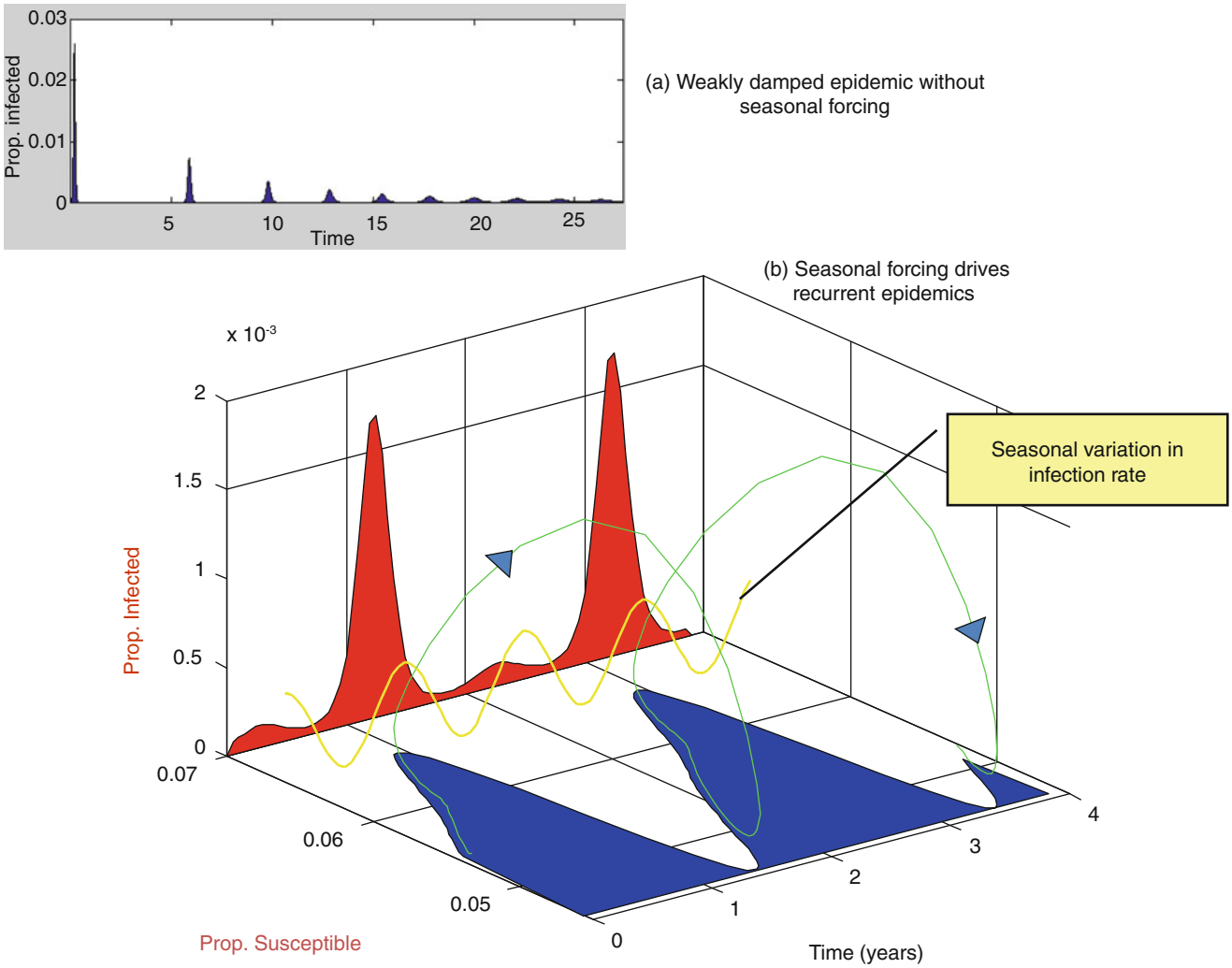

Fig. 5.3 (**a**) Simulated SEIR dynamics for measles with a birth rate, but in the absence of seasonal forcing of transmission rate; for full model specification and parameters, see Grenfell and Bolker [20]. (**b**) Same model, with sinusoidal forcing of the infection as shown (forcing amplitude set to 0.2; Grenfell and Bolker [20]). The green trajectory shows the joint dynamics of susceptible and infectious densities through time; area plots show the dynamics of infectious and susceptible individuals (Taken from Fig. 3 in above book chapter, found on p.39)

(Fig. 5.3a). The question of what maintains the recurrent epidemics [9] generally observed for immunizing childhood infections (e.g., Fig. 5.1) drove researchers to seek the key aspect of biological realism missing from the simplest SEIR model. For measles in England and Wales, seasonal variation in transmission driven by increased contact rates of children when schools were in session rapidly emerged as a possible candidate [12, 21] and has since received considerable empirical support [2, 3]. Stochastic fluctuations in incidence could in principle also contribute to the maintenance of cycles [22, 23]; however, for measles, the predominant driver is seasonality in transmission [2, 3]. Birth rate may modulate the periodicity of recurrent cycles driven by seasonality through its role in determining the rate of susceptible replenishment [24]. For example, for most of the postwar pre-vaccination era in London, seasonality generated sustained cycles by resonating with the biennial epidemic tendency of measles dynamics. However, during the postwar baby boom, births achieved sufficient levels to shift measles dynamics into annual cycles (Fig. 5.4).

2.4.2 Epidemic Dynamics in Developing Countries

It was realized early that seasonality could also result in more complex dynamics, including chaotic fluctuations, that is, very irregular dynamics with little long-term predictability. Contexts with both high and low birth rates (and both high and low transmission since birth rates and transmission act dynamically in very similar ways for immunizing infections [24]) can promote complex dynamics via coexisting attractors. Until recently, it was thought that chaotic measles dynamics were not likely to

be observed [3, 25], since observed seasonality in transmission was not strong enough to drive the associated violent epidemics. However, recent analyses of measles in Niger revealed very strong seasonality (driven by movement in and out of cities linked to rainfall); this, combined with high transmission rates and the highest birth rate in the world, results in irregular outbreaks consistent with expectations of chaos (Fig. 5.5). Erratic boom and bust outbreaks are expected to continue even as routine vaccination improves; and this suggests that high investment in reactive vaccination and surveillance is important, and pulsed vaccination approaches such as supplementary immunization activities could also play a helpful role in synchronizing dynamics [26].

