Polio

Herd immunity has played an important role in the ongoing attempts to erradicate polio. Interrupting transmission of the wild-type poliovirus is feasible because the oral polio vaccine (OPV) contains an attenuated live virus, a virus that cannot cause disease but reproduces in the body cells and stimulates immunity. Because certain individuals vaccinated with OPV can shed the vaccine-derived polioviruses (VDPV) to individuals who were not vaccinated, the number of polio-susceptible individuals in the population is reduced. However, OPV has some inherent risks. Although the vaccine strains are transmitted less efficiently than the wild-type poliovirus, by recombining with other enteroviruses (viruses that infect the gastrointestinal tract and nervous system), they can evolve to have the same transmission properties and virulence (Fine and Carneiro 1999; Dowdle *et al.* 2003).

While polio vaccination has reduced the risk of VDPV transmission, circulating VPDVs have initiated four known epidemics during periods when the proportion of vaccinated children was relatively low. This has raised concern over the finality of the polio eradication program and has lead to endgame planning – the decision-making process that will determine when and how polio vaccination will cease (Dowdle *et al.* 2003; Nathanson and Fine 2002). There is a serious risk that VDPV will persist into the post-vaccination era and initiate a new epidemic (Fine and Carneiro 1999; Nathanson and Fine 2002). This is because immunocompromised individuals may continue to shed VDPVs, generating new infections for several years following vaccination. Because the majority of polio cases do not exhibit the symptoms of disease, polio may persist through a silent chain of infections without detection (Eichner and Dietz 1996).

Malaria

In 1897, Ross made the groundbreaking discovery that malaria parasites are transmitted between vertebrates by *Anopheles* mosquitoes, and in 1911 developed the first mathematical model of malaria transmission (Ross 1911). He pointed out that in order to counteract malaria anywhere we need not banish *Anopheles* there entirely – we need only reduce their numbers below a certain figure (Ross 1911). Ross' theoretical research also led him to conclude that intervention campaigns based solely on larval-mosquito control, drugs, or bednets were less likely to succeed than campaigns using combinations of these measures (Ross 1911). Although a number of Ross' insights were confirmed by field studies and subsequently applied to intervention programs, the value of his theoretical achievements went largely unrecognized until the middle of the 20th century.

In the 1950s, Macdonald extended Ross' theoretical research, suggesting that the daily survivorship of adult *Anopheles* was the weakest link in the chain of malaria transmission (Macdonald 1956, 1957). This discovery provided support for the 1955–1969 DDT-based global eradication campaign by the World Heath Organization (WHO) that targeted precisely this link. The success of the campaign varied, leading to reduction and even elimination of malaria transmission in some areas, but minimal change in others. Unfortunately, MacDonald's model was not field-tested until the very end of the campaign, at which point it proved to be a poor predictor of malaria prevalence (Najera 1974). In the early 1970s, however, WHO sponsored the Garki project in northern Nigeria, which included baseline studies, intervention trials, and the development of a model that extended Macdonald's transmission model to incorporate human immunity. Using changes in the mosquito population as input, the Garki model was much more successful at predicting variation in malaria prevalence in the human population, and was employed in the analysis of control efforts that used both insecticide and drug intervention. However, the attempt to interrupt transmission at Garki failed due to unanticipated heterogeneities in mosquito and human populations. The failure of the project caused much of the policy community to conclude that future campaigns to control malaria in Africa were untenable, at least pending the development of a vaccine. Recent modeling efforts have begun to address heterogeneities in mosquito, human and parasite populations, environmental change, and other factors.

