PERSPECTIVES: EPIDEMIOLOGY

Simple Rules with Complex Dynamics

Sir Robert May

In the 19th century and the early years of the 20th century, deaths from infectious diseases fell dramatically in developed countries, well before the advent of antibiotics or vaccination. The pattern illustrated for measles (see the figure) can be repeated for scarlet fever, diphtheria, and other infections that carried off heroines in Victorian novels. The causes of the decline remain debatable, although a mixture of better hygiene, improved nutrition, and possible genetic changes in both human and viral or bacterial populations seems plausible (*1*, *2*).

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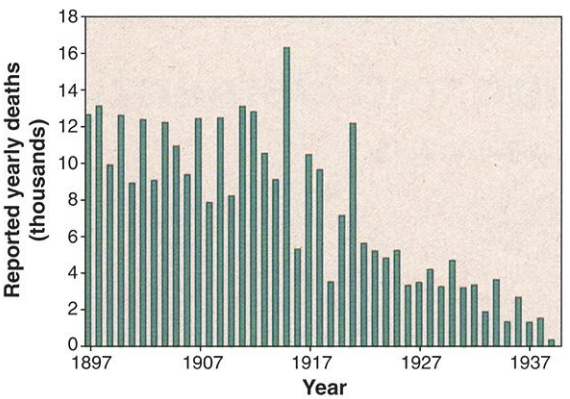
This decline prompted the U.S. Surgeon General to declare in 1967 that "the time has come to close the book on infectious diseases." However, this statement is not true in the developing world, where measles, for example, kills millions of children each year (albeit aided by malnutrition). And the advent of HIV/AIDS throughout the world, and of BSE ("mad cow disease") in some nonhuman animal populations in developed countries, along with strains of tuberculosis and other potentially lethal infections that are resistant to most antibiotics, underlines the continuing need for better understanding of the transmission and control of infectious diseases. To this end, Earn and colleagues (*3*) report on page 667 of this issue a simple mathematical model that explains the cycles of childhood measles epidemics and how they fluctuate in response to the introduction of vaccination and variations in birthrate.

The past 20 years or so have seen many advances in the use of mathematical models to study the dynamics of the engagement between populations of human hosts and infectious pathogens. Such models for viral and bacterial infections commonly divide the host population into categories or compartments—those who have not yet experienced infection ("susceptibles," S); infected but not yet infectious ("exposed," E); infectious (I); recovered and thereby immune (R)—with various rate processes determining the flows into and out of each category. Recent work on these so-called "microparasitic" models (*1*) builds on pioneering earlier studies in mathematical epidemiology in two principal ways. First (and often using newly available techniques), there is much more emphasis on assessing the models' parameters based on empirical data such as the transmission rates of a disease. An important complication here is that transmission rates will often vary over the year, depending on the opening and closing patterns of schools.



Understanding measles epidemics. Yearly numbers of deaths attributed to measles in England and Wales, 1897 to 1939 [from (*1*)].

Second, relatively recent work on chaos in systems exhibiting nonlinear dynamics has demonstrated how very simple sets of deterministic equations, such as those of the SEIR (Susceptible-Exposed-Infectious-Recovered) model, can explain exceedingly complex behavior.

Earn *et al.* (*3*) give a particularly revealing account of this mathematical frontier for measles incidence in four representative large cities (London, Liverpool, New York, and Baltimore) over a 30-year period that spans the introduction of vaccination. Before mass vaccination programs began in the 1960s, measles outbreaks showed different patterns in different places: annual cycles in many developing countries such as Kenya; roughly 2-year cycles in larger developed countries such as Denmark or the United Kingdom; and irregular outbreaks in small countries like Iceland. Under vaccination, patterns of measles outbreaks have tended to become more irregular, both in time and location. Earn and co-workers show that the relatively simple SEIR model can synthesize many of these epidemiological observations, and at the same time can provide population biologists with real-world examples of chaos and bifurcation in the patterns of infectious disease incidence.

A central ecological concept for any population is the "basic reproductive ratio," R_0. In essence, this measures the average number of offspring an individual is capable of producing. For a microparasitic infection, R_0 is more precisely defined as the average number of secondary infections produced by one infected individual in a population where everyone is susceptible. Biologically, R_0 can be written as $\langle\beta\rangle T$, where $\langle\beta\rangle$ is the average rate of producing infections per unit time, and T is the duration of infection. Empirically, for an endemic infection (such as measles before vaccination) R_0 can be estimated as the reciprocal of the fraction of the population who are susceptible, which can be estimated from serological surveys. For example, R_0 in a typical developed country before vaccination is around 5 to 10 for rubella, and around 20 for measles (*1*).

For the standard SEIR model, earlier studies (*4*) had emphasized that vaccinating a proportion, p, of the population had the effect of reducing $\langle\beta\rangle$ to $\langle\beta\rangle(1 - p)$. Correspondingly, R_0 is reduced by a factor of $(1 - p)$. The criterion for ultimate eradication of infection is to drive the effective value of the basic reproductive ratio below unity: hence the eradication criterion $p > 1 - 1/R_0$. Earn *et al.* make generalizations from this observation, noting that changes in the birthrate similarly can be incorporated as effective changes in $\langle\beta\rangle$. This means that, for a discussion of the dynamics of this SEIR system, all changes in either vaccination rates or birthrates can be incorporated in a single parameter—the effective value of the average transmission rate, $\langle\beta\rangle$.