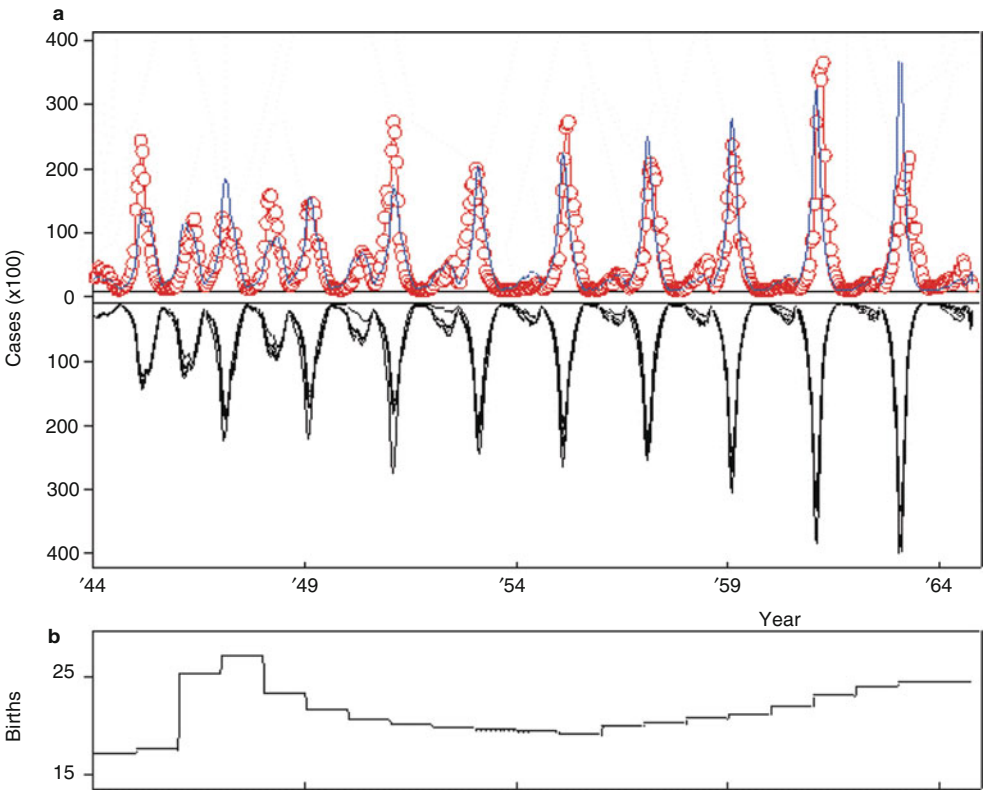

Fig. 5.4 (**a**) Observed pre-vaccinations measles dynamics for London (*red circles*), corrected for under-reporting, along with predictions of an autoregressive time series version of the SEIR model, starting at the observed initial density of cases and susceptibles (for more details, see [126]) (**b**) Birth rates accompanying the dynamics in panel (**a**) (Taken from Fig. 4 in above book chapter, found on p. 41)

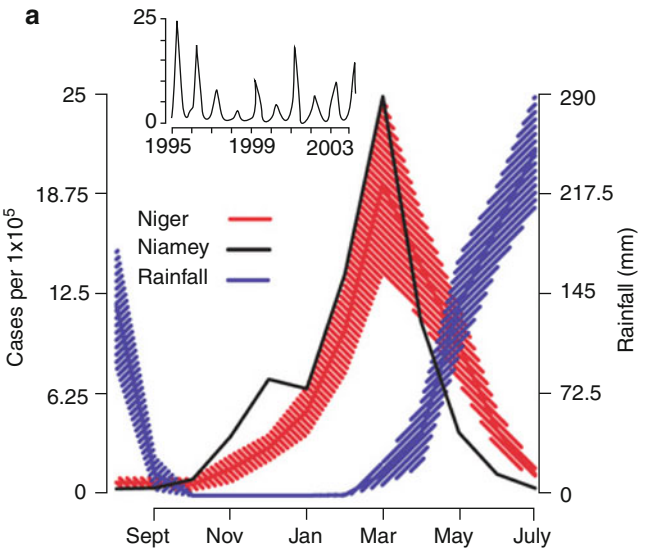

Fig. 5.5 Time series dynamics of measles outbreaks from Niger. (**a**) Mean number of reported measles cases per 10,000 nationwide in Niger from 1995 to 2004, and the mean monthly rainfall over the same time period (*blue*). Shaded regions give ±2 standard deviations. *Black curve*, mean monthly cases of measles in Niamey from 1986 to 2005. *Inset* monthly measles time series from 1995 to 2004. (**b**) Weekly measles case reports from seven departments of Niger, 2001–2005. *Red asterisk* Niamey. Each department is an aggregate of 3–8 arrondissements. (**c**) Case reports per month for the city of Niamey from 1986 to 2005. The *box* indicates the time frame shown in (**b**). *Black dots* months with 0 reported cases (Taken from Fig. 1, Ferrari et al. [26]; http://www.nature.com/nature/journal/v451/n7179/images/nature06509-f1.2.jpg)