Schistosomiasis

Efforts to eradicate schistosomiasis in the first quarter of the 20th century included the drying of irrigation canals, education in rural communities, and the application of copper sulfate molluscicide, all of which proved ineffective (Sturrock 2001; Engels *et al.* 2002). The failure of these control efforts was exacerbated by a lack of resources and the increasing number of habitats made available to the intermediate snail hosts through socio-economic improvements, such as river navigation and drainage (Sturrock 2001). By the end of the First World War, interest in field control waned when antimonial drugs were discovered and community distribution began. Success, unfortunately, was never achieved as the drugs proved costly and often caused severe side-effects (Khalil 1938). It was not until the launch of the WHO, in 1948, that global efforts to control schistosomiasis were spearheaded. The WHO's initial efforts to remedy the lack of environmental control and use of toxic chemotherapy included the development of an international research agenda that would incorporate scientific theory and finding in the planning of control and eradication programs (Sturrock 2001; Engels *et al.* 2002).

Beginning with the seminal work of Hairston and colleagues, an enormous amount of ecological modeling has

been used to understand the population dynamics of schistosomes and to control the transmission of schistosomiasis (Hairston 1961, 1965; Hairston *et al.* 1958). Much of this modeling has been aimed at analyzing the observed patterns of infection in snails and humans, and the likely effects of various intervention strategies. Expanding Hairston's early research efforts, Cohen (1973, 1977) developed sophisticated analyses of host-parasite population dynamics that determined the point in the schistosome transmission cycle when interventions strategies could be most successfully applied. A major insight came from the ecological understanding of the key role played by the statistical distribution of the worms in both their snail and vertebrate hosts. Because schistosomes are dioecious it was initially assumed that control might be achieved by reducing worm burdens to a level where the majority of infections in humans were of a single sex; this would substantially reduce the reproductive rate of the pathogen and cause its numbers to suddenly collapse. However, initial calculations of the mean parasite burden required to achieve this level of control assumed that worms were distributed in a Poisson fashion in the host population. Unfortunately, most parasitic helminthes have highly aggregated distributions that considerably increase the probability that any female worm is likely to be present in a host with a viable male (Shaw and Dobson 1995). This makes it considerably less likely that the parasite population will collapse even when mean worm burdens are less than unity.

If there is a general criticism that can be aimed at some of the earlier mathematical models for epidemics, it is that they often neglected important biological details (particularly spatial heterogeneities) in favor of more elegant mathematical formulations. This was partly a consequence of the primitive computational facilities available until comparatively recently. Nevertheless, there are still regular "new" publications where "backward bifurcations" and other mathematical delights are rediscovered and proposed to offer insights into control. As occurred with the schistosome work, spatial and other heterogeneities can quickly confound these insights.

Anderson and May (1978, 1982) produced a series of theoretical models to illustrate the effects of seasonality and the spatial clustering of infected snails on the success of the schistosome transmission cycle. The results of these modeling efforts were recognized by WHO and employed in the restructuring of schistosome control efforts. In concert with field data, these models were used to determine the season and location of highest snail density and intensity of infection so that molluscicides could be applied most effectively. This restructuring of the molluscicide program minimized, if not outright stopped, transmission in most regions well into the 1980s (Sturrock 2001). Unfortunately, the effect on the human worm burden was slow and interest in molluscicides declined when new drugs appeared, pesticide prices increased, and fears grew out of the potential for adverse environmental effects (Jordan 2000; Sturrock 2001). More recently, however, wider application of mathematical modeling to various aspects of schistosomiasis control has helped the WHO to adopt new intervention strategies (Bergquist *et al.* 1996). For example, schistosomiasis transmission models are currently being developed to facilitate the planning of public health intervention programs that include both vaccination and field-based initiatives, including biocontrol and education (Spear *et al.* 2002). Finally, ongoing efforts to reduce populations of the molluscan intermediate hosts of human schistosomes, via predation and competition by biocontrol species, offer additional hope for the future control of schistosomiasis (Mkoji *et al.* 1999).