On the other hand, the dynamics of the system depend on the details—the amplitude and the shape—of the annual variation in the measles transmission rate. The system is essentially a forced pendulum, with the pendulum's inherent period dependent on $\langle\beta\rangle$ (which embraces any effects of changing birthrates or vaccination rates) and with a complicated forcing function (set by the seasonal details of school schedules). Earn *et al.* can thus summarize the dynamics, for any speci-

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fied seasonal forcing pattern, in a single bifurcation diagram, which depends only on the effective value of the average transmission rate, $\langle\beta\rangle$ (Fig. 1 in their report) (*3*). In this way, they can then lay bare the otherwise bewilderingly different patterns of measles incidence seen (after the advent of vaccination) in London, Liverpool, New York, and Baltimore (*3*).

I think this does not, however, close the book on the topic. Earn *et al.* use the standard SEIR equations, with their "mass action" assumption that new cases arise in simple proportion to the product of the number of individuals who are susceptible and the number who are infectious. The social realities of family structures, housing conditions, and much else will be anecdotally familiar to anyone responsible for the staff in a large department (for example, parents with children in school are more likely to catch colds). Much relevant work remains to be done in teasing apart the social, genetic, age-related, and other complications that are smoothed out in the usual mass action assumption.

In a country such as the United Kingdom, where childhood vaccination remains voluntary, the practical questions have more to do with fundamental problems in the evolution of altruistic behavior than with the ecological dynamics so beautifully surveyed by Earn and colleagues. There may be risks—very, very tiny, but not zero—associated with vaccination. For example, the risk of meningitis/encephalitis associated with MMR (measles, mumps, and rubella) vaccination is estimated to be around 1 in 1,000,000 (*5*). The risks of infection itself are, however, much greater: from around 1 in 200 to 1 in 5000 for complications due to meningitis/encephalitis after natural infection with measles, mumps, or rubella (*5*). So, your best strategy is for everyone else's child to be vaccinated, thus eradicating the risk of infection, but for your own child to remain unvaccinated. But we are now trapped in the Prisoner's Dilemma: If too many parents "cheat" in this way, herd immunity will no longer protect their children. This is a real paradox, with no trick answer. I believe that the answer to such dilemmas, where individual and group interests ineluctably conflict, is a program of effectively compulsory immunization, backed by a clear and analytical understanding of the effects of population level or "herd" immunity, which are so admirably illustrated by the Earn study.

References

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PERSPECTIVES: AIDS

HIV Infection and Dementia

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Morbidity and mortality associated with HIV infection have declined in developed countries as a result of effective antiretroviral combination therapies that include protease inhibitors. However, the inability of protease inhibitors to effectively cross the blood-brain barrier and penetrate the brain parenchyma has raised concerns that although infected individuals may live longer, they may face a consequent increased risk of developing HIV-associated dementia. This speculation is based on the assumption that initial entry of HIV into the brain, which usually occurs early in infection (*1*), establishes lifelong persistence of the virus. Hence, although therapy effectively controls HIV replication elsewhere in the body, replication could continue in the brain unabated, ultimately initiating neurological disease.

Evidence contrary to this view comes from several lines of investigation:

1) The brains of asymptomatic HIV-infected individuals usually contain very low levels of HIV DNA, or none at all (*2–5*), and tissue expression of the virus—a presumed prerequisite for intracranial spread of the infection—is seldom detected in the former group (*2, 6*).

2) With the advent of protease inhibitors, the incidence of HIV dementia has declined (*7, 8*). This suggests that controlling systemic HIV replication limits the development of dementia.

3) HIV dementia typically does not present before the onset of AIDS. Why is this, if the virus is present within the brain from early infection and if it plays a key role in development of the disease? Perhaps a threshold level is required that takes years to attain (possibly a consequence of the limited range of host cells for HIV in the brain). Alternatively, HIV replication within brain tissue may be controlled before immunodeficiency begins, and when this control is lost, virus replication and spread proceed. There again, HIV replication may require a stimulus associated with later stages of infection, immune activation being a likely candidate. These explanations necessitate that HIV remains essentially dormant within the brain for many years—a conceivable proposition, given that retroviruses can integrate into the host cell genome, and that the primary host cells (microglia and macrophages) are long-lived. Not known, however, is whether a significant portion of the HIV DNA within brains of asymptomatic individuals is integrated into the genome of host cells, which is not the case in those dying with AIDS (*5, 9, 10*).

4) The abundance of macrophages in the brain appears to be a better correlate of HIV dementia than the presence or extent of brain infection (*11*); in the simian immunodeficiency virus (SIV) animal model, the number of macrophages correlates with the severity of central nervous system (CNS) lesions (*12*).

5) The cells expressing HIV in AIDS patients' brains, particularly the multinucleated giant cells, are frequently perivascular in location (that is, they are found in the space between the brain parenchyma and blood vessels) (*13*). The perivascular infiltrates in these brains are frequently composed primarily of macrophages (*14*). Also, neuroinvasion by SIV coincides with an increase in the number of perivascular macrophages (*15*), and these cells appear to be a major target cell for SIV in the brain not only during acute infection (*16–18*), but also later, when encephalitis is present (*18*).

6) SIV-associated neurological disease is more readily produced by intravenous, rather than intracranial, inoculation (*19*).

Together, these findings suggest that in late-stage HIV infection, an increase in trafficking of monocytes (the precursors of macrophages) to the brain may be associated with the development of HIV neurological disease (see the figure). This interpretation is further strengthened by results from a recent case study in our laboratory. We found that sequences of the gp160 gene (which encodes the highly variable HIV envelope protein) from the deep white matter of brain were more closely related to those from bone marrow than to those from other tissues. In fact, they were most closely related to sequences recovered from blood monocytes taken 5 months earlier (*20*).

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