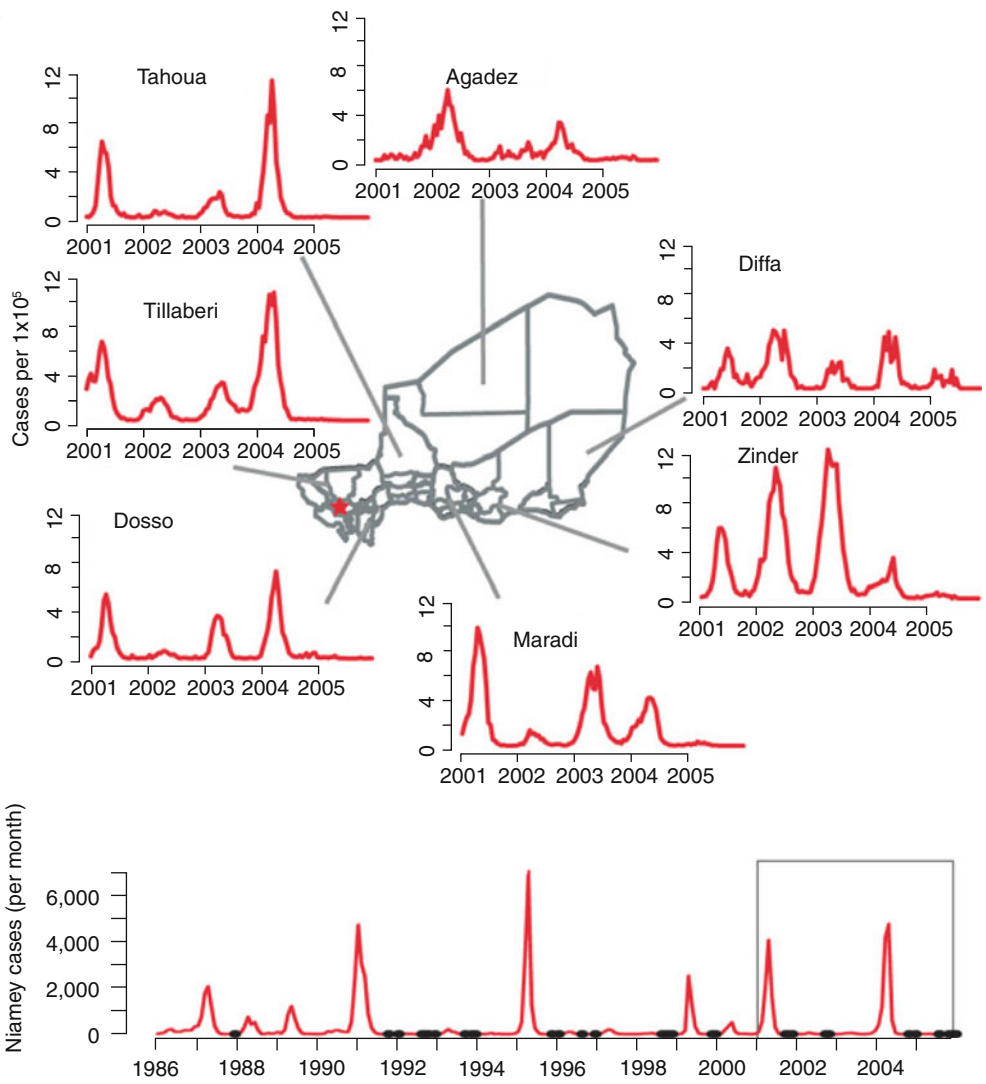

Fig. 5.5 (continued)

3 Age Structure, Demography, and Serological Profiles

The mean age at which individuals become infected by immunizing viral infection is generally lower for infections with higher rates of transmission or R_0 (defined above). Intuitively, this occurs because the faster an immunizing virus is spreading through a population, the younger the age at which individuals are likely to be exposed to it. Host demography modulates this relationship, and higher birth rate countries with an R_0 equivalent to that in lower birth rate countries will tend to have a lower average age of infection [27]. Maternal immunity, or protection of children after birth by transfer of maternal antibodies, will also have an impact, increasing the average age of infection for children whose mothers have been exposed to infection. Since maternal antibodies rarely persist for much more than a year, this effect will be greatest for infections with very low average ages of infection [4]. Beyond these broad descriptors, however, there is the added complication of possible relationships between age and probability of exposure to infection. Such relationships may arise for a variety of reasons. For example, only individuals beyond a certain age may work in areas where the disease is transmitted, or the disease may be only sexually transmitted. As a result, the force of infection, or probability that a susceptible individual will be infected, will show a distinct relationship with age.

For directly transmitted infections, like measles, mumps, rubella, and influenza, the age profile of the force of infection is determined by the rate at which individuals of different ages interact. There are two approaches to estimating this variation. The first is to use age profiles of seropositivity to infer the pattern of the force of infection and, from this, extrapolate to the pattern of contacts over age [28–31]. The link between these age profiles and the force of infection over age can be made since once an individual has been

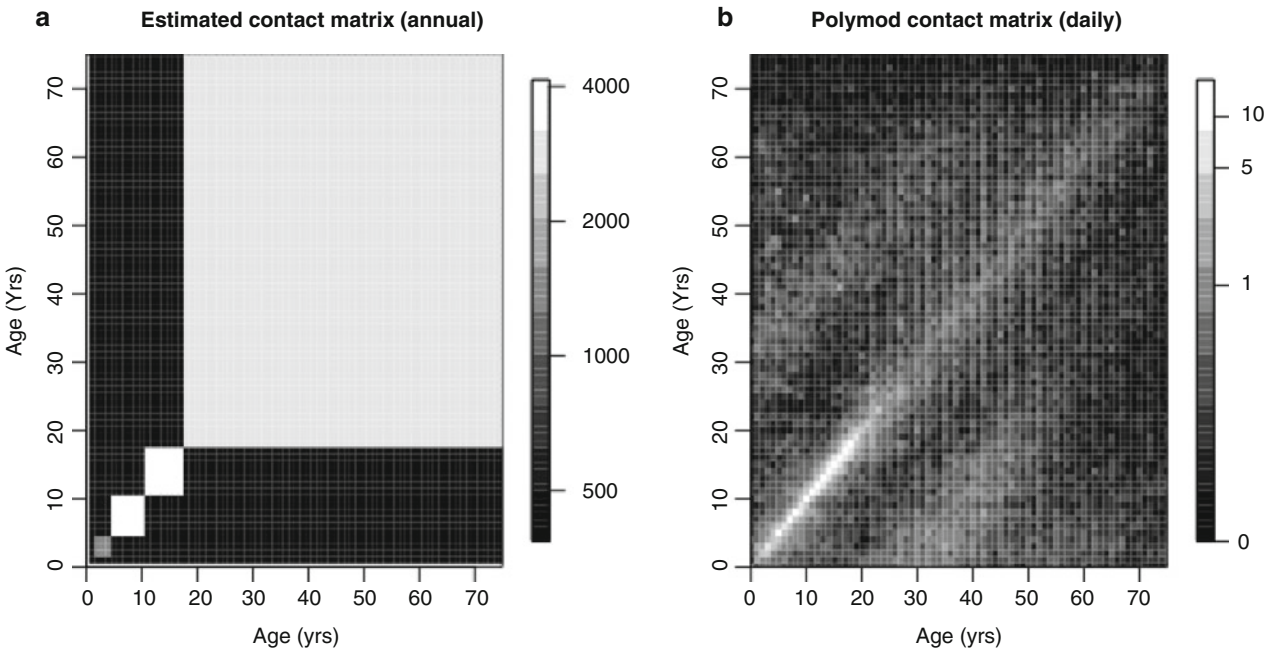

Fig. 5.6 (**a**) Contact matrix (annual) estimated from serology profiles and incidence data using maximum likelihood approaches (Ref. [30]), here showing a semi-assortative mixing matrix; (**b**) POLYMOD contact matrix (daily) obtained from diary studies showing records across all of Europe (Ref. [34])

infected, she/he can never be infected again. Therefore, to be immune at any age, the individual must have contracted the infection prior to that age. On a population level, cross-sectional seropositivity thus provides an indication of the total risk of infection for individuals up to a given age. (Longitudinal age-serological profiles can be even more powerful in quantifying epidemic risk [32]).