SARS

The SARS outbreak in the spring of 2003 caused global disruption of airline traffic and had a major impact on the economies of the Far East (Dye and Gay 2003). Many of the scientists involved in the British foot and mouth outbreak quickly became involved in collating and analyzing data for SARS. When new outbreaks occur the key step is isolating symptomatic individuals and tracing and quarantining their contacts (Fraser *et al.* 2004). A mathematical insight of major importance here is that the proportion of infective contacts that occur before symptoms appear is of major importance in determining the success of the control strategy (Fraser *et al.* 2004). For pathogens such as influenza and HIV, where around 40% and 90% of transmission may occur before symptoms appear, the success of isolation will be limited. Mercifully, for SARS and smallpox, symptoms appear before 5 to 10% of possible transmission has occurred.

Geohelminths

More than a third of the world's people are infected with parasitic worms (geohelminths) (Crompton 1989). These worms reside in the alimentary canals and lungs of people with limited access to sanitation and clean water. While they are rarely fatal, geohelminths have a continuous and substantial impact on growth and intellectual development (Crompton 1989; Chan *et al.* 1994). Mathematical models have been used to examine, develop, and understand the population dynamics of parasitic helminths since the early models of Crofton (Crofton 1971a,b). These models were developed and refined by Anderson and May (Anderson 1978; Anderson and May 1978; May and Anderson 1978) to provide a comprehensive framework that now guides much of our understanding of the dynamics and control of human geohelminths (Anderson and May 1982; Anderson and May 1985; Anderson and Medley 1985; Bundy 1988; Bundy 1990). The major public health

insight provided by these models was the realization that because the majority of the worm population resides in a small proportion of the host population, control should focus on identifying why particular individuals were at risk and how control (usually treatment with anthelmintics) could be focused on these individuals or age-classes (Guyatt and Evans 1992; Medley *et al.* 1993; Chan *et al.* 1995).

River blindness

In 1975, the World Health Organization initiated the Onchocerciasis Control Program (OCP) in western equatorial Africa to combat river blindness (onchocerciasis). OCP's initial efforts were grounded in the rotational application of insecticides intended to kill the black fly vector and ultimately delay disease transmission for a sufficiently long period to allow the human reservoir of infection to decrease to an insignificant level (Davies 1994). By 1983, the success of OCP's insecticide efforts came into question – had vector control really interrupted disease transmission, or was reinfection occurring at undetected levels? To address these concerns OCP developed a series of theoretical models, based on the ecology of black flies and epidemiology of the disease, to predict the number of years of vector control required before the parasite reservoir would fall to insignificant levels (Remme *et al.* 1986; Plaisier *et al.* 1990; Remme *et al.* 1990).

The first set of models confirmed that the initial decade of vector control had been successful and predicted that the prevalence of infection would fall to zero if efforts were continued for 4–5 more years. After 14 years of vector control and the predicted rate of decline in disease prevalence, OPC considered ending the expensive larvicide program (Remme *et al.* 1990; Remme *et al.* 1995). To determine when insecticide operations could be stopped without a serious risk of recrudescence, OCP developed a comprehensive transmission model called ONCHOSIM (Plaisier *et al.* 1990). ONCHOSIM allowed OCP to simulate the effects of human and parasite population densities, the dynamics of vector populations, and interventions via insecticide and chemotherapy on disease prevalence (Remme *et al.* 1995). ONCHOSIM was particularly useful because it was able to test the effects of ivermectin, a popular treatment agent donated by Merck Pharmaceutical Co, as an independent control agent and in concert with larvicide (Habbema and Oortmarssen 1995, Mackenzie 2000). The resulting ONCHISIM predictions indicated that control of river blindness would be possible with committed long-term ivermectin treatment and without additional larvicidal control (Plaisier *et al.* 1990; Remme *et al.* 1995). Employing the methodology suggested by ONCHOSIM, OCP managed the successful control of river blindness in 11 African countries by the end of the program in 2002. Today, disease is no longer considered a public health problem throughout the area and the parasite reservoir has been virtually eliminated.

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