The age profile of infection can be framed mathematically [33], and parameters describing contacts between individuals of different ages inferred [31]. The resulting estimated matrix of contacts over age is known as the Who-Acquires-Infection-from-Whom or WAIFW matrix. Alternatively, patterns of contacts between individuals can be directly measured [34], for example, using diary studies (Fig. 5.6); and by combining this with the age profile of infection within the population, the force of infection over age can be inferred [35].

The infection dynamics themselves may also influence the relationship between age and force of infection. If outbreaks are separated by long intervals during which little exposure occurs, individuals may remain susceptible for many years and thus contract the infection at a later age than might be predicted from the age profile of contacts alone [36]. More subtly, detailed network analyses show that even within a single influenza outbreak, the burden of disease can cascade from children (where contacts are highest) to the less connected adults as immunity accumulates within the children, with implications for optimal vaccination distribution [37].

Understanding the processes underlying the average age of infection has a practical importance for any infection where the burden of disease shows an age profile. Rubella is a classic example. Infection during early childhood tends to be mild, but infection during pregnancy may result in birth of a child with congenital rubella syndrome, consisting of a range of birth defects (see Ref. [38]). A realistically complex age structure of mixing, as detailed in empirical studies, may thus be of crucial importance in establishing the burden of disease [39] but also how the burden of disease is likely to change as a result of vaccination.

4 Spatial Dynamics

So far, we have assumed that deterministic, spatially homogeneous dynamics govern infectious disease outbreaks. In fact, epidemics often spread across a heterogeneous landscape of human cities, towns, or rural communities, and this spread depends partly on the links between those locations. This leads us to move from the *deterministic* SIR model described above to *stochastic* models, which account for the random nature of individual infection dynamics and demography – for instance, individuals may or may not become infected with a given average probability, so that by chance, particularly in small populations, no new infections may occur, and the chain of transmission may be broken. During the troughs between epidemic outbreaks in smaller communities, incidence may fall to such low numbers that local extinction is likely.

Based on this observation, Bartlett [9, 40] used analyses of epidemiological data and stochastic models to develop the notion of critical community size (CCS), or population size below which stochastic extinction is expected, which was further developed by Black [41] in studies of measles persistence in insular populations. Bartlett demonstrated the existence of a CCS of around 300,000–500,000 for measles in England and Wales. For measles to persist in locations with a population size smaller than this CCS, immigration of infected immigrants from elsewhere in the metapopulation is necessary. The result is that the spread of measles across England and Wales in the pre-vaccine era resembled traveling waves spreading out from London [6], with a substantial epidemic lag in locations further away. The duration of the lag was also shaped by the size of the local populations. The duration of fade-outs following local extinction contains information on the degree to which a particular location is connected to the metapopulation as a whole [42]. Generally, this points to larger places being more connected. More detailed parametric analyses tend to confirm this (e.g., the gravity model [43]).

Similar processes may operate for immunizing or lethal infections in animal populations, with, for example, the spread of rabies through raccoon populations acting as an invasion wave structured by large landscape features such as rivers [44]. For more complex human infections, features such as imperfect immunity (see Sect. 5.2 below) will tend to shift the age class of hosts who disperse the infection. That shift may impact on the main mechanism of dispersal [45] and move the scenario away from invasion into a locally coupled landscape to a more demographically driven dynamic [46].

5 Comparative Dynamics

So far, we have explored the epidemiological dynamics of acute, immunizing viral infections. Though the resulting dynamics are both important and fascinating from a dynamical perspective, the natural (life) history of most viral infections departs, in one way or another, from this simple case. We review these complexities, and their epidemiological and control implications, in succeeding Sections.

5.1 From Acute to Chronic

A dramatically different life history from the transient infection paradigm represented by measles is observed with infections that are much more persistent (even lifelong). This difference may be expressed in terms of infectious period in individual hosts [4]. To illustrate how increasing infectious period alone modifies the violent epidemics of childhood infections, we retain the assumption of lifelong immunity of the SEIR model and vary the infectious period, from the roughly 1 week of measles to 10 years, corresponding to the approximate average pre-HAART treatment infectious period of HIV [4].

Figure 5.7 explores this comparison, simulating an infection which invades a partly susceptible population (full details are given in Ref. [6]; note that for clarity, the epidemic curves for 1- and 10-year infectious periods are raised above the curves for the more acute infections). Each simulation refers to a virus with a different infectious period. We assume that R_0 is identical for each of these infections. R_0 is roughly given by the product of mean *per capita* infection rate and infectious period; thus, to keep R_0 constant:

- A short infectious period implies a relatively high infection rate.
- A longer infectious period requires a lower infection rate.

This assumption imposes a simple evolutionary constraint on our set of model pathogens in Fig. 5.7, in that fitness (roughly equating to R_0) is kept constant as we increase the infectious period. Figure 5.7 indicates, first, that increasing the infectious period reduces, and eventually eliminates, the tendency for cyclical epidemics [48]; essentially, a longer infectious period "fills in the troughs" following major epidemics. As infectious period increases, we therefore see a transition from seasonally driven biennial epidemics (at the measles extreme of a 1-week infectious period) to low-amplitude annual epidemics (at 1 month). For longer infectious periods (1 year), we see slowly evolving epidemics with little seasonal activity and a modest post-epidemic overshoot. Finally, for a 10-year infectious period, we see a smooth slow epidemic, with an essentially "logistic" rise to a stable endemic plateau of incidence. Though crude, this exercise captures the essential dynamical transmission from the violent epidemics of acute infections to the much smoother and slower epidemic invasion of HIV [4]. Note that the seasonal variation in infection rate is assumed similar for the "measles" and "HIV" cases; however, the latter completely eliminates associated seasonal fluctuations in incidence due to the smoothing effect of prolonged infectious carriage.

Figure 5.7 also illustrates a second major dynamical impact arising from the trade-off of increased infectious period against lowered infection rate. "Fast" infections are much more prey to local stochastic extinction in the deep troughs between epidemics (Sect. 2.4) than the much more endemic incidence promoted by longer infectious period. On the other hand, acute immunizing infections can invade populations much more quickly than chronic infections for the same R_0 (Note that very imperfect immunity (corresponding to 'SIS' dynamics) could generate 'fast' invasion even for relatively chronic infections (Figure 5.7, inset), because of the increased supply of susceptible individuals (Sect. 5.2)). Note that, despite these great variations in dynamics, the assumption of a common R_0 means that the herd immunity

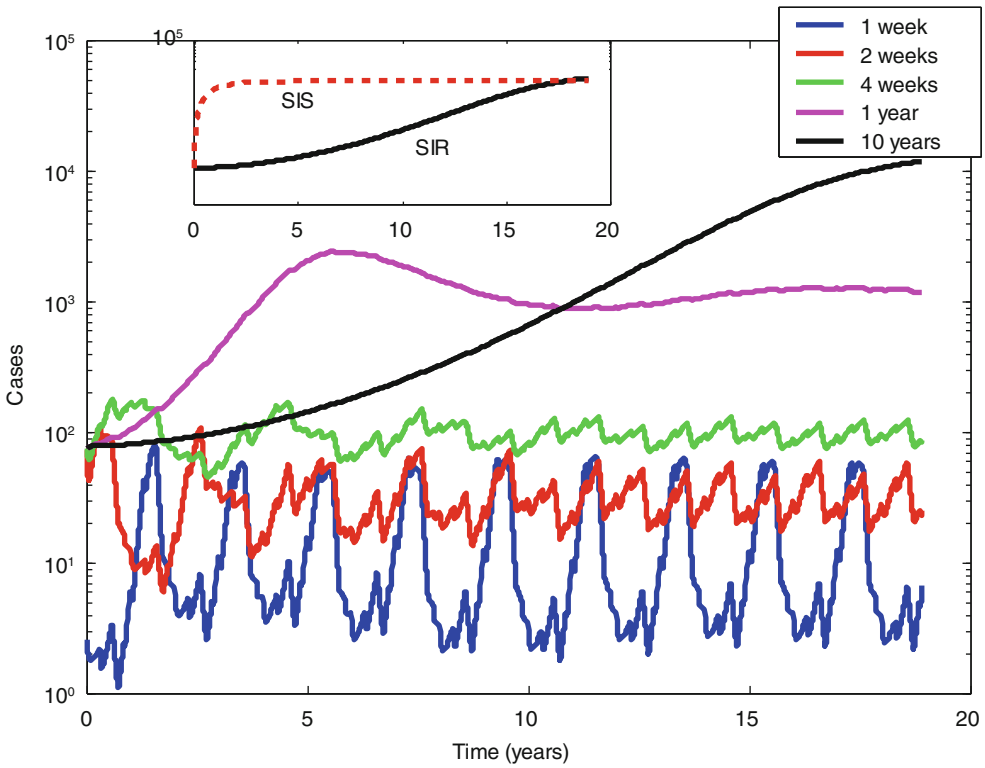

Fig. 5.7 Numerical solutions of seasonally forced SEIR models (see Fig. 5.3b), showing changes in the dynamics of infection caused by increasing the infectious period (see *color key*) while maintaining the basic reproduction number of infection at a constant level. To simulate crudely the initial dynamics of a "novel" infection, the system starts by introducing 6 % infectives into a 20 % susceptible population (a real novel epidemic might be much more violent if everyone is susceptible). *Inset*: Comparing the "slow" dynamics generated by a 10-year infectious period with a (sketched) solution of an SIS model with much faster dynamics (Taken from Figure in Box 2, Grenfell and Harwood [47])

threshold for elimination of infection is the same across this range of behaviors Sect. (2.3).

5.2 Departures from the SEIR Paradigm

We have seen that the SEIR framework (Fig. 5.1b) can be a powerful tool for capturing the dynamics of perfectly immunizing infections such as measles. With its various refinements to incorporate structure in the host population (such as age and spatial distribution), it yields a rich variety of dynamical behavior (Fig. 5.7). Given the range of immunological complexities and different viral life histories, however, it is clear that SEIR dynamics are only part of the story. In such cases, it is often possible to adapt Fig. 5.1b to more faithfully reflect such important biological complexities.

5.2.1 Waning Immunity

Many viruses are capable of reinfecting a host. This may be due to the waning of host immunity over time, as with respiratory syncytial virus (RSV) [49], or due to viral evolution for immune escape (e.g., with norovirus [50] and influenza) [51, 52]: see Sect. 6 for a more in-depth treatment of the latter. In either case, the overall dynamical effect is for recovered, immune individuals to eventually reenter the susceptible pool, as illustrated by Fig. 5.8a.

Where such waning of immunity is appreciable, the implications for vaccination can be profound. As the susceptible pool is replenished not only by births but also by previously immune individuals, the critical vaccination threshold (Sect. 2.3) is raised, making it more difficult to control the spread of infection. For this reason, vaccination against many imperfectly immunizing infections is aimed at direct protection of those receiving vaccine, rather than at raising indirect protection.

5.2.2 Partial Immunity

So far, the models we have considered assume that immune individuals have solid, transmission-blocking immunity, even if this should wane through time. In reality, however, it is common for immunity to be clinically protective (i.e., against symptomatic disease) but only partially protective from infection. This applies, for example, in the case of rotavirus, the leading cause of severe diarrhea in infants worldwide [53, 54]. Figure 5.8b illustrates a model structure developed to capture these dynamics [46].

5.2.3 Host Heterogeneity in Transmission

Recalling the qualitative differences between the dynamics of acute and chronic infections (Fig. 5.7), some viruses show a "mixed" character on the host population level: while some individuals clear infection relatively quickly, others may continue to harbor the virus as "carriers," either in a latent phase or in a chronic infectious state, for a longer period. An example is hepatitis B, in which 5–10 % of adult patients show chronic infection. As illustrated in Fig. 5.8c, this can be represented mathematically by identifying two infectious classes: one acute and the other chronic.

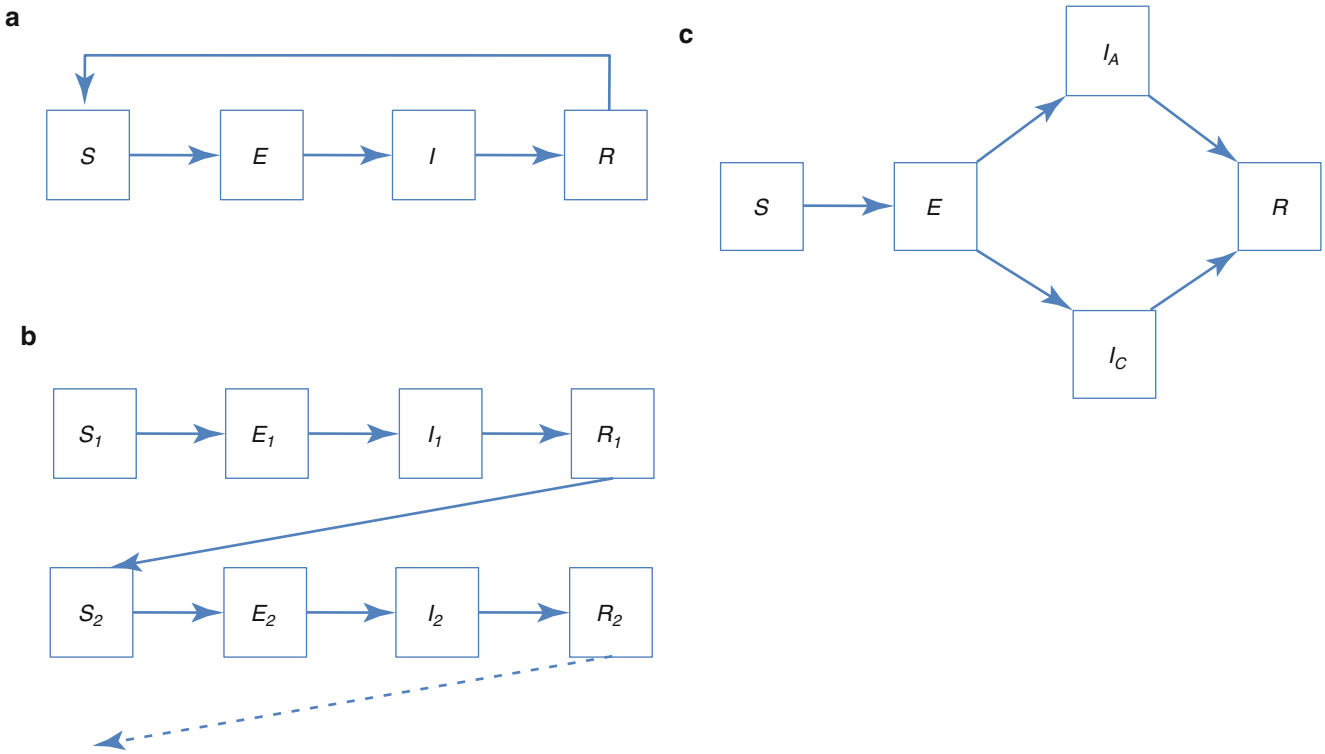

Fig. 5.8 Examples for extensions of the basic SEIR model (Fig. 5.1b). (**a**) Waning immunity can be represented by allowing individuals to return from recovered (R) to susceptible (S) status at a given rate. (**b**) If acquired immunity affords clinical but not sterilizing (transmission-blocking) protection, then additional SEIR stages may be incorporated to capture the corresponding effects on transmission dynamics. (**c**) An example of population heterogeneity, distinguishing "acute" cases (I_A) from "carriers" (I_C), the latter recovering at a slower rate than the former

Such factors can have implications for the dynamics and persistence of infections in a population [55]. In particular, where a disease shows epidemic cycles, facing the possibility of local extinction in the epidemic troughs, the presence of a small number of carrier hosts can facilitate viral persistence in the population, through these troughs. For example, in some cases infection with varicella zoster virus can be followed decades later by infectious shingles, an occurrence which could maintain the virus in small populations [56].

5.2.4 Complex Viral Strain Interactions

Strain structure, vector dynamics, and seasonality in transmission offer yet more complexities, as in the example of dengue [57]. Spread by *Aedes* mosquitoes, dengue has shown a significant emergence worldwide in the last 50 years.

Dengue dynamics are notable for the global circulation of four distinct serotypes (see Fig. 5.9a). Notably, prior immunity to a given serotype can elevate the risk of severe disease from subsequent infection by a different serotype [60–62]. It has been proposed that this arises from antibody-dependent enhancement (ADE) between different serotypes [63, 64], and modeling studies suggest that ADE could play an important role in shaping the epidemiological and strain dynamics of dengue, on the host population level [65–67].

However, there are also indications of a short period of cross-protective immunity (i.e., against all serotypes) for 2–9 months following infection [68], potentially mediating some degree of competition between serotypes. Several studies have addressed the dynamical implications of interactions between ADE and such immunity [69, 70]. Dengue dynamics are therefore complex and multifactorial: an understanding of these effects is important in understanding the potential for unexpected effects from transmission-reducing interventions [71].

6 Dynamics and Evolution of Immune Escape

Had viruses been discovered by the time that Darwin proposed "descent with modification" in the mid-nineteenth century, they may quickly have been recognized as fine examples of evolution in action. Indeed, today there is wide acknowledgment of the inextricable role that evolution plays in viral dynamics [58] and in the control of many different viral infections. RNA viruses in particular, lacking the replication fidelity of a DNA genome, are capable of considerable mutation rates [72]. In the presence of host immunity, natural selection

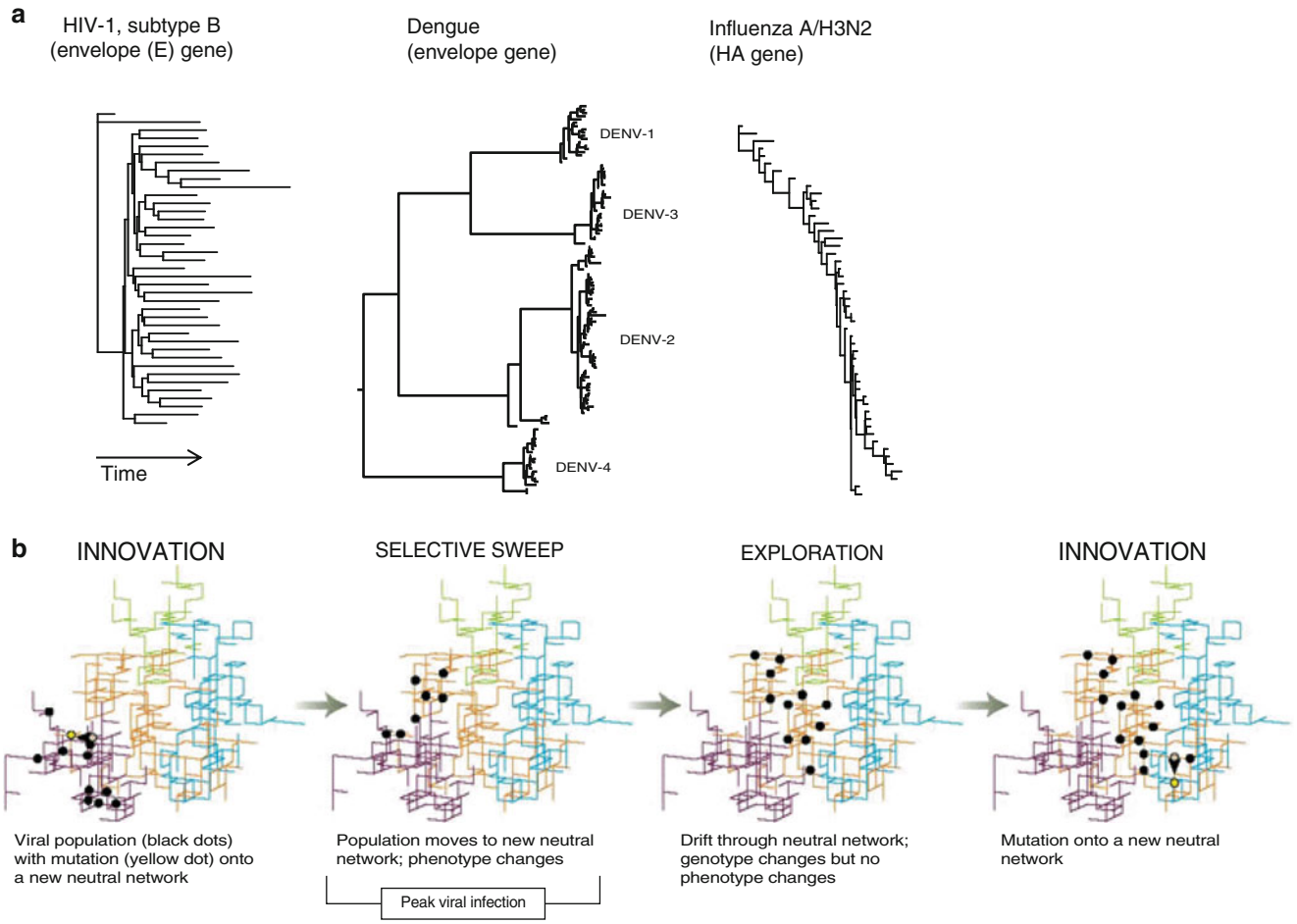

Fig. 5.9 (**a**) A diversity of viral diversity: examples of major human infections showing different patterns of evolution (Taken from (Ref. [58]), and references therein; Adapted from Fig. 1, Grenfell et al. [58]) (**b**) Schematic illustration of the "epochal evolution" model, which seeks to explain notable features in the phylogeny of human influenza A (panel **a**, rightmost phylogeny) (Taken from figure in van Nimwegen [59])

will favor those mutants most capable of evading immunity while still being capable of spreading between hosts.

As a result of these high mutation rates, population-level evolutionary patterns that can arise are quite diverse. Figure 5.9a illustrates how some infections, such as HIV, show significant population-level diversity [73], while others, notably seasonal influenza A, exhibit a markedly different pattern, with a "trunk-like" phylogeny on the population level [74].

The case study of influenza demonstrates not only interesting evolutionary patterns but also the following important features:

(i) The challenges that evolution can pose for infection control
(ii) The complex interplay, across a range of physical scales, between the evolution of a pathogen and its success in spreading in a host population
(iii) The many outstanding questions that remain, in understanding how viruses adapt to continue reinfecting their hosts

In what follows, we explore both within-host and population-level aspects of influenza evolution, with an emphasis on seasonal (interpandemic) influenza. We then set out the prevailing paradigms that seek to explain how these patterns arise, through complex interactions between viral evolution and epidemiology.

6.1 Immune Escape and Herd Immunity

Classic theoretical principles [4] provide a useful framework in which to think about viral evolution, where "evolutionary fitness" is determined ultimately by the capacity for transmission in a given host population. Recall from Sect. 2.3 that in the presence of prior immunity in the population, the effective reproduction number, R, serves as a compact measure of transmission potential. Vaccination aims to lower R through reducing the number susceptible in the population; however, evolving pathogens introduce the complexity of countering this effect, by evading immunity and thus acting

to restore R. Note the combination of immune escape and transmissibility encapsulated in R. In particular, on the scale of the host population and with a given level of existing immunity, the escape mutant with the greatest evolutionary fitness is that which maximizes R [5].

6.2 Molecular Aspects of Viral Evolution

As discussed in Chap. 21, the influenza surface protein hemagglutinin (HA) is a key immune target, with anti-HA antibodies capable of offering sterilizing immunity, that is, the potential to block host infection altogether. Indeed, raising such immunity is a central function of current influenza vaccines. However, HA is also the most variable viral component, continually under selective pressure to escape antibody binding [51]. For these reasons, while influenza evolution is by no means limited to HA, this viral component has attracted the most attention.

An important mechanism of immune escape is through conformational changes of HA epitopes to abrogate antibody binding, without compromising the ability of the virus to attach to host cells [75]. More recently, however, results from mouse experiments suggest that escape mutants can also acquire increased viral avidity for host cells [76]. Another potential immune escape strategy [77] is glycosylation, or the attachment of oligosaccharides to the HA molecule, to occlude epitopes from antibody binding. Such strategies are not without potential functional costs for replication [78], and yet there are indications that human influenza A/H3N2 has been accumulating glycosylation since its introduction into the human population in 1968 [79, 80].

6.3 Population-Level Manifestations of HA Evolution

On a genetic level, the evolutionary pattern for influenza HA (Fig. 5.9a), showing serial replacement of strains through time, is often characterized as "drift." The limited standing diversity, or "trunk-like" phylogeny, is especially paradoxical in light of the relatively high mutation rate of influenza A, where instead several lineages might have been expected to emerge and coexist in the population.

Moreover, how do such *genetic* patterns translate to *antigenic* properties, that is, viral interaction with anti-HA antibodies? In 2004, new techniques allowed a characterization of the antigenic evolution of the influenza subtype H3N2 [74] during the years since its introduction into humans in 1968. The resulting pattern is characterized by "punctuations" in antigenic evolution, occurring roughly every 2–8 years, in contrast with the more gradual pattern of genetic change shown in Fig. 5.9a. These punctuations have great importance for public health, often necessitating major reformulation of current, HA-based vaccines [81].

Two prevailing paradigms explaining these important phenomena, on both the genetic and antigenic levels, are the *epochal evolution* model [82] and that of *strain-transcending immunity* [83]. Both may be considered "phylodynamic" models [58], in the sense of aiming to capture the complex interactions between viral immune escape, viral population genetics, and epidemiology.

The picture of "strain-transcending immunity" [83] invokes a temporary mode of immunity, which immediately follows recovery from infection and protects the individual against infection by all influenza strains. Such broad immunity is postulated to arise, for example, either from T cells or from innate immunity [83]. Over the course of months, this broad immunity gives way to more long-lived, more narrowly acting immunity that is specific to the immunizing strain. On the population level, a key dynamical effect of such immunity structure is to impose population-level constraints on viral diversity, sufficiently strong to maintain a single dominant lineage through time.

The epochal evolution model [82] provides an alternative view. It builds on the proposal by Kimura in 1968 [84] that many amino acid substitutions in nature do not alter evolutionary fitness and are thus *phenotypically neutral*. If influenza HA evolution can be thought of as tracing a series of paths through a space of genotypes, the epochal evolution model proposes that, in phenotypic terms, such a space has a modular structure (Fig. 5.9b) in which each "module" is a group of genotypes sharing the same antigenic phenotype and a transition between modules corresponds to the observed antigenic "jumps." In particular, HA evolution diffuses through the local genotype space, accumulating neutral substitutions and thus genotypic diversity, over several years. Ultimately, a single strain accumulates the substitutions required to transition to a new antigenic phenotype. At this point, the emergent strain – owing to its antigenic novelty – causes a peak in infection and undergoes a selective sweep in the host population, to the exclusion of other strains. Such an event thus acts to periodically control antigenic diversity, maintaining the "trunk-like" shape of the influenza phylogeny.

Alongside these two prevailing paradigms of influenza evolution, yet another model [85] proposes that observed strains are drawn from a limited set of antigenic types, with their selection dependent on niches in host population immunity. While each of these models succeeds in capturing important features of influenza dynamics, they also highlight important gaps in our understanding of viral evolution and how to manage it.

7 Coevolution and the Evolution of Virulence

The degree to which viruses harm hosts varies considerably. Both within and between virus species, some variants may barely affect hosts at all, while others have significant health

impacts, up to and including host mortality [86]. An evolutionary perspective indicates that variation in virulence across clones should be shaped by the costs and benefits of virulence for parasite transmission [87]. The spread and persistence of virulence mutations may be favored if they covary with transmission. However, since host mortality can interrupt transmission, a range of values of virulence may lead to equivalent levels of overall fitness for the parasite [88]. While it is broadly agreed that the theoretical framework and empirical evidence on the existence of virulence-transmission trade-offs need to be further developed and extended [87], there are some systems where the general predictions appear to be borne out (e.g., [89, 90]). Perhaps most famously, the introduction of the myxoma virus into Australia was at first devastating to rabbit populations, causing near 100 % mortality. However, over subsequent years, the virulence of the infection decreased. Various lines of evidence suggest that this occurred in response to selection for increased transmission via decreased virulence – swift rabbit mortality was not an efficient mode of transmission for the virus.

8 Within-Host Dynamics

While we have so far largely discussed virus dynamics on the level of the host population, there are equally important processes to be considered on the within-host level. The "kinetics" of viral infection arise from a complex array of factors including viral replication and variability, the dynamics of the immune response, and pathogenicity to the host [91]. Over the past two decades, mathematical models have played an important role in studying these dynamics, often motivated by the need to understand the actual and potential impact of interventions such as treatment or immunization [91–93].

A major example is HIV infection (see Chap. 43); its clinical course is characterized by an initial acute phase of viral replication, lasting on the order of weeks, followed by an asymptomatic latent phase that can last decades before ultimately progressing to AIDS [94]. Major advances in the 1990s showed that despite the long clinical timescale involved, in vivo HIV replication is in fact a rapid process, with the viral life cycle being on the order of days [95, 96]. Subsequent studies modeling the dynamics of drug resistance underlined the need for early and aggressive drug therapy [97]. Conversely, more recent work capturing the dynamics of the immune response has illustrated how immunity raised by CD8+ T-cell vaccination elicits a response that is too weak and too late to achieve sterilizing immunity [98].

Hepatitis C virus (HCV) represents another major public health challenge and, like HIV, is a rapidly mutating virus capable of continually evading immunity to establish chronic infection [99]. HCV infection is currently treated with broad-spectrum combination antiviral therapy including interferon-alpha, ribavirin, and protease inhibitors, with upwards of 50 % of treated patients being responders; however, there is a need for a more rationally optimized approach. Models capturing viral dynamics in treated and untreated patients have contributed to an understanding of the action of these therapies [100–102], estimates of parameters such as rates of viral growth and of viral RNA clearance [102, 103], and correlates of long-term response to therapy [104].

Modeling approaches have been used to study the kinetics of acute infections too, notably in the context of influenza infection [105]. A key interest, for example, has been the relative importance of target cell depletion, innate immunity, and adaptive immunity in shaping the dynamics of viral infection [106–108].

Overall, while there remain significant gaps in our understanding of these and other major viral infections [103, 109], this work demonstrates the clinically relevant insights that can be derived from a careful study of within-host dynamics [91, 110].

9 Summary and Future Directions

This chapter has broadly outlined the multitude of factors shaping viral dynamics, as well as the role of mathematical approaches in elucidating these factors and their interactions. This growing body of work sets the stage for future directions.

The link between epidemiological modeling and policy is long-standing. Bernoulli's work provides perhaps the earliest case study [1]; recent high-profile examples include the use of models to guide responses to foot and mouth disease in the UK [111], smallpox [112], and influenza [113]. The key criterion of the effective deployment of models for policy is that they are embedded in testable hypotheses, embodying the best possible science. Continuing progress in this area thus calls for better understanding of the basic principles.

Especially in the context of viral evolution, whether in relation to immune escape or virulence, a complete biological framework calls for a linkage of processes across disparate scales, from the macroscopic structure of the host population to the molecular basis of viral replication and transmission. A key task at the heart of this challenge is arguably to quantify transmission potential in terms of immune escape, that is, to measure empirically how changes at the molecular level impact R (see Sect. 6.1). Indeed, recent equine influenza experiments provide some important steps in this direction [114].

New and emerging ways of tracking disease may also help to shed new light on the global spread of viruses and on how they may be better controlled. To name three examples, while disease surveillance continues to operate largely through public health channels, there is increasing interest in the use of alternative sources, including automated

tracking of Internet and social media trends [115, 116]. Second, genetic sequencing and analysis complements existing epidemiological approaches. The advent of high-throughput whole-genome sequencing is expected to shed new light on within-host viral diversity [117], an important aspect in our understanding of viral evolution. Third, any viral infection leaves its mark on the host immune system. Serological studies thus offer another valuable source of information in monitoring diseases [32] and already play an important role in many national surveillance programs (see Chap. 4). While in some cases there remain challenges in the clinical interpretation of quantitative serological data (e.g., Ref. [118]), its future use in estimating, for example, the prevalence of subclinical, but infectious, cases could be of significant value to public health efforts [119–121].

Finally, it is important to consider the role of the hosts themselves. With the host population providing the medium through which viruses spread, important factors in viral dynamics include heterogeneities among individuals (e.g., host genetic variation [122] and "superspreaders" of infection [123]) and patterns of human connectivity and mobility. Various approaches are beginning to unravel some of these patterns, both in the developed [34, 124] and in the developing world [125]. Future developments in such techniques will provide valuable new data for understanding the human role in viral dynamics.

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